Diagnostic accuracy of structural and visual function tests to detect age-related eye disease

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Contents

Chapter 2: Non-contact methods for the detection of people at risk of primary angle closure glaucoma: a systematic literature review and meta-analysis

List of Tables

Lists of Figures

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Declaration

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Abstract

Global trends in population ageing will lead to an exponential increase in age-related eye disease. If undetected, and in the absence of timely treatment, these diseases could result in significant visual impairment. New technologies for the assessment of ocular structure and function could potentially improve disease identification, but it is paramount that their diagnostic performance is fully evaluated before they can be employed in a routine clinical setting.

Chapter 2 describes the results from a systematic review of the diagnostic accuracy of five non-invasive tests to detect those at risk of primary angle closure glaucoma. The tests evaluated were the van Herick test of limbal anterior chamber depth, flashlight test, Scanning Peripheral Anterior Chamber Depth Analyser, Scheimpflug photography and Anterior Segment Optical Coherence Tomography. A meta-analysis was performed and summary estimates of sensitivity and specificity were calculated for each test. In addition, test comparisons were conducted based on the thresholds with the best performing diagnostic odds ratio. Overall, most tests performed well and showed equivalent accuracy. However, care should be taken in applying the summary estimates in clinical practice due to the observed heterogeneity and high risk of bias found in most studies.

Chapter 3 describes a diagnostic accuracy study to investigate the performance of a prototype flicker perimeter (Accelerator 4-Alternative Forced-Choice Flicker Test prototype (A4FTp)) to detect primary open angle glaucoma (POAG). Participants with glaucoma (n=38) were compared to normal controls (n=40). The diagnosis of POAG was confirmed by a reference standard ophthalmic examination and the performance of the A4FTp was compared with two available screening tests: Frequency Doubling Technology perimeter and optical coherence tomography (OCT). The clinician performing these tests was masked to the results of the reference standard examination. Diagnostic accuracy of all three tests was equivalent in the detection of POAG. Time taken to complete the A4FTp was relatively short with good subject acceptability. Initial results are promising and with further development, the test could have a role in glaucoma detection.

Chapter 4 reports on the diagnostic value of OCT to detect glaucomatous disc damage or retinal pathology using a clinical vignette methodology. A sample of 50 community optometrists undertook online training followed by completion of a computer-based vignette assessment, showing either a single fundus/disc photographic image (n=26) or a combination of a fundus/disc image with the corresponding OCT scan (n=26). Comparing the OCT combination to fundus imaging alone improved overall diagnostic performance by approximately 20%, with fewer false positives and false negatives recorded. These findings suggest that OCT could augment case-finding, but further research is needed to evaluate its value in a real-world setting.

Abbreviations

AAC	Acute angle closure
ACA	Anterior chamber angle
A4FTp	Accelerator 4-Alternative Forced-Choice Flicker Test prototype
ACD	Anterior chamber depth
ACG	Angle closure glaucoma
ACV	Anterior chamber volume
AJ	Anish Jindal
AMD	Age-related macular degeneration
AOD	Angle opening distance
ARA	Angle recess area
AS-OCT	Anterior Segment Optical Coherence Tomography
AUROC	Area under receiver operator characteristic curve
BF	Bruno Fidalgo
CI	Confidence Interval
CO	Corneal opacities
COAG	Chronic open angle glaucoma
CoO	College of Optometrists
CT	Christopher Tyler
dB	Decibel
DC	Dioptric Cylinder
dL	Decilog
DOR	Diagnostic odds ratio
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Screening Service
DS	Dioptric Sphere
EGS	European Glaucoma Society
EL	Ersilla Lucenteforte
FDT	Frequency Doubling Technology

GCC	Ganglion cell complex
GOC	General Optical Council
GP	General practitioner
GSS	Glaucoma Staging System
HFA	Humphrey Field Analyser
IC	Irene Ctori
IG	Iris Gordon
IOP	Intraocular pressure
IQR	Interquartile range
ISGEO	International Society Geographical Epidemiological Ophthalmology
ITC	Irido-trabecular contact
JL	John Lawrenson
LACD	Limbal anterior chamber depth
LOCS	Lens Opacity Classification System
LPI	Laser peripheral iridotomy
LV	Lens vault
MD	Mean deviation
MSVI	Moderate/severe visual impairment
NA	Narrow angle
NICE	National Institute for Health and Care Excellence
NLR	Negative likelihood ratio
NPV	Negative predictive value
NR	Not recorded
NSC	National Screening Committee
OCT	Optical coherence tomography
PAC	Primary angle closure
PACG	Primary angle closure glaucoma
PACS	Primary angle closure suspect
PAS	Peripheral anterior synechiae

PLR	Positive likelihood ratio
POAG	Primary open angle glaucoma
PPV	Positive predictive value
PSD	Pattern standard deviation
PTM	Posterior trabecular meshwork
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RE	Refractive error
RevMan	Review Manager
RGC	Retinal ganglion cells
RNFL	Retinal nerve fibre layer
RNIB	Royal National Institute of Blind People
ROC	Receiver operator characteristic curve
SAP	Standard Automated Perimetry
SD	Standard deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SIGN	Scottish Intercollegiate Guidelines Network
SITA	Swedish Interactive Thresholding Algorithm
SPAC	Scanning Peripheral Anterior Chamber Depth Analyser
SROC	Summary receiver operator characteristic curve
SS	Scleral spur
SS-OCT	Swept-Source Optical Coherence Tomography
STARD	Standards for Reporting of Diagnostic Accuracy Studies
SWAP	Short Wave Automated Perimetry
TISA	Trabeculo-iris space area
UBM	Ultrasound biomicroscopy
UK	United Kingdom
USA	United States of America
VMT	Vitreo-macular traction

Chapter 1 Introduction

1.1 Epidemiology of age-related posterior segment diseases

It is estimated that there are 253 million people worldwide who live with a visual impairment; its distribution is affected by age and 81% of people who are blind or have moderate/severe visual impairment (MSVI) are aged 50 years and above (Bourne et al., 2017). In 2019, there was an estimated 702 million people who were aged 65 years or over, accounting for 9.1% of the global population and by 2050, this number is forecasted to increase to 1.5 billion (15.9%) (UN, 2019). It was previously thought that population ageing was confined to high income countries, however a recent report has found that virtually all countries are now experiencing this phenomenon (UN, 2019).

It is predicted by 2020 there will be 237.1 million people globally who will have MSVI and 38.5 million who will be blind, increasing by 20 million and 2.5 million respectively from 2015 (Flaxman et al., 2017). Anterior segment eye diseases account for a greater proportion of age-related blindness than posterior segment eye diseases (Figure 1.1). However, the two leading causes of irreversible MSVI and blindness affect the posterior segment, which are glaucoma and age-related macular degeneration (AMD) where age is the predominant risk factor for both diseases. Glaucoma is the leading cause of irreversible blindness worldwide (Kapetanakis et al., 2016), accounting for 2% of global visual impairment and 8% of blindness in those aged 50 years or older (Flaxman et al., 2017). AMD prevalence is high in the elderly population, particularly in high income countries, where it is the leading cause of irreversible blindness (Bressler, 2004, Congdon et al., 2004, Chakravarthy, 2006, Jager et al., 2008, Bourne et al., 2018). Globally, AMD accounts for 4% of MSVI and 6% of blindness (Congdon et al., 2004, Flaxman et al., 2017). It has been forecasted that from 2015 to 2020, there will be an increase of almost 1 million people with MSVI and 0.2 million people suffering from blindness from these two conditions alone (Flaxman et al., 2017).

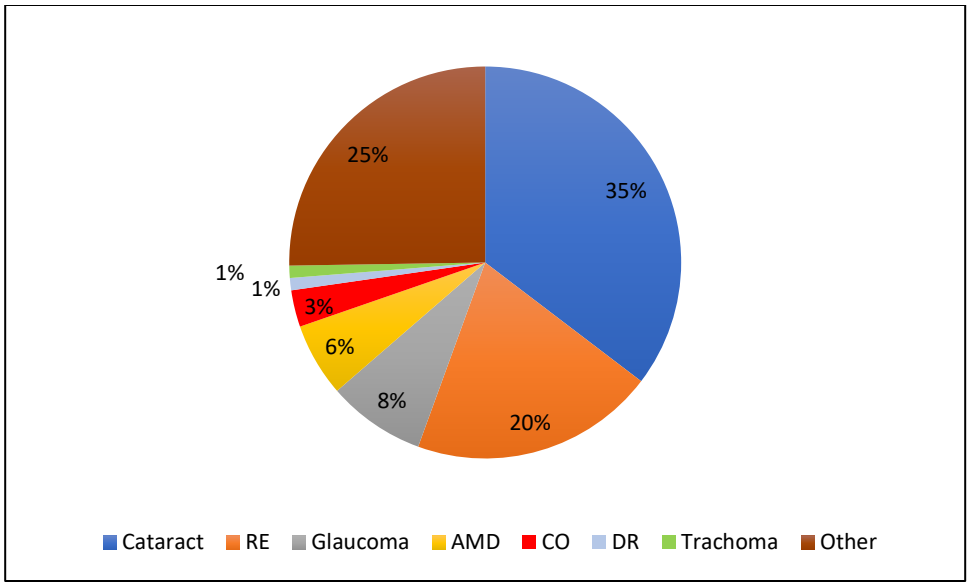


Figure 1.1. Global causes of blindness in those aged 50 years and older (Flaxman et al., 2017). RE: Refractive Error (uncorrected); AMD: Age-Related Macular Degeneration; DR: Diabetic Retinopathy, CO: Corneal Opacities.

1.1.1 Glaucoma

Glaucoma can be defined as 'a group of optic neuropathies characterised by progressive degeneration of retinal ganglion cells' (Weinreb et al., 2014). There are several classifications used to define the subtypes of glaucoma. It can be initially classified as primary or secondary. Primary glaucomas are not associated with any other ocular or systemic diseases, whereas secondary glaucomas show these associations. Further sub-classification is based on the status of the anterior chamber angle (ACA) as determined by gonioscopy. In the presence of glaucomatous optic neuropathy; primary open angle glaucoma (POAG) is diagnosed when the posterior trabecular meshwork (PTM) within the ACA is not obscured by the peripheral iris whereas in primary angle closure glaucoma (PACG) the PTM is mechanically blocked by the peripheral iris. Figure 1.2 describes the classification of glaucoma.

For this thesis, the term POAG has been predominantly used. Occasionally, reference is made to chronic open angle glaucoma (COAG), which was the terminology adopted by the National Institute for Health and Care Excellence (NICE) glaucoma clinical guideline committee (NICE, 2017). Both terms are effectively synonymous.

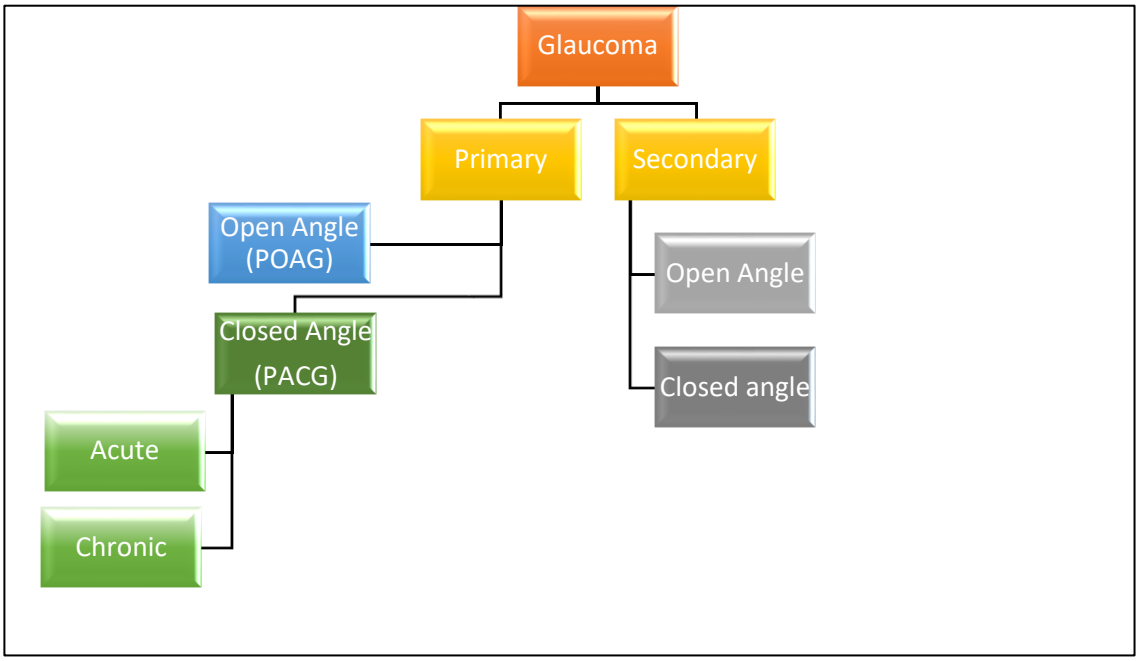


Figure 1.2. Classification of glaucoma.

A systematic review identified the pooled global prevalence of POAG and PACG was 3.05% and 0.50%, where prevalence is highest in those residing in Africa and Asia, respectively (Tham et al., 2014). With an ageing population and increased longevity, the number of individuals globally affected by POAG is forecasted to increase from 57.5 million in 2015 to 65.5 million by 2020 (Kapetanakis et al., 2016). In the case of PACG, it is likely to affect 23.4 million by 2020 and 32 million by 2040 in those aged 40 to 80 years old (Tham et al., 2014). Glaucoma can cause visual disability (Johnson et al., 2017), as it can affect the patients' ability to drive (Ramulu et al., 2009a), read (Ramulu et al., 2009b) and navigate (Baig et al., 2016). In 2015, there were 4 million people worldwide suffering

from glaucomatous MSVI and this is projected to increase by 0.5 million by 2020 (Flaxman et al., 2017).

There are numerous risk factors that can be attributed to either POAG or PACG, important demographical risk factors include age and family history. A number of epidemiological studies have demonstrated that the prevalence of POAG increases exponentially with age, depending on the population studied (Tielsch et al., 1991a, Wormald et al., 1994, Mitchell et al., 1996, Varma et al., 2004, Leske et al., 2008); as well for PACG (Foster et al., 1996, Foster et al., 2000b, Yamamoto et al., 2005, He et al., 2006a, Liang et al., 2011). If there is a first degree relative with POAG, studies have identified the odds of the individual having this disease increases by up to 9 times (Tielsch et al., 1991a, Wolfs et al., 1998, Doshi et al., 2008). For PACG, the heritability of a narrow angle has been reported as high as 60%, where siblings of those affected by PACG have been estimated to be 7 times more likely to have a narrow angle (Amerasinghe et al., 2011). Another well-documented risk factor is ethnicity, the prevalence of POAG is higher in those of African origin than in any other racial/ethnic groups (Tielsch et al., 1991b, Leske et al., 1994, Rotchford & Johnson, 2002, Rotchford et al., 2003), as African-Americans are 6 times more likely to develop glaucoma compared to whites (Tielsch et al., 1991b). In the case of PACG, higher rates of the disease occur with Inuit and Asian populations (Clemmesen & Alsbirk, 1971, Drance, 1973, Tham et al., 2014). Intraocular pressure (IOP) is the only modifiable risk factor for the development and progression of POAG, where hypotensive treatment has been shown to have a positive effect on disease progression (Cartwright & Anderson, 1988, Schulzer et al., 1998, Heijl et al., 2002).

1.1.2 Age-related retinal diseases

Age is a significant risk factor in a number of retinal diseases that can cause visual impairment such as age-related macular degeneration (Evans, 2001, Chakravarthy et al., 2010, NICE, 2018), epiretinal membrane (Mitchell et al., 1997, Miyazaki et al., 2003, McCarty et al., 2005, Kawasaki et al., 2008), central retinal vein occlusion (Rogers et al., 2010, Sartori et al., 2013) and vitreo-retinal conditions such as macula holes and vitreo-macular traction (Garcia-Layana et al., 2015). AMD affects the central retina (macula) and it has been documented that nearly all late AMD cases occur in people older than 60 years (Meuer et al., 2014, Mitchell et al., 2018). There were 8.4 million people globally that had MSVI from AMD in 2015 and this is forecasted to increase to 8.8 million by 2020 (Flaxman et al., 2017). Global projections for the number of people affected with AMD by 2020 are 196 million, increasing to 288 million in 2040 (Wong et al., 2014).

With a global increase in population ageing, health systems will need to adapt in order to serve the growing number of older people to maximise health and well-being (UN, 2015). In many cases, timely detection and treatment of posterior segment eye diseases can lower the risk of vision impairment in the patient's lifetime (Heijl et al., 2002, Chakravarthy et al., 2010, Kersey et al., 2013). There is increasing recognition that detecting age-related eye diseases can be augmented by the application of new structural and visual function technologies. Recent evidence has shown these devices can be effective in identifying glaucoma (Dabasia et al., 2015b, Azuara-Blanco et al., 2016a, NICE, 2017) and retinal diseases (Ouyang et al., 2013). Therefore, establishing the diagnostic accuracy of these tests is vital to ensure successful implementation into clinical practice.

1.2 Diagnostic accuracy

Diagnostic test accuracy is a key component of health care and is critical to the initial diagnosis, staging, screening, monitoring and surveillance of disease. Diagnostic information can be obtained from several sources that include imaging, biochemical technologies, pathological and psychological investigations (Sackett et al., 1991).

Diagnostic accuracy studies usually report sensitivity, specificity, receiver-operator characteristics curves and/or positive and negative predictive values as measures of diagnostic performance from a test (Deeks, 2001). These studies compare test results from those with a disease and those without. The accuracy of the test being assessed is usually termed the 'index test' and is compared to a 'reference standard'; which is usually a test or group of tests where a diagnosis of the target or 'true' disease for each patient is made. Thus, when an index test threshold has been specified, results can be then categorised as true positive, false positive, true negative, and false negative (Table 1.1) (Mallett et al., 2012).

	Reference standard test	
Index Test	Disease Positive	Disease Negative
Test Positive	True Positive	False Positive
Test Negative	False Negative	True Negative

Table 1.1. Diagnostic table (2x2).

Paired diagnostic measures determine the sensitivity and specificity of an index test. Sensitivity is the proportion of true positives that are correctly identified by the index test and specificity is the proportion of true negatives identified. By comparing the diagnostic accuracy of tests in terms of their sensitivities and specificities relative to a reference standard, this ensures the most appropriate tests are deployed in the clinical setting (Swets & Pickett, 1982, Freedman, 1987, Zhou et al., 2009). However, these indices used alone provide limited information regarding the test's applicability to a wider population. Predictive values can be used that account for the prevalence of a

disease in a given population. The positive predictive value is the probability that an individual with a positive screening result has the disease and negative predictive value is the probability that an individual with a negative screening result doesn't have the disease (Altman & Bland, 1994). Other paired diagnostic measures include positive and negative likelihood ratios which describe the discriminatory properties of positive and negative test results, respectively (Deeks & Morris, 1996). Likelihood ratios state how many times more likely the test results are in patients with disease than in those without. A positive likelihood ratio above 10 and a negative likelihood ratio below 0.1 are considered to provide convincing diagnostic evidence, whereas those above 5 and below 0.2 give strong diagnostic evidence (Jaeschke et al., 1994). Likelihood ratios can be directly applied to give probabilistic statements concerning the likelihood of disease in an individual (Deeks, 2001).

Diagnostic accuracy studies report the performance of a test or group of tests and their potential application. Yet, if studies are not conducted properly or reporting is found to be inconsistent, there is potential for bias (internal validity) or difficulty in estimating the generalisability of the findings (external validity) (Fidalgo et al., 2015). Bias can lead to a systematic distortion that can result in the premature adoption of a poorly performing test. To improve the quality and reporting of studies, two tools were developed, a quality assessment tool known as QUADAS (Quality Assessment of Diagnostic Accuracy Studies) (Whiting et al., 2003) and STARD (Standards for the Reporting of Diagnostic Accuracy Studies) (Bossuyt et al., 2003). Since their conception, there have been evolutions in both tools with revised and updated versions of STARD 2015 (Cohen et al., 2016) and QUADAS-2 (Whiting et al., 2011).

QUADAS-2 is a multi-domain checklist recommended by the Cochrane Collaboration and NICE for assessing the methodological quality of diagnostic accuracy studies in systematic reviews. QUADAS-2 consists of four key domains, where the risk of bias and concerns of applicability are judged on patient selection, index test, reference standard, and flow of patients. The STARD 2015 checklist was developed to standardise reporting of diagnostic test accuracy studies. The STARD 2015 tool has a list of 30 items that should

be checked, which includes the use of a flow diagram to present the design of the study and key reporting of facts.

An evaluation of the original STARD and QUADAS by Fidalgo et al (Fidalgo et al., 2015), found 58 studies that were suboptimal in reporting automated perimetry testing in glaucoma. Comparing a ten-year period before and after the introduction of both tools, the authors concluded that reporting did not substantially improve following the introduction of STARD. Evaluation using STARD 2015 for glaucoma diagnostic test accuracy (Virgili et al., 2017) found similar results to Fidalgo et al, however Virgili and colleagues did find a slight improvement in reporting over time.

1.3 Reference standard

In ophthalmology, the structural and functional assessment of the eye is integral for the detection of ocular abnormalities. The reference standard(s) for identifying and diagnosing ocular diseases are discussed below.

1.3.1 Anterior segment

The slit lamp bio-microscope allows the anterior segment of the eye to be examined in high detail using various types of illumination and magnification by a trained clinician. Since its invention over 100 years ago, the stereoscopic slit lamp examination still remains the reference standard in assessing the anterior segment from the ocular adnexa through to the anterior vitreous.

ACA evaluation is important for the classification of glaucoma (SIGN, 2015, Prum et al., 2016, EGS, 2017, NICE, 2017). Yet, direct visualisation of the ACA is not possible using the slit lamp alone, as the angle is masked by total internal reflection. Gonioscopy is a technique that allows the clinician to view the irido-corneal angle using a gonio-lens with a slit lamp. This lens contains a mirror which is applied to an anaesthetised cornea with

the possible use of coupling fluid, thus allowing visualisation of the ACA (Figure 1.3). This technique should be performed under dark room conditions with the eye in the primary position, to view the angle structures (Figure 1.4), presence of irido-trabecular contact, peripheral anterior synechiae or both (Bhargava et al., 1973).

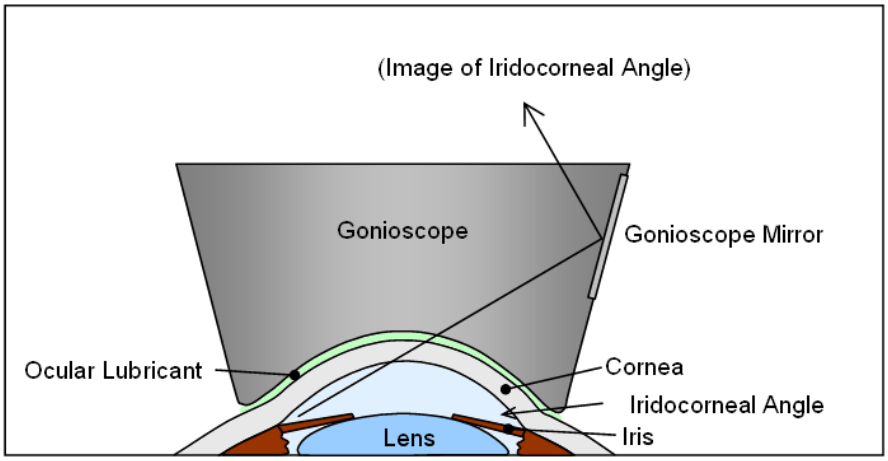


Figure 1.3. Ray diagram of the optics associated with gonioscopy (Lucas, 2006).

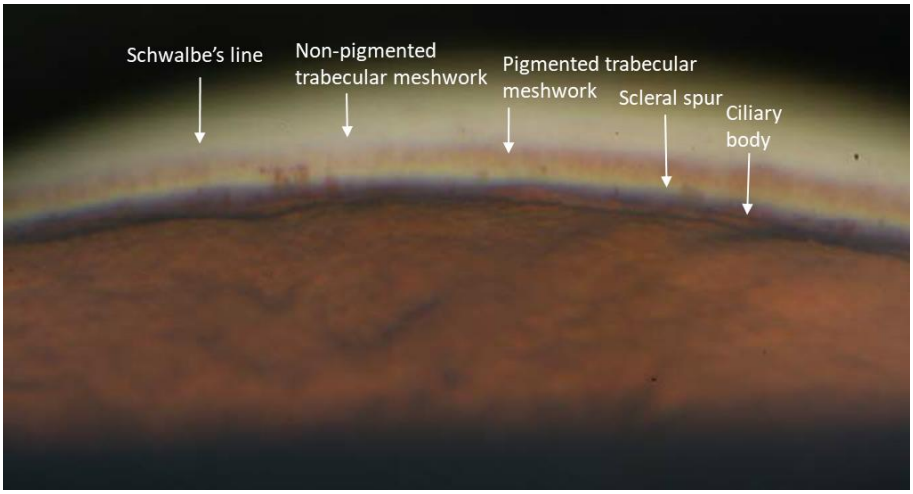


Figure 1.4. Gonioscopy of an open anterior chamber angle with all the structures visible. Image adapted from (Castañeda-Díez et al., 2011).

1.3.2 Posterior segment structural assessment

Indirect ophthalmoscopy is usually the primary method that is performed in most ophthalmic settings to diagnose posterior segment eye diseases. This technique involves a slit lamp coupled with a supplementary lens, usually a Volk lens. This method offers greater fields of view when compared to traditional direct ophthalmoscopy and also provides a stereoscopic examination of the posterior segment. For glaucoma, it is recommended that structural examination of the optic disc requires dilated binocular indirect ophthalmoscopy (SIGN, 2015, Prum et al., 2016, EGS, 2017, NICE, 2017). In retinal diseases such as AMD, this method is also recommended to document the size, number and location of lesions detected (NICE, 2018).

Optic nerve head examination involves the observer assessing the structure of the neuroretinal rim. Glaucomatous damage to the optic nerve may start as localised or generalised loss of neural tissue. Early damage to the optic nerve head frequently occurs in the superior and inferior quadrants which can cause a notch within the neural retinal rim of the optic disc. This can also be accompanied or be preceded by a focal or diffuse loss of the retinal nerve fibre layer (Sommer et al., 1991, Quigley et al., 1992, Lee et al., 2016), that will lead to an associated area of reduced of sensitivity in the patient's visual field (Figure 1.5). As damage of the retinal ganglion cells (RGC) and supporting optic nerve tissues progresses, this will lead to further excavation of the neural tissues and deepen the level of cupping, until there is total loss of optic nerve tissue that results in a complete loss of the visual field.

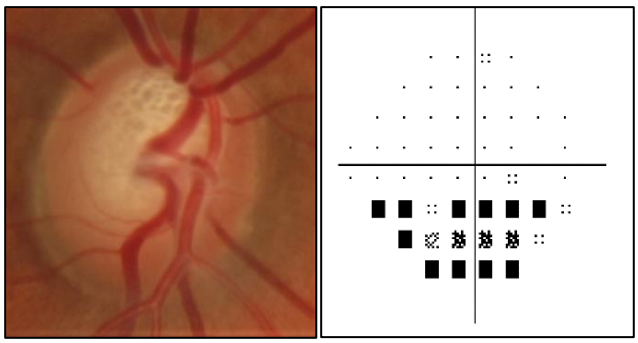


Figure 1.5. Superior excavation of the optic nerve head with an associated inferior visual field defect. Image sourced from (Jindal et al., 2019).

1.3.3 Functional assessment

The normal field of vision in a human eye is 160 degrees horizontally and 120 degrees vertically. The visual pathway begins with light being detected by photoreceptors comprising of rods and cones within the neurosensory retina. This causes a cascade of chemical reactions where the signal is then transmitted to the bipolar cells and RGC which lie mainly in the retinal nerve fibre layer (Fortune et al., 2015). The nerves then leave the eye via the optic nerve, which then projects onto the lateral geniculate nucleus and subsequent visual cortex.

Visual field assessment tests the function of the visual pathway where any damage may result in a functional deficit that is either relative or absolute; nearly all pathological abnormalities are detected in central 20–30 degrees (Wong & Plant, 2015). Perimetry is a technique that assesses the visual field. Gross field assessment by traditional confrontation can detect large and dense visual field defects, for smaller/relative defects, Standard Automated Perimetry (SAP) is usually required. SAP projects a white stimulus onto a white background, the luminance of the stimulus increases and decreases incrementally to determine a threshold value, where this has been defined as a stimulus that has a 50% chance of being perceived.

SAP thresholding is generally acknowledged as the reference standard for visual field assessment. Functional abnormalities resulting from RGC damage can be identified by SAP. A popular SAP device known as the Humphrey Visual Field Analyser (HFA), is commonly used in secondary care in the United Kingdom (UK), where it employs the Swedish Interactive Thresholding Algorithm (SITA). SITA significantly reduced the time taken to complete the original HFA programme from 12 minutes to 6 minutes per eye (Bengtsson et al., 1998). Such algorithms modernised field testing by achieving good levels of sensitivity and reduced test times (Sekhar et al., 2000).

The reference standard is the conclusive diagnostic examination to confirm a disease. However, barriers that may prevent such an examination being performed include the time taken to obtain a result, practicality, requirement of space, skilled personal or costs

to administer. With advances in technology and methods in both structural and functional assessment, these may overcome these limitations and provide suitable diagnostic performance, but before these new techniques are incorporated into practice, their test accuracy should be assessed.

1.4 Index tests

Evaluation of diagnostic accuracy requires a comparison between the test being evaluated ('index' test) and the accepted reference ('gold') standard, where subsequent application could potentially identify those with or at risk of disease.

1.4.1 Anterior chamber assessment

Gonioscopy is not routinely performed outside a specialist setting since it is invasive, time consuming and requires a high level of skill. A number of methods have been developed that can assess the anterior chamber configuration that are non-invasive, relatively quick to perform and require less training when compared to gonioscopy. A systematic review (Smith et al., 2013) evaluated some of these devices to ascertain their correlation to gonioscopy. They found that these machines provided useful information regarding the dimensions of the anterior chamber depth/angle, but none provided enough information to be considered a substitute for gonioscopy. In addition, they recommended more research is needed to validate the diagnostic significance of these tests in identifying those at risk of PACG. Other tests that were designed to evaluate the risk of PACG and necessitate the requirement of gonioscopy include the van Herick method that estimates the limbal anterior chamber depth (LACD) and the flashlight test (Van Herick et al., 1969, Vargas & Drance, 1973).

1.4.2 Posterior segment structural assessment

Dilated indirect ophthalmoscopy is required to suitably examine the optic nerve head and retina. However, this method is relatively time consuming, subjective and requires the use of mydriatic drops that can affect the patient's vision for several hours.

Glaucoma

Assessment of the optic nerve head and retinal nerve fibre layer relies on direct observation, however it has been estimated that up to 40% of retinal nerve fibres may be lost before glaucomatous damage is detected (Quigley et al., 1980). This could be attributed to subtle thinning being missed or obscuration by media opacities and/or fundus pigmentation. Over the past twenty years, the introduction of computerised imaging has led to supplementary assessment of the posterior segment. Some of these devices can provide objective and quantitative measurements that are highly reproducible; as well as showing very good agreement with clinical estimates of the optic nerve head structure and visual function (Greenfield & Weinreb, 2008). A systematic review that investigated the diagnostic accuracy of some of these devices, suggested that they could be used to inform glaucoma decision making in primary care and triaging referrals (Michelessi et al., 2015).

Retina

For retinal examination, a recent cross-sectional study in the United States of America found that 25% of eyes were misdiagnosed using indirect ophthalmoscopy as 'normal', whereas they had macular characteristics that indicated AMD that was revealed by fundus photography (Neely et al., 2017). In another study, investigators examined the value of scanning laser ophthalmoscopy in combination with traditional fundal examination; they found that this technology enhanced the detection of retinal lesions such as naevi, retinal pigment epithelial changes and retinal haemorrhages (Brown et al., 2013).

It has been suggested that case-finding for age-related eye diseases can be augmented by the application of imaging technologies (Brown et al., 2013, Ouyang et al., 2013, Dabasia et al., 2015b, Azuara-Blanco et al., 2016a). One device that has been rapidly adopted in secondary care ophthalmology and more recently in primary care is optical coherence tomography (OCT) (Dabasia et al., 2014b, Jamous et al., 2014, Kiely et al., 2017, Ly et al., 2017). OCT was first described in 1991 (Huang et al., 1991), it is an interferometric non-invasive imaging modality that enables in-vivo imaging of biological tissues that can provide objective and rapid measurements of the posterior segment (Michelessi et al., 2015, Kashani et al., 2017). This has resulted in its ability to facilitate in the diagnosis of a number of diseases that affect the optic nerve and retina (Jeong et al., 2016). Early OCT devices that used the time-domain principle have evolved into the current clinical standard of Spectral-Domain Optical Coherence Tomography (SD-OCT). SD-OCT incorporates Fourier domain strategies that offer higher sensitivity, improved scan acquisition speeds as well as higher axial and transverse resolutions (Leitgeb et al., 2003, Bengtsson et al., 2012), when compared to time-domain OCT. SD-OCT projects a wavelength beam of approximately 830nm into the eye and the frequency information of the back reflected light is used to generate an image of the structure. The image acquisition rate of the device ranges between 25,000-75,000 axial scans/second, enabling the acquisition of three-dimensional data from the area of interest due to new light sources and fast sensors (Leitgeb et al., 2014, Kostanyan et al., 2015). More recent developments include Swept-Source Optical Coherence Tomography (SS-OCT) that uses a single tunable laser that sweeps through different frequencies to cover the entire broad spectrum, where scanning speeds of up to 400,000 axial scans/second can be captured (Potsaid et al., 2010). As SS-OCT systems use a more complex light source than SD-OCT, this allows better tissue penetration and in detailed visualisation of structures such as the choroid (Mrejen & Spaide, 2013, Adhi et al., 2014) and lamina cribosa (Wang et al., 2014) that was previously inaccessible. However, SS-OCT is currently limited to either research or secondary care clinics due to its' prohibitive cost.

1.4.3 Functional visual field assessment

SAP threshold testing can cause fatigue and reduced reliability due to the time taken to complete, especially in those with advanced disease as it would take longer to reach endpoint. In addition, a trained operator must monitor the patient when performing SAP, which can be prohibitive when allocating resources. Based on histological analysis and glaucoma modelling, it has been estimated that up to 50% of the RGC may be damaged before a defect can be identified using SAP (Quigley et al., 1989, Kerrigan-Baumrind et al., 2000, Harwerth & Quigley, 2006), hence early functional loss may be missed (Nouri-Mahdavi et al., 2011).

It was originally thought that glaucoma preferentially damages large diameter retinal ganglion cells (Quigley et al., 1987, Kerrigan-Baumrind et al., 2000) namely M cells. However, studies reported that the apparent attenuation of large ganglionic fibres in glaucoma patients, is purely a result of shrinkage of the entire cell population, where morphological studies appear to support this claim (Morgan, 1994, Osborne et al., 1999, Morgan, 2002). Furthermore, recent research has cast doubt on the exclusive vulnerability of RGC with large somata to glaucoma, as it is now estimated that there are more than 30 different RGC types and research is still ongoing to ascertain the selectivity of cell loss (Santina & Ou, 2017). Nonetheless, knowledge that M cells were sensitive to high temporal frequency stimuli combined with reports that this method could potentially improve sensitivity to functional glaucomatous damage when compared to SAP (Tyler, 1981, Lachenmayr & Drance, 1992, Horn et al., 1997), led to many studies designing tests that employed stimuli that moved or flickered in some way at a high temporal frequency in an attempt to 'isolate' this magnocellular pathway. These studies found that by employing temporal modulation flicker, flicker sensitivity was reduced in those with glaucoma (Tyler, 1981, Kondo et al., 1998, Spry et al., 2005, Prokosch & Eter, 2014, Reznicek et al., 2015, Horn et al., 2016).

Frequency doubling perimetry has been incorporated into the Frequency Doubling Technology (FDT) perimeter and the subsequent Matrix perimeter. Psychophysical

investigations using a vertical sinusoidal grating that is flickered at a high frequency resulted in a frequency doubling phenomenon (Kelly, 1966). This method was originally thought to isolate a subpopulation of My cells from the magnocellular pathway, whereby these cells exhibited non-linear properties to increasing temporal frequency. However, it has been argued that this method may not be targeting a particular cell type (Johnson, 1994, Sample et al., 2000, White et al., 2002a) and maybe even attributed to non-retinal mechanisms within the visual cortex (White et al., 2002b, Zeppieri et al., 2008). Nevertheless, whatever the exact mechanism, studies have found that frequency doubling perimetry could potentially detect glaucomatous field loss earlier than SAP, and possibly even predict future SAP defects (Medeiros et al., 2004, Kim et al., 2007, Leeprechanon et al., 2007, Fan et al., 2010, Liu et al., 2014), however this remains controversial (Patel et al., 2007, Redmond et al., 2013). Further details regarding the FDT stimuli are described in chapter 3.

1.5 Detection of eye disease

Eye diseases can be identified either by case-finding or formal screening programmes. Case-finding describes a process of opportunistic detection of disease, whereby the population screened is self-selected. By contrast, formal screening invites all participants who are considered to be at risk of developing a disease, by virtue of age or other risk factors.

1.5.1 Screening

The UK National Screening Committee (NSC) defines screening as “a process of identifying apparently healthy people who may be at increased risk of a disease or condition” (NSC, 2016), otherwise known as ‘targeted screening’; whereas a universal screening programme requires all individuals within a given population to be screened. It is recommended that screened individuals that have been identified at risk of disease,

are then “offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition” (NSC, 2016). The aims of both types of screening are similar, to detect the disease where subsequent treatment can be provided.

When determining screening suitability, the condition must meet an eligibility criteria in order to be medically and financially acceptable. Criteria described by Wilson & Jungner (Wilson & Jungner, 1968) outlines the principles of screening that needs to be fulfilled (Table 1.2). This has defined the basis of preventive medicine and is largely considered the standards needed, by which screening tests are judged and determined (Sheehy et al., 2009).

1.	The condition being screened for should be an important health problem
2.	The natural history of the condition should be well understood
3.	There should be a detectable early stage
4.	Treatment at an early stage should be of more benefit than at a later stage
5.	A suitable test should be devised for the early stage
6.	The test should be acceptable
7.	Intervals for repeating the test should be determined
8.	Adequate health service provision should be made for the extra clinical workload resulting from screening
9.	The risks, both physical and psychological, should be less than the benefits
10.	The costs should be balanced against the benefits

Table 1.2. The principles of screening criteria outlined by Wilson & Jungner (Wilson & Jungner, 1968).

In the UK, the NSC is responsible for advising ministers and the National Health Service about screening and its implementation of screening programmes. They have established an internationally agreed set of criteria categorised by the condition, test, treatment and screening programme. In addition to the Wilson and Jungner criteria, they

recommend that a screening programme should be evidence-based; where high-quality randomised controlled trials have demonstrated a reduction in mortality and/or morbidity; offering of treatment policies; and evidence that the programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public (NSC, 2016).

A clear benefit of screening is that it may reduce the risk of developing a condition, however it cannot offer a guarantee of protection, as there will always be an unavoidable number of false negative and positive results. Consequently, a false negative result would lead to false reassurance by both patients and clinicians and may even dissuade patients from returning for future screening tests. In the case of a false positive, the patient may experience anxiety and this would also impact the screening's cost efficiency due to the unnecessary referral. Another problem of screening is the overall cost to society that includes; equipment, services, treatment and time taken off work for people to attend, where the allocated funds could be spent elsewhere.

In response to the potential burdens of screening, analysis must be conducted to evaluate the cost-effectiveness of such programme which includes; screening and treatment costs per quality-adjusted life-year gained and years where sight is saved with respect to eyes, however even when provisionally costed, this is based on a number of assumptions. Targeted screening programmes developed to detect diabetic retinopathy (Javitt & Aiello, 1996, Jones & Edwards, 2010) were based on ideal levels of attendance and access to examination. Yet, data found that the screening coverage and attendance was below recommended levels for this disease (Millett & Dodhia, 2006, Paz et al., 2006, Saadine et al., 2008); as such this can have major financial consequences (Lawrenson et al., 2018).

1.5.2 Case-finding

With the lack of available screening programmes, most posterior eye diseases are detected when the patient self-presents themselves to a medical practitioner, optometrist, or ophthalmic nurse in either a primary or secondary care setting.

A general practitioner (GP) is typically the first point of care and treatment for medical concerns in the UK. In 2013 eye health accounted for 4.5 million GP consultations and cost the UK economy £22 billion (RCGP, 2016). However, a GP would not normally assess an asymptomatic eye due to either time constraints, lack of detailed ophthalmic knowledge and/or possess the necessary equipment for an in-depth ocular examination. Furthermore, non-specialist healthcare professionals may have a low threshold for referring patients to an optometrist or ophthalmologist (Hornby, 2013).

Optometrists are primary healthcare practitioners of the eye and visual system, who provide comprehensive eye and vision care (WCO, 2018). As the major provider of primary eye care in the UK, optometrists play a key role in the opportunistic detection of both symptomatic and asymptomatic eye disease. It is well recognised that glaucoma is dependent on opportunistic case-finding amongst those attending for a routine eye examination (Lawrenson, 2013). When patients self-present for an eye examination in primary care, usually an optometrist would assess an at-risk glaucoma patient by examining the optic disc, LACD, measure visual fields and perform tonometry to measure the IOP and would refer cases of suspect glaucoma, usually to a glaucoma sub-specialist ophthalmologist. If glaucoma is detected early, subsequently cost savings could be realised as management costs are higher in those with advanced disease (Traverso et al., 2005, Lee et al., 2006, Stein et al., 2012, Lorenz et al., 2013, Chan et al., 2014, Gazzard et al., 2019), although this could be offset if there are a high number of false positives.

Optometrists have the necessary equipment and knowledge to provide some primary care ophthalmology services and their role has been systematically reviewed (Hawley, 2011, Baker et al., 2016). Furthermore, optometrists are expanding their scope of practice by engaging in therapeutic prescribing and management of diseases in high

income countries (Krumholz et al., 2001, Roth, 2007, Needle et al., 2008). With the growing demand for eye care services and limited medical professionals providing ophthalmic services, it's foreseeable that optometrists will play a greater role in the detection and management of eye diseases.

1.6 United Kingdom

In the UK it has been projected by 2035 the population over 75 years will increase to 8.9 million, representing an 80% increase compared to 2010 (Rutherford, 2012). Population ageing is leading to substantial increases in visual impairment (Pezzullo et al., 2018); the burden of sight loss disproportionally affects the elderly with 1 in 5 people aged 75 or over (Evans & Rowlands, 2004), and 1 in 2 people aged 90 and over (RNIB, 2009).

Currently, AMD is the largest cause of registration for sight impairment and severe sight impairment in England and Wales accounting for 52% and 42% respectively (Rees et al., 2014). This is followed by glaucoma accounting for 8.4% sight impairment and 7.4% of severely sight impairment registrations (Bunce et al., 2010). The overall prevalence of late AMD is 2.4% in those aged 50 years or more, increasing to 12.2% in individuals greater than 80 years of age in the UK (Owen et al., 2003, Minassian & Reidy, 2009, Owen et al., 2012, Rudnicka et al., 2012). This equates to an estimated 513,000 people currently affected by late AMD, which is set to rise to 679,000 by 2020 (Owen et al., 2012). In the UK the overall prevalence of POAG is 2.1%, where this increases from 0.3% in people aged 40 years to 3.3% in those aged 70 years and older and it is estimated that 11,000 new cases are diagnosed annually (Burr et al., 2007). For PACG, prevalence in European-derived populations aged 40 years and older is 0.4%, which corresponds to 130,000 cases in the UK, and it is predicted to increase by 19% within the next decade due to increased longevity (Day et al., 2012). Recent projections have forecasted that from 2015 to 2035, there will be an almost 60% and 44% rise in late AMD and glaucoma cases in the UK, respectively (RCO, 2017a, RCO, 2017b).

1.7 Rationale

Evidence has shown that 50% of sight loss could be avoided through improved eye care and early detection (RNIB, 2009). With slowly progressing eye diseases, medical consultation is usually sought when symptoms occur, which can result in irreversible structural and/or functional damage being observed on examination. As case-finding relies on self-presentation, diseases such as glaucoma or chronic retinal diseases requires awareness of the patient to attend routine eye examinations. Various public health campaigns have been successful in raising awareness of glaucoma within at-risk populations; but this has not necessarily translated into a change in health seeking behaviour by attending an optometrist for an eye examination (Baker & Murdoch, 2008). Therefore, newer strategies are needed in order to improve detection in order to reduce the risk of age-related sight loss.

With the advent of new structural and visual function testing technologies, these devices could potentially improve detection in those at risk of visual impairment in their lifetime. For the detection of PACG, there are several tests that are currently available to identify those at-risk but there has been no systematic evaluation of their diagnostic accuracy in identifying the disease. Undetected glaucoma in those who have limited access to eye care remains to be problematic, where the risk of ocular morbidity is high. In addition, there is currently no individual test or group of tests that have shown to be superior for POAG screening in the general population (Mowatt et al., 2008, Geimer, 2013, Dabasia et al., 2015b). Successive surveys have found OCT gaining popularity with optometrists, where adoption has increased seven-fold within a decade (Myint et al., 2011, Dabasia et al., 2014b). However, at present there is a lack of evidence regarding the diagnostic benefit offered by OCT in case-detection in primary care in a range of age-related posterior segment diseases.

1.8 Aims of this thesis

The primary aims of this thesis are:

1. Conduct a systematic review and meta-analysis evaluating the diagnostic accuracy of non-contact methods for the detection of people at risk of primary angle closure glaucoma.

2. Investigate the diagnostic accuracy of a newly developed test to detect primary open angle glaucoma and compare it with current screening technology.

3. Determine the value of OCT when diagnosing posterior segment eye diseases by community optometrists.

Chapter 2: Non-contact methods for the detection of people at risk of primary angle closure glaucoma: a systematic literature review and meta-analysis

2.1 Introduction

2.1.1 Background

Glaucoma is the leading cause of irreversible blindness worldwide, the global prevalence of primary angle closure glaucoma (PACG) in a population aged 40 to 80 years is 0.5% (Tham et al., 2014). Although, globally open angle glaucoma is more common (3.0%) than PACG (Tham et al., 2014), PACG is more likely to result in bilateral blindness (Quigley, 1996, Resnikoff et al., 2004). It was estimated that PACG caused bilateral blindness in 3.9 million people in 2010, rising to 5.3 million by 2020 where it will account for 50% of global glaucoma blindness (Quigley & Broman, 2006).

Primary angle closure is characterised by appositional or adhesional (synechial) narrowing and eventually occlusion of the drainage angle in the anterior chamber of the eye, resulting in elevated intraocular pressure (IOP) and optic neuropathy. If the occlusion occurs rapidly with symptomatic IOP elevation, this is termed acute angle closure (AAC) where patients are treated medically followed by laser peripheral iridotomy (LPI), where the fellow eye is also prophylactically treated using LPI (Emanuel et al., 2014). Alternatively, angle closure may develop insidiously with chronically raised IOP that is often asymptomatic. If not treated, the increased IOP leads to damage to retinal ganglion cells and glaucomatous optic neuropathy, otherwise known as PACG. In those presenting with PACG, a recently published multicentred randomised controlled trial has provided evidence that clear lens extraction is associated with better clinical and patient-reported outcomes than LPI and may therefore be a better first-line treatment option (Azuara-Blanco et al., 2016b). With timely detection in those with an anatomically narrow anterior chamber angle (ACA), the risk of further occlusion, subsequent PACG and blindness can be reduced with appropriate treatment.

2.1.2 Gonioscopy

Gonioscopy is the acknowledged reference standard for the assessment of the ACA (Prum et al., 2016, EGS, 2017, NICE, 2017). Gonioscopy should be performed on both eyes in any individual with suspected angle closure. Dynamic assessment can be performed and is helpful in distinguishing irido-trabecular contact (ITC) from peripheral anterior synechiae (PAS) using a four-mirror lens, which is applied to the cornea creating pressure via the gonio-lens. There are several grading systems that are used to document the angle viewed on gonioscopy, commonly used schemes are the Shaffer, Scheie and Spaeth. The Shaffer grading system (Shaffer, 1960) is the most widely adopted ACA classification scheme, this records the ACA width in four quadrants, from grade 0 (closed) to grade 4 (wide open) (Figure 2.1). Angle morphology can be described using the Scheie grading system (Scheie, 1957). This scheme describes the angle according to the anatomical structures observed (grade IV: Schwalbe's line not visible; grade III: Schwalbe's line visible; grade II: anterior trabecular meshwork visible; grade I: visible scleral spur; and grade 0: ciliary body band visible). The Spaeth classification is the most detailed of the three grading systems where this allows grading of the geometric angle, iris profile and level of iris insertion (Spaeth, 1971).

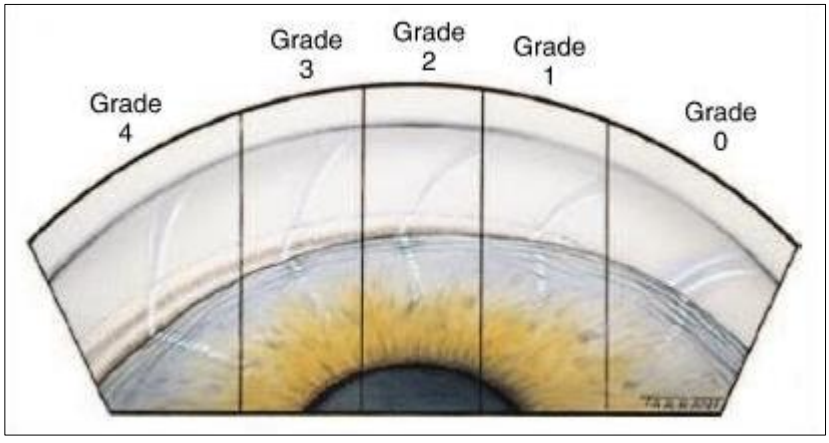


Figure 2.1. Shaffer grading of the angle width using gonioscopy. This figure was published with permission from Elsevier (Kanski, 2003).

The clinical course of PACG has been described in a modern International Society Geographical & Epidemiological Ophthalmology (ISGEO) classification scheme for use in prevalence surveys and epidemiological research (Foster et al., 2002). This identifies three stages in the natural history of angle closure from initial ITC to anterior segment signs of disease (raised IOP, peripheral anterior synechiae, or both), culminating in glaucomatous optic neuropathy.

1. Primary angle closure suspect (PACS): an eye in which appositional contact between the peripheral iris and posterior trabecular meshwork (irido-trabecular contact) is considered in two or more quadrants, in dark room conditions using static gonioscopy.

2. Primary angle closure (PAC): an eye with an occludable drainage angle and features indicating that trabecular obstruction by the peripheral iris has occurred, such as PAS, elevated IOP (>21 mmHg), iris whorling (distortion of the radially orientated iris fibres), glaucomfleken lens opacities or excessive pigment deposition on the trabecular surface. There is no evidence of glaucomatous optic neuropathy or associated glaucomatous field loss.

3. Primary angle closure glaucoma: signs of PAC as described above and evidence of glaucomatous optic neuropathy.

2.1.3 Incidence and prevalence

Longitudinal incidence studies are helpful in understanding the natural history and causes of a disease. Longitudinal studies in those with no previous diagnosis of angle closure have found different rates of development. A study of an Mongolian population aged 50 years and older, found a PACS incidence of 20.4% among participants with a central anterior chamber depth (ACD) of <2.53 mm over 6 years (Yip et al., 2008) and a 10 year follow up study in an urban Chinese population aged 50 years and older found the cumulative incidence of PACS was 16.9% (Wang et al., 2019). For those with

established angle closure, a 5-year Indian cohort study found 22% of those with PACS progressed to PAC and 28.5% of those with PAC converted to PACG (Thomas et al., 2003). Among Inuit individuals with a shallow anterior chamber, 16% developed PACG at a 10-year follow-up visit (Alsbirk, 1992). Among 129 primary angle closure suspects (94% Caucasian), 19.4% developed a study endpoint during a mean 2.7-year follow-up in a clinical setting (Wilensky et al., 1993). However, in a community cohort of 485 Chinese individuals with PACS, only 4.1% progressed to PACG over 6 years of follow-up (Ye et al., 1998). Furthermore, a recent study in another Chinese population aged 50-70 years, found that only 4.8% of those with untreated PACS converted to PAC/AAC over 6 years (He et al., 2019). However, differences found may be attributed to the different populations studied, sample sizes used, and the definitions used to define angle closure.

The prevalence of PACG varies across geographic regions and ethnic groups, the prevalence of PACG is highest in Asia (1.09%), where more than three-quarters of those affected with PACG reside (Tham et al., 2014). Another review reported a lower PACG pooled prevalence of 0.75% in Asia, however they noted an increased prevalence in those aged 70 years or older of 2.32% (Cheng et al., 2014). The prevalence of PACG in African and European populations are lower than the values found in Asia, where the later population was found to have a prevalence of approximately 0.4% (Day et al., 2012, Tham et al., 2014).

2.1.4 Target condition

Many population-based surveys have adopted the ISGEO classification. In practice, a key issue is the definition of a narrow (occludable) angle (Sun et al., 2017). While the ISGEO classification is comprehensive, it has been argued that this definition would still exclude many people deemed at risk of developing angle closure glaucoma, such as those with less than 180 degrees of irido-trabecular contact, appositional angle closure or primary PAS (Foster et al., 2002). An alternative term that has been suggested for clinicians was a ‘narrow angle,’ this would indicate those at risk of the disease where they would have

an anatomical predisposition to angle closure using gonioscopy (Weinreb, 2006). For the purpose of this review, we have defined the target condition of a narrow angle using gonioscopy as either:

1. An eye with any appositional contact between the peripheral iris and posterior trabecular meshwork in two or more quadrants (≥180 degrees); or
2. An eye with or at risk of angle closure as judged by a trained and experienced eye care professional using gonioscopy with or without indentation.

Currently, narrow angles are typically diagnosed by opportunistic case-finding, where patients present in either primary or secondary care to a healthcare practitioner with an ophthalmic subspecialty using gonioscopy. While gonioscopy is the current reference standard to diagnose a narrow angle, this technique is not routinely performed outside of a specialist setting. Furthermore, it is not ideal for angle closure screening since its invasive, time consuming and requires a high level of skill that can result in moderate agreement even amongst expert clinicians (Foster et al., 1996, Foster et al., 2000a, Aung et al., 2001). In addition, gonioscopic interpretation can be affected by gonio-lens pressure, direction of gaze, lighting and patient co-operation (Forbes, 1966, Sakata et al., 2008). Therefore, other approaches need to be considered when working outside a traditional ophthalmic environment.

2.1.5 Index tests

There have been various anatomical and demographic risk factors identified for PAC (Lowe, 1970, Congdon et al., 1996, Weinreb, 2006). Anatomical risk factors include a shallow ACD, thickening of the crystalline lens, lens vault, small corneal diameter, hyperopia and a short axial length (Nolan et al., 2006). Major demographical risks factors include older age and female gender (Weinreb, 2006). Also, those of Inuit and Asian ancestry are of greater risk of angle closure (Clemmesen & Alsbirk, 1971, Drance, 1973, Tham et al., 2014), where it is thought that those of Chinese origin have a greater

shallowing of the anterior chamber with age than Europeans or Africans (Wojciechowski et al., 2003). Furthermore, all the prior risk factors have been associated with a shallower ACD. It is thought that this anatomical shallowing of the anterior chamber depth is the highest risk factor in most ethnic groups for the development to angle closure glaucoma (ACG) (Nolan et al., 2006). Studies that have evaluated PACG screening have established the effectiveness of measuring anterior chamber dimensions to identify occludable angles (Congdon et al., 1996, Devereux et al., 2000, Kurita et al., 2009). As gonioscopy is not routinely done in a primary setting, a variety of non-contact devices with varying degrees of sophistication have been developed to evaluate the risk of angle closure that can measure the ACD, ACA, or both.

Anterior Segment Optical Coherence Tomography

Anterior Segment Optical Coherence Tomography (AS-OCT) allows both qualitative and quantitative analysis of the angle. This technique is based on low-coherence interferometry whereby the delay and intensity of light reflected from the ocular tissue structures is measured. There are currently several optical coherence tomography (OCT) devices that can measure the anterior chamber; depending on the device, they use one of the following domains to obtain clinical data: time-domain, spectral-domain or the more recent swept-source domain method that may or may not require a special lens adapter. Spectral and swept-source domain methods have a higher scan speed and axial resolution than time-domain methods. While a wavelength of approximately 830nm is required to image the posterior segment, a longer wavelength of 1310nm is used to image the anterior segment where inbuilt software can be used to quantitatively assess the angle parameters, which include: the trabeculo-iris space area (TISA), angle recess area (ARA) and angle opening distance (AOD) (Quek et al., 2011) as well as ACD and ACA (Figure 2.2). Qualitative interpretation by a clinician has been typically defined by contact between the peripheral iris and any part of the angle wall anterior to the scleral spur (Figure 2.3). Studies state different AODs of 500 or 750 microns in the detection or diagnosis of narrow angles or an ACA of less than 20 degrees (Smith et al., 2013).

However, there is no current consensus on any parameter with its associated cut-off to identify a narrow angle.

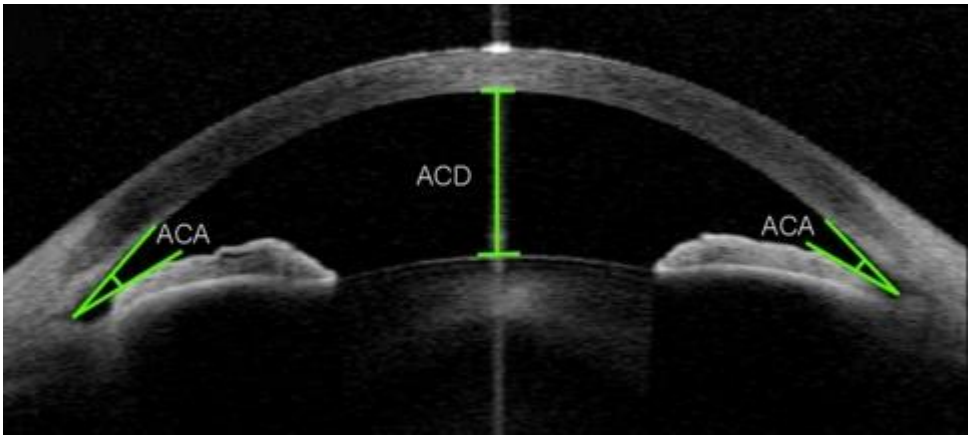


Figure 2.2. AS-OCT image illustrating areas of measurement with respect to ACD and ACA. Image sourced from (Kim et al., 2011).

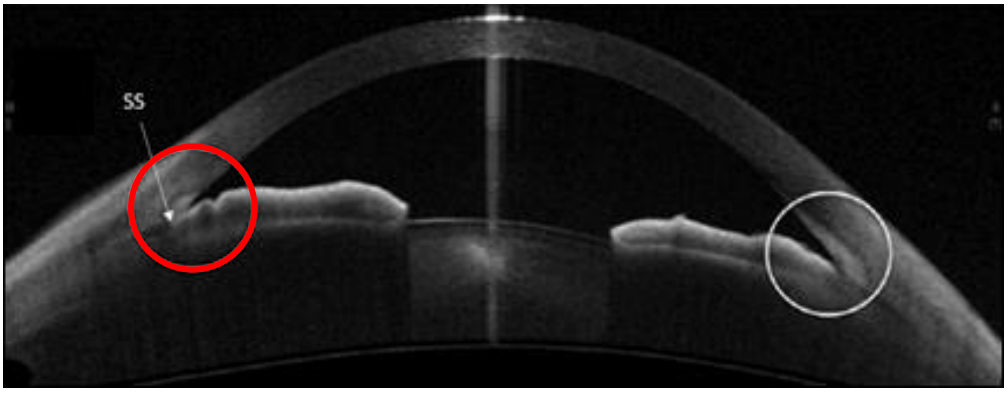


Figure 2.3. Qualitative interpretation of AS-OCT output. The red circle shows a closed angle and the white circle highlights a narrow angle. Image adapted from (Angmo et al., 2016). SS: Scleral Spur.

Scheimpflug photography

The Scheimpflug principle is used to correct perspective distortion in aerial photographs and has been adapted for ocular imaging. The Oculus Pentacam (Oculus, Wetzlar, Germany) device employs this principle using monochromatic blue light at a wavelength of 475nm. By rotating the apparatus around the optical axis of the eye, a series of radially oriented images are generated in three dimensions around 360 degrees 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 2 second acquisition frame. This generates a set of measurements that provide a detailed description of the biometric configuration of the anterior segment, which includes the ACA, ACD and the anterior chamber volume (ACV) (Figure 2.4). When calculating the ACA, it should be noted that this is not a direct measurement but is extrapolated from the measurements taken. Currently, there is no consensus on which parameter or cut-off value that should be used for the determination of a narrow angle.

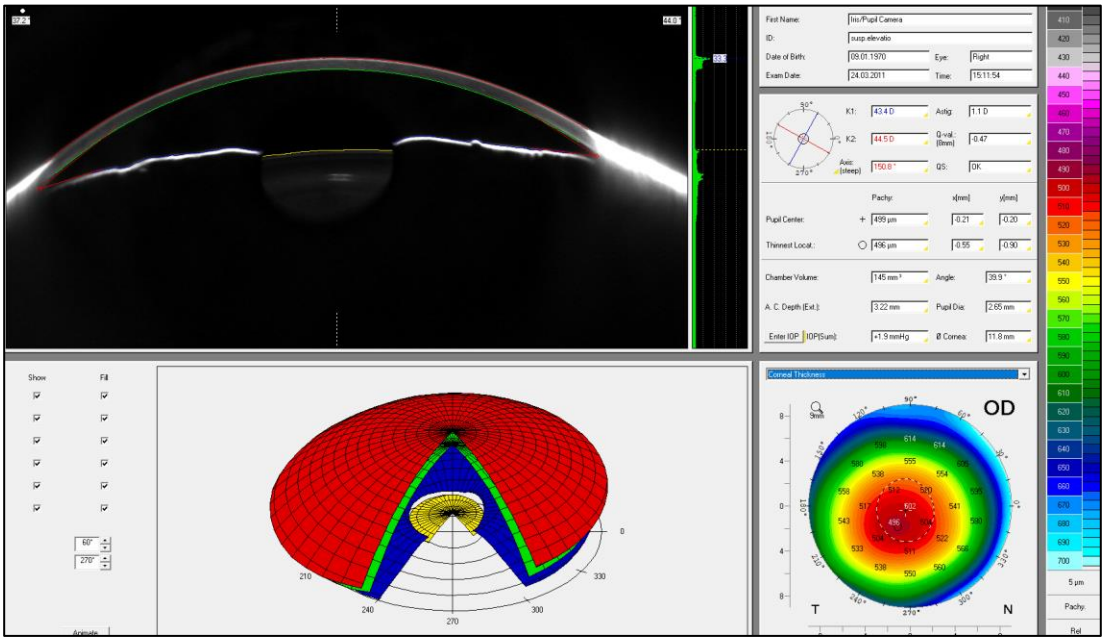


Figure 2.4. Image of Pentacam image capture. Reproduced with permission of OCULUS.

Scanning Peripheral Anterior Chamber Depth Analyser

Scanning Peripheral Anterior Chamber Depth Analyser (SPAC) is an objective method for measuring the peripheral ACD by automatically taking 21 slit lamp images of the anterior chamber using a 1 mm-wide slit at 0.4-mm intervals from the optical axis towards the limbus (Kashiwagi et al., 2006). These measurements are compared to a normative database and converted into a numerical scale ranging from 1 to 12, with 12 representing the deepest ACD. In addition, the output provides a categorical grading (as a suffix to the numerical grade) reporting the risk of angle closure: S (suspect angle closure), P (potential angle closure) and no suffix (normal). The device has been shown to be reproducible and easy to operate, therefore making it suitable for use by non-clinicians (Kashiwagi et al., 2004).

Limbal anterior chamber depth assessment (van Herick technique)

The van Herick technique is used to assess the anterior chamber depth at the limbus using a slit lamp bio-microscope (Van Herick et al., 1969). The illumination system is set at 60 degrees from the observation system. A focused vertical slit-beam is positioned at the limbus and moved just onto the cornea until the beam separates into a corneal section and reflection of the beam onto the iris. An estimate of the thickness of the dark space between the beams (which corresponds to the limbal anterior chamber depth (LACD)) is recorded as a fraction (or percentage) of the corneal section thickness over the central portion of the beam. Van Herick originally described a four-point grading scheme (Van Herick et al., 1969), which was extended to a seven-point scale by Foster et al (Foster et al., 2000a). Foster and colleagues used an intuitive percentage scale, in an effort to improve the precision of the measurement. Van Herick et al considered that an eye with a LACD of grade 2 or less required gonioscopy (≤25%) (Figure 2.5) and that a grade 1 angle (<25%) was at a high risk of angle closure. Foster et al, further subdivided grade 1 into 5% and 15% cut-off values and found that the augmented scale was associated with improved test accuracy. Table 2.1 describes the van Herick grading with the 7-point grading system described by Foster and colleagues.

van Herick Grade	Corneal section thickness (fraction)	Corneal section thickness (extended percentages)
Grade 1	<1/4	0%, 5% 15%
Grade 2	1/4	25%
Grade 3	>1/4 to 1/2	40%, 75%
Grade 4	≥1	≥100%

Table 2.1. Van Herick grading using the traditional four-point system alongside the modified seven-point LACD grading.

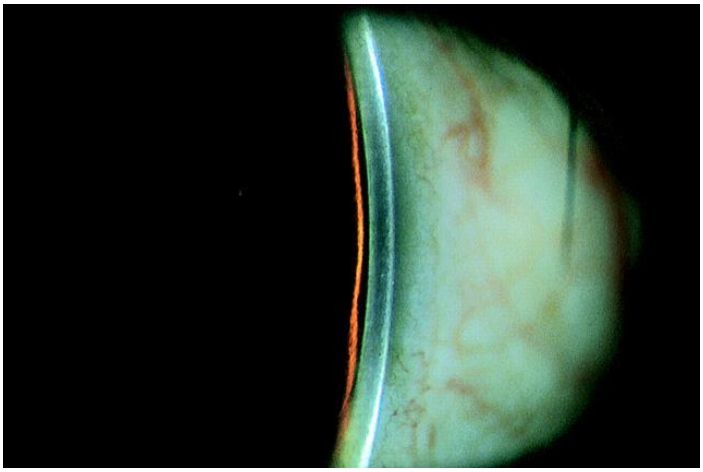


Figure 2.5. Limbal chamber depth grade 2 (25%) of peripheral corneal thickness. Reproduced from (Foster et al., 2000a) with permission from BMJ publishing group Ltd.

Flashlight

The flashlight test is an accessible screening method if no other equipment is available. The test can be carried out in a primary or secondary care setting and involves shining a pen torch from the temporal limbus parallel to the iris to assess the ACD. Quantitative grading uses a 4 point scale that corresponds to the proportion of the nasal iris in shadow from the pen torch, between the limbus and the pupillary edge (Vargas & Drance, 1973) (grade 4=minimal/none of the nasal iris in shadow to grade 1=nasal iris is in complete shadow); grade 1 is associated with a high risk of angle closure (Figure 2.6b). Qualitative

grading can also be used to describe the amount of shadow falling on the iris as shallow, medium or deep which is further described by He and colleagues (He et al., 2007).

Figures 2.6a and 2.6b, a) left image: flashlight shone from the temporal limbus showing a deep anterior chamber with no nasal shadow (grade 1) and b) right image: a shallow anterior chamber with the nasal iris in complete shadow. Reproduced from (Gracitelli et al., 2014) with permission from Springer Nature.

2.1.6 Clinical pathway

With the high prevalence of PAC and the burden of blindness attributable to PACG in high-risk populations, this opens up the possibility of using non-contact devices for population or opportunistic screening (Nolan et al., 2003, Nolan et al., 2006). Non-invasive assessment of the dimensions of the anterior chamber depth and/or angle are part of a standard ophthalmic examination (Figure 2.7). If the screening test is positive such individuals are identified as being 'at-risk' then the patient is referred for further assessment, usually to a glaucoma sub-specialist ophthalmologist or specialist optometrist. The clinician will then carry out gonioscopy (the reference standard for qualitative and quantitative assessment of the ACA) and further tests such as IOP measurement by Goldmann Applanation Tonometry, optic nerve head examination and automated threshold visual field testing to diagnose PACS/PAC/PACG. Depending on the

clinical presentation, the affected individual may be monitored or undergo medical and/or surgical treatment.

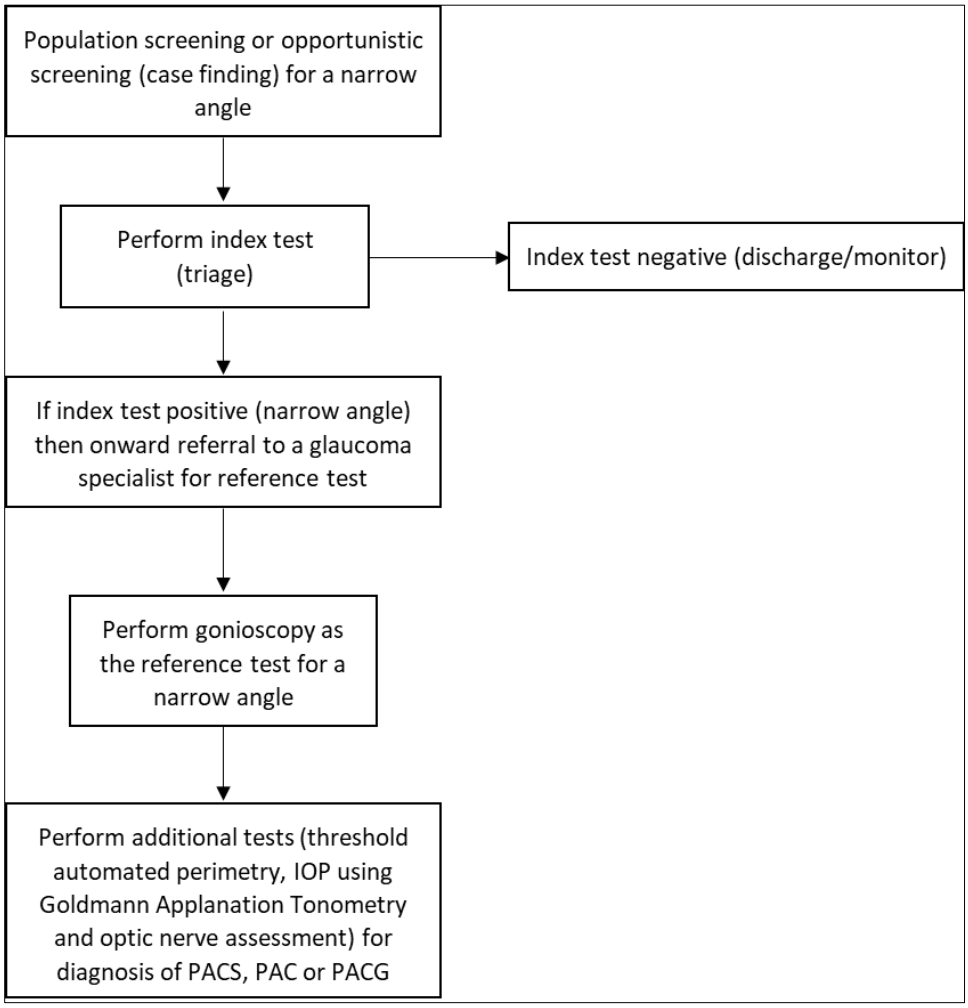


Figure 2.7. Clinical pathway.

2.1.7 Rationale

Non-contact screening tests are relatively quick and can be carried out by appropriately trained healthcare professionals or technicians as a triage test when screening or case-finding, to identify eyes at risk of angle closure. These non-contact tests cannot replace gonioscopy as they do not provide sufficient information on the ACA anatomy (Smith et al., 2013). However, in cases, when gonioscopy is not possible or fails to visualise the anterior chamber configuration/depth, some of these techniques (AS-OCT) can be used

to measure the area of interest (Kang et al., 2013) or can be used as an alternative (LACD) to facilitate in the diagnosis of glaucoma (NICE, 2017). Furthermore, objective devices such as AS-OCT and Scheimpflug photography can be used to supplement existing clinical documentation by providing objective measurements (Smith et al., 2013).

At present, there are no screening programmes specifically designed for PACG detection. In the United Kingdom (UK) and Finland, costed population-based screening programmes for primary open angle glaucoma (POAG) were found not to be cost-effective, but screening may be more effective if targeting at-risk populations (Burr et al., 2007, Vaahtoranta-Lehtonen et al., 2007, Hernández et al., 2008). While PACG is less prevalent than POAG in patients of European ancestry, it is unlikely that screening at present would be cost-effective in this population, however in the UK, ACG is predicted to increase by 19% within the next decade due to increased longevity (Day et al., 2012). Additionally, in countries where PACG prevalence is higher, the risk of blindness presents a potential problem, for example in China, PACG accounts for 91% of bilateral glaucoma blindness (Foster & Johnson, 2001). Therefore, screening those who are at risk of PACG may prove cost-effective and could play an important role in identifying and treating those early to prevent blindness. Presently, there is a lack of high-quality evidence on the value of non-invasive screening methods to detect those at risk of PACG. Such data could be potentially used to inform future economic models in determining the cost effectiveness of screening and/or clinical guidelines.

The primary objective of this systematic review was to determine the diagnostic accuracy of non-contact screening methods for identifying eyes with a narrow angle. Secondary objectives included; the comparison of non-contact screening tests, assessing the accuracy of each test for detecting the most severe referable condition or PACG (versus PAC, PACS or a non-occludable angle) and to explore potential causes of heterogeneity in diagnostic accuracy.

Study Contributions

Title registration and drafting of the Cochrane protocol was completed by Anish Jindal (AJ). Electronic searches of the databases were performed by Iris Gordon (IG). Assessment of the studies for inclusion and exclusion were conducted by AJ and Irene Ctori (IC). Risk of bias, data extraction, data entry and authoring of the first draft of the Cochrane review was undertaken by AJ and John Lawrenson (JL). The statistical methods section and analysis was completed by Ersilla Lucenteforte (EL). Comments of the text were reviewed by AJ, JL, IC, EL and Gianni Virgili.

2.2 Methods

2.2.1 Inclusion criteria

Non-contact methods for the detection of narrow angles are mainly of interest in screening and primary-care settings as a triage test, aiming to guide referrals to ophthalmologists, however the overall accuracy of these tests is not known in any care setting. We therefore included all prospective and retrospective cohort studies ('single-gate' design) and case-control studies ('two-gate' design) that were conducted in either primary or secondary care; where the accuracy of the non-contact method for diagnosing a narrow angle was compared to a gonioscopic reference standard. Studies that compared each method separately and studies that compared more than one method, to the reference standard in the same population were included. Participants in these studies received all the tests or were randomised to receive different tests. We included studies that provided sufficient data to allow the calculation of sensitivity and specificity.

Participants

Participants who met the inclusion criteria for studies conducted in any setting, which evaluated any of the index tests against the reference standard.

Index tests

The non-contact methods that were assessed were: flashlight, LACD using the van Herick technique, SPAC, Scheimpflug photography and AS-OCT.

Target condition

A narrow angle, as a referable condition that can include PACS, PAC or PACG, as described earlier.

Reference standard

Gonioscopy was the reference standard for the diagnosis of a narrow angle. When the information was available, we further classified a narrow angle into one of three subgroups PACS, PAC, PACG, if the following measurements have been taken; IOP measurement, visual field assessment and optic disc examination.

2.2.2 Search methods for identification of studies

The Cochrane Eyes and Vision Information Specialist (IG) searched the following electronic databases. Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, MEDLINE Ovid, Embase Ovid, BIOSIS, System for Information on Grey Literature in Europe (OpenGrey), Aggressive Research Intelligence Facility database, ISRCTN registry, US National Institutes of Health Ongoing Trials Register and World Health Organisation International Clinical Trials Registry Platform. There were no language or publication year restrictions imposed. Searches were conducted on the reference lists of included studies to identify further studies. We did not hand search journals or conference proceedings.

2.2.3 Selection of studies

Two review authors (AJ and IC) independently screened the titles and abstracts of all studies identified by the electronic searches. Each record at this stage was labelled as "definitely relevant", "possibly relevant" or "definitely not relevant." Records labelled as "definitely not relevant" by both review authors were excluded. A pilot stage was completed where both authors screened 100 titles independently then discussed any inconsistencies in labelling to reduce potential disagreements. After the pilot, all titles and abstracts were screened and disagreements were resolved by discussion at the end of the screening process.

Full text reports of records labelled as "definitely relevant" or "possibly relevant" were retrieved and the two reviewers independently assessed whether these met the inclusion criteria. Agreements on inclusion were reached by consensus and disagreements were resolved by the involvement of a third reviewer (JL).

2.2.4 Data extraction and management

Two review authors (AJ and JL) independently extracted the following data from the included studies regarding the characteristics of each study (see Appendix 1a) and where possible: the number of true positives, false positives, true negatives and false negatives using 2x2 contingency tables. From the 2x2 tables, sensitivity (true positive rate) and specificity (true negative rate) with 95% Confidence Intervals (CI) were calculated.

One review author entered data into Review Manager 5 (RevMan) (RevMan, 2015) and a second review author verified the entered data. Independent data extraction was piloted on 5 studies, modifications were then made to streamline the extraction process to improve consistency and translation of data into RevMan. We resolved any disagreement when presented through discussion. AJ contacted the study investigators if there was missing data or for clarification, a two weeks allowance was given for a response. If there was no response, data extraction proceeded using the information available via the published reports.

2.2.5 Assessment of methodological quality

Two review authors (AJ and JL) independently assessed each included study for risk of bias using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) to assess the susceptibility to bias of the included studies, based on guidance (Whiting et al., 2011). Assessment of each study was conducted and judged each bias criterion to be at 'high', 'low' or 'unclear' risk of bias (lack of information or uncertainty over the

potential for bias). Concerns regarding applicability in studies that included patients that had a previous diagnosis of a narrow angle were rated as 'high' (Table 2.2).

2.2.6 Statistical analysis and data synthesis

We extracted and analysed the available data at fixed thresholds for each index test, in order to ease the interpretability of our summary measures of accuracy. Our preferred thresholds were:

- Flashlight technique: grades 1 and 2.
- LACD using the van Herick technique: percentages or van Herick grades 1 and 2 (≤25%).
- SPAC: categorical grading of suspect angle closure or potential angle closure and numerical grading, as provided by the device.

There is no current consensus regarding thresholds for Scheimpflug photography and AS-OCT, data was extracted using reported thresholds, where a 2x2 diagnostic table could be constructed.

When four or more studies provided data at fixed thresholds; a bivariate model was fitted by a statistician (EL) using the metaDAS macro in SAS to provide summary point estimates of sensitivity and specificity. For all index tests, comparisons of diagnostic accuracy were made with the threshold that yielded the highest diagnostic odds ratio (DOR) for each test. DOR summarises the diagnostic accuracy of the index test as a single number that describes how many times higher the odds are of obtaining a test positive result in a diseased rather than a non-diseased person, were it depends significantly on the sensitivity and specificity of a test (Šimundić, 2009, Macaskill et al., 2010). We also reported positive predictive values (PPV) and negative predictive values (NPV) in relation

to disease prevalence with regards to the estimations of test accuracy, as these are useful measures of test performance for population screening.

Since narrow angles are often bilateral, this complication may result in unit of analysis issues. We included studies that evaluated only one eye of each participant or, in participants with two affected eyes, studies that randomly selected only one eye. We also included studies that pooled data from both eyes in the review, however we acknowledge that these studies would suffer from unit of analysis issues that would overestimate the precision in test accuracy, but this was controlled in some cases.

2.2.7 Investigations of heterogeneity and sensitivity analysis

Initial investigation of heterogeneity in sensitivity and specificity was performed by visual inspection of the forest plots. Formal analysis was planned (Jindal et al., 2018) using the following study-level covariates: study design (e.g. single-gate and two-gate designs); diagnostic reference thresholds (gonioscopy grading (e.g. number of quadrants occluded)); and characteristics of the study population (e.g. high versus low prevalence, ethnicity) for the diagnostic tests.

A sensitivity analysis was also planned to assess the impact of risk of bias on test accuracy by repeating the analysis after removing studies at high risk of bias. Subgroup analysis was proposed to compare the accuracy of each test between healthcare settings, as well as test performance to detect the most severe referable condition or PACG (versus PAC, PACS or non-occludable angle).

DOMAIN	LOW	HIGH	UNCLEAR
PARTICIPANT SELECTION	**Describe methods of participant selection; describe included participants (prior testing, presentation, intended use of index test and setting)**		
Was a consecutive or random sample of participants enrolled?	Consecutive sampling or random sampling of people according to inclusion criteria	Non-consecutive cohort of referrals (from primary care) or (in screening setting) sampling based on volunteering or referral	Unclear whether consecutive or random sampling used
Was a case-control design avoided?	No selective recruitment of people with or without narrow angles, or nested case-control designs (systematically and randomly selected from a defined population cohort)	Selection of either cases or controls in a predetermined, non-random fashion; or enrichment of the cases from a selected population	Unclear selection mechanism
Did the study avoid inappropriate exclusions?	Exclusions are detailed and felt to be appropriate (e.g. people with corneal opacities, ocular malformation causing bulbar derangement)	Inappropriate exclusions are reported (e.g. people with borderline index test results)	Exclusions are not detailed (pending contact with study authors)
Risk of bias: could the selection of participants have introduced bias?	All signalling questions = 'Yes'	Any signalling question = 'No'	Unclear
Concerns regarding applicability: are there concerns that the included participants do not match the review question?	Inclusion of participants without a previous diagnosis of a narrow angle	Inclusion of participants with a previous diagnosis of a narrow angle	Unclear inclusion criteria
INDEX TEST	**Describe the index test and how it was conducted and interpreted**		
Were the index test results interpreted without knowledge of the results of the reference standard?	Test performed blinded or independently and without knowledge of reference standard results are sufficient and full details of the blinding procedure are not required; or clear temporal pattern to the order of testing that precludes the need for formal blinding	Reference standard results were available to those who conducted or interpreted the index tests	Unclear whether results are interpreted independently
If a threshold was used, was it prespecified?	The study authors declare that the selected cut-off used to dichotomise data was specified a priori; or a protocol is available with this information	A study is classified at higher risk of bias if the authors define the optimal cut-off post hoc, based on their own study data	No information on preselection of index test cut-off values
Risk of bias: could the conduct or interpretation of the index test have introduced bias?	All signalling questions = 'Yes'	Any signalling question = 'No'	Unclear
Concerns regarding applicability: are there concerns that the index test, its conduct or interpretation differ from the review question?	Tests used and testing procedure clearly reported and tests executed by personnel with sufficient training	Tests used are not validated or study personnel was insufficiently trained	Unclear execution of the tests or unclear study personnel profile, background and training

Table 2.2. Guidance for QUADAS-2 assessment of risk of bias.

DOMAIN	LOW	HIGH	UNCLEAR
REFERENCE STANDARD	**Describe the reference standard and how it was conducted and interpreted**		
Is the reference standard likely to correctly classify the target condition?	Not applicable. Score 'Yes' for all studies		
Were the reference standard results interpreted without knowledge of the results of the index test?	Reference standard performed blinded or independently and without knowledge of index test results are sufficient and full details of the blinding procedure are not required; or clear temporal pattern to the order of testing that precludes the need for formal blinding	Index test results were available to those who conducted the reference standard	Unclear whether results were interpreted independently
Risk of bias: could the reference standard, its conduct or its interpretation have introduced bias?	All signalling questions = 'Yes'	Any signalling question = 'No'	Unclear
Concerns regarding applicability: are there concerns that the target condition as defined by the reference standard does not match the review question?	Not applicable. Score 'Low' for all studies		
FLOW AND TIMING	**Describe any participants who did not receive the index test(s) or reference standard, or either, or who were excluded from the 2x2 table; describe the time interval and any interventions between index test(s) and reference standard**		
Was there an appropriate interval between index test(s) and reference standard?	No more than three months between index and reference test execution	More than three months between index and reference test execution	Unclear whether test results were executed within three months
Did all participants receive a reference standard?	All participants receiving the index test were verified with the reference standard	Not all participants receiving the index test were verified with the reference standard	Unclear whether all participants receiving the index test were verified with the reference standard
Did all participants receive the same reference standard?	Not applicable. Score 'Yes' for all studies		
Were all participants included in the analysis?	The number of participants included in the study match the number in the analysis	The number of participants included in the study does not match the number in the analysis	Insufficient information on whether the number of participants included in the study matches the number in the analysis
Risk of bias: could the participants' flow through the study have introduced bias?	All signalling questions = 'Yes'	Any signalling question = 'No'	Unclear

Table 2.2 (continued). Guidance for QUADAS-2 assessment of risk of bias.

2.3 Results

2.3.1 Results of the search and characteristics of included studies

Searches of the literature were conducted on the 10th of November 2017. The electronic searches yielded 5844 records, the Cochrane Information Specialist removed 2246 duplicate records and we screened the titles and abstracts of the remaining 3598 records. We obtained full-text reports of 142 references for further assessment and excluded 99 reports (Figure 2.8). We identified 43 reports of 38 studies (see Appendix 1b for full characteristics of the included studies) that met the inclusion criteria and provided data from 19,425 participants for quantitative analysis. Fifteen of the included studies were cohort studies, 13 were cross-sectional and 10 used a case-control design. Most studies were conducted in Asia (29, 76.3%), followed by Europe (4, 10.5%), North America (2, 5.2%), South America (2, 5.2%) and Africa (1, 2.6%). Over half the studies (23, 60.5%) were conducted in a secondary care setting, with the remainder in a community setting (Table 2.3). The sample size ranged from 24 to 2052 patients (median 201) with most studies enrolling one eye per person (26, 68%) (see Appendix 1c, for demographics of the included studies).

Twenty-three studies assessed AS-OCT (13,335 patients), 14 studies LACD (6257 patients), 7 studies Scheimpflug photography (974 patients), 6 studies SPAC (5239 patients) and 5 studies evaluated the flashlight test (974 patients). Twenty-four of the studies evaluated a single index test and the remainder evaluated two or more tests on the same population. For the gonioscopic reference standard, 34 studies reported either the number of quadrants or degrees occluded, 2 studies used unique definitions such as the mean of four quadrants or an ACA angle less than 20 degrees in one quadrant and 1 study used the clinician's subjective opinion of occludability. The gonioscopic reference criterion was unclear in one study (Table 2.4).

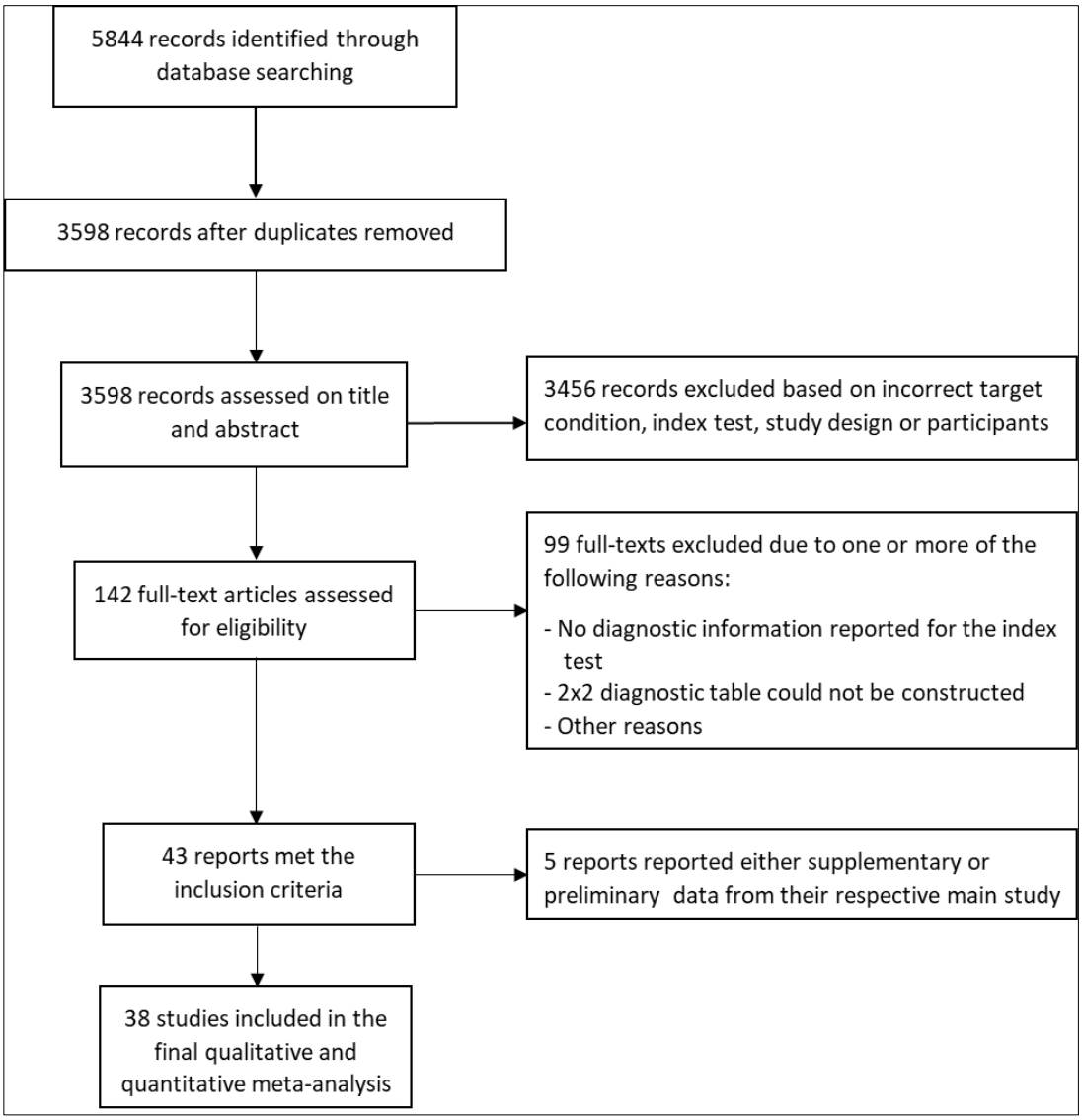


Figure 2.8. Flow diagram.

Study Identification	Study design	Country	Setting	Recruitment
(Alonso et al., 2010)	Cohort	Brazil	Secondary	NR
(Andrews et al., 2012)	Case-control	China	Secondary	Consecutive
(Ashaye, 2003)	Cohort	Nigeria	Secondary	Consecutive
(Baskaran et al., 2007)	Cohort	Singapore	Secondary	Consecutive
(Baskaran et al., 2012)	Cohort	Singapore	Secondary	Consecutive
(Campbell et al., 2015)	Cohort	UK	Primary	Triaged
(Chang et al., 2011)	Cross-sectional	Singapore	Primary	Consecutive
(Congdon et al., 1996)	Cross-sectional	Taiwan	Primary	Consecutive
(Dabasia et al., 2015a)	Case-control	UK	Secondary	NR
(Foster et al., 2000a)	Cross-sectional	Mongolia	Primary	Consecutive
(Gracitelli et al., 2014)	Cohort	Brazil	Secondary	NR
(Grewal et al., 2011)	Cohort	India	Secondary	Consecutive
(He et al., 2007)	Case-control	China	Primary	Random
(Hong et al., 2009)	Case-control	Korea	Secondary	NR
(Khor et al., 2010)	Cross-sectional	Singapore	Primary	Consecutive
(Kim et al., 2014)	Case-control	Korea	Secondary	Consecutive
(Ko et al., 2015)	Cross-sectional	Taiwan	Primary	Random
(Kurita et al., 2009)	Cohort	Japan	Secondary	Consecutive
(Lavanya et al., 2008)	Cross-sectional	Singapore	Primary	Consecutive
(Melese et al., 2016)	Case-control	USA	Secondary	NR
(Narayanaswamy et al., 2010)	Cross-sectional	Singapore	Primary	Consecutive
(Nolan et al., 2006)	Cross-sectional	Singapore	Secondary	Consecutive
(Nolan et al., 2007)	Case-control	Singapore	Secondary	NR
(Nongpiur et al., 2011)	Case-control	Singapore	Secondary	NR
(Okabe et al., 1991)	Cross-sectional	Japan	Primary	Random
(Park et al., 2011)	Cohort	Korea	Secondary	Consecutive
(Radhakrishnan et al., 2005)	Case-control	USA	Secondary	NR
(Rossi et al., 2012)	Case-control	Italy	Secondary	Consecutive
(Sakata et al., 2010)	Cohort	Singapore	Secondary	Consecutive
(Tan et al., 2012)	Cross-sectional	Singapore	Primary	Consecutive
(Thomas et al., 1996)	Cohort	India	Secondary	Consecutive
(Tun et al., 2017)	Cohort	Singapore	Secondary	Consecutive
(Wirbelauer et al., 2005)	Cohort	Germany	NR	NR
(Wong et al., 2009a)	Cohort	Singapore	Secondary	Consecutive
(Wong et al., 2009b)	Cohort	Singapore	Secondary	Consecutive
(Wu et al., 2011)	Cross-sectional	Singapore	Primary	Consecutive
(Yu et al., 1995)	Cross-sectional	China	Primary	Random
(Zhang et al., 2014)	Cross-sectional	China	Primary	Consecutive

Table 2.3. Study design and recruitment method of the included studies. NR: Not recorded.

Study Identification	Tests and Thresholds evaluated	Target condition	Gonioscopic occlusion (No. degrees)
Alonso 2010	Scheimpflug photography: ACA and ACD	NR	NR
Andrews 2012	LACD: ≤25%; SPAC: ≤6	PACS	≥180
Ashaye 2003	LACD: ≤25%	Gonioscopic occlusion	≥270
Baskaran 2007	LACD: 0%, ≤5%, ≤15%, ≤25%, ≤40%; SPAC; S and S or P	Gonioscopic occlusion (with or without PAS)	≥180
Baskaran 2012	AS-OCT: Subjective ≥2 quadrants closed	Gonioscopic occlusion	≥180
Campbell 2015	LACD: <25%; AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion	≥90
Chang 2011	SPAC: ≤4 and ≤5; AS-OCT: Temporal AOD750 and subjective ≥2 quadrants closed	Gonioscopic occlusion (with or without PAS)	≥180
Congdon 1996	LACD: <25% and >25% to ≤50%; flashlight grade 1 and 2	Gonioscopic occlusion (PACS, PAC, PACG grouped)	≥90
Dabasia 2015	LACD: 0%, ≤5%, ≤15%, ≤25%; AS-OCT: ACA, ACD; Scheimpflug photography: ACA, ACD and ACV	Gonioscopic occlusion (PACS, PAC, PACG grouped)	≥270
Foster 2000	LACD: 0%, ≤5%, ≤15%, ≤25%, ≤40%	Gonioscopic occlusion (PACS, PAC, PACG grouped)	≥270
Gracitelli 2014	Flashlight: Grade 1	Gonioscopic occlusion	≥180
Grewal 2011	AS-OCT: Temporal AOD500, TISA500; Scheimpflug photography: ACD and ACV	Gonioscopic occlusion (PACS and PAC grouped)	360
He 2007	Flashlight: Grade 1	Gonioscopic occlusion	≥180
Hong 2009	AS-OCT: ACA and ACD; Scheimpflug photography: ACA and ACD	Gonioscopic occlusion	≥270
Khor 2010	AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion	≥90
Kim 2014	AS-OCT: ACD and LV	Gonioscopic occlusion (PAC and PACG grouped)	≥180
Ko 2015	LACD: >25% to ≤50%	Gonioscopic occlusion (PACS, PAC, PACG grouped)	≥270
Kurita 2009	Scheimpflug photography: ACD	Gonioscopic occlusion (PACS and PAC grouped)	≥270

Table 2.4. Index tests and reference standard of the included studies. LV: Lens vault.

Study Identification	Tests and Thresholds evaluated	Target condition	Gonioscopic occlusion (No. degrees)
Lavanya 2008	SPAC: S or P, S or P and/or ≤5, ≤5; AS-OCT: Subjective ≥2 quadrants closed	Gonioscopic occlusion (with or without PAS)	≥180
Melese 2016	AS-OCT: Temporal AOD500, AOD 750, TISA500, TISA750	Gonioscopic occlusion	≥90
Narayanaswamy 2010	AS-OCT: Temporal AOD500, AOD750, TISA500, TISA750, ARA750	Gonioscopic occlusion	≥180
Nolan 2006	LACD: 0%, ≤5%, ≤15%, ≤25%	Gonioscopic occlusion	≥270
Nolan 2007	AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion	≥90
Nongpiur 2011	AS-OCT: LV	Gonioscopic occlusion (PACS, PAC, PACG grouped)	≥180
Okabe 1991	LACD: ≤25%	Gonioscopic occlusion	360 (mean of 4 quadrants Shaffer ≤2)
Park 2011	LACD: <25%; AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion (with and without PAS)	≥60
Radhakrishnan 2005	AS-OCT: AOD500, ARA500, ARA750, TISA500, TISA750	Gonioscopic occlusion	360
Rossi 2012	Scheimpflug photography: ACA, ACD, ACV	Gonioscopic occlusion (PACG excluded)	≥180
Sakata 2010	AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion	≥90
Tan 2012	AS-OCT: ACA, ACV and LV	Gonioscopic occlusion (with or without PAS)	≥180
Thomas 1996	LACD: <25%; flashlight grade 1 and 2	Gonioscopic narrow	Clinical opinion
Tun 2017	AS-OCT: Subjective ≥2 quadrants closed	Gonioscopic occlusion	≥180

Table 2.4 (continued). Index tests and reference standard of the included studies.

Study Identification	Tests and Thresholds evaluated	Target condition	Gonioscopic occlusion (No. degrees)
Wirbelauer 2005	LACD: ≤25%; AS-OCT: ACA, AOD500	Gonioscopic narrow	Narrow (ACA ≤20 degrees in 1 quadrant)
Wong 2009a	SPAC: S or P, S or P and/or ≤5, ≤5; AS-OCT: Subjective ≥2 quadrants closed	Gonioscopic occlusion	≥180
Wong 2009b	AS-OCT: Subjective ≥1 quadrants closed	Gonioscopic occlusion	≥90
Wu 2011	AS-OCT: ACA and ACV	Gonioscopic occlusion	≥180
Yu 1995	Flashlight: Grade 1 and 2	Gonioscopic occlusion	≥90
Zhang 2014	LACD: ≤15%, ≤25%, ≤40%; SPAC: S or P and/or ≤5, S or P and/or ≤6; AS-OCT: Subjective ≥2 quadrants closed; Scheimpflug photography: ACD, ACA and ACV	Gonioscopic occlusion	≥180

Table 2.4 (continued). Index tests and reference standard of the included studies.

2.3.2 Methodological quality of included studies

A summary of the methodological quality assessment is shown in Figure 2.9 which illustrates the risk of bias and applicability concerns for the 38 included studies.

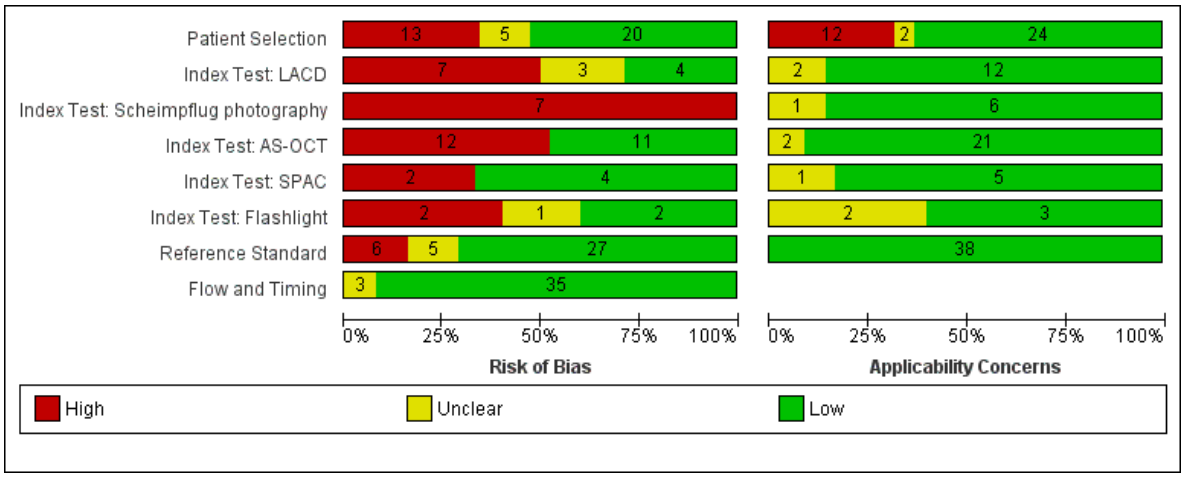


Figure 2.9. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

Patient Selection domain

Thirteen of the included studies (34.2%) were judged to have a high risk of patient selection bias, where one or more of the signalling questions answered negatively. Ten studies adopted a diagnostic case-control design that recruited patients with the target condition (cases) and a group of control patients without the target condition. Two studies reported using inappropriate exclusions, and 1 study enriched their sample by recruiting patients who had been previously examined who either had or were at risk of glaucoma. Five studies (13%) were categorised as having an unclear risk of bias; 3 studies did not report their exclusion criteria coupled with the method of sampling and 2 studies did not report their exclusion criteria.

The purpose of the index tests is to triage at-risk populations or for use in opportunistic screening to identify eyes at risk of angle closure. The inclusion of patients with a

previous diagnosis of the target condition therefore raised applicability concerns, as the spectrum of patients in these studies was not representative of those who would receive the test in practice.

Index test domain

There was a high risk of bias in studies where index test thresholds were not pre-defined. Optimal cut-offs were determined *post hoc* in all of the studies that evaluated Scheimpflug photography (7 studies, 100%), over half for AS-OCT (12 studies, 52%), and 2 of the 6 studies that evaluated SPAC. In the majority of studies, the index test was interpreted without knowledge of the reference standard results. However, for LACD, five studies (35.7%) were judged at high risk of bias since the same observer performed the index and reference test, which may have influenced the interpretation of the index test result. For the flashlight test masking was performed in 4 out of the 5 included studies.

Applicability of the test was generally of low concern across all the index tests, as the tests and testing procedures were clearly described and executed by personal who were sufficiently trained.

Further classification regarding the risk of bias and applicability per test is provided in Appendix 1d.

Reference standard domain

For the reference standard domain, 27 studies (71%) were judged to be at a low risk of bias, 6 studies (16%) were classified as high risk as gonioscopy was not masked to the index test result and in 5 studies (13%) masking was unclear. Concerns regarding applicability were not applicable for this review, since gonioscopy was used as the reference standard for the diagnosis of a narrow angle in all of the included studies.

Flow and Timing domain

For the flow and timing domain, the majority of studies (35, 92%) were classified as having a low risk of bias. In these studies, all participants receiving the index test were verified with the reference standard, the number of participants included in the study matched the number in the analysis and there was less than a three-month interval between the execution of the index test and reference test. There were 2 studies (5%) where the time interval between the index and reference test was not reported and in 1 study it was unclear whether all patients were included in the analysis.

The overall number of subjects/eyes excluded from all the studies due to gonioscopy was negligible (44, 0.2%); for LACD, flashlight, SPAC and Scheimpflug photography it was small (0% to 1.9%). The number of eyes/participants excluded from the final analysis using AS-OCT was relatively high (14.7%), due to the non-interpretation of the data owing to either the clinician or the internal software inability to identify the scleral spur (see Appendix 1e for full details regarding the number of eyes/subjects excluded per study).

2.3.3 Conflict of interest

Conflict of interest was of high concern in 15 studies, unclear concern in 8 studies, and of no concern in 15 studies. Conflicts of interest were reported for 13 studies that evaluated AS-OCT (56.5%) where the authors described receiving financial support from the manufacturer and/or loan of the device. For SPAC, 4 studies (66%) involved the patent holder of the device who was also a co-author, hence this was considered of high concern.

2.3.4 Diagnostic accuracy findings

Thirty-eight studies reported sensitivity and specificity values for one or more index tests. Sensitivities and specificities were very heterogeneous, as observed from the forest plots (see Appendix 1f) due to the number of different thresholds, target definition consensus, population studied, study designs and/or unit of analysis issues. Table 2.5 presents the diagnostic accuracy of the index test parameters that were used to conduct a meta-analysis using the bivariate model. Fixed thresholds for the tests were analysed and the thresholds for each index test that had the highest DOR were: LACD (≤25%); flashlight (grade 1); SPAC combination numerical and categorical grading (≤5 and/or S or P); Scheimpflug photography (ACD) and AS-OCT (subjective). Twelve studies analysed data from both eyes, however 4 studies corrected for the clustering of data (Congdon et al., 1996, Foster et al., 2000a, Lavanya et al., 2008, Rossi et al., 2012).

Test (parameter)	No. studies, No. patients (range)	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
LACD				
0%	4, 2920 (78-1632)	0.08 (0.03-0.18)	1.00 (0.99-1.00)	28.28 (8.78-91.11)
≤5%	4, 2920 (78-1632)	0.43 (0.31-0.55)	0.97 (0.96-0.97)	21.42 (12.12-37.86)
≤15%	5, 3345 (78-1632)	0.61 (0.36-0.81)	0.93 (0.83-0.97)	20.43 (6.21-67.21)
≤25%	**13, 6412 (78-1632)**	**0.85 (0.74-0.92)**	**0.88 (0.82-0.92)**	**41.26 (22.48-75.72)**
Scheimpflug photography				
ACV	4, 832 (36-299)	0.84 (0.79-0.89)	0.79 (0.65-0.88)	19.94 (9.31-42.73)
ACD	**7, 1056 (34-299)**	**0.91 (0.20-0.96)**	**0.79 (0.69-0.86)**	**38.65 (11.74-127.3)**
ACA	5, 725 (36-299)	0.72 (0.60-0.82)	0.91 (0.67-0.98)	25.84 (5.70-117.12)
SPAC				
≤5 and/or S or P	**4, 4677 (153-2052)**	**0.81 (0.70-0.89)**	**0.80 (0.77-0.83)**	**17.29 (9.45-31.63)**
AS-OCT				
Subjective	**12, 7385 (45-2052)**	**0.87 (0.77-0.93)**	**0.69 (0.60-0.77)**	**15.14 (9.63-23.82)**
Flashlight				
Grade 1	**5, 1188 (45-390)**	**0.53 (0.31-0.74)**	**0.92 (0.77-0.97)**	**12.33 (6.05-25.11)**

Table 2.5. Accuracy of parameters for each test. Summary estimates calculated when ≥4 studies were available for meta-analysis.

2.3.5 Diagnostic accuracy of the index tests

LACD

Fourteen studies (6257 patients) assessed LACD, with 7 studies evaluating a single threshold, 2 studies reporting two or more thresholds and the remainder providing data on three or more thresholds (Table 2.4). With an increasing LACD cut-off criterion (0%, ≤5%, ≤15%, ≤25%), there were gains in sensitivity from the summary point estimates of 0.08 (LACD 0%) to 0.85 (LACD ≤25%) and a corresponding reduction in specificity (1.00 to 0.88). The most commonly used threshold was ≤25% (used in 13 studies), which produced pooled sensitivity and specificity estimates of 0.85 (95% CI 0.74 to 0.92) and 0.88 (95% CI 0.82 to 0.92) respectively. Significant heterogeneity in sensitivity can be observed in the forest plot from the reported studies (Figure 2.10), with values ranging from 0.54 to 0.99. A summary receiver-operator characteristics curve (SROC) for LACD ≤25% is shown in Figure 2.11.

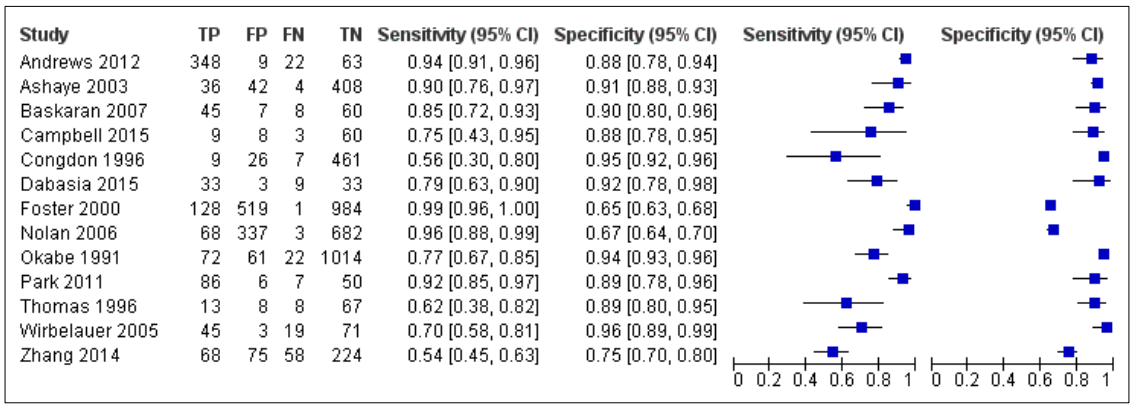


Figure 2.10. Forest plot for LACD threshold '≤25%.'

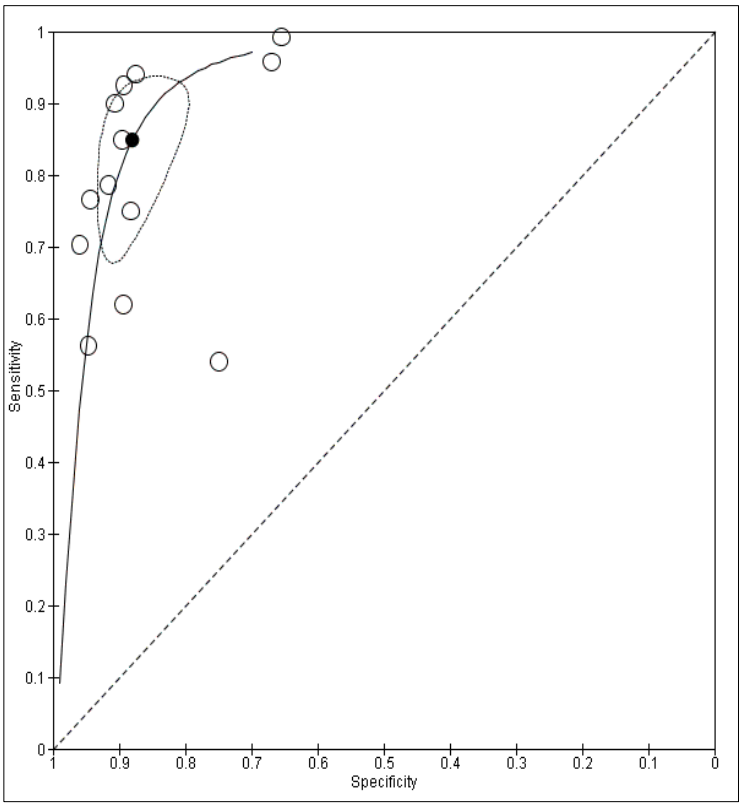


Figure 2.11. LACD threshold '≤25%,' SROC curve and summary point (with associated 95% confidence region).

Scheimpflug photography

Seven studies (974 patients) evaluated Scheimpflug photography. Four studies reported all three anterior segment parameters (ACA, ACD and ACV), 2 studies evaluated 2 parameters and 1 study evaluated only ACD (Table 2.4). Although different thresholds were used for each parameter, these were grouped for the meta-analysis. Point estimates of summary sensitivity varied between 0.72 and 0.91 across the parameters, where ACD had the highest sensitivity estimate and DOR (Table 2.5); the range in specificity and sensitivity values for this parameter was similar (Figure 2.12 and Figure 2.13).

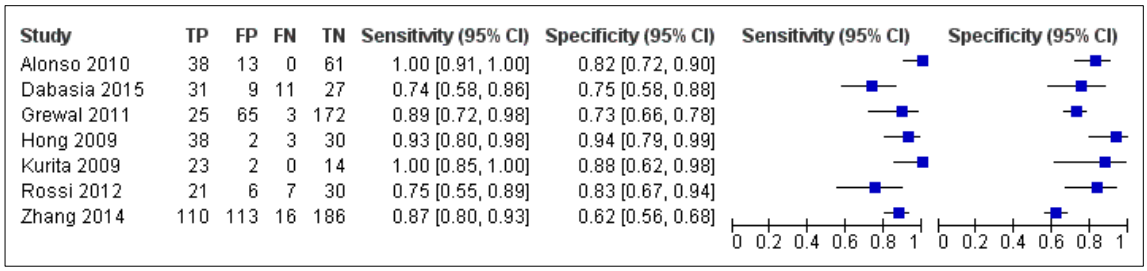


Figure 2.12. Forest plot for Scheimpflug photography threshold 'ACD.'

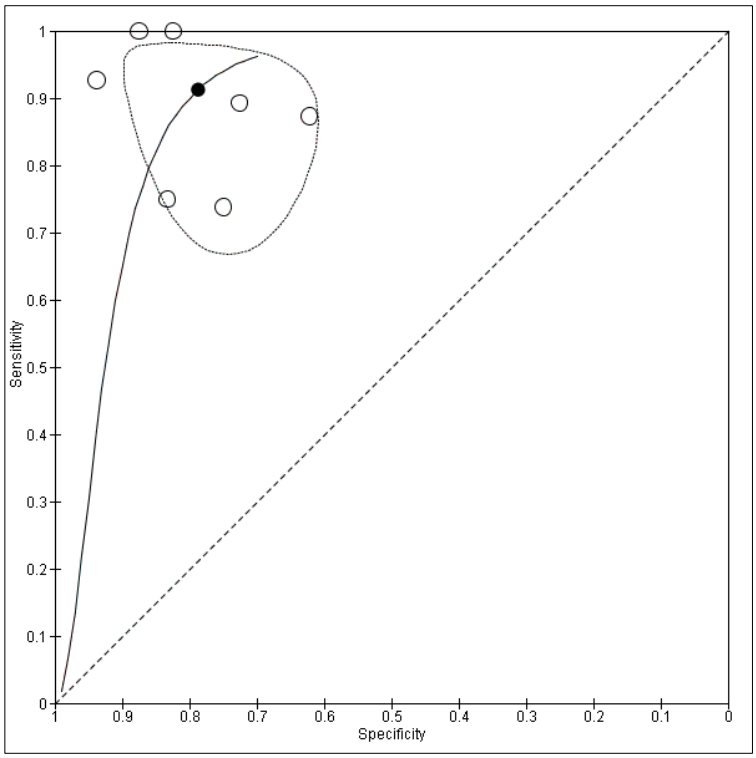


Figure 2.13. Scheimpflug photography threshold 'ACD,' SROC curve and summary point (with associated 95% confidence region).

SPAC

Six studies (5239 patients) examined SPAC, 3 studies reported both categorical and numerical grades, 2 studies presented only the numerical grading and 1 study described categorical thresholds (Table 2.4). With a variety of grading both categorical, numerical and combinations were used across the studies, the most common numerical grading was a SPAC threshold of ≤5, for the current analysis, this was amalgamated with the equivalent categorical grades suspect (S) and potential (P) risk of angle closure to produce a summary estimate (sensitivity 0.81; specificity 0.80) (Table 2.5), with sensitivities from the studies ranging from 0.63 to 0.90 (Figure 2.14 and Figure 2.15).

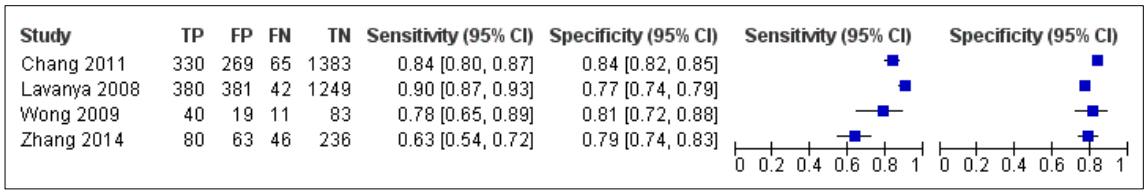


Figure 2.14. Forest plot for SPAC threshold '≤5 and/or S or P.'

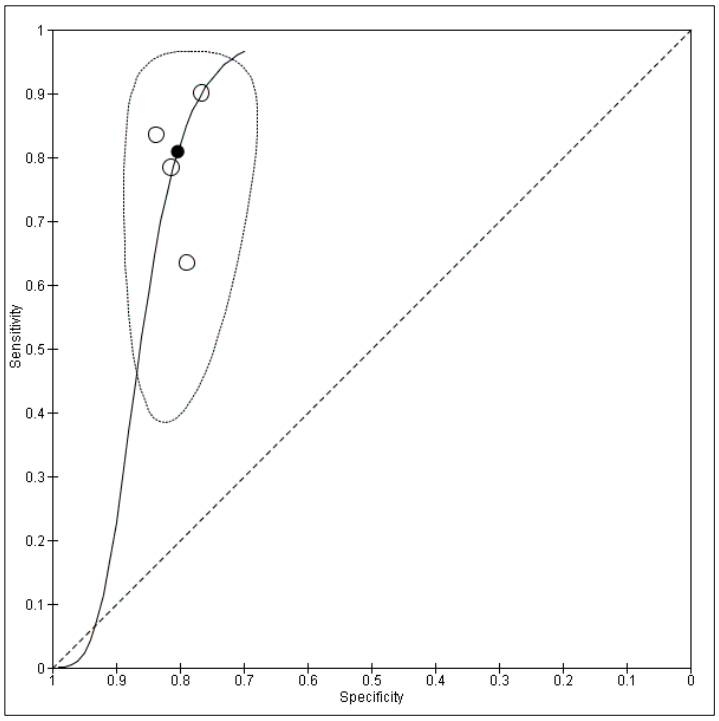


Figure 2.15. SPAC threshold '≤5 and/or S or P,' SROC curve and summary point (with associated 95% confidence region).

AS-OCT

Twenty-three studies (13,335 patients) assessed AS-OCT, 16 studies used the Visante time-domain AS-OCT; 3 studies, slit lamp OCT; 2 studies spectral-domain OCT with a lens adapter and 1 study utilised swept-source OCT. Sixteen AS-OCT parameters were reported; using either quantitative or qualitative thresholds or both. Point estimates of sensitivity and specificity could only be calculated for the subjective judgement of occludability (12 studies, 7385 patients). This revealed a high sensitivity (0.87) but lower specificity (0.69) (Table 2.5). There were large variabilities in sensitivity (0.50-1.00) and specificity (0.42-0.89) from the studies, as observed from the forest plot and summary point confidence estimates (Figure 2.16 and Figure 2.17).

Quantitative parameters reported unique cut-off values that were derived post-data collection, despite grouping the cut-off values per parameter, there were insufficient studies for meta-analysis.

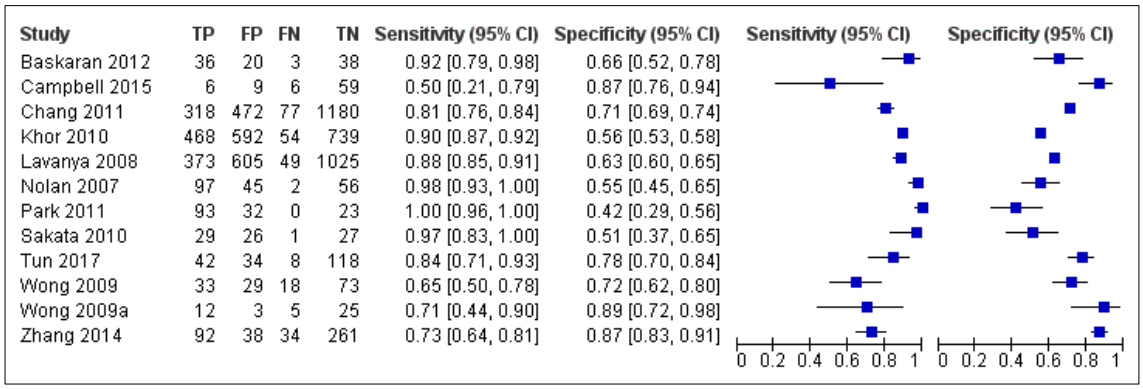


Figure 2.16. Forest plot for AS-OCT 'subjective judgement.' N.B. Wong 2009 and Wong 2009a are associated with the referenced 'Wong et al., 2009a' and' Wong et al., 2009b' studies respectively.

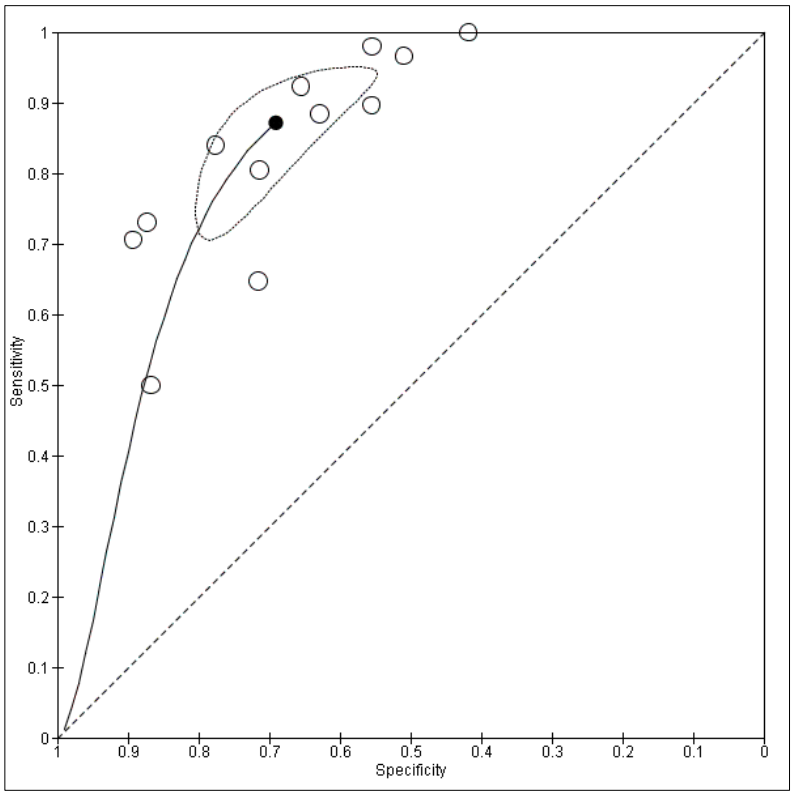


Figure 2.17. AS-OCT 'subjective judgement,' SROC curve and summary point (with associated 95% confidence region).

Flashlight

Five studies (974 patients) evaluated the flashlight test, 3 studies evaluated grades 1 and 2 and two studies evaluated only grade 1 (Table 2.4). Flashlight grading uses a 4-point scale; grades 1 and 2 are clinically more informative when diagnosing a narrow angle since they describe angles that are critically narrow or narrow respectively. A meta-analysis was conducted for grade 1, with an estimated sensitivity of 0.53 and specificity of 0.92 (Table 2.5). Visual inspection of the forest plot revealed heterogeneity with respect to sensitivity ranging from 0.20 to 0.89 (Figure 2.18). There was considerable uncertainty in the summary estimate as observed from the large size regarding the 95% confidence region in Figure 2.19. There were insufficient studies to generate a summary estimate for grade 2.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Congdon 1996	2	19	8	333	0.20 [0.03, 0.56]	0.95 [0.92, 0.97]		
Gracitelli 2014	8	12	1	24	0.89 [0.52, 1.00]	0.67 [0.49, 0.81]		
He 2007	142	21	44	88	0.76 [0.70, 0.82]	0.81 [0.72, 0.88]		
Thomas 1996	9	13	12	62	0.43 [0.22, 0.66]	0.83 [0.72, 0.90]		
Yu 1995	12	0	60	318	0.17 [0.09, 0.27]	1.00 [0.99, 1.00]		

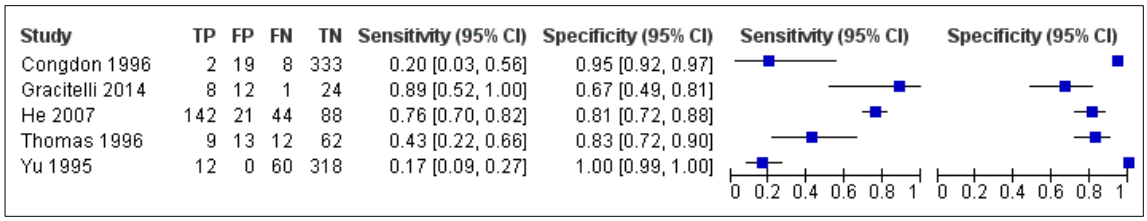


Figure 2.18. Forest plot for flashlight 'grade 1.'

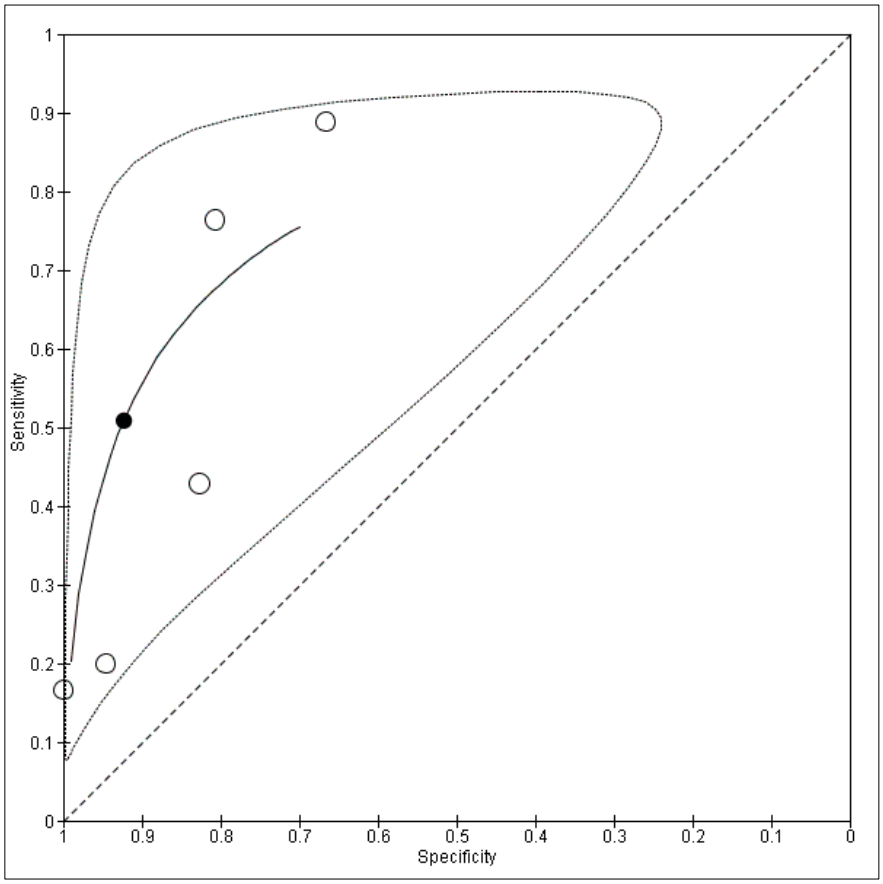


Figure 2.19. Flashlight threshold 'grade 1,' SROC curve and summary point (with associated 95% confidence region).

2.3.6 Test comparisons

For each test, the parameter yielding the highest DOR was compared in the bivariate model, using LACD (≤25%) as the reference test (Table 2.6). Sensitivity comparisons were similar across all the index tests except for the flashlight test, where a grade 1 threshold had a significantly lower sensitivity than the reference test. Specificity evaluation was also similar for all the best performing index test parameters apart from AS-OCT, which showed a significantly lower specificity than LACD.

Test (parameter)	No. studies, No. patients (range)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (p value)	Specificity (p value)
LACD (≤25%)	**13, 6412 (78-1632)**	**0.85 (0.74-0.91)**	**0.88 (0.82-0.92)**	**Reference**	**Reference**
Scheimpflug photography (ACD)	7, 1056 (34-299)	0.90 (0.78-0.96)	0.79 (0.67-0.88)	0.31	0.10
SPAC (≤5 and/or S or P)	4,4677 (153-2052)	0.81 (0.58-0.93)	0.80 (0.65-0.90)	0.65	0.16
AS-OCT (Subjective)	12, 7385 (45-2052)	0.88 (0.78-0.93)	0.70 (0.59-0.79)	0.62	<0.001
Flashlight (Grade 1)	5, 1188 (45-390)	0.53 (0.31-0.74)	0.92 (0.77-0.97)	0.02	0.55

Table 2.6. Relative accuracy of the best parameter (based on DOR) for each test.

2.3.7 Investigation of heterogeneity and sub-group analysis

There were insufficient studies to evaluate test accuracy for detecting the most severe referable condition (PACG) versus a narrow angle or to compare test performance between primary and secondary care. There were also insufficient studies to conduct the pre-specified formal investigation of heterogeneity. We had planned to perform a sensitivity analysis to assess the impact of risk of bias on test accuracy by repeating the analysis after removing studies at high risk of bias, however nearly all the studies were judged to have at least one domain that was labelled as high/unclear risk of bias or had an applicability concern.

2.3.8 Interpretation of findings

Published prevalence estimates for angle closure disease (PACS, PAC and PACG) in Asian populations are variable, ranging from 6-20% of those aged 40 and over (Foster et al., 2000a, Bourne et al., 2003, He et al., 2006a, Nolan et al., 2006, Lavanya et al., 2008, Vijaya et al., 2008, Liang et al., 2011, Sawaguchi et al., 2012, Tang et al., 2019, Wang et al., 2019). We have used the summary estimates for each index test derived from the bivariate model to simulate the performance of these tests for population screening (Table 2.7), based on prevalence values of 5% and 10%. For example, using the LACD threshold ≤25%, if 50 people out of 1000 had a narrow angle, the test would only miss 7 cases and 114 patients would be unnecessarily referred for specialist investigation.

What is the accuracy of LACD, Scheimpflug photography, SPAC, AS-OCT and flashlight for diagnosing a narrow angle?	
Patient/population	Patients ≥40 years with a narrow angle compared to open angle controls
Studies	15 cohort, 13 cross-sectional and 10 studies were a case-control design
Prior testing	Present in 20 studies (Unclear in 4 studies)
Setting	Primary or secondary care
Index tests	LACD, Scheimpflug photography, SPAC, AS-OCT and flashlight
Reference standard	Clinical assessment of a narrow angle using gonioscopy
Role and purpose	Identify those at risk of a narrow angle for subsequent gonioscopy examination by a glaucoma specialist
Quality concerns	Patient selection bias and index test threshold not being pre-defined were common concerns
Limitations	Insufficient studies to explore heterogeneity or subgroup analysis

Test (parameter)	**No. studies, patients (range)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Implications in 1000 patients undergoing community triage**									
				NA prevalence 5% 50 cases out of 1000					**Narrow angle prevalence 10% 100 cases out of 1000**				
				NA detected	NA Missed	Referred (no NA)	PPV	NPV	NA detected	NA Missed	Referred (no NA)	PPV	NPV
LACD (≤25%)	13, 6412 (78-1632)	0.85 (0.74-0.92)	0.88 (0.82-0.92)	43	7	114	0.27	0.99	85	15	108	0.44	0.98
Scheimpflug photography (ACD)	7, 1056 (34-299)	0.91 (0.20-0.96)	0.79 (0.69-0.86)	46	4	199	0.19	0.99	91	9	189	0.33	0.99
SPAC (≤5 and/or S or P)	4, 4677 (153-2052)	0.81 (0.70-0.89)	0.80 (0.77-0.83)	41	9	190	0.18	0.99	81	19	180	0.31	0.97
AS-OCT (Subjective)	12, 7385 (45-2052)	0.87 (0.77-0.93)	0.69 (0.60-0.77)	44	6	295	0.13	0.99	87	13	279	0.24	0.98
Flashlight (Grade 1)	5, 1188 (45-390)	0.53 (0.31-0.74)	0.92 (0.77-0.97)	27	23	76	0.26	0.97	53	47	72	0.42	0.95

Table 2.7. Summary of findings. NA: Narrow angle.

2.4 Discussion

Future projections indicate that those with PACG aged 40-80 years will reach 23.4 million by 2020, accounting for 50% of glaucoma blindness and disproportionally affect those who reside in Asia (Quigley & Broman, 2006, Tham et al., 2014). The current reference standard to detect a narrow angle is gonioscopy. Whilst this technique offers comprehensive visualisation of the ACA and adjacent structures, it is invasive, requires a high degree of skill to perform and is not usually performed outside a specialist ophthalmic setting. Gonioscopy is therefore unsuitable for population screening. As a shallow ACD is the cardinal risk factor in most ethnic groups for the development of PACG, tests that can evaluate the risk of angle closure by measuring the anterior chamber dimensions could potentially be used to identify those at risk of the disease.

This systematic review evaluated the diagnostic accuracy of non-contact screening methods including LACD (van Herick test), flashlight, SPAC, Scheimpflug photography and AS-OCT for detecting individuals at risk of PACG. These tests were evaluated as stand-alone screening methods that could be used by specialist or non-specialist healthcare professionals in a primary care or triage setting. In the proposed clinical pathway, screen positive cases would be referred for gonioscopic assessment by a glaucoma specialist.

2.4.1 Summary of main results

We analysed data from a total of 19,425 participants in 38 studies reporting the diagnostic accuracy of one or more index tests for the detection of a narrow angle. The majority of studies were conducted in Asia. Pre-specified thresholds were reported for LACD, flashlight, SPAC and the subjective judgement of occludability using AS-OCT. However, all the reported thresholds for Scheimpflug photography and quantitative AS-OCT thresholds were calculated *post-hoc* and were based on the best performing cut-points derived from each study population. The heterogeneity of sensitivity and

specificity estimates for each test was large and could not be adequately explained. Furthermore, 25 of the 38 included studies (66%) were judged to have a high risk of bias in at least one domain, most commonly due to patient selection bias and/or not pre-defining the index test threshold. This suggests that we should be cautious in our interpretation of the results.

A meta-analysis was conducted to generate summary estimates of diagnostic accuracy based on thresholds with the highest DOR for all of the index tests. We found that the overall accuracy of LACD assessment based on a threshold of ≤25% was good (sensitivity 0.85 (0.74 to 0.92); specificity 0.88 (0.82 to 0.92) and similar to Scheimpflug photography and SPAC. The flashlight test had a significantly lower sensitivity and the subjective judgement of occlusion by AS-OCT was associated with a lower specificity than LACD.

2.4.2 Comparison with previous reviews

Two systematic reviews have previously evaluated the diagnostic accuracy of anterior segment imaging to detect angle closure (Smith et al., 2013, Porporato et al., 2018). Neither of these reviews conducted a meta-analysis.

The review by Smith and colleagues formed part of an Ophthalmic Technology Assessment conducted by the American Academy of Ophthalmology, included data from 79 articles published to July 2011 that provided quantitative and qualitative data on ultrasound biomicroscopy (UBM), AS-OCT, Scheimpflug photography and SPAC. A more recent review by Porporato et al, evaluated the role of AS-OCT in angle closure disease where this review included 71 studies, published to June 2017.

For AS-OCT, both reviews commented on its non-contact nature and ease of obtaining images when compared to invasive methods. They also concluded that it correlated well with the information provided by gonioscopy in terms of sensitivity and highlighted its potential for primary angle closure screening, however as in the current review, concerns were raised regarding its specificity. In addition, they discussed the AS-OCT's

inability to clearly define the scleral spur, which is located deep within the anterior chamber recess, in a high proportion of participants; that led to a large number of uninterpretable results. This limitation was also echoed in a number of narrative reviews (Friedman & He, 2008, Lin & Huang, 2012, Dabasia et al., 2014a, Chansangpetch et al., 2018). In the current review, the overall number of exclusions for AS-OCT was unacceptably high, with approximately 15% of participants excluded, due to either poor image quality or inability to identify the scleral spur.

For Scheimpflug photography, Smith and colleagues commented that its non-contact approach is appealing for screening, but emphasised that the device does not allow detailed visualisation of angle structures, making it difficult to estimate the ACA (Smith et al., 2013). Consequently, the ACA had the poorest correlation with gonioscopy, compared to the ACD and ACV parameters. This limitation was also commented in other narrative reviews, (Dabasia et al., 2014a, Nguyen et al., 2016, Shinoj et al., 2016).

SPAC captures information about the peripheral anterior chamber depth, where it is essentially an automated quantitative van Herick test (Smith et al., 2013), which is appealing for non-clinical personnel to operate and interpret. Smith et al described that SPAC correlated well with AS-OCT, based on its performance in a large cross-sectional study (Lavanya et al., 2008).

The UK National Institute for Health and Care Excellence (NICE) published a national clinical guideline for the diagnosis and management of chronic open angle glaucoma (COAG) (NICE, 2017), which applies in England, Wales and Northern Ireland. As part of the evidence synthesis for this guideline, the accuracy of tests to identify a narrow angle was evaluated for the purpose of differentially diagnosing COAG. The index tests included: AS-OCT, Scheimpflug imaging, UBM and LACD. The search was restricted to studies that used the ISGEO definition for gonioscopic occlusion (posterior trabecular meshwork not visible for ≥180 degrees). There were insufficient studies to conduct the planned meta-analysis, however they reported that a LACD threshold of ≤25% achieved the highest specificity, compared to AS-OCT and Scheimpflug photography, whereas AS-

OCT achieved the highest sensitivity. The guideline committee concluded that none of the index tests met the pre-specified sensitivity level of 95% needed to recommend the test as an alternative to gonioscopy, however they recommended that AS-OCT or LACD could be used when clinical circumstances rule out gonioscopy. The Scottish Intercollegiate Guidelines Network (SIGN) have produced specific guidance on glaucoma referral and safe discharge (SIGN, 2015). This guideline discusses the relatively high specificity associated with LACD and low specificity with AS-OCT, as well as their accessibility by community optometrists. The guideline committee recommended that gonioscopy or LACD could be used when case-finding. SIGN further stated the specific thresholds that would trigger a referral into secondary eye care services, irrespective of any other findings. They endorsed a gonioscopic threshold of ≥270 degrees of PTM not visible and a LACD threshold of ≤25%. The latter recommendation was based on two cohort studies in Asia (Thomas et al., 1996, Baskaran et al., 2007). Our comprehensive review provides further validation for the ≤25% LACD threshold, which gave the best balance between sensitivity and specificity.

2.4.3 Applicability of findings to the review question

Non-invasive techniques for the evaluation of the ACA are commonly performed as part of a standard eye examination by ophthalmic clinicians. These tests could potentially be used for population screening to identify those at risk of angle closure. Given that the tests could be applied in either primary or secondary care, we did not place any restriction on setting, although in both pathways consecutive undiagnosed patients would be evaluated or triaged. However, approximately one-third of the included studies recruited participants with a previous diagnosis of a narrow angle, which was mainly attributed to the use of a case-control design. These designs are known to over-estimate the performance of screening tests and therefore our estimates of test accuracy could be higher than would be expected in unscreened populations.

Three-quarters of the included studies were performed in Asia, which carries the greatest burden of PACG and its associated blindness (Tham et al., 2014). The prevalence of PACG in Asian populations is up to three times higher than in European derived groups (Day et al., 2012, Cheng et al., 2014). Consequently, population screening for angle closure in these populations is more likely to be cost-effective (Tang et al., 2019). The review findings are therefore particularly applicable for the design of screening programmes in these high-risk groups.

Non-contact methods for identifying narrow angles include both subjective (flashlight, LACD) and objective tests (SPAC and Scheimpflug photography). AS-OCT imaging can be interpreted subjectively or objectively. Subjective tests in the included studies were generally interpreted by ophthalmologists, who are usually based in a secondary care setting. Previous studies evaluating LACD have found no difference in performance between ophthalmologists and non-medical healthcare professionals, with moderate inter-observer agreement for each group (Jindal et al., 2015, Johnson et al., 2018). Similarly, a small study assessing AS-OCT qualitative judgements by glaucoma specialists also found moderate agreement (Tay et al., 2015).

Angle closure disease represents a spectrum of disorders from angle closure suspect to PACG. Angle closure is defined by the degree of appositional contact between the peripheral iris and trabecular meshwork and the presence or absence of trabecular damage (PAS). Although all the studies used gonioscopy as the reference standard, a variety of diagnostic definitions were used. Our review allowed for flexibility in the clinical definition and accepted the classification of a narrow angle adopted by the investigators. Almost half of the studies (42.1%) used the widely accepted ISGEO classification (2 or more quadrants occluded), the remainder used either a more (26.3%) or less (26.3%) stringent definition, the classification was unclear in 2 studies (5.3%).

2.4.4 Implication for practice

Although PACG is less common than primary open angle glaucoma, it is often more severe and is associated with a greater likelihood of visual morbidity. Nearly half of the people affected by PACG worldwide are of Chinese descent (Quigley & Broman, 2006), where in China 3.1 million are blind in at least one eye due to the condition (Foster & Johnson, 2001). Angle closure often develops insidiously and is frequently asymptomatic in this and other East Asian populations. Early detection is therefore crucial to avoid visual impairment. Although the studies included in the current review have a number of methodological shortcomings, we nonetheless consider the results valuable. The finding that the estimation of LACD performed as well as highly sophisticated imaging technologies, confirms the potential for this test for screening for narrow angles in high-risk populations. The test is simple to perform and can be learned with relatively little training. A recent health economic analysis concluded that combined population screening for open and closed angle glaucoma in Chinese adults aged 50 years or above is likely to be cost-effective (Tang et al., 2019). In their decision-analytic model, the authors included diagnostic estimates for the combined sensitivities and specificities of LACD and optic nerve photography. Using a LACD threshold of ≤25% alone and based on our summary estimate of test accuracy, approximately 40% of those who would be identified as test positive would have a narrow angle (PPV=0.44; narrow angle prevalence 10%).

Sixty percent of the included studies evaluated AS-OCT. This technology has a number of theoretical advantages, including the rapid and non-invasive acquisition of high-resolution images of the entire circumferential ACA. These images can be interpreted qualitatively or quantitatively. Although the included studies provided data on 16 separate AS-OCT parameters, the lack of consistency in the thresholds meant that summary estimates could only be calculated for the subjective judgement of occludability. Comparative analysis for this parameter showed similar sensitivity to LACD but an inferior specificity. However, OCT technology is continuing to develop with

ongoing improvements in image resolution. It is likely that the superior resolution of newer devices e.g. swept-source OCT, will overcome the current problem of scleral spur visualisation, which is an important anatomical landmark for ACA evaluation.

2.4.5 Strengths and weaknesses of the review

Strengths of this systematic review included its methodological rigour, which included the following:

- A comprehensive search strategy to identify as many potential studies for inclusion with no language, clinical setting, study design or publication year restrictions.
- All titles and abstracts were independently screened by two reviewers (AJ and IC).
- Two reviewers (AJ and JL) independently extracted data and conducted a quality assessment of studies (using QUADAS-2).
- We obtained translations of two Asian studies that met the inclusion criteria, undertook data extraction and conducted risk of bias assessments.
- Sufficient studies were available to conduct a meta-analysis and produce summary estimates of sensitivity and specificity for all five index tests.

There were a number of limitations of the review. Comparisons between index tests are best conducted using direct (within study) comparisons, as direct comparisons are considered to be more reliable than indirect comparisons (between studies) (Takwoingi et al., 2013). Since relatively few of the included studies reported more than one test or parameter, indirect comparisons were conducted throughout. Indirect comparisons can potentially lead to confounding due to between study differences in the characteristics of participants, reference standards and study design (Bossuyt et al., 2013). The majority of studies had a high or unclear risk of bias in at least one domain and substantial heterogeneity was observed between studies. This should be taken into consideration when interpreting the review findings. Finally, there were insufficient studies to compare

test performance in different clinical settings and disease severity, in addition we were unable to conduct the planned sensitivity analysis on the risk of bias, as this may have impacted the applicability of such tests.

2.4.6 Conclusion

The global burden of PACG is mainly associated with those who reside in Asia, where the majority of the studies included in this review were conducted. As such, our findings would be applicable to the design of screening programmes in these high-risk groups. Meta-analysis of the assessed non-contact methods showed relatively good performance for most tests for the detection of a narrow angle. Indirect comparisons in diagnostic accuracy were similar, but flashlight and AS-OCT had a lower sensitivity and specificity, respectively. However, care is advised when interpreting these estimates for clinical decision making, due to the observed heterogeneity in test performance and high risk of bias found in most studies.

There is still a need for high-quality studies to evaluate the performance of non-invasive tests for angle assessment. These studies should adopt consecutive or random sampling using pre-specified thresholds. Furthermore, investigators performing the index test and reference standard should be masked. The diagnostic accuracy of index tests to identify angle closure in subgroups (PACS, PAC, PACG) would also provide useful additional information that would be relevant for the development of care pathways for angle closure.

Disclaimer

This chapter is based on a pre-peered review version of a Cochrane Review. Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews (www.cochranelibrary.com).

Chapter 3: Diagnostic accuracy of a new thresholding glaucoma programme using temporally modulated flicker

3.1 Introduction

Functional assessment using visual field testing remains one of the most important tools for identifying and monitoring vision loss in glaucoma (Jampel et al., 2011). Glaucoma detection currently relies on opportunistic case-finding, however epidemiological studies have shown that up to a half of glaucoma is undiagnosed in high income countries (Tielsch et al., 1991a, Klein et al., 1992, Mitchell et al., 1996, Quigley & Vitale, 1997, Weih et al., 2001, Chan et al., 2017) and over 90% in low income countries (Ramakrishnan et al., 2003, Vijaya et al., 2008, Garudadri et al., 2010, Thapa et al., 2012, Budenz et al., 2013). Glaucoma fulfils many of the standard criteria (Wilson & Jungner, 1968) needed to justify the development of a population-based screening programme. However several studies have reported that primary open angle glaucoma (POAG) screening in the general population is not cost-effective in high income countries such as the United Kingdom (UK) and Finland, but screening may be more effective if targeting at-risk populations (Burr et al., 2007, Vaahtoranta-Lehtonen et al., 2007, Hernández et al., 2008). Two recent studies evaluating glaucoma screening in rural India (John & Parikh, 2018) and China (Tang et al., 2019) have found that combined screening for open and closed angle glaucoma could be cost-effective due to lower overhead costs and the high risk of blindness in untreated cases of primary angle closure glaucoma.

Since the introduction of automated perimetry in the early 1970s, developments have included improving the following; sensitivity of the tests to detect early visual field damage; test efficiency; test reliability and the ability to ascertain progressive field loss (McKendrick, 2005, Wu & Medeiros, 2017). Perimeters have been developed to use different stimuli that have attempted to 'isolate' retinal ganglion cell (RGC) mechanisms in order to improve test performance to glaucoma such as the use of 'flicker'. The first commercially available perimeters utilising this phenomenon were the first generation 'Frequency Doubling Technology '(FDT) perimeter and the subsequent Matrix perimeter,

manufactured by Carl Zeiss Meditec, whereby both machines contain in-built algorithms which can be used for screening or case-finding. Newer flicker strategies such as Pulsar and Flicker Defined Form perimetry have been incorporated into the Octopus 600 perimeter and the Heidelberg Edge Perimeter, respectively. Pulsar performance has been shown to be comparable with FDT (Gonzalez de la Rosa, 2011), however it is affected by refractive blur (Gonzalez-Hernandez et al., 2007). Flicker defined form perimetry has been demonstrated to distinguish healthy from those with early glaucoma, however its ability to make this distinction reduces with more advanced disease (Horn et al., 2015). Alternate strategies to flicker include Short Wave Automated Perimetry (SWAP) and motion displacement thresholding. The former uses a blue on yellow stimuli that attempts to isolate the koniocellular pathway (Dacey & Packer, 2003) and the later uses a temporal form of hyperacuity. The main disadvantage of SWAP is that its performance is affected by the natural age-related yellowing of the crystalline lens and subsequently this has probably limited the widespread use of this strategy. Motion displacement thresholding has been incorporated into the Moorfields Motion Displacement Thresholding perimeter, this uses white vertical line stimuli, where the smallest displacement of the line is observed as the threshold. The programme was designed to overcome the effects of cataract and uncorrected refractive error (Bergin et al., 2011, Dabasia et al., 2015b, Che Hamzah et al., 2020). It's initial diagnostic capabilities were found to be promising (Ong et al., 2014), but a subsequent cross-sectional study found its performance to be lower when tested in an elderly population (Dabasia et al., 2015b), in addition this test at present is not commercially available.

With the advent of touch screen and tablet-technology, this has created new opportunities for the development of a portable low-cost glaucoma-screening test that could be used in those at risk of disease, home setting or in underserved communities. For example, an iPad-based threshold perimeter using stimulus locations based on the Humphrey Field Analyser (HFA) 24-2 test grid showed good diagnostic performance for the detection of glaucoma (Vingrys et al., 2016, Schulz et al., 2018). In addition, the newly developed 'Eyecatcher' portable perimeter uses an inexpensive eye tracker and tablet

computer, where it was found it could clearly discriminate between glaucomatous and normal eyes and it may be used for case-finding or where testing remains difficult (Jones et al., 2019).

A new device termed the Accelerator 4-Alternative Forced-Choice Flicker Test prototype (A4FTp) has been developed for the purpose of screening POAG. This device incorporates temporally modulated flicker whereby the temporal modulation uses a flicker stimulus that is matched in luminance to the background, the contrast of the stimulus is then temporally modulated at a fixed spatial frequency, and the amplitude of the flicker modulation to detect the stimulus is determined (Tyler, 1991). Sensitivity to temporal modulation flicker has been shown to be effective in separating normal subjects from glaucoma patients, and flicker stimuli have been utilised in a number of perimeters (Tyler, 1981, Lachenmayr & Drance, 1992, Horn et al., 1997, Yoshiyama & Johnson, 1997). Another advantage of these flicker methods is that they are relatively unaffected by optical blur due to uncorrected refractive error (Tyler, 1991, Lachenmayr & Gleissner, 1992), where it has been demonstrated that an optical defocus of up to +6 dioptres has little effect on FDT perimetry, in terms of sensitivity in normal observers (Anderson & Johnson, 2003b). The stimuli are displayed in a uniform red field (610nm) which was designed to minimise transmission losses in the optic media (Wyszecki & Stiles, 1982). Another feature of the A4FTp test design is the use of extended stimulation areas at a small number of test locations. Previous studies have shown that the large numbers of stimulus locations used in current threshold perimeters are not always necessary to achieve high levels of sensitivity; good diagnostic performance can be achieved using relatively few test locations, confined to areas that are particularly prone to glaucomatous damage (Bosworth et al., 1997, Westcott et al., 1999, Wang & Henson, 2013). Moreover, one of the most common indices of glaucomatous loss is the mean deviation (MD) of the HFA, which focuses on the average loss across large areas of the retina (Hodapp et al., 1993). The philosophy of the stimulus design in the A4FTp test is therefore to use large stimuli that integrate information across extended retinal regions

to detect those who are at higher risk of visual disability in their lifetime; that will then lead to subsequent referral for further investigation and diagnosis.

The aim of the present study was to assess the diagnostic performance of the A4FTp, using a new psychophysical thresholding algorithm that could potentially be used to detect functional vision loss outside the normal clinical setting and in those who are at risk of glaucomatous visual disability in their lifetime. Performance of the A4FTp was also compared with commercially available screening glaucoma technologies that detect structural or functional glaucomatous damage.

Study Contributions

Development of the A4FTp design and algorithm involved Christopher Tyler (CT), Bruno Fidalgo (BF), JL. Ethics application and the study protocol was written by AJ. Recruitment of all participants, study logistics and user acceptability survey was organised by AJ. AJ conducted the reference standard ophthalmic examination and BF performed the index tests for all study participants. Statistical analysis and study findings were conducted and written by AJ. Comments on the peer-reviewed paper were reviewed by BF, AJ, IC, CT and JL.

3.2 Methods

This prospective diagnostic accuracy study was conducted in a university-based primary eye clinic in London, UK, between January and July 2017. The study was approved by the School of Health Sciences Research Ethics Committee, City, University of London, and complied with the tenets of the Declaration of Helsinki. Written and informed consent was obtained from all participants prior to taking part in the study.

3.2.1 Study participants

Participants eligible for inclusion were consecutive adults (≥40 years) with a clinical diagnosis of POAG and were recruited either from the university eye clinic or via a request for volunteers in the 'International Glaucoma Association' newsletter. The control participants were consecutive non-glaucomatous adults (≥40 years), who were recruited from the university eye clinic and local optometry practices.

3.2.2 Inclusion and exclusion criteria

There is no universally-accepted reference standard for the diagnosis of glaucoma; however optic disc and visual field damage are typically used to diagnose the presence of the disease (Michelessi et al., 2015). For the current study, the diagnosis of POAG was based on a reference standard examination and included the following diagnostic criteria: open anterior chamber angles, presence of glaucomatous optic neuropathy (classified as localised absence of neuroretinal rim, cup-to-disc ratio of 0.7, or interocular asymmetry in vertical cup-to-disc ratio of 0.2 in similar sized discs); and the presence of a concordant glaucomatous field defect using the 24-2 Swedish Interactive Thresholding Algorithm (SITA) programme on the HFA. The classification of a field defect was based on criteria amended from Anderson (Anderson & Patella, 1999) (a cluster of 3 points on the pattern deviation plot having $p<5\%$, with at least 1 point with $p<1\%$, none of which

could be edge points unless located immediately above or below the nasal horizontal meridian, and a pattern standard deviation at p<5%).

The inclusion criteria for the control participants included: normal appearance of the optic disc, normal fundus, intraocular pressure ≤21mmHg and full visual fields on the reference examination. Any participant with a history of angle closure or significant ocular co-morbidity was excluded e.g. diabetic retinopathy, retinal vascular occlusions, peripheral retinal abnormalities, optic atrophy, clinically significant cataract (indexed by the Lens Opacity Classification System III (Chylack et al., 1993) (LOCS III) (N≥4.0, C≥2.0, P≥2.0) or a neurological field defect (based on HFA perimeter criteria).

3.2.3 Procedures

Figure 3.1 shows the flow of patients through the study. All participants underwent testing on both eyes with the three index tests specified below, performed in a random order by an experienced optometrist (BF) who was unaware of the participants' ocular status. This was then followed by a reference standard ophthalmic examination by a clinician (AJ) masked to the index test results. Participants were included in the analysis if they underwent both reference and index tests; those with uninterpretable results were excluded.

Thresholds of abnormality for the index tests were based on cut-offs commonly reported in the literature and were pre-defined before data analysis except for the A4FTp.

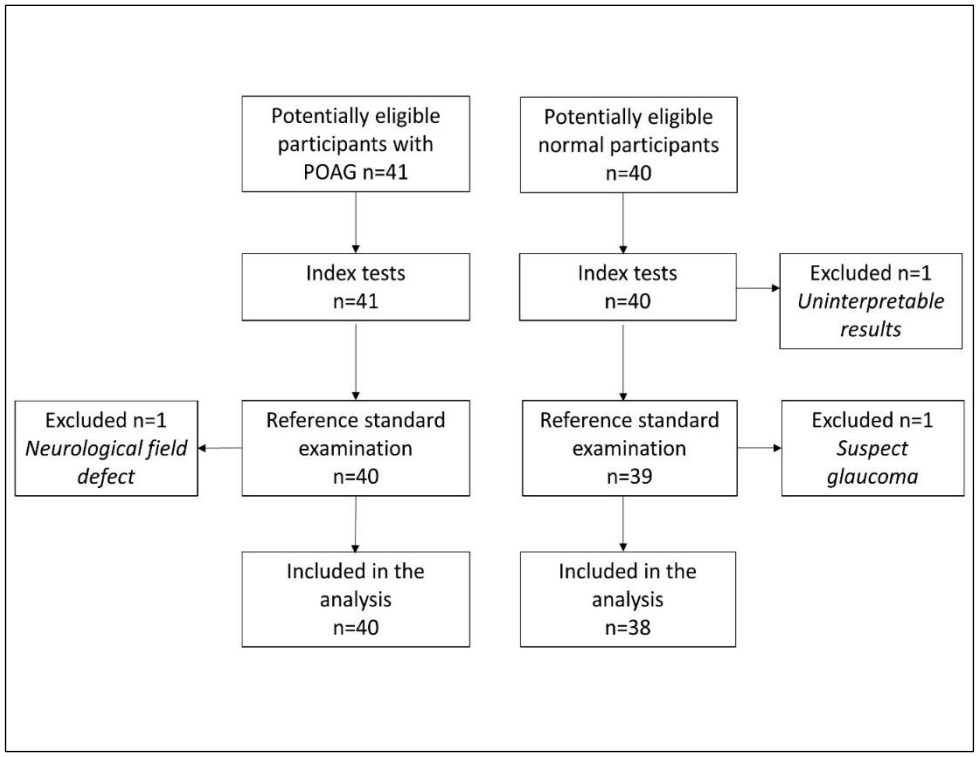


Figure 3.1. Study flow diagram.

3.2.4 Index tests

The index tests included: A4FTp; FDT; and the iVue Spectral-Domain Optical Coherence Tomography (SD-OCT).

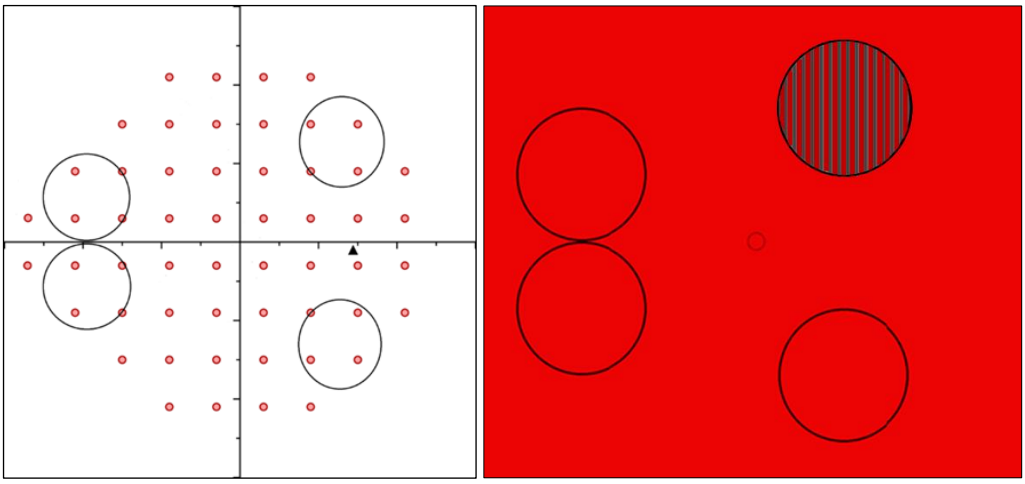
A4FTp

The A4FTp (software version 1.0) is a computer-based full threshold test, which uses a four-alternative forced-choice staircase termination paradigm to determine sensitivity to temporally modulated sinusoidal flicker. Studies have found that by employing temporal modulation flicker, flicker sensitivity was reduced in those with glaucoma (Tyler, 1981, Kondo et al., 1998, Spry et al., 2005, Prokosch & Eter, 2014, Reznicek et al., 2015, Horn et al., 2016). The first commercial perimeter to incorporate a flicker strategy was the FDT, where studies found it achieved moderate to high diagnostic performance in those with established glaucoma (Quigley, 1998, Trible et al., 2000, Horn et al., 2002,

Müskens et al., 2004, Stoutenbeek et al., 2004, Geimer, 2013, Dabasia et al., 2015b). Previous studies have suggested that the large numbers of test locations in current threshold perimeters are not necessary to achieve high levels of sensitivity; good diagnostic performance can be achieved by using relatively few test locations, confined to areas that are particularly susceptible to glaucomatous damage (Henson et al., 1988, Wang & Henson, 2013). Whilst the informational value of stimulus locations in susceptible areas of the visual field may be high, the correlation between adjacent test locations limits the value of adding multiple stimuli in these areas. The choice of stimulus location for this first iteration of the A4FTp was based on the study by Wang and Henson (Wang & Henson, 2013) who used optimised sub-sets of the standard 24-2 test pattern, based on the positive predictive value (PPV) of each test location that broadly corresponded to the typical patterns of glaucomatous visual field loss (Nicholas & Werner, 1980, Keltner et al., 2003).

The A4FTp stimuli are located in the superior and inferior arcuate regions of the visual field, with two temporal stimuli (11 degrees diameter) positioned 9-21 degrees from fixation and two nasal (11.7 degrees diameter) targets 14-26 degrees from fixation, situated at the endpoints of the arcuate sweep of the retinal nerve fibre layer, the visual field location subject to the well-known 'nasal step'. Stimuli were displayed at a viewing distance of 33cm on a high refresh rate screen (120 Hz) on a uniform background (Figures 3.2a-3.2b). The target stimulus in each of four test fields was a burst of 30 Hz effectively sinusoidal flicker with the same mean luminance as the background (19 cd/m^2) that was ramped on and off according to a 1 second raised cosine envelope in order to avoid onset and offset transients. After each stimulus, a 2-beep audio signal was cued to indicate that the stimulus had been presented and that the user then had to input their response onto a 4-button keypad, that translated to the presented stimuli location. Thresholds for each location were measured by a 2-up, 1-down staircase in log modulation steps of 1 deciLog (dL) (1/10^{th} of log10 base intervals, following the simplifying convention relative to decibel (dB) units adopted by Tyler (Tyler, 1991)) based on an incorrect/correct choice of the four regions, which was flickering on each trial. The staircase ended when

performance reached the stable criterion level of σ<1 decilog in terms of both slope and variability over the last 8 trials of the staircase (Fidalgo et al., 2018). Results were plotted in decilog units. The participant's refractive error was corrected for the working distance if the participant habitually wore a distance correction. In the absence of a pre-defined threshold for abnormality, the optimal threshold for the A4FTp was derived from the data and corresponded to the criterion value that maximised both sensitivity and specificity.



Figures 3.2a and 3.2b, a) Left image: A4FTp stimuli locations translated onto an HFA 24-2 visual field plot of the right eye and b) right image: A4FTp presentation of the flickering stimuli in one of the 4 locations in the right eye.

FDT perimeter

The FDT was introduced into clinical practice in the late 1990s (Anderson & Johnson, 2003a). The first generation FDT (Carl Zeiss Meditec Inc., Dublin CA, software version 4.00.0) incorporates both suprathreshold and threshold algorithms; it measures contrast sensitivity at 0.25 cycles/degree, which is counterphase flickered at 25Hz (Anderson & Johnson, 2003b). There are two suprathreshold probability algorithms which are matched to the machine's normative database which can test the central 20 or 30 degrees of the visual field, both can be used for screening; the most common are the

C20-5 or C20-1 programmes. Both these test patterns have been systematically evaluated in the literature (Burr et al., 2007). For comparative performance against the A4FTp, the first generation FDT perimeter using C20-5 supra-threshold mode was chosen as this is widely used for glaucoma detection in primary care and both machines use similar stimuli that allow a more direct comparison of the visual field function compared to other perimeters.

The contrast levels for C20-5 are measured at 17 locations within the central 20 degrees of the visual field and are compared to an age-corrected normative database. Test results for each location are classified into probability levels that are represented by a greyscale (Figure 3.3). Trial lens correction was provided as per the manufacturer's recommendations for high refractive errors. Classification of an abnormal result was based on the following criteria: any location missed at the p<5% significance level or any location missed at the p<1% level. If any of the indices were unreliable, which included false positives, false negative or fixation losses ≥33% or any point missed, the test was repeated, with the repeated test result analysed.

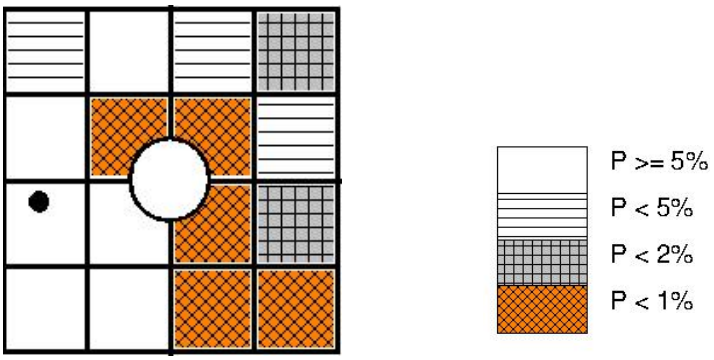


Figure 3.3. FDT plot with the associated probability levels.

IVue Spectral-Domain-Optical Coherence Tomography

Optical coherence tomography (OCT) is a non-invasive imaging method, which provides an *in-vivo* examination of the eye by constructing high-resolution cross-sectional images following the principle of low-coherence interferometry.

The iVue SD-OCT (Model iVue 100, Optovue Inc, Fremont CA) incorporates spectral-domain technology to provide an axial and transverse resolution of 5µm and 15µm respectively. The capture rate is 26,000 A-scans/sec using a wavelength of 840nm ±10µm. Segmentation algorithms allow the identification and quantification of individual retinal layers, for example the retinal nerve fibre layer (RNFL) or the combined ganglion cell and inner plexiform layers of the ganglion cell complex (GCC) whereby thinning has been observed in glaucoma (Tan et al., 2009, Na et al., 2012, Sevim et al., 2013). The glaucoma optic nerve head scan protocol provides a measure of the 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) (Figure 3.4). The GCC thickness data (Figure 3.5) is acquired from the inner limiting membrane to the outer plexiform layer in the macula area of 7mm by 7mm, centred 1mm temporal to the fovea to sample a greater area of the temporal retina (Dabasia, 2014).

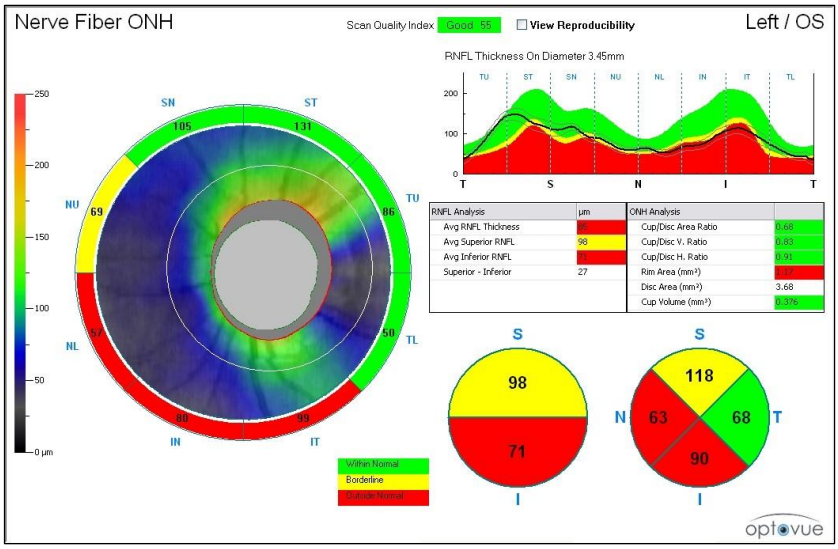


Figure 3.4. IVue SD-OCT RNFL profile analysis report.

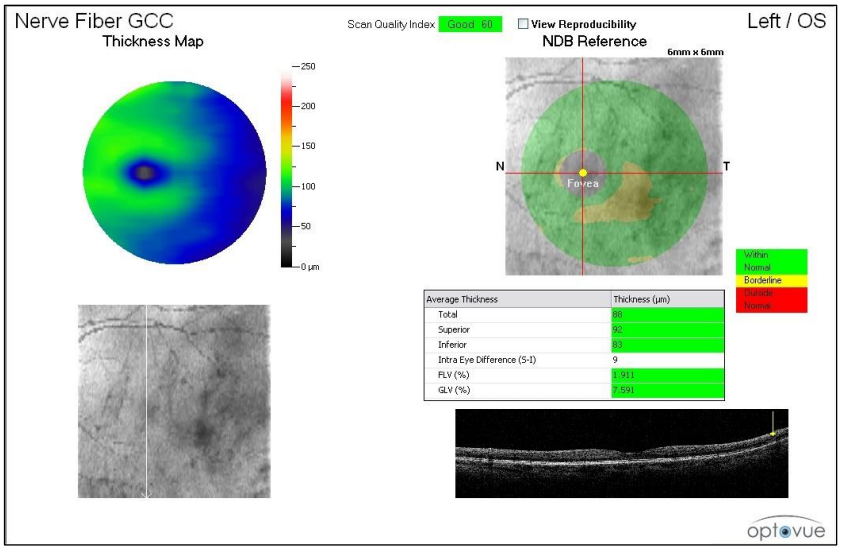


Figure 3.5. IVue SD-OCT GCC analysis report.

The IVue SD-OCT (software version 3.2.0.42) was used to scan the posterior segment of the eye, capturing data from the optic nerve head RNFL and GCC average thickness. Scans were taken through un-dilated pupils under dark room conditions. If the scan quality (scan quality index was below 50) was inadequate or data uninterpretable, the pupil was dilated and the scan was repeated, if the scan did not meet this criterion the eye was excluded. Cut-offs for abnormality were for any RNFL quadrant or GCC average thickness identified at p<1% or p<5% from the manufacturers' normative database.

3.2.5 Reference test

All participants underwent a reference standard ophthalmic examination on the same day as the index tests by an experienced glaucoma-specialist optometrist (AJ) (with training and accreditation within glaucoma clinics in the UK Hospital Eye Service), masked to the index tests results. The ocular examination comprised: LogMAR best correct visual acuity; refraction; intraocular pressure measurement (IOP) with a Goldmann Applanation Tonometer; slit lamp biomicroscopy including grading of the crystalline lens with the LOCS III and van Herick assessment of limbal anterior chamber depth (Van Herick et al., 1969) (with potentially occludable angles examined using

gonioscopy); dilated fundus examination and detailed disc assessment using indirect ophthalmoscopy. Visual fields were measured using a Humphrey Field Analyser (Carl Zeiss Meditec Inc) using the SITA 24-2 standard pattern (model 720i software version 5.1.2). Humphrey field testing was repeated for false positives >15%, false negatives or fixation losses >33%. Glaucomatous visual field loss was classified using the Hodapp Parrish-Anderson criteria, where a participant with a mean deviation of <6dB was defined as having early glaucoma, ≥6db to <12dB as moderate glaucoma and ≥12dB as advanced glaucoma, the full classification has been described elsewhere (Hodapp et al., 1993).

The Hodapp criteria allows rapid classification of glaucomatous field loss in a clinical setting, however it may be inappropriate for finer categorisation of visual field loss. A newer glaucoma staging system (GSS2) described by Brusini and Filacorda uses a 7-stage system that may be better suited for classifying localised defects compared to traditional systems (Brusini & Filacorda, 2006). The GSS2 stages glaucoma severity by plotting the visual field indices onto a graph by taking both pattern standard deviation (PSD) and MD into account (Brusini & Filacorda, 2006). Exploratory analysis using the GSS2 was conducted on the glaucoma cohort regarding the performance of the functional index tests and classification.

3.2.6 Evaluation of user acceptability

Subjects were asked to complete a questionnaire regarding the acceptability of the index tests and the HFA at the end of the reference examination. The questionnaire evaluated the ease of use, test duration and test comfort using a seven-point Likert scale (see Appendix 2).

3.2.7 Sample size calculation

The sample size was based on precision and the A4FTp's anticipated sensitivity reaching 0.85. It was considered that the 95% confidence limit should not fall below 0.60 with a 0.95 probability. This level required a minimal sample of 33 participants with glaucoma (Flahault et al., 2005).

3.2.8 Statistical analysis

Statistical analysis was performed using SPSS 23.0 (www.ibm.com/analytics/spss-statistics-software) and MedCalc 17.4 (www.medcalc.org). All tests were performed on both eyes for comparison with the clinical assessment of individual eyes and the data from one eye used in the analysis. In the case of glaucoma participants, this was the eye with the greater glaucomatous visual field loss and the right eye for the controls. If this eye did not meet the inclusion criteria, the other eye was selected; however, if neither eye met the inclusion criteria, the participant would have been excluded.

Receiver operator characteristics curves (ROC) were plotted for the ability of the index tests to discriminate glaucomatous from non-glaucomatous eyes. Differences in the area under the receiver operator characteristics curves (AUROC) for each test parameter at the 95% confidence interval (CI) was compared statistically using the DeLong method (DeLong et al., 1988), a p-value of 0.05 was considered as the threshold for significance. Sensitivity, specificity, positive and negative likelihood ratios were also calculated. Parametric and non-parametric tests were used to compare the differences between the two groups with respect to participant characteristics and user acceptability of the tests. Linear regression was used to assess the correlation between A4FTp threshold and the age of the controls.

3.3 Results

3.3.1 Participant characteristics

Eighty-one participants were assessed for initial eligibility and were invited to participate. Three participants were excluded from the analysis: 1 had uninterpretable results on all the visual function tests, 1 had suspected glaucoma and 1 participant with glaucoma had a bilateral neurological visual field defect. Thirty-eight controls and 40 participants diagnosed with glaucoma were included in the final analysis. There were no uninterpretable OCT scans of the 78 eyes that were analysed. The glaucoma group contained more pseudophakics (n=22, 55%) compared to the controls (n=2, 5.3%). There was no statistical difference between the two groups in visual acuity, refractive error or gender. Most participants were of Caucasian origin and the average ages for the control and glaucoma groups were 61.6 years (95% CI 58.1-65.0) and 71.9 years (68.8-74.9), respectively. A summary of the demographic and clinical data for the controls and glaucoma participants is provided in Table 3.1. There were no adverse events when performing any of the index tests or reference examination.

Glaucoma cases were categorised by glaucoma severity using the criteria from Hodapp criteria as: early (n=13, 32.5%), moderate (n=14, 35%) and advanced glaucoma (n=13, 32.5%). Using the GSS2 criteria, cases were categorised as: stage 0 (n=1, 2.5%), borderline (n=2, 5%), stage 1 (n=5, 12.5%), stage 2 (n=5, 12.5%), stage 3 (n=10, 25%), stage 4 (n=8, 20%) and stage 5 (n=9, 22.5%).

	Control	Glaucoma	p value
No. Participants	38	40	
Age (years) (Mean±SD)	61.6±10.6	71.9±9.4	<0.001
No. Female (%)	22 (57.9%)	24 (60%)	0.85
Ethnicity (No. %) Caucasian Asian Indian African Origin	 28 (73.7%) 10 (26.3%) 0 (0%)	 37 (92.5%) 2 (5%) 1 (2.5%)	
Visual Acuity (LogMar) (Mean±SD)	0.04±0.17	0.09±0.12	0.092
IOP (mmHg) (Mean±SD)	17.5±2.5	15.3±5.5	0.023
Refractive Error (DS) (Mean±SD)	-0.26±3.59	-0.72±2.81	0.53
Refractive Error (DC) (Mean±SD)	-0.72±0.71	-1.01±0.93	0.13
HFA SITA 24-2 MD (dB) (Mean±SD)	-0.71±1.55	-10.53±7.61	<0.001

Table 3.1. Demographical and summary clinical data for the participants in each group. DS: Dioptric Sphere; DC: Dioptric Cylinder; MD: Mean Deviation; SD: Standard Deviation. Independent t-tests were performed for each category except for gender, where chi-squared was used.

3.3.2 Diagnostic performance of the A4FTp

The threshold that optimised sensitivity and specificity (Youden index), with the respective AUROC was determined per stimuli location or an average of either two or four locations from the A4FTp. The best performing thresholds (as determined by the greatest AUROC) were; single location, superior nasal quadrant mean AUROC 0.77 (95%CI 0.66-0.86); hemifield location, nasal hemifield 0.80 (95% CI 0.70-0.88) and the mean threshold from all four stimulus locations 0.82 (95% CI 0.73-0.92). The best performing parameter for the A4FTp was the mean threshold from all four stimulus locations (Table 3.2).

Index Test	Test Parameter	Optimal Threshold (dL)	Se (%)	Sp (%)	PLR	NLR	AUROC (95% CI)
A4FTp	**Mean of 4 Locations**	**>12.3**	**82.5**	**73.7**	**3.1**	**0.2**	**0.82 (0.73-0.92)**
	Superior hemifield	>10.8	95.0	55.3	2.1	0.1	0.79 (0.69-0.88)
	Inferior hemifield	>13.1	75.0	73.7	2.9	0.3	0.78 (0.67-0.87)
	Nasal hemifield	>13.3	82.5	73.7	3.1	0.2	0.80 (0.70-0.88)
	Temporal hemifield	>10.5	95.0	57.9	2.3	0.1	0.79 (0.68-0.87)
	Superior nasal quadrant	>10.4	92.5	50.0	1.9	0.2	0.77 (0.66-0.86)
	Superior temporal quadrant	>10.9	77.5	68.4	2.5	0.3	0.76 (0.65-0.85)
	Inferior nasal quadrant	>14.1	67.5	73.7	2.6	0.4	0.74 (0.63-0.84)
	Inferior temporal quadrant	>10.3	97.5	47.4	1.9	0.1	0.75 (0.64-0.84)

Table 3.2. A4FTp diagnostic performance of the locations tested. Se: Sensitivity; Sp: Specificity; PLR: Positive Likelihood ratio; NLR: Negative Likelihood Ratio; CI: Confidence Interval.

The A4FTp optimal parameter achieved a sensitivity and specificity of 83% and 74% respectively. Sensitivity of the test could potentially be increased by lowering the log threshold, however this would lead to an unacceptable reduction in specificity; Figure 3.6 plots the A4FTp thresholds with their respective sensitivity/specificity. Figure 3.7 shows a histogram of the mean log flicker thresholds for the control and glaucoma subgroups with their 95% confidence intervals. Mean log thresholds increased with disease severity, although there was overlap in the distributions for control participants

and those with early glaucoma. In the control group, there was no statistically significant correlation (p=0.24), using the A4FTp optimal threshold against age.

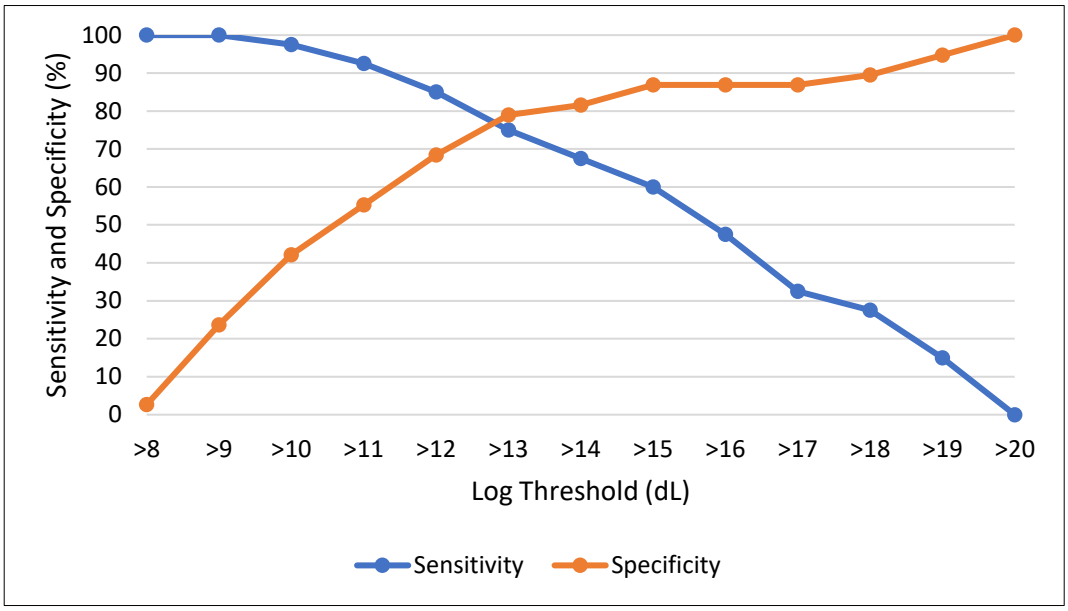


Figure 3.6. Sensitivity and specificity plot of the A4FTp thresholds.

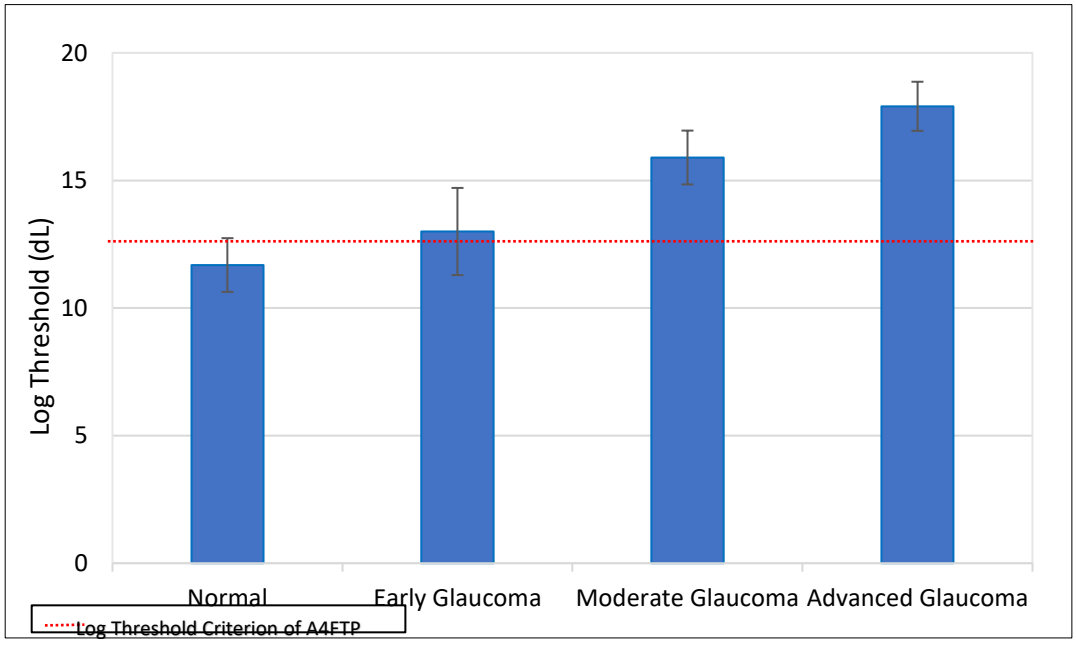


Figure 3.7. Histogram of the mean log thresholds of control and glaucoma subgroups. Error bars represent the 95% confidence interval.

3.3.3 Comparison of the A4FTp with other index tests

Table 3.3 displays the diagnostic performance of all the index tests, the best performing threshold for each index test was, A4FTp; mean of the 4 locations, FDT; any location missed at p<5% level and for the SD-OCT; any quadrant at the p<1% level in the RNFL.

Index Test	Test Parameter	Optimal Threshold	Se (%)	Sp (%)	PLR	NLR	AUROC (95% CI)
A4FTp	**Mean of 4 Locations**	**>12.3dL**	**82.5**	**73.7**	**3.1**	**0.2**	**0.82 (0.73-0.92)**
FDT	**Any point missed at p<5% level**	**>0**	**90.0**	**92.1**	**11.4**	**0.1**	**0.91 (0.82-0.96)**
	Any point missed at p<1% level	>0	82.5	97.4	31.7	0.2	0.90 (0.81-0.96)
iVue SD-OCT RNFL	**Any quadrant at p<1%**	**-**	**87.5**	**84.2**	**5.5**	**0.1**	**0.90 (0.83-0.97)**
	Any quadrant at p<5%	-	95.0	68.4	3.0	0.1	0.82 (0.74-0.90)
iVue SD-OCT GCC	Mean GCC p<5%	-	70.0	78.9	3.3	0.4	0.75 (0.63-0.84)
	Mean GCC p<1%	-	57.5	92.1	7.3	0.5	0.75 (0.64-0.84)

Table 3.3. Diagnostic performance of A4FTp, FDT and iVue SD-OCT.

Table 3.4 shows pairwise comparisons of the AUROC between A4FTp and other index test parameters. There was no statistical significance between the A4FTp and FDT cut-offs. Comparisons between the A4FTp and the SD-OCT parameters showed no statistically significant difference for either the GCC average thickness or RNFL any quadrant identified at the p<1% level and p<5% level.

Test comparisons	Difference between the AUROC's (95% CI)	p value
A4FTp vs FDT p<1% any point missed	0.08 (-0.03-0.18)	0.15
A4FTp vs FDT p<5% any point missed	0.09 (-0.02-0.02)	0.12
A4FTp vs SD-OCT RNFL p<1%	0.07 (-0.04-0.18)	0.18
A4FTp vs SD-OCT RNFL p<5%	0.01 (-0.11-0.12)	0.91
A4FTp vs SD-OCT GCC mean p<5%	0.08 (-0.06-0.22)	0.27
A4FTp vs SD-OCT GCC mean p<1%	0.08 (-0.05-0.20)	0.23

Table 3.4. Pairwise comparison of AUROC between A4FTp and the other index parameters.

Figure 3.8 shows a Venn diagram for the best performing criteria of each index test in identifying the glaucoma participants. The A4FTp detected slightly fewer glaucoma cases (n=33, 83%) than the FDT (n=36, 90%) or SD-OCT (n=35, 88%). Two cases (5%) were missed by all three index tests. The diagram also shows that a screening strategy that combines a structural test (SD-OCT RNFL) with a functional test (FDT or A4FTp) increases the likelihood of detecting the disease.

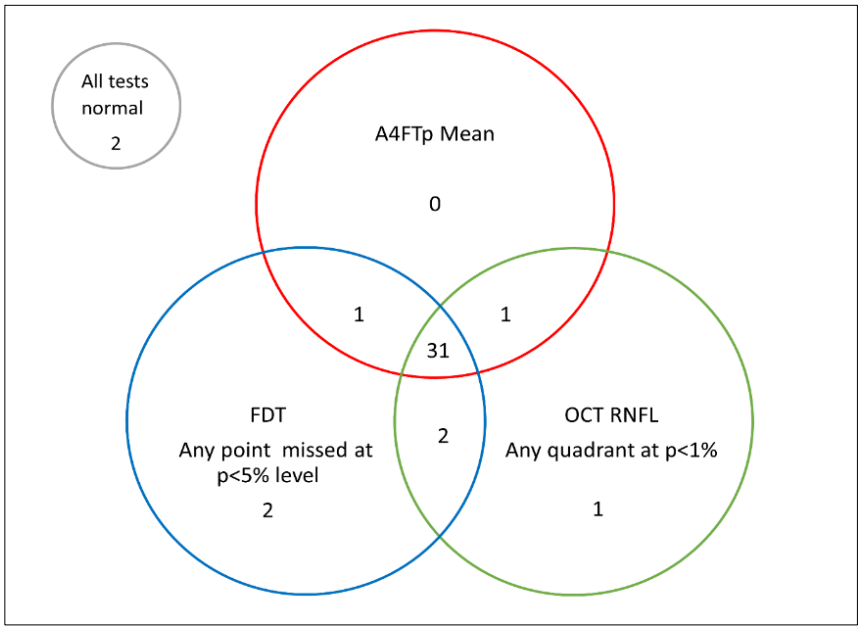


Figure 3.8. Venn diagram of the best performing parameter from the index tests in identifying the glaucoma cases alone or combined with the other tests.

3.3.4 Glaucoma detection between A4FTp and FDT

Using the optimal thresholds, the A4FTp test identified 93% and 100% of moderate and severe glaucoma respectively, it identified half of those diagnosed with early glaucoma as defined using the Hodapp classification (Figure 3.9). The FDT detected all cases of early glaucoma, where 87% and 85% of those with moderate and advanced glaucoma were identified, respectively (Figure 3.10).

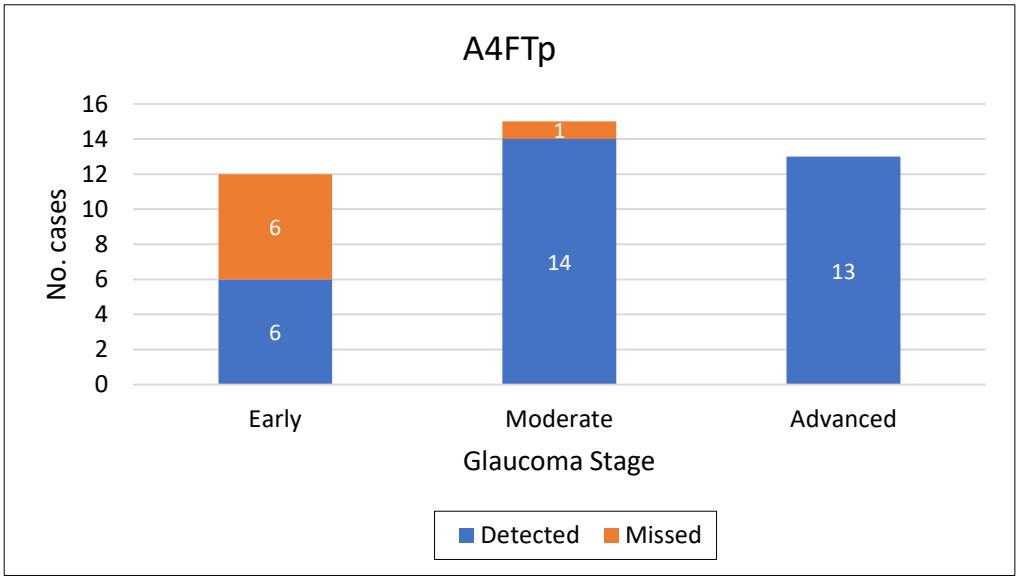


Figure 3.9. Histogram of the glaucoma severity detected by the A4FTp.

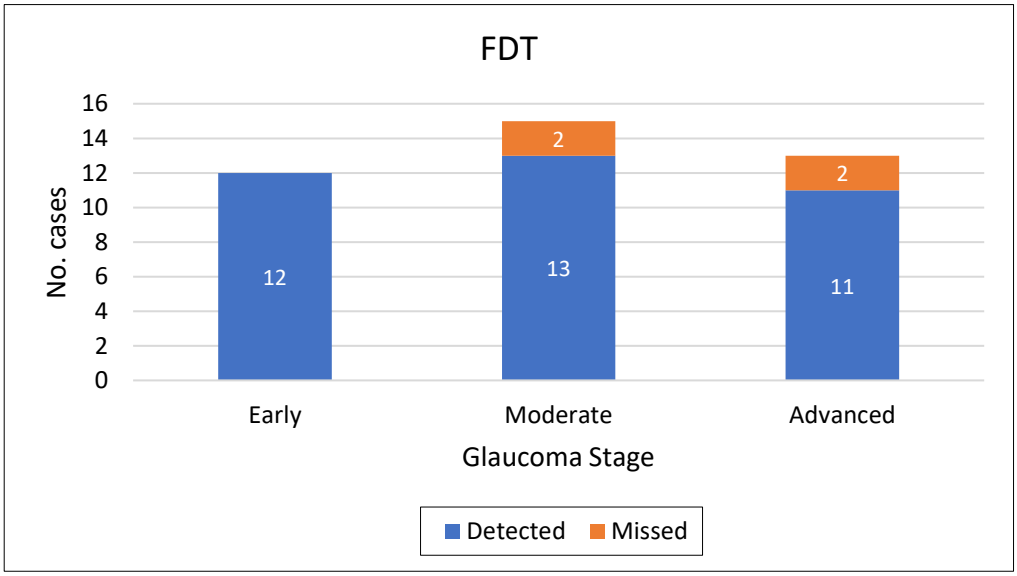


Figure 3.10. Histogram of the glaucoma severity detected by the FDT.

Using the GSS2 criteria, performance between the A4FTp and FDT were similar across all the glaucomatous stages except for stage 1. FDT detected all stage 1 cases but the A4FTp detected 2 out of 5, stage 1 cases. Performance of the A4FTp and FDT using GSS2 are plotted in Figure 3.11.

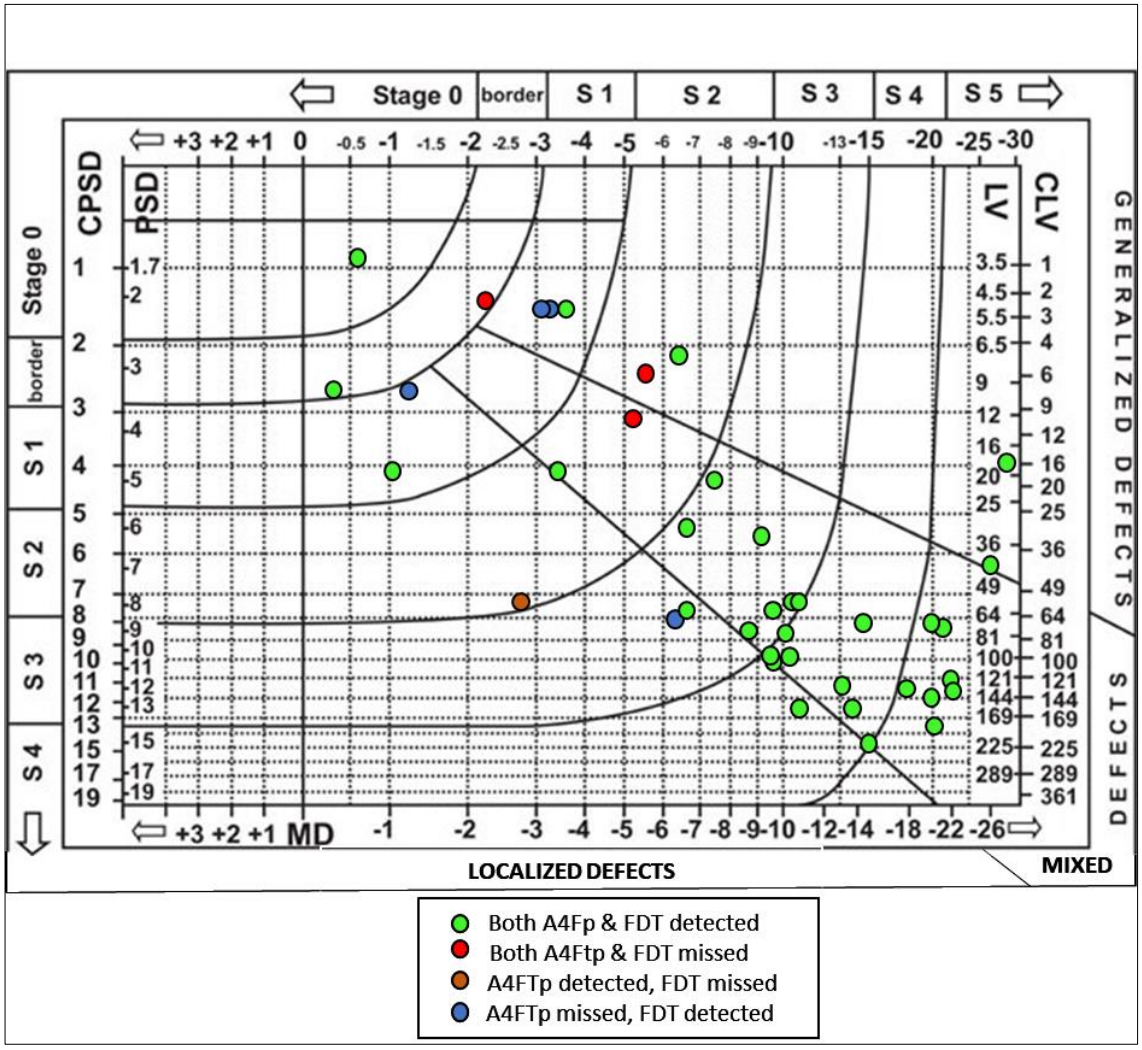


Figure 3.11. GSS2 plot of glaucoma detected by the A4FTp and FDT.

In total, there were 4 glaucomatous eyes that the FDT detected but the A4FTp missed. Using the GSS2 classification, 2 cases were defined as having generalised loss and 2 with focal loss; 3 out of 4 cases were classified as stage 1 and 1 case as stage 3. Examination of the 4 printouts from the FDT and HFA revealed only one subject had generalised loss,

where the A4FTp's tested locations were not sensitive enough to detect this loss (Figure 3.12a); 3 subjects had focal damage in locations where the A4FTp stimuli did not test (Figures 3.12b-3.12d).

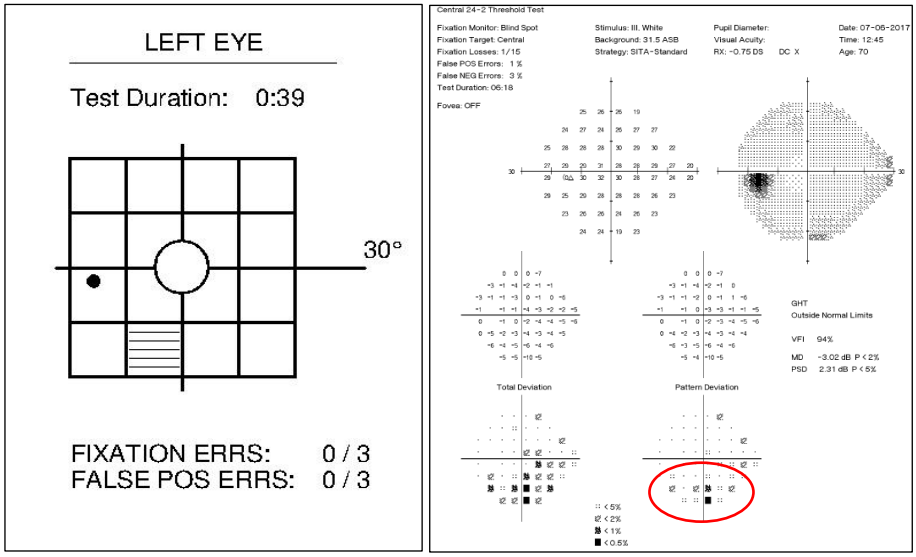


Figure 3.12a. Inferior generalised loss detected on FDT and HFA but missed on the A4FTp.

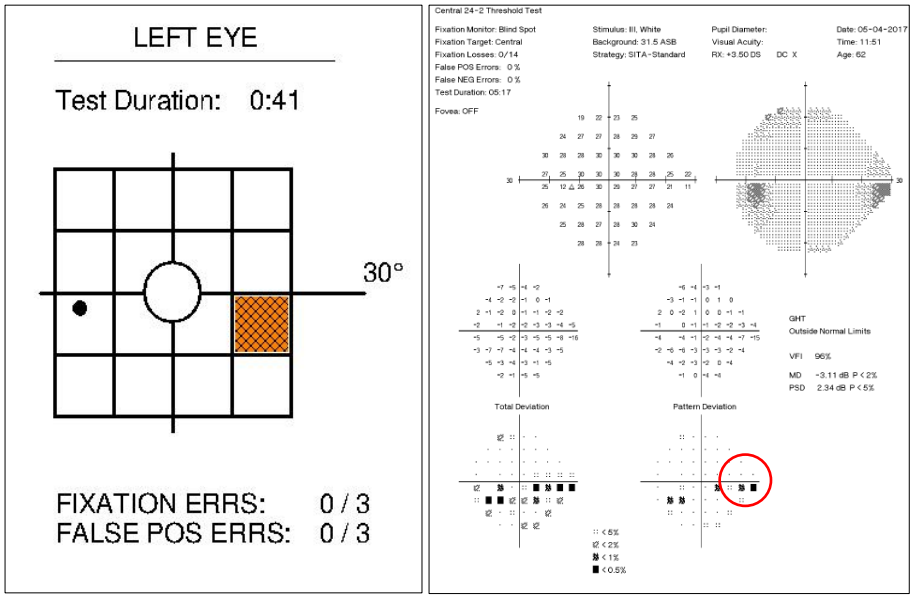


Figure 3.12b. Extreme 'nasal step' focal loss missed on A4FT but detected on FDT and HFA.

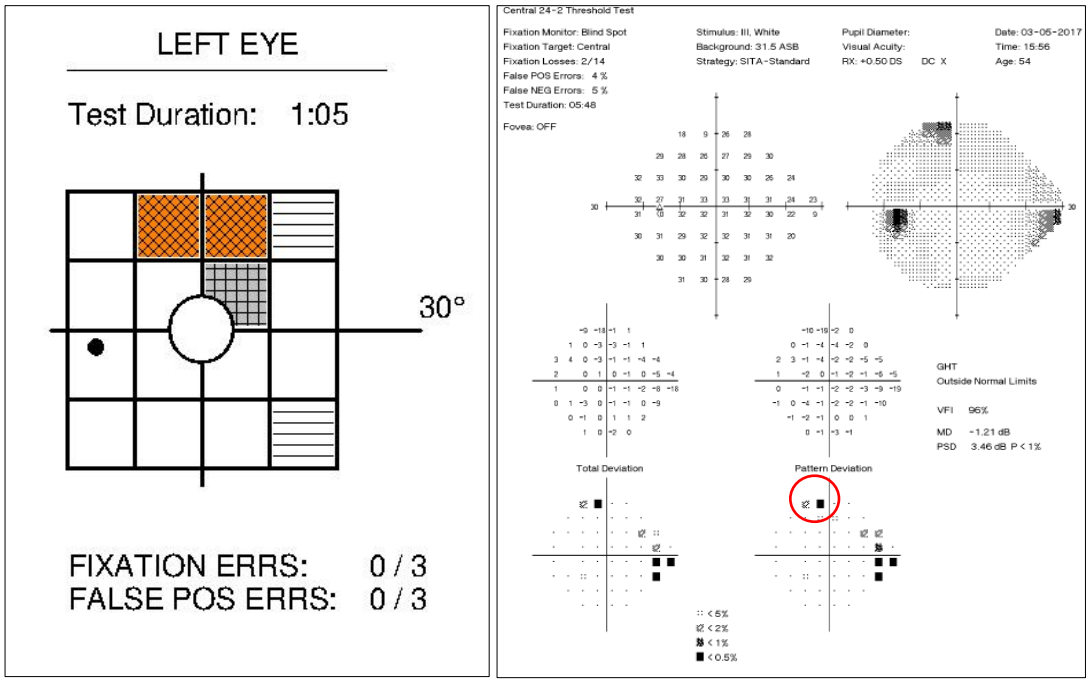


Figure 3.12c. Superior focalised loss missed on A4FTp but detected on FDT and HFA. Note: nasal step was missed on both A4FTp and FDT.

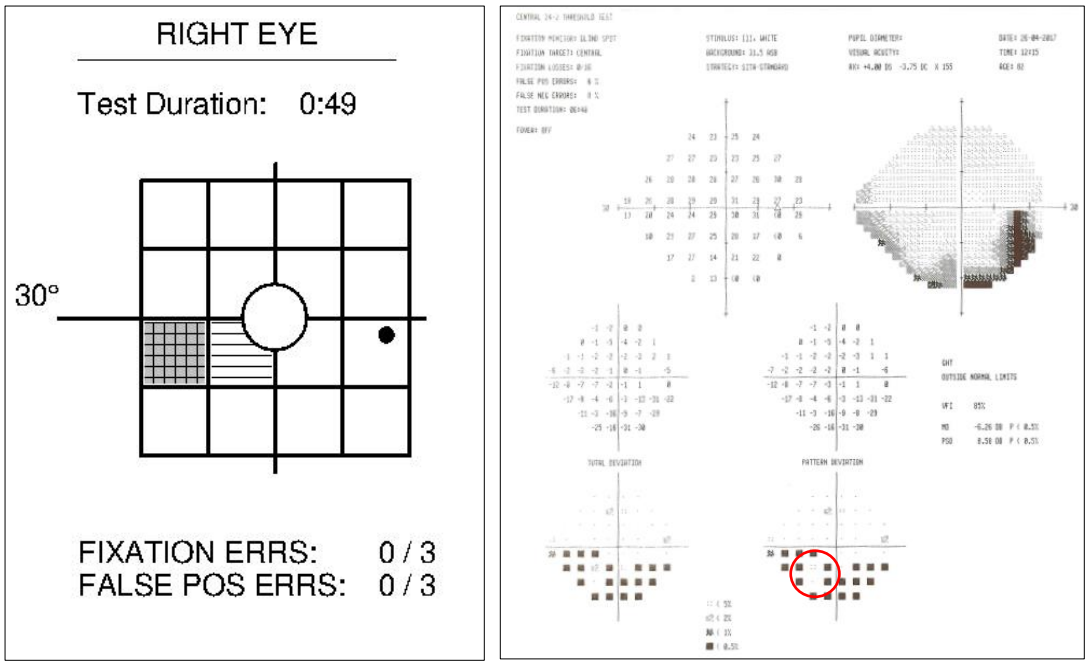


Figure 3.12d. Inferior nasal focalised loss missed on A4FTp but detected on FDT and HFA. Note: inferior temporal loss was missed on both FDT and A4FTp.

3.3.5 A4FTp outliers

Analysis of A4FTp performance identified 3 control participants with flicker sensitivity outside the 95% confidence interval of the mean. These participants were confirmed as healthy on the reference examination and were within normal limits on all the other index tests. A recalculation of the diagnostic accuracy of the A4FTp with these 3 outliers removed improved specificity to 80% and the AUROC to 0.88 (95% CI 0.79-0.95) (Figure 3.13). However, there was no statistical significance in AUROC with and without the outliers (p=0.11).

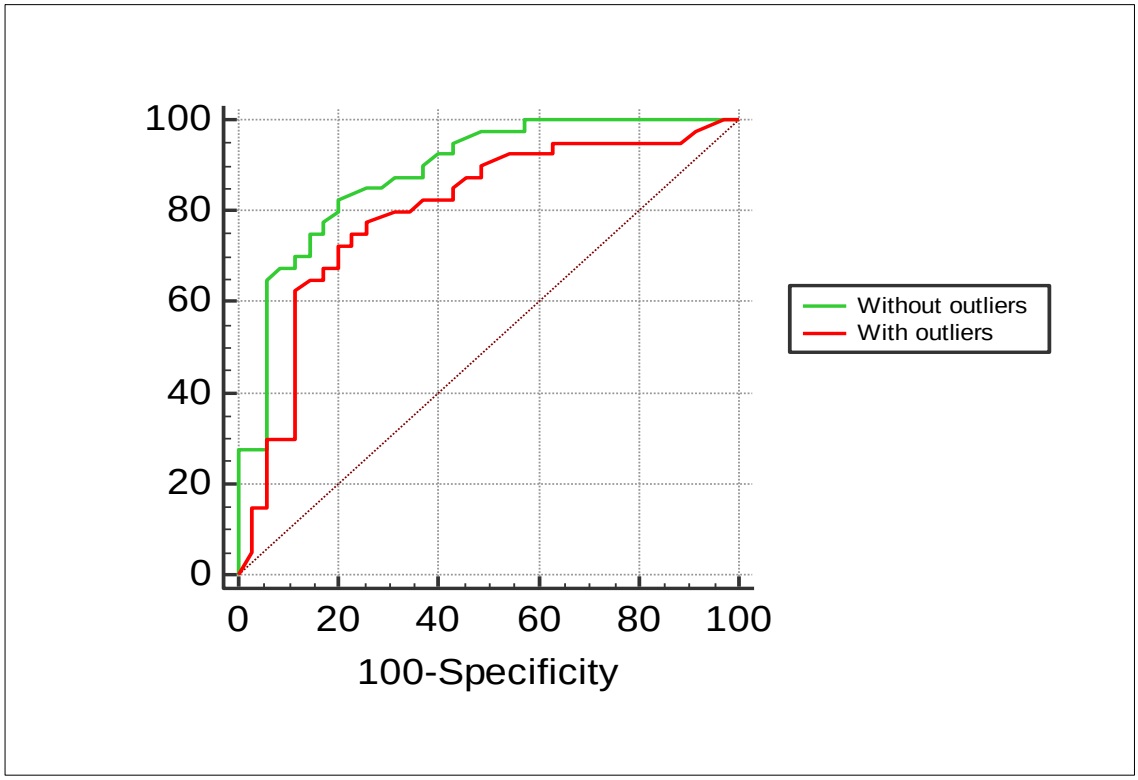


Figure 3.13. ROC of the A4FTp with and without outliers.

3.3.6 Test duration

Table 3.5 and Figure 3.14 shows the time taken to perform the functional tests (including the HFA 24-2, which was undertaken as part of the reference examination). The mean time taken for all participants in the tests were FDT C20-5 (62±35 seconds), A4FTp (142±86 seconds) and HFA (364±79 seconds), which was statistically significantly different between all three tests ($p<0.001$). There were also statistically significant differences between the control and glaucoma groups for the HFA ($p<0.001$), FDT C20-5 ($p<0.001$) and A4FTp ($p<0.008$).

	All participants Time Taken (secs)	**Control Time Taken (secs)**	**Glaucoma Time Taken (secs)**	**p value**
HFA SITA 24-2 Threshold (Mean±SD)	364±79 (~6 mins)	307±29 (~5.2 mins)	419±73 (~7 mins)	<0.001
FDT time (Supra-threshold C20-5) (Mean±SD)	62±35 sec (~1 mins)	37±9.0 (~0.6 mins)	86±33 (~1.4 mins)	<0.001
A4Tp Threshold (Mean±SD)	142±86 sec (~2.4 mins)	116±45 (~1.9 mins)	167±106 (~2.8 mins)	0.008

Table 3.5. Time taken to perform each functional test.

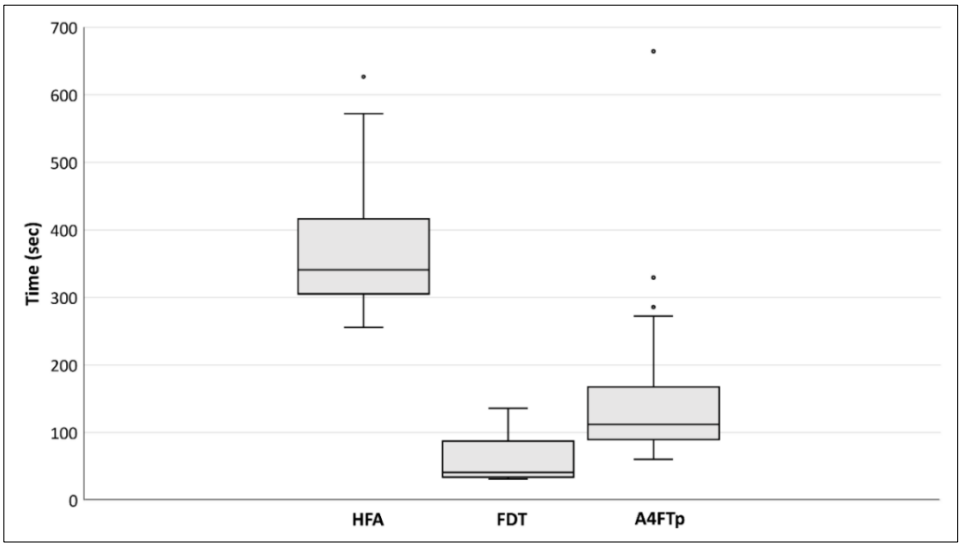


Figure 3.14. Box and whiskers plot of time taken to perform each functional test.

3.3.7 User acceptability

Figure 3.15 shows the Likert test scores from the acceptability survey. There was a higher proportion of participants who found the HFA uncomfortable and time taken to complete when compared to all the other index tests. There was no statistical difference regarding difficulty to perform when compared to the A4FTp ($p=0.877$) but there was with the FDT ($p=0.002$) and OCT ($p<0.001$).

The A4FTp, FDT and OCT had a similar proportion of participants (>90%) rating the tests as not uncomfortable or not too long. There were more participants who found the A4FTp more difficult to perform which was statistically significant when compared to the FDT ($p<0.001$) and OCT ($p<0.001$). Comparisons between the glaucoma and controls, found those with glaucoma experienced statistically more difficulty with the A4FTp when compared to the controls ($p=0.015$). There was no significant difference between the two groups between any of the other tests when reporting discomfort or the time taken to complete.

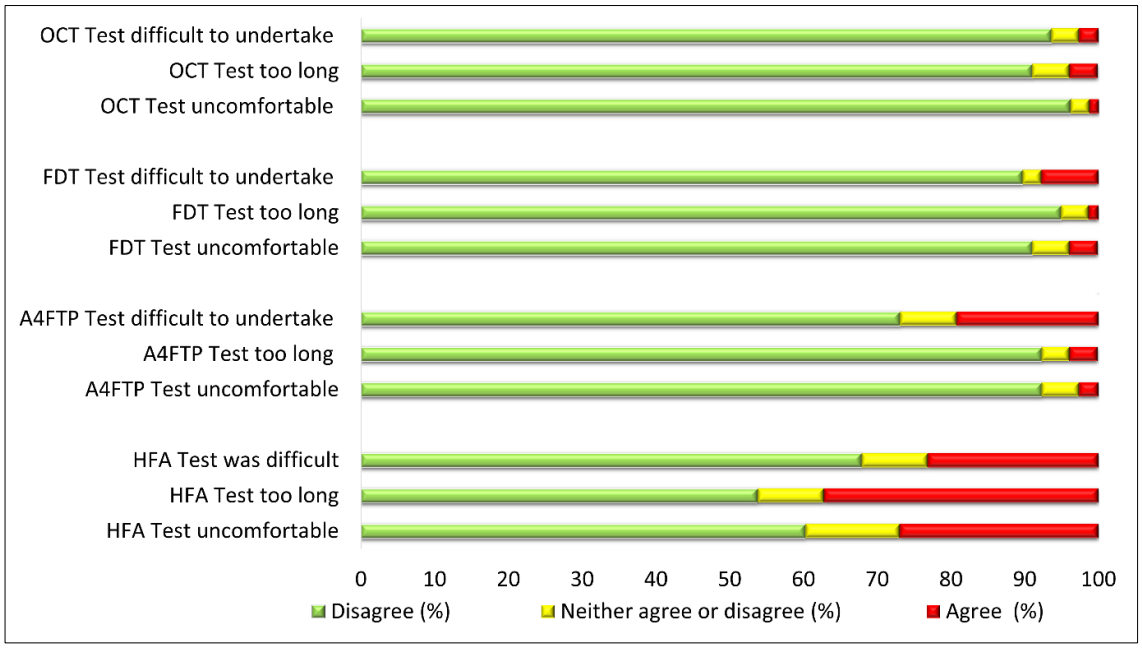


Figure 3.15. Likert responses from user acceptability survey from all participants.

3.4 Discussion

Glaucoma is the leading cause of irreversible blindness worldwide; in a recent systematic review it was estimated that glaucoma was responsible for 6.6% of total global blindness and 2.2% of all moderate and severe visual impairment (Bourne et al., 2016). The lack of symptoms in its early stages, coupled with inequitable access to healthcare contributes to high rates of undiagnosed glaucoma, especially in those deemed at risk of glaucoma.

The introduction of mobile technology has created new opportunities for the development of low-cost glaucoma-screening tests for use in at-risk populations. The current study evaluated the diagnostic performance of a simple screening test (A4FTp) for potential use in areas where glaucoma detection remains an issue and to evaluate those at higher risk of visual disability from glaucoma in their lifetime. This diagnostic case-control study evaluated 40 cases of glaucoma and 38 controls (≥40 years) and compared A4FTp performance with two commercially available glaucoma screening technologies.

3.4.1 A4FTp characteristics

The flicker rate in the A4FTp was set at the value found to be effective for glaucoma detection in previous studies (Tyler, 1981, Tyler et al., 1994). The A4FTp measured flicker thresholds at 4 fixed locations, strategically placed to detect the arcuate or nasal step defects that are commonly seen in manifest glaucoma. By selecting a reduced number of locations, it was hypothesised that this would lead to a reduction in time taken to complete but also to maintain suitable diagnostic performance in those with moderate disease. At each test location, a flickering field was displayed and the sensitivity to sinusoidal flicker modulation at a fixed temporal frequency (30Hz) was determined. Flicker sensitivity has been shown to be resilient to optical blur (Tyler, 1991) and the large stimulus size minimised the impact of fixation losses. Furthermore, presenting the stimuli in a red field reduces optical scatter due to opacities in the ocular media.

The best performing threshold for the A4FTp was the mean threshold of all 4 stimulus locations, which was based on the highest AUROC. Comparison of AUROC's found the performance of the A4FTp to be similar to the best performing parameters of the FDT (C20-5 algorithm) and the SD-OCT (RNFL thickness outside normal limits). Using this optimal threshold criterion, the A4FTp identified 33 out of the 40 glaucoma cases in our sample (83%) and correctly classified 28 out of the 38 of the controls (74%). All cases of advanced glaucoma were detected, and all but one of the subjects with moderate glaucoma. However, a high proportion (50%) of early glaucomas were not detected (Hodapp et al., 1993). The test took on average just over 2 minutes per eye to complete and the user acceptability survey found the test positive, in terms of comfort and participant's opinion on the duration of the test.

3.4.2 A4FTp comparison with FDT

Both the A4FTp and FDT assess visual function by using similar stimuli, the A4FTp took on average just over 2 minutes per eye to complete using a novel staircase termination criterion. The time taken to complete the A4FTp test was within the clinically recognised '3-minute period of vigilance'; this is advantageous in terms of response variability, as beyond this time the variability increases (Henson & Emuh, 2010). The FDT time taken in the current study for both controls and glaucoma was similar to other studies (Johnson et al., 1999, Detry-Morel et al., 2004). Overall, FDT testing using the C20-5 algorithm took approximately half the time to complete when compared to the A4FTp. This finding was not surprising, as supra-threshold algorithms commence testing at pre-defined thresholds set by the machine's internal database; where a minimal number of stimuli presentations are required to confirm a defect, however this at the expense of measuring retinal sensitivity precisely at each location (Takahashi et al., 2017).

Diagnostic performance regarding FDT have reported sensitivities between 80–100% for perimetric glaucoma and specificities of 80–95% (Quigley, 1998, Trible et al., 2000, Horn et al., 2002, Müskens et al., 2004, Stoutenbeek et al., 2004, Geimer, 2013, Dabasia et al.,

2015b) which complements the current study findings. More specifically, FDT AUROC in this study achieved similar performance to previous studies using the C20-5 and C20-1 programmes (Müskens et al., 2004, Stoutenbeek et al., 2004) of 0.92 and 0.93, respectively.

While there was no difference in overall diagnostic performance between the FDT and A4FTp, there was a difference in performance in those with early disease. Glaucoma classification regarding disease severity was staged using the Hodapp classification (Hodapp et al., 1993), that offers a quick and simple categorisation of glaucoma using the mean deviation. Using this classification, the FDT identified proportionally more individuals with early glaucoma than the A4FTp (100% vs 50%). Performance between FDT and A4FTp for the detection of moderate and advanced glaucoma was similar. Using the GSS2 staging system (Brusini & Filacorda, 2006), further analysis was undertaken to investigate whether the A4FTp was missing cases with localised defects. Although the numbers were small, there were no obvious differences when compared to the FDT based on the pattern of glaucomatous loss, which was supported by manual inspection of the field plots. Interestingly, there were two cases where glaucomatous damage occurred within the central 10 degrees, where both FDT and A4FTp missed but the HFA detected, this is of particular relevance considering new evidence of early glaucoma affecting the central visual field (Grillo et al., 2016, De Moraes et al., 2017).

3.4.3 A4FTp comparison with SD-OCT

Objective imaging modalities are being increasingly used to facilitate the diagnosis and monitoring of glaucoma (Chong & Lee, 2012). OCT provides a rapid, non-invasive method of evaluating the structural integrity of the posterior segment. AUROC comparison found no statistical significance between the A4FTp and SD-OCT where abnormalities were identified in the RNFL or GCC at the 5% or 1% probability level. In a recent systematic review, RNFL parameters were still preferable to GCC for diagnosing manifest glaucoma (Oddone et al., 2016), which was echoed in the current study where RNFL yielded a

higher AUROC than GCC. Diagnostic performance of the RNFL in the current study was similar to other studies evaluating iVue 100 SD-OCT regarding sensitivity (79%-90%) and specificity (88%-95%) (Seong et al., 2010, Huang et al., 2011, Kim et al., 2013, Bertuzzi et al., 2014).

Whilst the OCT is a structural examination, advantages over functional assessment include its objectivity, repeatability and the time taken to acquire rapid quantitative data that can be easily interpreted by a non-clinician; its use of colour coded maps, with red being flagged as abnormal at the p<1% level. However, it is recognised that caution is needed when interpreting red disease as this is dependent on the machine's normative databases (Chong & Lee, 2012). A review of OCT as a single test in population-based screening is still not well understood (Ervin et al., 2012); it has been proposed that OCT could be used to complement other diagnostic tests in a primary care, or triage setting (Michelessi et al., 2015). Nonetheless, with its ease of use and ability to gather diagnostic data it has been proposed that SD-OCT could be used for screening glaucoma in high-risk populations (Bengtsson et al., 2012). However, as with FDT, both devices are relatively expensive and not currently portable. It has been proposed that if OCT was more compact and less expensive, this might render it suitable for screening (Geimer, 2013), and as such these developments are currently being experimented (Chopra et al., 2018).

3.4.4 User acceptability

A user acceptability survey was given to all participants. The HFA took the longest time to perform, where it was outside the '3-minute period of vigilance', unsurprisingly it registered the largest proportion of participants agreeing that it was 'too long' (37.2%) or 'uncomfortable' (26.9%).

As part of the survey, there was an additional comments section where 43 (55.1%) participants completed. Responses were coded into 4 categories that related to; FDT; A4FTp; HFA and researchers plus other comments. A fifth of the responses contained

negative comments regarding HFA describing discomfort, fatigue and difficulty in performing the test that was reflected in the acceptability scores. From the 21 comments relating to the A4FTp, 5 positively referred to the test 'as easier than the HFA'. From the remaining 16 responses, 3 were from the controls and the rest had glaucoma where participants described confusion in either; registration of the user response and/or use of the keypad operation in translating the observed stimuli. When the data was unmasked, none of the patients were found to have a medical history that may have affected their co-ordination, hearing or dexterity in operating any of the tests. In addition, specificity for the A4FTp was the lowest of all three tests, there were 3 controls that had A4FTp threshold values well outside the 95% confidence interval, suggesting they were poor performers of only the A4FTp. Therefore, both the acceptability survey and lower specificity support the higher difficulty experienced in undertaking the A4FTp, suggesting its current interface requires improvement.

3.4.5 Application of A4FTp

Patients who are at higher risk of visual field impairment generally present with greater field damage on presentation (Saunders et al., 2014). The initial design of the A4FTp was based on a minimal number of locations that could be tested and theoretically retain an adequate diagnostic performance to moderate visual damage. This would best suit those at risk of developing visual disability in their lifetime, with the current study supporting good performance in those with moderate and advanced glaucoma. If the test strategy was to improve sensitivity to detect early glaucoma, additional stimuli locations could be added, but this may cause the specificity to be lowered as described by Wang and colleagues (Wang & Henson, 2013). However, in Wang and Henson's report, they based their assumptions on the HFA SITA 24-2 white stimuli size of 0.43 degrees diameter, whereas the flicker stimuli used in the A4FTp is considerably larger (approximately 11 degrees). Therefore, by modifying the A4FTp stimulus size and increasing the number of locations tested, this could improve sensitivity without causing a significant reduction in specificity.

An ideal screening test should be safe, quick, easy to administer and interpret, acceptable to the people who are to be tested and valid to distinguish between those who do and do not have glaucoma (Burr et al., 2007). The A4FTp has been shown to be acceptable to patients in terms of comfort, time taken and easy to administer. While the A4FTp had comparable diagnostic accuracy to current glaucoma diagnostic technology, test performance from the evaluated index tests did not reach the sensitivity and specificity needed for glaucoma population screening due it's relatively low prevalence (Mowatt et al., 2008), whereas targeting those at high risk may prove beneficial (Fleming et al., 2005, Burr et al., 2007, Hernández et al., 2008, Bengtsson et al., 2012). Based on a glaucoma prevalence of 5% in high-risk populations (Kapetanakis et al., 2016) and a test with 90% sensitivity and 90% specificity, only one in three persons screening positive would have the disease. As sensitivity and specificity are inversely proportional, by lowering the A4FTp threshold to maximise sensitivity leads to a corresponding reduction in specificity, therefore this test as with other tests would lead to an unacceptable rise in false positives. It has been proposed that future glaucoma screening strategies will employ combinations of tests and target those most likely to be affected by vision loss in their lifetime (Friedman, 2007, Boland et al., 2016), as described by two models in India and China (John & Parikh, 2018, Tang et al., 2019). Combining structural and functional testing can be used to improve the sensitivity or specificity for glaucoma detection in either a screening or case-finding setting, depending on whether the priority is to maximise true positives or minimise false positives (Shah et al., 2006). For example, if structural and functional tests are used and disease positives are defined as those who test positive by either test, there will be a net increase in sensitivity; conversely, a strategy where disease negatives are defined as those who test negative on both tests will maximise specificity. For example, in the current study a combination of the functional A4FTp and the structural OCT using the optimal thresholds would have achieved a sensitivity of 90% which is better than either of tests used alone.

3.4.6 Strengths and limitations

This study has a number of strengths: the design, analysis and reporting of the study complied with the principles of the Standards for Reporting of Diagnostic Accuracy (STARD 2015). The performance of the index tests was compared in a representative sample of participants with the target condition, with a range of disease severities. The reference standard and index tests were conducted on the same day as the index tests by an experienced clinician masked to the index test results. The reference standard for POAG was based on a comprehensive ophthalmic examination typical of that conducted in a hospital glaucoma unit.

The study contained several limitations, it was not a population-based study, the use of a case-control design may have artificially overestimated the performance of all the index tests. For example, both sensitivity and specificity reduced with the FDT when tested in larger population-based studies (Detry-Morel et al., 2004, Robin et al., 2005, Boland et al., 2016); a meta-analysis of two high-quality studies using the FDT C20-5 to detect open angle glaucoma found a pooled sensitivity of 72% and specificity of 60% (Burr et al., 2007). This is not surprising, considering flicker sensitivity can be affected by non-glaucomatous diseases such as cataract (Tanna et al., 2004, Swanson et al., 2005, Casson & James, 2006) and other posterior segment conditions (Cioffi et al., 2000, Kopplin & Mansberger, 2015, Boland et al., 2016, Fidalgo et al., 2019). This is the first time the A4FTp has been evaluated, as with most initial studies an initial enriched population is sought to optimise preliminary performance before testing in wider populations and allocating the appropriate resources to further develop the test.

For the reference standard, both established visual field loss and glaucomatous disc damage were required to be present for the case definition in the current study. Therefore, those with pre-perimetric glaucoma were not included and would have affected real-world diagnostic performance, however given the comparative nature of the study, the same degree of bias would apply for all the index tests. Similarly for the A4FTp, the age of the control and glaucoma groups differed by approximately a decade, hence the relative effect of an age-related loss in flicker sensitivity would have also

applied to the FDT. The majority of glaucoma cases were Caucasian with over 80% of the study population of European origin, therefore this may limit the generalisability of the findings, and performance may differ in other ethnic groups where glaucoma is more prevalent (e.g. patients of African origin).

3.4.7 Conclusion

The A4FTp was designed to detect those at risk of developing visual disability from glaucoma in their lifetime, with the current study supporting its ability to detect those with moderate and advanced disease. Application of such a tool may be advantageous for populations in which the immediate priority is to slow aggressive visual field loss. The A4FTp features comparable performance to currently available glaucoma diagnostic technologies, easy administration, ready interpretation, relatively short testing time and robustness to the effects of refractive error. With further development in usability and performance, the A4FTp could have a future role in glaucoma detection.

Chapter 4: Impact of optical coherence tomography on diagnostic decision-making by UK community optometrists

4.1 Introduction

As the major provider of eye care in the United Kingdom (UK), optometrists play a key role in the opportunistic detection of both symptomatic and asymptomatic eye disease. They also initiate the vast majority of referrals into secondary care (Bell & O'Brien, 1997, Bowling et al., 2005, Azuara-Blanco et al., 2007, Davey et al., 2011, Kelly et al., 2011, Muen & Hewick, 2011, O'Connor et al., 2012). Although optometrists' referral accuracy seems to improve with clinical experience (Davey et al., 2015, Parkins et al., 2018), decision-making in the diagnosis of glaucoma and retinal disease is often associated with considerable uncertainty. In practice, the health of the optic disc or macula is judged subjectively based on direct or indirect fundoscopy. High false positive and false negative rates have been reported in disc assessment by optometrists (Keenan et al., 2015, Ratnarajan et al., 2015). Similarly, a prospective study of optometrist referrals for neovascular age-related macular degeneration (AMD) reported satisfactory performance in identifying symptoms, but poorer performance in recognising clinical signs (Muen & Hewick, 2011).

Optical coherence tomography (OCT) is an interferometric imaging modality that enables in-vivo imaging of biological tissues and provides an objective, rapid and non-invasive method of evaluating the structural integrity of the posterior segment (Michelessi et al., 2015, Kashani et al., 2017). This technology has the potential to improve clinical decision making in a primary care or triage setting for glaucoma and other age-related eye diseases (Ouyang et al., 2013, Dabasia et al., 2015b, Michelessi et al., 2015, Azuara-Blanco et al., 2016a).

Successive surveys in the UK have shown that utilisation of OCT by optometrists have increased from 2% in 2008 to 15% within a decade (Myint et al., 2011, Dabasia et al., 2014b). Whilst OCT is becoming more popular in primary care, there is a lack of high-

quality evidence to support this technology in improving diagnostic performance in case-finding. Furthermore, there is currently no formal requirement for optometrists to demonstrate competency in interpreting its diagnostic data post qualification. A recent study in Australia using case vignettes found that the diagnostic accuracy of macular disease is only marginally improved with the incorporation of advanced imaging techniques when compared to colour fundus photography alone; the additional information from advanced imaging led to increased numbers of false positives and a greater tendency to refer cases to secondary care (Ly et al., 2018).

Clinical vignettes can simulate realistic patient interactions and are widely used to measure variation in the diagnosis and management of disease across a range of medical specialities (Veloski et al., 2005). Vignettes have been validated against unannounced standardised patients and case record abstraction as a measure of quality of care (Peabody et al., 2000, Peabody et al., 2004). They offer a number of advantages including control of case mix and the economies of scale, which means that they can be administered simultaneously to a large group of clinicians.

The benefit of the widespread adoption of OCT on case-finding for ocular disease by community optometrists in the UK is unclear. The aim of the current study was to determine the value of OCT in a representative sample of community optometrists, by evaluating their performance and confidence to detect posterior segment diseases, using a clinical vignette methodology.

Study Contributions

Ethics application, study protocol and the selection of images required for the clinical vignettes was written and carried out by AJ. Establishment of the expert panel and their findings was organised by AJ. The clinical vignette software package was developed by Ripley systems and the clinical data was inputted by AJ. The pilot and the OCT training was organised by AJ and IC, online training was delivered by AJ. Study eligibility, recruitment of all the participants, study logistics, statistical analysis and study findings were performed and written by AJ. Comments on the peer-reviewed paper were reviewed by AJ, IC and JL.

4.2 Methods

4.2.1 Participating optometrists

UK registered community optometrists were recruited from several sources. An invitation to participate in the study was sent either directly by email, via posters distributed to local community practices or through contacting Local Optical Committees. Optometrists expressing an interest were asked to complete an online questionnaire to determine their eligibility for the study. The questionnaire also asked for information on mode of practice (locum, independent, and multiple group), postgraduate qualifications and any further training or professional development undertaken (see Appendix 3). To be included in the study, participants had to be registered in the UK and employed in community optometry practice for at least 2 days per week. Optometrists were excluded if they had ever participated in any AMD shared care schemes, or had previously worked in a medical retina or glaucoma secondary care clinic.

The study was approved by the School of Health Sciences Research Ethics Committee, City, University of London, and complied with the tenets of the Declaration of Helsinki. Written and informed consent was obtained from all participants prior to taking part in the study.

4.2.2 Standardised online training

It was anticipated that participating optometrists would vary in their experience of interpreting OCT data and it was decided *a priori* to develop a bespoke online training programme to familiarise participants with the principles of OCT interpretation and specifically, the characteristics of the data output from the iVue Spectral-Domain Optical Coherence Tomography (SD-OCT). The training consisted of a 1-hour online lecture (delivered via the universities virtual learning system) and links to relevant publications on OCT interpretation. The lecture was written and delivered by AJ and covered the

principles of OCT, interpretation of quantitative and qualitative data outputs and clinical examples of retinal and optic nerve pathology.

4.2.3 Sourcing of clinical data

Fundus and OCT images selected for the study were taken from a dataset, which was previously collected in a prospective community-based cross-sectional study (Dabasia et al., 2015b); all the patients had consented for their anonymised clinical information to be shared for the purpose of future research. OCT scans of the disc and macula were captured using the IVue SD-OCT (Optovue Inc, www.optovue.com, software version 3.2.0.42) (details of scan protocols have been described elsewhere (Aref & Budenz, 2010). Forty-five-degree fundus photographs were taken through dilated pupils using the Topcon mydriatic/non-mydriatic retinal camera (Topcon Medical Systems Inc., www.topconmedical.com, model TRC-NW8F) at a resolution of 3008x2000. The patients were diagnosed at the time of data capture following a reference standard ophthalmic examination. The reference examination was conducted by an experienced clinician who had undertaken validated training in glaucoma and completed grader accreditation in diabetic retinopathy and age-related macular degeneration at the Reading Centre, Moorfield's Eye Hospital, UK. The definitions regarding glaucoma classification that were used in this study have been described elsewhere (Dabasia et al., 2015b).

Twenty-six fundus images were chosen from the dataset, consisting of a mixture of normal eyes and eyes showing disc or retinal pathology; a similar, independent set of 26 images with their corresponding OCT data files were also selected (Table 4.1). The image sets were of good quality and free from artefacts. Seventy percent of the images in each set contained an ocular abnormality (Figure 4.1); this proportion was similar to the posterior segment abnormalities detected in the original cross-sectional study (Dabasia et al., 2015b).

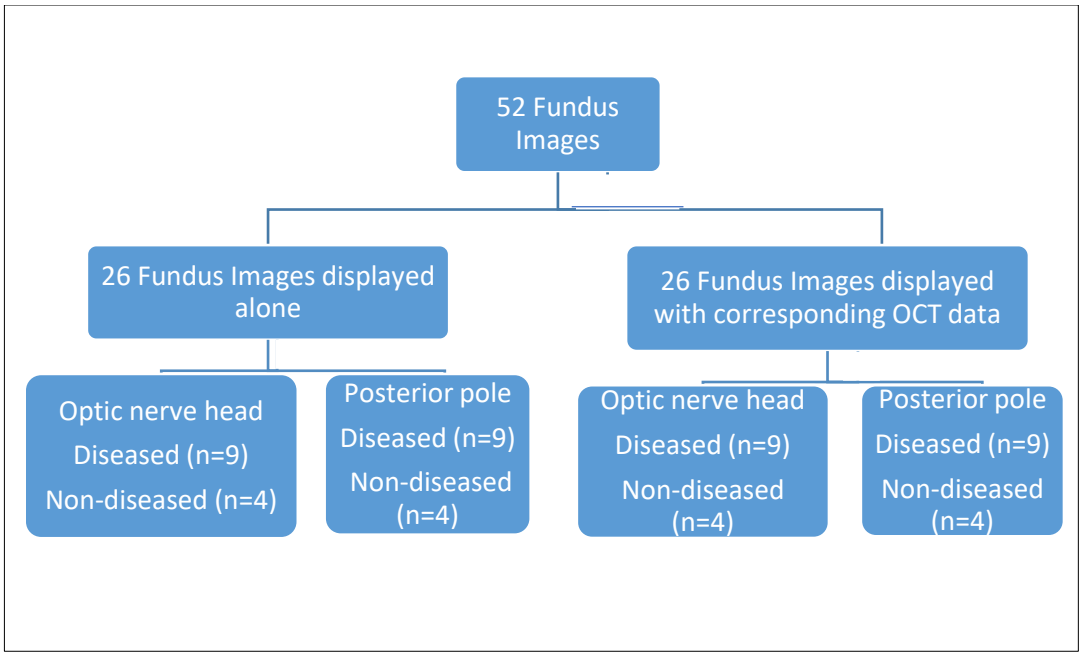


Figure 4.1. Flow diagram of the image allocation for the assessment.

Fundus alone (n=26)		**OCT combination (n=26)**	
Median age (IQR)	66 (65-72)	66 (65-74)	
Ethnicity No. (%) Caucasian African origin South Asian Asian	 24 (92%) 1 (4%) 0 (0%) 1 (4%)	 17 (65%) 5 (19%) 3 (12%) 1 (4%)	
Diagnosis	No.	Diagnosis	No.
Healthy disc	4	Healthy disc	4
Glaucoma suspect	5	Glaucoma suspect	4
Glaucoma	4	Glaucoma	5
Healthy retina	4	Healthy retina	4
Vitreo-macular traction	1	Vitreo-macular traction	1
Epiretinal membrane	2	Epiretinal membrane	2
Diabetic maculopathy	1	Diabetic maculopathy	2
Choroidal naevus	1	Choroidal naevus	1
Advanced dry AMD	1	Advanced dry AMD	1
Macular hole	1	Macular hole	1
Early AMD	1	Early AMD	0
Intermediate AMD	1	Intermediate AMD	1

Table 4.1. Case mix of the conditions shown in the clinical vignettes. IQR: Interquartile range.

4.2.4 Expert panel

An independent expert panel was convened to ensure that a) the fundus images to be presented alone and those presented in combination with OCT data were of a similar level of difficulty and b) confirm that the cases were typical of those seen in primary care. The panel comprised 5 clinicians with expertise in medical retina and glaucoma, including two consultant ophthalmologists, an academic optometrist, an experienced community optometrist and a hospital optometrist. The panel were asked independently to view both sets of fundus photographs and grade the level of difficulty of each set to diagnose the condition from the photographs using a 10-point Likert scale (Figure 4.2). They were also asked to state whether the conditions were representative of a primary care case mix. All members of the panel agreed that the conditions were representative with 4 out of 5 clinicians agreeing the case mix was appropriate. Similarly, the level of difficulty scored by the expert panel was equivalent for the optic nerve and retinal disease cases between the two image sets.

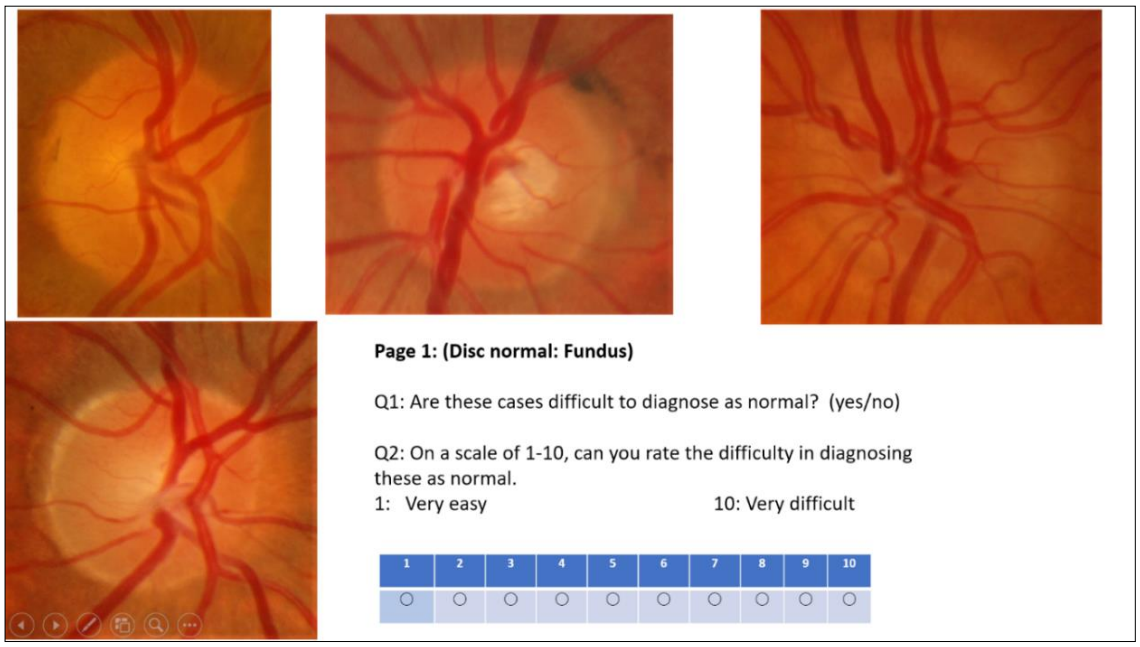


Figure 4.2. A set of normal discs presented to the expert panel to determine the difficulty of diagnosis.

4.2.5 Case vignettes

Case vignettes displayed a monoscopic fundus image, the age of the patient, best-corrected visual acuity and pinhole acuity gathered at the time of the original data capture. The fundus image showed either an optic disc or posterior pole of the retina, 26 of the vignettes were combined with the corresponding SD-OCT analytical report. For the disc image, they were asked to classify the disc as either 1. Healthy, 2. Probably healthy, 3. Probably damaged, or 4. Damaged (Figure 4.3). For the posterior pole images, participants were asked to select a diagnosis from a pull-down menu containing a list of 11 retinal conditions including a 'healthy' option (Figure 4.4). Following each clinical decision, participants were asked to rate their confidence in their decision using a 10-point Likert scale. The order of vignettes was randomised by a random number generator and presented using a specifically developed software package produced by Ripley Systems Ltd (www.ripleysystems.co.uk).

4.2.6 Pilot

The vignettes were independently piloted for clarity, questions, layout and time taken to complete a sample of 4 questions from the assessment by 28 optometrists undertaking the MSc in Clinical Optometry at City, University of London. The time taken to complete the pilot was within 5 minutes for all participants. The cohort reported that clarity, questions and layout were appropriate for the assessment. Suggestions included; facility to enlarge the images as this would be reflective of current clinical practice and to incorporate a demonstration of the assessment before formal commencement. The interface was subsequently modified based on these suggestions and the full assessment (52 vignettes) was then piloted by 3 optometrists. All three optometrists completed the assessment well within an hour. None of the piloted data from the 31 optometrists was used in the final analysis.

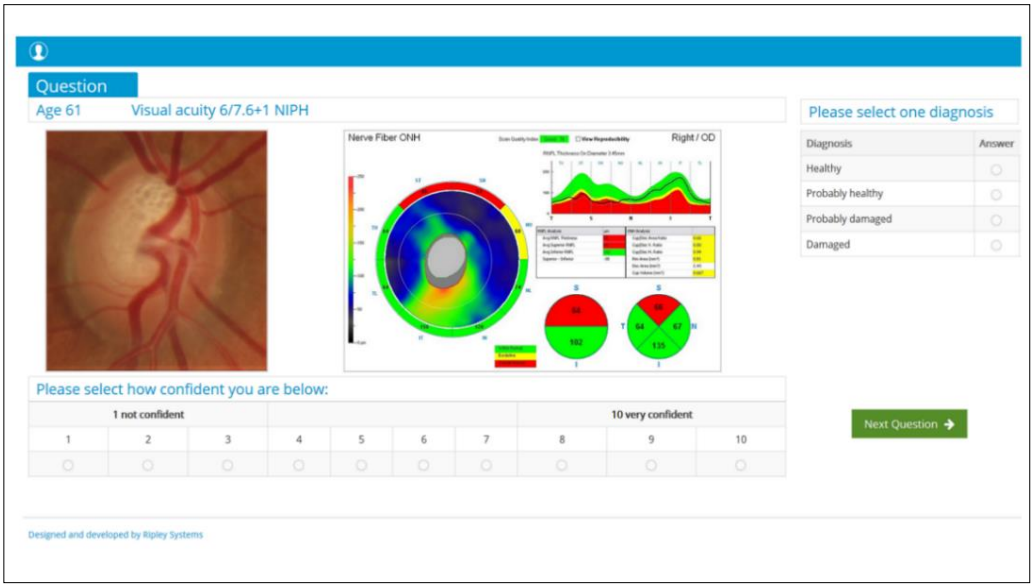


Figure 4.3. Optic disc vignette with corresponding OCT data; RNFL thickness with colour coded comparisons to the normative database in their respective quadrants; average overall RNFL thickness and hemifield thickness; optic nerve head analysis displaying cup to disc ratios and volumetric analysis.

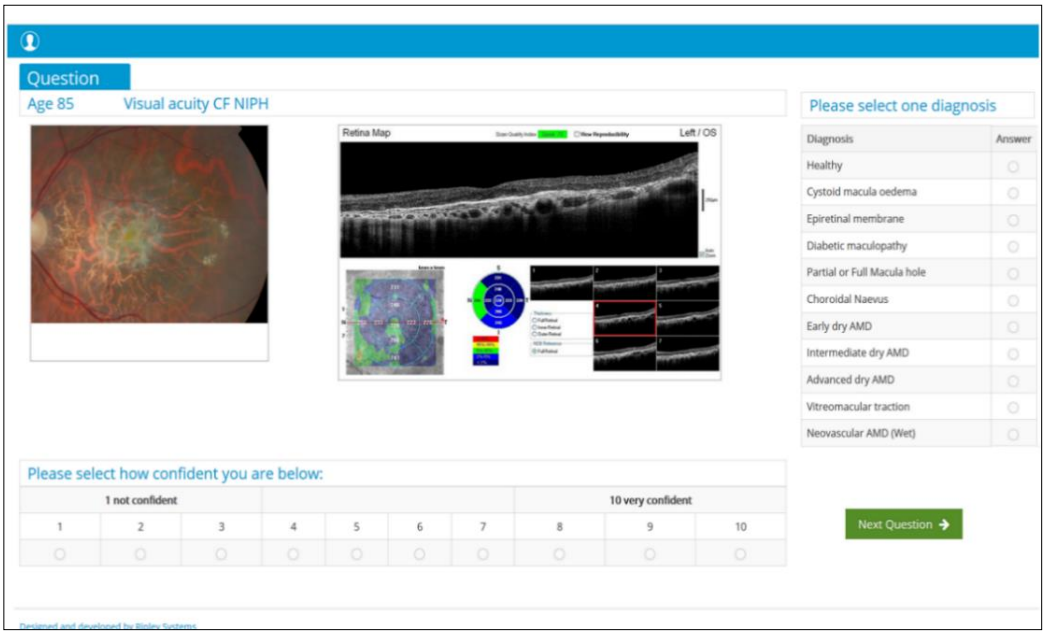


Figure 4.4. Vignette illustrating the central retina with the corresponding OCT data; seven B-scans displaying sections of the macula from superior to inferior; macular thickness map that is colour coded according to the machines normative database.

4.2.7 Computer-based assessment

Participants completed the assessment during a single 1-hour session, held at City, University of London. The vignettes were viewed under standardised viewing conditions on calibrated 21.5-inch computer monitors at a resolution of 1920x1080. Before the assessment, participants were instructed on the nature of the examination and were shown demonstration vignettes. Participants were also briefed on the classification system used when categorising age-related macular degeneration (Ferris et al., 2013). In addition, they were informed that each vignette related either to a normal eye or an eye showing a single ophthalmic diagnosis. Furthermore, it was confirmed that there was no evidence of amblyopia and that the only risk factor provided was age.

4.2.8 Sample size

A minimum of 51 images was needed to detect a statistically significant difference of 20% in performance; between the 2 diagnostic methods with 95% confidence and 80% power (Hajian-Tilaki, 2014). For the sample size calculation, a median specificity of 74% was assumed based on previous studies involving community optometrists in detecting glaucomatous discs using disc images (Hadwin et al., 2013, Myint et al., 2014). For the number of participants making a clinical decision, a formal sample size calculation was not performed. However, we aimed to recruit a suitable number of community-based optometrists who are representative of those working in the UK. From a previous study of glaucoma decision-making using a similar computer-based assessment, a sample of 53 optometrists provided a sufficiently narrow confidence interval (CI) for diagnostic performance in a disc assessment task (Myint et al., 2014).

4.2.9 Statistical analysis

Statistical analysis was performed using SPSS 24.0 (www.ibm.com/analytics/spss-statistics-software). To calculate the overall diagnostic performance for each participant, responses for each case vignette were converted into a binary score (one mark for a correct diagnosis and zero for an incorrect diagnosis).

In cases where the original diagnosis was either suspect glaucoma or definite glaucoma, a correct mark was given in both cases if the user answered either damaged or probably damaged, similarly if the disc was healthy, 'probably healthy' was an acceptable answer. For cases of early or intermediate AMD, a mark was given if the participant classified the disease as either diagnosis. For all other retinal conditions, only the correct diagnosis was acceptable and alternative diagnoses were deemed to be incorrect.

For incorrect responses, the false positive and false negative rates were determined. A false negative was defined as a case showing an ocular disease incorrectly diagnosed as healthy; a false positive was a normal case incorrectly diagnosed as diseased. Secondary analysis was undertaken to determine the sensitivity and specificity of the two modalities with respect to disease presence and absence.

Parametric paired t-tests were used to compare diagnostic performance and Wilcoxon tests for the confidence scores between fundus and OCT combination data sets. The Mann-Whitney test was used for subgroup analyses based on participant gender, practice setting or years of experience post-qualification. Linear regression was used to compare practitioner confidence and diagnostic performance to years qualified. For all tests, $p<0.05$ was considered statistically significant.

4.3 Results

4.3.1 Participant characteristics

Sixty-two participants completed the eligibility questionnaire and 12 participants were excluded: 3 participants worked less than 2 days a week in community practice and 9 optometrists had previously worked in a medical retina or glaucoma secondary care clinic. Fifty optometrists were included in the final analysis and completed all case vignettes.

Characteristics of participants are summarised in Table 4.2. Participants had a median of 10 years post-registration experience with the majority female (62%). Approximately equal numbers were either working as locums or based in independent or multiple practices. Less than a fifth of participants had additional qualifications related to either glaucoma or medical retina. Although the majority (84%) used fundus photography routinely, less than a third had used OCT in their practice or had undertaken previous training in OCT interpretation.

	Median (IQR)	No. (%)
A. No. years qualified	10 (4-19)	
B. Gender		
Female		31 (62%)
Male		19 (38%)
C. Setting of primary practice		
Independent		16 (32%)
Multiple		17 (34%)
Locum		17 (34%)
D. No. optometrists working in community primary care		50 (100%)
E. No. days working in community practice in a week	4 (3-5)	
F. No. optometrists working in secondary care		5 (10%)
G. No. days working in secondary care in a week	2 (1-2.5)	
H. Optometrists using fundus photography routinely		42 (84%)
I. Optometrists using OCT routinely		15 (30%)
J. Optometrists with postgraduate qualifications specific to glaucoma		8 (16%)
K. Optometrists with postgraduate qualifications specific to medical retina		1 (2%)
L. Previous attended training/courses regarding OCT		
OCT manufacturer		6 (12%)
Distance learning continued education and training		2 (4%)
Own Practice/company		7 (14%)

Table 4.2. Demographic characteristics of the participants (n=50). For practice setting 'multiple' refers to high street chains with practices throughout the UK.

4.3.2 Overall diagnostic performance

The mean percentage of case vignettes correctly identified using fundus imaging alone was 62% (16/26 cases) (95% CI 59%-64%), increasing to 80% (21/26 cases) (95% CI 77%-82%) for the fundus image/OCT combination, which was statistically significant ($p<0.001$). Statistically significant improvements were also seen for the OCT combination for both disc ($p<0.001$) and retinal cases ($p<0.001$) (Figure 4.5). Nearly all the optometrists performed better with the supplementary OCT clinical data (94%), one

participant (2%) showed no improvement and two participants (4%) performed worse (Figure 4.6).

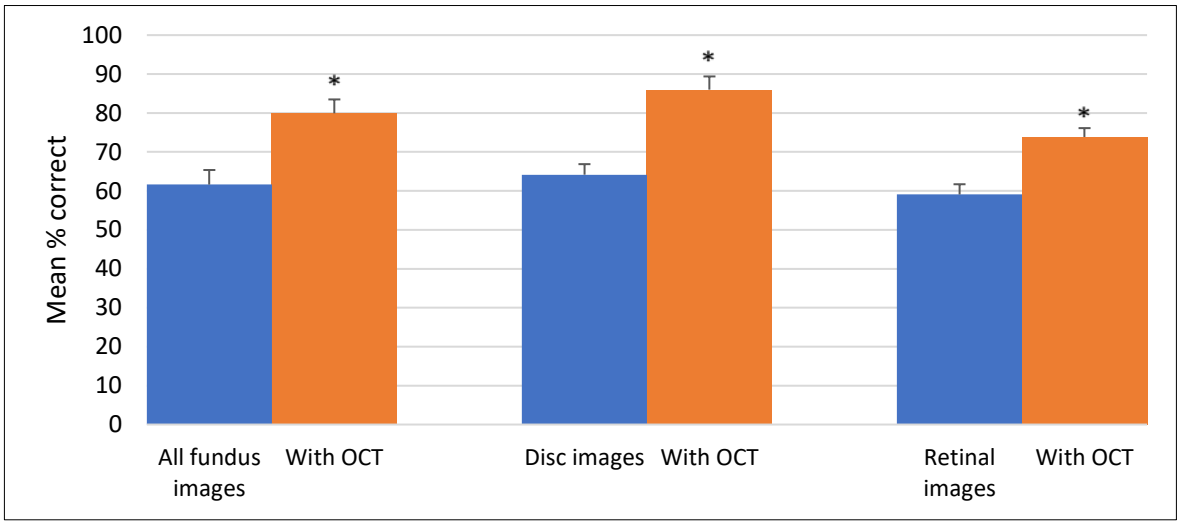


Figure 4.5. Correctly identified mean percentage score of total, optic discs and retinal cases using fundus alone and combination OCT. Error bars represent the upper 95% confidence interval. * indicates a statistically significant difference (p<0.001).

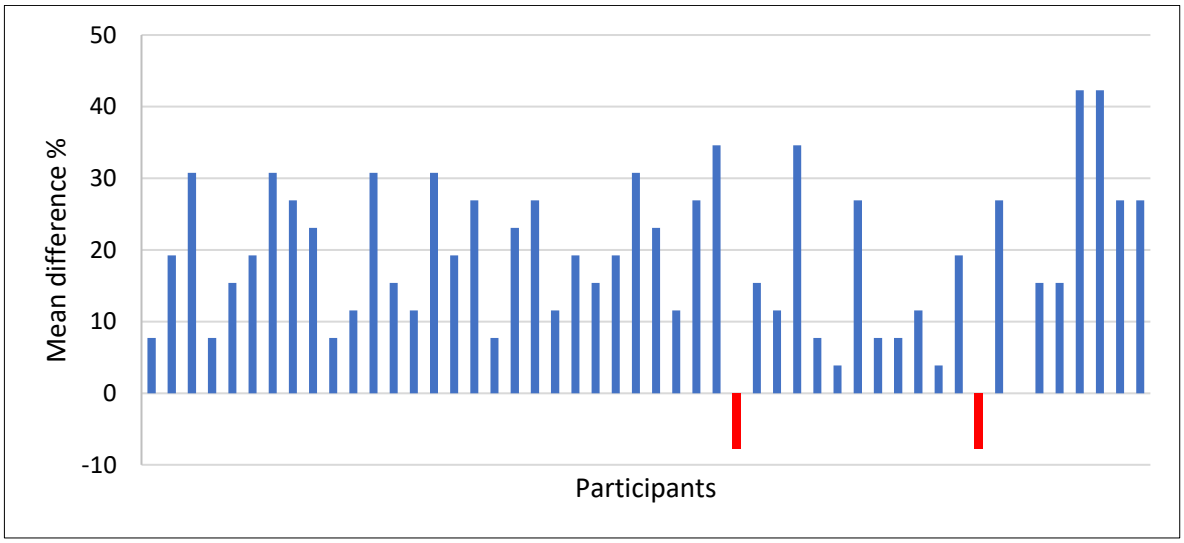


Figure 4.6. Difference in scores between the OCT combination and fundus alone. Positive scores indicate improvement with the combination.

4.3.3 Performance to disease

The mean sensitivity and specificity of all participants regarding the case vignettes to any disease for fundus imaging alone was 73% and 80% respectively, increasing to 87% and 92% for the fundus image/OCT combination (Table 4.3). Overall and disc pairwise comparisons regarding sensitivity and specificity between these two sets of images were all statistically significant ($p<0.001$). Sensitivity for the retinal cases did not improve statistically for the OCT combination, however specificity did improve ($p=0.002$).

	Sensitivity (95% CI)	**Specificity (95%CI)**
All Fundus images	73% (70%-76%)	80% (75%-84%)
All Fundus images with OCT	87% (84%-90%)	92% (89%-94%)
Discs images	54% (48%-60%)	87% (81%-92%)
Disc images with OCT	80% (76%-85%)	99% (96%-100%)
Retina images	92% (90%-95%)	73% (67%-79%)
Retina images with OCT	94% (91%-96%)	85% (80%-90%)

Table 4.3. Sensitivity and specificity values of cases using fundus alone and combination OCT.

4.3.4 False negative and false positive rates

The overall false negative rate was 27% for cases consisting of a fundus image alone. This reduced to 13% for the fundus image/OCT combination. Although this difference was statistically significant ($p<0.001$), a significant reduction was seen only for the disc scenarios (Figure 4.7).

The mean false positive rate using fundus image alone and for the combination with OCT was 27% and 9% respectively, which was statistically significant ($p<0.001$). Significant reductions were observed for both discs and retinal cases, ($p<0.001$) and ($p=0.002$) respectively (Figure 4.8).

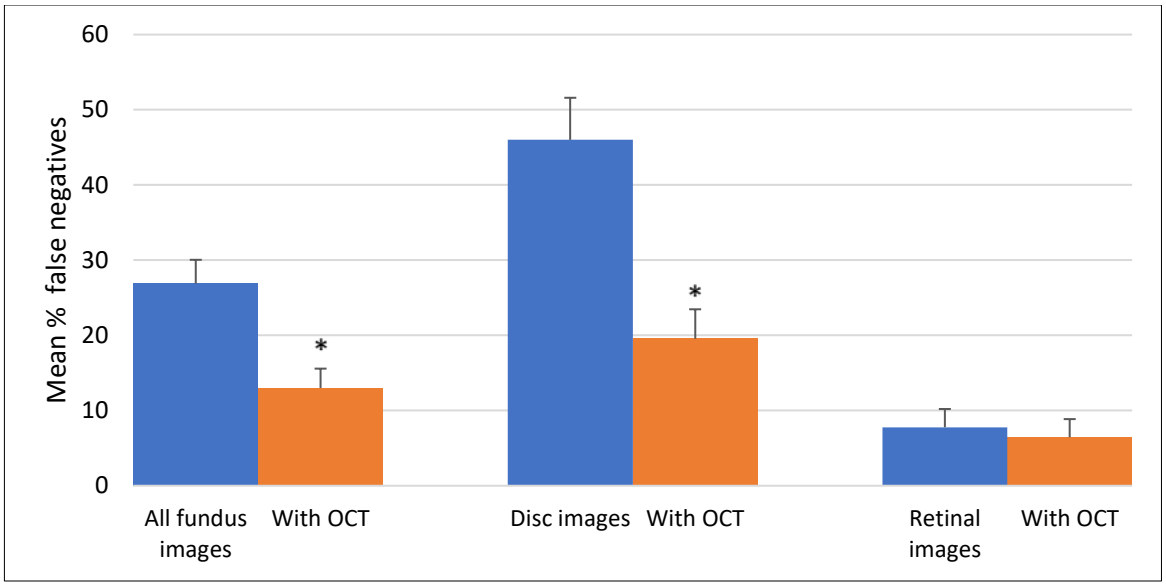


Figure 4.7. False negative rates of total, optic discs and retinal cases using fundus alone and combination OCT. Error bars represent the upper 95% confidence interval. * indicates a statistically significant difference ($p<0.05$).

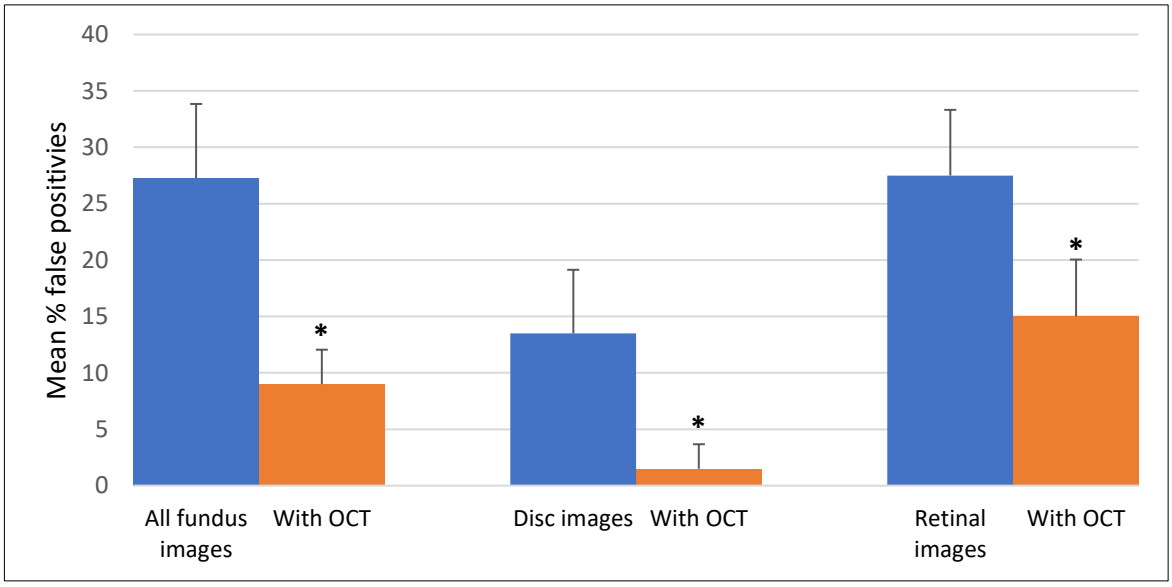


Figure 4.8. False positive rates of total, optic discs and retinal cases using fundus alone and combination OCT. Error bars represent the upper 95% confidence interval. * indicates a statistically significant difference ($p\leq0.002$).

4.3.5 Subgroup analysis of diagnostic performance

There was no difference in diagnostic performance based on participant gender, practice setting, OCT experience or years qualified post qualification. Further analysis regarding those qualified ≥10 years (n=26) and <10 years (n=24) showed no statistically significant difference in diagnostic performance between the two modalities. Although prior OCT training did not have an impact on overall performance, there was a statistically significant improvement for retinal conditions with OCT (p=0.026) but not for discs. The overall performance of optometrists with additional qualifications in either glaucoma or medical retina with the OCT combination was better than those without (p=0.024).

4.3.6 Confidence scores

The median confidence of diagnostic decisions was high (median 8 out of 10), and confidence only marginally improved with the addition of the OCT data for both retinal and disc cases (Table 4.4). There was no statistically significant difference in diagnostic confidence between the genders or practice setting. Similarly, further qualifications, training or experience in using OCT did not influence confidence. There was a positive correlation between the number of years qualified and confidence in decisions for all vignettes consisting of the fundus image alone, (Pearson correlation, r=0.324, p=0.022), but not for the OCT combination.

	Fundus confidence	Combination confidence	p value
Total confidence median (IQR)	8.0 (7.0-8.0)	8.3 (8.0-9.0)	<0.001
Disc confidence median (IQR)	8.0 (7.0-8.0)	9.0 (8.0-9.0)	<0.001
Retina confidence median (IQR)	8.0 (7.0-8.0)	9.0 (8.0-9.0)	<0.001

Table 4.4. Confidence scores of participants; p values were calculated using the Wilcoxon sign rank test.

4.4 Discussion

The global distribution of visual impairment is affected by age, where it is a significant risk factor in the development of a number of eye diseases including: glaucoma (Tielsch et al., 1991a, Wormald et al., 1994, Mitchell et al., 1996, Varma et al., 2004, Leske et al., 2008), age-related macular degeneration (Meuer et al., 2014, Mitchell et al., 2018), epiretinal membrane (Mitchell et al., 1997, Miyazaki et al., 2003, McCarty et al., 2005, Kawasaki et al., 2008) and vitreo-retinal conditions such as macular holes and vitreo-macular traction (VMT) (Garcia-Layana et al., 2015). Timely detection is key and visual loss in these conditions can be prevented, with up to 50% of sight loss potentially avoided (RNIB, 2009).

With the ease in using OCT and its ability to gather a huge amount of diagnostic information rapidly, it has been widely adopted to diagnose a number of eye diseases (Jeong et al., 2016). It has been proposed that OCT could fulfil the test acceptability requirement needed for eye disease screening (Wilson & Jungner, 1968, NSC, 2016). A recent systematic review found that OCT achieved a pooled specificity of 95% and sensitivity of 75% in the diagnosis of glaucoma (Oddone et al., 2016). However, nearly all the studies in the review were case-control studies, where these can over-estimate diagnostic accuracy (Medeiros et al., 2007, Rao et al., 2012), whereas different study designs with larger cohorts demonstrated lower specificity (Dabasia et al., 2015b, Virgili et al., 2018). Furthermore, based on the relatively low prevalence of glaucoma in the general population, the diagnostic capability of OCT alone is probably insufficient to meet the requirements needed for general glaucoma screening. However it has been proposed that it could be used to screen glaucoma in high-risk populations (Bengtsson et al., 2012), but this has not been formally evaluated. A review investigating macular oedema in patients with diabetic retinopathy, recognised OCT as the new reference standard for its detection (Virgili et al., 2015). When OCT was applied prior referral to the Diabetic Retinopathy Screening Service (DRSS), it was found it could lower health

service costs (Olson et al., 2013) and when used adjunct to current DRSS modalities, it was considered cost-effective (Leal et al., 2019).

With the absence of age-based population screening programmes, the majority of eye diseases are detected by case-finding where advances in imaging technology can provide additional diagnostic information. A systematic review suggested OCT could be used to inform glaucoma case-finding in primary care (Michelessi et al., 2015), where community optometrists are well placed for the detection and referral of ocular abnormalities. The College of Optometrists-funded 'impact of equipment in eye care' project showed there was widespread investment in modern imaging technologies by optometrists in primary care, especially OCT (Dabasia et al., 2014b). This is expected to substantially increase following the announcement that the largest optometry chain in the UK will be incorporating OCT in all of their practices within the next few years (AOP, 2017).

With the widespread adoption of OCT, its benefit in case-finding for ocular disease by community optometrists is unclear. The current study investigated the value of OCT in the diagnosis of posterior segment diseases in a representative sample of community optometrists by evaluating their performance and confidence in clinical decision making. The performance of 50 community optometrists was assessed in diagnosing a range of pathologies affecting the posterior segment, using 26 case vignettes containing fundus images alone and 26 vignettes showing fundus images with their corresponding OCT data.

4.4.1 Disc assessment

Several authors have previously investigated the performance of community optometrists in the subjective assessment of optic discs (Hadwin et al., 2013, Myint et al., 2014, Yoshioka et al., 2015). The disc images and OCT scans used in the present study were taken from participants recruited into a community-based cross-sectional study to assess the performance of technologies for glaucoma case-finding (Dabasia et al., 2015b). Within each image set, 70% of discs were from patients with confirmed or

suspect primary open angle glaucoma (presence of glaucomatous optic neuropathy and a concordant glaucomatous field defect or a disc showing glaucomatous features and a normal field, respectively) and 30% were normal. The overall diagnostic performance based on monoscopic observation of disc images alone was approximately 65%, with a sensitivity of 54% and specificity of 87%. Diagnostic performance was similar to previous studies of optometrists in Australia (Yoshioka et al., 2015) and the UK (Myint et al., 2014).

Since the original diagnoses of glaucomatous optic neuropathy was based on dilated indirect ophthalmoscopy, it is possible that diagnostic accuracy may have improved with stereoscopic visualisation. A UK study, using stereoscopic photographs of healthy and glaucomatous discs reported an overall accuracy of 80% (Hadwin et al., 2013). Although it could be argued that in standard clinical practice, a diagnosis of glaucoma is usually based on a combination of disc observation and visual field assessment; optic nerve damage is often the first clinically detectable sign of the disease. For example, in randomised controlled trials of patients with ocular hypertension, 40-60% of cases converting to glaucoma showed optic disc changes before reproducible visual field damage (Keltner et al., 2006, Miglior et al., 2007).

In the current study, there was a significant improvement in classification and diagnostic performance with the OCT combination alongside reductions in false positive and false negative rates. Similarly, Yoshioka and colleagues (Yoshioka et al., 2015), found that when OCT was combined with an image of the optic disc, overall performance and sensitivity increased with a reduction in false negatives. The current study provides evidence that disc evaluation can be augmented by additional information on the integrity of the retinal nerve fibre layer provided by the OCT.

4.4.2 Diagnosis of retinal disease

A major advantage in using OCT to diagnose retinal and macular diseases is its ability to provide high-resolution cross-sectional images of the retina and perform quantitative segmental analysis of retinal layers (Ontario, 2009). The Retinal Disease Screening Study compared fundus photography with OCT imaging in 158 asymptomatic subjects and concluded that OCT was more sensitive than fundus photography for the detection of retinal irregularities and was able to detect significantly more clinically relevant disease (Ouyang et al., 2013). The present study showed an improvement in performance for the diagnosis of retinal conditions with the additional data from OCT and a corresponding reduction in the false positive rate. The false negative rate was low (<10%) for both sets of vignettes.

To the author's knowledge, this is the first study to look at the impact of OCT on optometrist's diagnostic decisions for a range of retinal and macular diseases. A recently published vignette study from Australia evaluated the effect of advanced imaging (including OCT) on optometrist's decision-making for the diagnosis and management of AMD (Ly et al., 2018); the use of fundus photography alone resulted in an accurate diagnosis of AMD in 61% of cases, this was similar to the current study where participants detected 59% of cases correctly in a range of retinal conditions. Ly and colleagues (Ly et al., 2018) found overall diagnostic accuracy improved by a modest five per cent with advanced imaging and the additional information led to an increased false positive rate and a greater tendency to refer to secondary care. The authors concluded that a lack of training in interpreting the results of advanced imaging might explain the findings. Although participants in the current study had varying experience of OCT interpretation upon recruitment, we attempted to mitigate this via standardised online training prior to carrying out the assessment.

4.4.3 Participant variables affecting performance

In the current study, almost a fifth of participants had higher professional qualifications in glaucoma or medical retina. The overall diagnostic performance of this group was superior with the overall OCT combination to those who did not have these qualifications. This is consistent with the findings of Hadwin and colleagues (Hadwin et al., 2013), who reported that optometrists with higher qualifications had a higher overall accuracy in stereoscopic optic disc assessment.

The overall diagnostic performance was found to be unaffected by the number of years post-registration experience, which was also found by Hadwin and colleagues (Hadwin et al., 2013). Although optometrist's referral accuracy has been shown to improve slightly with clinical experience (Davey et al., 2015, Parkins et al., 2018), the greatest improvement occurs within the first two years post-qualification, after which a plateau is reached in terms of diagnostic performance, which may explain the present study's findings as the median number of years qualified for the participants in the current study was 10 years and 94% of participants had been qualified for at least two years.

4.4.4 Diagnostic confidence

Participant confidence in their diagnostic decisions was high for both image sets. Although there was a small numerical improvement that was statistically significant with the OCT combination, this finding is not clinically significant. As with other clinical studies, this study risked the attraction of optometrists who were more confident in their diagnostic skills (Myint et al., 2011, Theodossiades et al., 2012, Parkins et al., 2018), which probably induced a 'ceiling effect' and could explain the high confidence scores with both image sets.

4.4.5 OCT implication

OCT use in secondary care ophthalmology and potential for primary care has led to the recognition that case-finding may be enriched in glaucoma (Dabasia et al., 2015b, Azuara-Blanco et al., 2016a) and the identification of retinal disease (Ly et al., 2018). The current study found that with the OCT combination, the overall percentage of cases that were correctly classified increased by an average of approximately 20%, with over 90% of participants showing an improvement in their overall diagnostic accuracy when the fundus images were combined with OCT. The performance of some individuals increased by over 40%. One particular case was associated with the greatest improvement, where only one optometrist correctly diagnosed VMT from the fundus image alone, where this improved to 38 optometrists (76%) correctly diagnosing a case when combined with OCT. This highlights the problem of diagnosing this condition based on limited symptoms and absence of OCT (Johnson, 2005).

Poor diagnostic accuracy has been reported in disc assessment by optometrists (Bowling et al., 2005, Keenan et al., 2015, Ratnarajan et al., 2015) and retinal conditions (Muen & Hewick, 2011, Parkins et al., 2018). Subsequently, there has been a shift towards integrating advanced imaging technologies in the hope of improving the conventional assessment. The current study reports that with the additional objective information provided with OCT with fundus examination, the proportion of false negatives and false positives were significantly reduced; this would inevitably lead to improved disease detection and reduce the induced cost-resource implications of unnecessary referrals.

With OCT uptake increasing over the last decade (Myint et al., 2011, Dabasia et al., 2014b), our sample demonstrated 30% of optometrists had access to OCT, which suggests its popularity is continuing. In agreement with other studies, the current study reported that optometrists with further professional qualifications showed improved diagnostic performance (Hadwin et al., 2013). With the increased incorporation of OCT in primary care, there is a concern that if clinicians do not receive the necessary training, this may result in reduced diagnostic performance, leading to an increase in inappropriate referrals. OCT outputs provide colour coded maps which are based on the

machine's normative databases, if practitioners are unaware of the limitations of this data this may lead to under or overdiagnosis (Chong & Lee, 2012).

The current study mainly focused on the detection of diseases using clinical vignettes, it did not explore management. There are few studies that have investigated triaging using OCT (Talks et al., 2007, Kelly et al., 2011, Ly et al., 2016). They concluded that OCT has the potential to assist triage and improve interdisciplinary professional working relationships, but even if the disease has been successful detected, triaged and referred, are there are enough resources to enable management of these conditions in an already over-stretched secondary care setting. It may be therefore appropriate that optometrists in primary care will shift the traditional management of diseases from secondary care into the community by acquiring higher qualifications (CoO, 2019) and purchase the relevant technology. However, with the volume and complexity of diagnostic imaging increasing faster than human expertise to interpret it, in addition to the time and cost needed to train optometrists; artificial intelligence may be the next step in facilitating the detection and management of eye diseases. Artificial intelligence that use deep learning strategies can analyse a significant amount of diagnostic data from a variety of sources such as OCT, fundus imaging and/or visual field data, and have been applied to detect diabetic retinopathy, glaucoma and age-related macular degeneration. With advancing algorithms, it has been proposed that deep learning methods coupled with telemedicine in primary eye care, could provide a financially long term solution to either screen, triage and/or monitor patients (Ting et al., 2019)

4.4.6 Strengths and limitations of the study

One of the strengths of the current study was the relevance of the case mix. The clinical vignettes were drawn from real clinical cases who participated in a large cross-sectional study of elderly subjects with a range of pathologies that would be typical of those seen in routine optometric practice (Dabasia et al., 2015b). The two sets of vignettes were externally validated to ensure a similar level of difficulty and the assessment was pilot

tested. In addition, all participants received a standardised online training package in OCT interpretation, that is similar to training given to new OCT users and in the assessment, they were forced to select a diagnosis as they would in clinical practice. In terms of demographics and mode of practice, the study participants were broadly representative of community optometrists working in the UK (CoO, 2015, GOC, 2017).

Since the aim of the study was to investigate the ability of optometrists to recognise disc damage and features on retinal images, the vignettes did not contain all of the diagnostic information that would normally be available to the optometrist e.g. presence of risk factors, data from visual field plots and intraocular pressure readings. Studies evaluating UK optometric practice patterns found that community optometrist's use of direct ophthalmoscopy was more common than indirect ophthalmoscopy (Shah et al., 2009, Myint, 2013). As non-stereoscopic images were used in the assessment, this is likely to reflect the view of the disc obtained by most UK community optometrists, but it should be noted that both these surveys were conducted almost a decade ago. A systematic review comparing stereoscopic and monoscopic disc methods found that monoscopic assessment generated a lower sensitivity than the stereoscopic (Newman-Casey et al., 2014). With the advent of updated clinical guidelines (SIGN, 2015, NICE, 2017), it is therefore possible that optometrists in UK community practice may be making greater use of binocular indirect ophthalmoscopy for detecting and referring optic nerve head disease. Another issue that could have been induced was the framing of some of the disc photographs in the vignettes. This may have prohibited participants in identifying peripapillary signs of RNFL damage that could have affected the diagnostic performance gained using OCT. In addition, the inclusion of unequivocally 'normal' vignettes may have unintentionally improved the diagnostic performance of the OCT. It has previously been demonstrated that effectiveness of the OCT in detecting glaucoma significantly decreases when evaluated against a more clinically relevant control group with suspicious-looking discs compared to a control group with no suspicious findings (Rao et al., 2012). The results may therefore not be fully representative of the participants' diagnostic performance in a 'real world' setting; this assumption is also relevant to the

artificially raised prevalence of certain eye diseases presented in the current study such as disc pathology. Subsequently, this may have influenced the decision making of participants attending an assessment that evaluated their ability to detect disease; with a perception that there would be a greater number of those with disease, that could have led to an over-classification of pathology.

4.4.7 Conclusion

There has been widespread investment in imaging technologies by UK community optometrists, most notably OCT. The results of this study suggest that OCT improves optometrist's diagnostic performance and confidence. These initial results imply that OCT provides valuable additional data that could augment case-finding for glaucoma and retinal disease. Whilst the improvement in diagnostic performance is encouraging, the OCT should still be employed judiciously in a routine clinical practice setting. It is also important that clinicians are appropriately trained in OCT data interpretation and appreciate the limitations as well as the strengths of the technology.

Chapter 5: Summary and directions for future work

5.1 Summary

With global shifts towards an ageing population, there will be an exponential increase in age-related eye diseases that could result in unavoidable sight loss if left undetected. The emergence of new imaging and visual assessment technologies has provided opportunities for improved detection and assessment of ocular disease. However, before these technologies can be incorporated in a routine clinical setting, it is crucial that their performance is fully evaluated.

In high income countries, epidemiological studies have shown that up to a half of glaucoma is undiagnosed (Tielsch et al., 1991a, Klein et al., 1992, Mitchell et al., 1996, Quigley & Vitale, 1997, Weih et al., 2001, Chan et al., 2017) and over 90% is undiagnosed in low income countries (Ramakrishnan et al., 2003, Vijaya et al., 2008, Garudadri et al., 2010, Thapa et al., 2012, Budenz et al., 2013). In the United Kingdom (UK) a cost based analysis that built-in the relatively low costs of 'technicians' for primary open angle glaucoma (POAG) screening using current technologies, was found to be not cost-effective in the general population (Burr et al., 2007), which concurs with similar findings from a Finnish study (Vaahtoranta-Lehtonen et al., 2007). In both studies, the authors concluded that whilst POAG is the predominate form of glaucoma in their studied population, the diagnostic accuracy of the reviewed technologies coupled with the low prevalence of the disease did not satisfy the requirements needed for population screening. However, they suggested that targeting those at risk of the disease may be economically viable (Burr et al., 2007, Vaahtoranta-Lehtonen et al., 2007, Hernández et al., 2008). With the emergence of primary angle closure glaucoma (PACG) contributing to a greater proportion of global glaucoma blindness, it will be those in Asia who will be greatest affected by this disease (Quigley & Broman, 2006, Tham et al., 2014). Two recent economic models found that screening for glaucoma which encompassed both POAG and PACG in rural India and China, could be cost-effective due to the higher

prevalence and risk of blindness associated with PACG (John & Parikh, 2018, Tang et al., 2019), however at present there are no screening programmes that are in operation.

For the definitive detection of those at risk of PACG, this requires gonioscopic assessment of the angle. This technique is not appropriate for population screening however, several non-invasive methods are available to identify eyes at risk of occlusion. Studies evaluating the diagnostic performance of these techniques are increasingly being published, however there have been relatively few attempts to synthesise this evidence. Systematic reviews of diagnostic test accuracy provide a quantitative summary of test accuracy, risk of bias assessment and compare the performance of alternative tests. Chapter 2 systematically reviews the diagnostic performance of five tests in the identification of a narrow angle: flashlight test, limbal anterior chamber depth (LACD), Scanning Peripheral Anterior Chamber Depth Analyser, Scheimpflug photography and Anterior Segment Optical Coherence Tomography (AS-OCT). Thirty-eight studies provided quantitative data for the review and a quality assessment (using QUADAS-2) was conducted for each study. The majority of studies were conducted in Asia, where the findings would be particularly applicable. Meta-analysis was conducted for all five tests; overall there was relatively good performance for most tests for the detection of a narrow angle, based on the test threshold with the highest diagnostic odds ratio. A comparison of diagnostic test accuracy using the LACD ≤25% threshold as the reference, revealed similar performance between the tests although flashlight and AS-OCT had a lower sensitivity and specificity, respectively. The studies included in the current review had a number of methodological shortcomings, for example a third of the studies recruited subjects with a previous diagnosis of narrow angle and all thresholds for Scheimpflug photography and quantitative AS-OCT thresholds were calculated *post-hoc* rather than being pre-determined. While these limitations could have led to an over-estimation of test performance, we nonetheless consider the results valuable. An important finding from the review was that LACD performed as well as sophisticated imaging technologies and confirms it's potential for screening narrow angles in high-risk populations. Although, care should be taken when interpreting and applying these

estimates for clinical decision making due to the observed heterogeneity in test performance and high risk of bias found in most studies.

In low income countries, the proportion of undetected glaucoma and the risk of associated blindness is high due to inadequate access to eye care and poor public awareness. Furthermore, with limited availability of low-cost technologies that can be deployed in such settings with minimal operator training, detection will always remain problematic. Chapter 3 describes the development and evaluation of a newly developed test named the 'Accelerator 4-Alternative Forced-Choice Flicker Test prototype (A4FTp)' to detect POAG; that could be used by non-clinical personnel outside the normal clinical setting for those at risk of glaucomatous visual disability in their lifetime. Its performance was evaluated and compared to current screening technologies (Spectral-Domain Optical Coherence Tomography (SD-OCT) and Frequency Double Technology (FDT) perimeter in a case-control study that recruited 78 consecutive adults with (n=40) and without (n=38) glaucoma. These three tests were performed by an experienced optometrist and masked to a reference ophthalmic examination conducted by the author. The overall diagnostic performance of the A4FTp was found to be equivalent for the detection of POAG. The A4FTp thresholding algorithm generated a relatively short testing time of approximately 2 minutes per eye for all participants. Detection of those with moderate and advanced glaucoma was similar to the FDT, however the FDT was more likely to detect early glaucomatous loss. A user acceptability survey was given to all participants and the A4FTp was reported to be acceptable in terms of test duration and comfort, but participants found the test more difficult to operate than the FDT. None of the index tests used alone met the high sensitivity and specificity needed for population screening due to the low prevalence of the disease in European based populations, as described in previous studies of glaucoma screening tests (Mowatt et al., 2008, Geimer, 2013, Dabasia et al., 2015b). However, with rates of undiagnosed glaucoma reaching as high as 95% in low income countries, the need to provide affordable and accessible strategies for testing in the community are still warranted.

Hence, with further development the A4FTp could have a future role alongside other tests in glaucoma detection in these at-risk populations.

In the UK and internationally, there has been a shift in integrating optical coherence tomography (OCT) from secondary care ophthalmology to primary care (Dabasia et al., 2014b, Jamous et al., 2014, Kiely et al., 2017, Ly et al., 2017). Successive surveys have found OCT gaining popularity with UK community optometrists (Myint et al., 2011, Dabasia et al., 2014b) however, there is a lack of evidence regarding the diagnostic benefit offered by OCT in primary care. Chapter 4 reports on a vignette case study comparing the diagnostic performance of 50 community-based optometrists using fundus imaging alone (as a proxy for a conventional ophthalmoscopic examination) compared to a set of cases where fundus imaging was supplemented by SD-OCT. Optometrists completed an online educational package on OCT interpretation that was followed by attendance of a computer-based assessment. The mean percentage of correct diagnoses for the combination of fundus image/OCT improved by approximately 20% when compared to fundus imaging alone. Nearly all the optometrists (94%) performed better with the supplementary OCT clinical data. In addition, those with higher qualifications had superior performance in clinical decision making with the OCT combination when compared to those without. The current study also reports that the additional OCT information resulted in a reduction in the proportion of false negatives and false positives. These observations suggest that OCT provides valuable additional data that could augment case-finding for glaucoma and retinal disease. Whilst the improvement in diagnostic performance is encouraging, more research is needed to assess the diagnostic benefit of OCT in a routine clinical setting.

5.2 Directions for future work

Chapter 2 evaluated the diagnostic accuracy of triage tests to identify a narrow angle. The employment of these tests for population screening or opportunistic case-finding could identify eyes at risk of angle closure that could then be referred for prophylactic treatment to reduce the risk of developing PACG. A recent large study in a Chinese population found that 4.8% of untreated primary angle closure suspects (PACS) and 2.5% of treated PACS using laser peripheral iridotomy (LPI) converted to primary angle closure (PAC)/acute angle closure (AAC) over a 6-year period (He et al., 2019). With the relatively low numbers of individuals converting to PAC/AAC, the authors advised against the widespread use of LPI in PACS and concluded that resources should be directed at those with more blinding forms of angle closure. This could include the selective use of clear lens extraction, which has been shown to be an effective intervention for reducing the risk of PACG (Azuara-Blanco et al., 2016b). The authors did concede that their findings may vary in other populations, due to the anatomical variations of the anterior segment (He et al., 2006b).

While this review established the diagnostic accuracy of non-contact methods to identify a narrow angle, there was no economic evaluation to determine the cost-effectivity of screening. A recent economic analysis found that glaucoma screening could be potentially cost-effective in Chinese adults aged 50 years or older (Tang et al., 2019), by harnessing the combined sensitivities and specificities of LACD and optic nerve photography. The estimates of test performance obtained from our meta-analysis could be used in future economic models to determine the cost-effectiveness of LACD or other test combinations and/or risk factors. Methodological limitations in the studies contributing to this analysis indicate that there is still a need for further high-quality studies to evaluate the performance of non-invasive tests for angle assessment. The following recommendations are suggested, that could reduce heterogeneity, increase validity and improve the generalisability of the results.

- Test thresholds should be pre-defined.
- A case-control design should be avoided.
- Investigators performing the index test and reference standard should be masked.
- Target condition using gonioscopy should conform to the ISGEO definition of primary angle closure, where diagnostic accuracy of the tests should analyse each stage of the disease (PACS, PACS and PACG) and overall. This would provide useful information for the development of care pathways.
- Evaluation of test performance in a variety of populations.
- Diagnostic test performance of the newer generation anterior segment devices should be evaluated i.e. spectral and swept source domain OCT.
- The number of exclusions with reasons should be reported where the index test result was not possible/uninterpretable.

Chapter 3 described the diagnostic accuracy of the A4FTp. Although the performance of this prototype was equivalent to currently available screening technologies, there were a number of elements that were identified that could improve it's test duration and usability. One of the key differences between the FDT and A4FTp was the use of the supra-threshold algorithm and the number of locations tested. It is well known that suprathreshold programmes are considerably quicker than thresholding (Katz et al., 1993, Weber & Klimaschka, 1995, Matsumoto et al., 2006, Iwase et al., 2007, Hirasawa et al., 2016). It's therefore envisaged that the next version of the A4FTp will employ a supra-threshold mode that should see testing times substantially reduced. The use of a supra-threshold algorithm would also allow the use of a greater number of stimulus locations whilst maintain a short test duration.

With these refinements, future work would be required to evaluate the performance of the A4FTp in a larger cohort that would be representative of the target population. The use of a touch screen display in place of the keypad used in the current prototype, could improve the usability and accessibility of the test.

Chapter 4 provided evidence that OCT improved clinical decision making by community optometrists in a range of posterior segment diseases. Recruited optometrists were generally representative of those working in the UK, however it mainly comprised of relatively experienced clinicians. It is known that less experienced clinicians can create a significant proportion of unnecessary referrals (Parkins et al., 2018). Considering newly qualified optometrists are unlikely to have higher qualifications and are known to be responsible for higher numbers of referrals, the diagnostic benefit of OCT may not extend to this cohort, even with the greater exposure of recent graduates to OCT during their undergraduate training. With the number of newly qualified optometrists rising in the UK (Harper & Lawrenson, 2018), this could lead to increased false positives that may confound the potential diagnostic value offered, therefore it may be worthwhile evaluating the value of OCT on clinical decision-making in a newly qualified cohort. Vignettes have been validated against unannounced standardised patients as a measure of quality of care (Peabody et al., 2000, Peabody et al., 2004). However, the vignettes in the current study limited the clinical information that would normally be present in practice such as intraocular pressure, visual field data and medical history. In addition, management of the scenarios presented to the participants was not evaluated. Previous studies have investigated the diagnostic performance of community optometrists in a real world setting by appraising the pattern and quality of referrals into secondary care (Bell & O'Brien, 1997, Bowling et al., 2005, Parkins et al., 2018). With the recent popularity of OCT amongst UK community optometrists, there is growing concern amongst secondary care providers that this will precipitate into an increase in unnecessary referrals, despite the current study suggesting otherwise. With the largest UK optometry chain announcing that they will be incorporating OCT into all of their practices within the next few years (AOP, 2017); this could provide an opportunity to investigate whether OCT has indeed impacted the number of referrals. In a triage audit conducting by Parkins and colleagues (Parkins et al., 2018), a similar approach could be adopted to evaluate referrals patterns before and after this mass OCT roll out, which

could provide further insight into the role OCT has on clinical decision making in primary care.

References

ADHI, M., LIU, J. J., QAVI, A. H., GRULKOWSKI, I., LU, C. D., MOHLER, K. J., FERRARA, D., KRAUS, M. F., BAUMAL, C. R. & WITKIN, A. J. 2014. Choroidal analysis in healthy eyes using swept-source optical coherence tomography compared to spectral domain optical coherence tomography. *Am J Ophthalmol,* 157**,** 1272-1281. e1.

ALONSO, R. S., AMBROSIO JUNIOR, R., PARANHOS JUNIOR, A., SAKATA, L. M. & VENTURA, M. P. 2010. Glaucoma anterior chamber morphometry based on optical Scheimpflug images. *Arq Bras Oftalmol,* 73**,** 497-500.

ALSBIRK, P. H. 1992. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. *Int Ophthalmol,* 16**,** 265-72.

ALTMAN, D. G. & BLAND, J. M. 1994. Diagnostic tests -2-Predictive values. *BMJ,* 309**,** 102-102.

AMERASINGHE, N., ZHANG, J., THALAMUTHU, A., HE, M., VITHANA, E. N., VISWANATHAN, A., WONG, T. Y., FOSTER, P. J. & AUNG, T. 2011. The heritability and sibling risk of angle closure in Asians. *Ophthalmology,* 118**,** 480-485.

ANDERSON, A. J. & JOHNSON, C. A. 2003a. Frequency-doubling technology perimetry. *Ophthalmology Clin,* 16**,** 213-225.

ANDERSON, A. J. & JOHNSON, C. A. 2003b. Frequency-Doubling Technology perimetry and optical defocus. *Invest Ophthalmol Vis Sci,* 44**,** 4147-4152.

ANDERSON, D. & PATELLA, V. 1999. *Automated static perimetry.* 2nd ed. Mosby, St Louis 147-159.

ANDREWS, J., CHANG, D. S., JIANG, Y., HE, M., FOSTER, P. J., MUNOZ, B., KASHIWAGI, K. & FRIEDMAN, D. S. 2012. Comparing approaches to screening for angle closure in older Chinese adults. *Eye,* 26**,** 96-100.

ANGMO, D., NONGPIUR, M. E., SHARMA, R., SIDHU, T., SIHOTA, R. & DADA, T. 2016. Clinical utility of anterior segment swept-source optical coherence tomography in glaucoma. *Oman J Ophthalmol,* 9**,** 3-10.

AOP. 2017. *OCT rollout in every Specsavers announced* [Online]. Optometry Today. Available: https://www.aop.org.uk/ot/industry/high-street/2017/05/22/oct-rollout-in-every-specsavers-announced [Accessed 26th November 2018].

AREF, A. A. & BUDENZ, D. L. 2010. Spectral domain optical coherence tomography in the diagnosis and management of glaucoma. *Ophthalmic Surg, Lasers Imaging,* 41**,** S15-S27.

ASHAYE, A. 2003. Use of limbal and central anterior chamber depth measurements in detecting eyes with gonioscopically occludable angles and primary angle closure glaucoma in Ibadan. *Afr J Medicine Med Sci,* 32**,** 413-416.

AUNG, T., ANG, L. P., CHAN, S.-P. & CHEW, P. T. 2001. Acute primary angle-closure: long-term intraocular pressure outcome in Asian eyes. *Am J Ophthalmol,* 131**,** 7-12.

AZUARA-BLANCO, A., BANISTER, K., BOACHIE, C., MCMEEKIN, P., GRAY, J., BURR, J., BOURNE, R., GARWAY-HEATH, D., BATTERBURY, M. & HERNÁNDEZ, R. 2016a. Automated imaging technologies for the diagnosis of glaucoma: a comparative diagnostic study for the evaluation of the diagnostic accuracy, performance as triage tests and cost-effectiveness (GATE study). *Health Technol Assess,* 20**,** 1-168.

AZUARA-BLANCO, A., BURR, J., RAMSAY, C., COOPER, D., FOSTER, P. J., FRIEDMAN, D. S., SCOTLAND, G., JAVANBAKHT, M., COCHRANE, C. & NORRIE, J. 2016b. Effectiveness of

early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. *Lancet,* 388**,** 1389-1397.
AZUARA-BLANCO, A., BURR, J., THOMAS, R., MACLENNAN, G. & MCPHERSON, S. 2007. The accuracy of accredited glaucoma optometrists in the diagnosis and treatment recommendation for glaucoma. *Br J Ophthalmol,* 91**,** 1639-1643.
BAIG, S., DINIZ-FILHO, A., WU, Z. & ET AL. 2016. Association of fast visual field loss with risk of falling in patients with glaucoma. *JAMA Ophthalmol,* 134**,** 880-886.
BAKER, H. & MURDOCH, I. 2008. Can a public health intervention improve awareness and health-seeking behaviour for glaucoma? *Br J Ophthalmol,* 92**,** 1671-1675.
BAKER, H., RATNARAJAN, G., HARPER, R. A., EDGAR, D. F. & LAWRENSON, J. G. 2016. Effectiveness of UK optometric enhanced eye care services: a realist review of the literature. *Ophthalmic Physiol Opt,* 36**,** 545-557.
BASKARAN, M., AUNG, T., FRIEDMAN, D. S., TUN, T. A. & PERERA, S. A. 2012. Comparison of EyeCam and anterior segment optical coherence tomography in detecting angle closure. *Acta Opthalmologica,* 90**,** e621-e625.
BASKARAN, M., OEN, F. T., CHAN, Y. H., HOH, S. T., HO, C. L., KASHIWAGI, K., FOSTER, P. J. & AUNG, T. 2007. Comparison of the scanning peripheral anterior chamber depth analyzer and the modified van Herick grading system in the assessment of angle closure. *Ophthalmology,* 114**,** 501-506.
BELL, R. & O'BRIEN, C. 1997. The diagnostic outcome of new glaucoma referrals. *Ophthalmic Physiol Opt,* 17**,** 3-6.
BENGTSSON, B., ANDERSSON, S. & HEIJL, A. 2012. Performance of time-domain and spectral-domain optical coherence tomography for glaucoma screening. *Acta Ophthalmol,* 90**,** 310-315.
BENGTSSON, B., HEIJL, A. & OLSSON, J. 1998. Evaluation of a new threshold visual field strategy, SITA, in normal subjects. Swedish Interactive Thresholding Algorithm. *Acta Ophthalmol Scand,* 76**,** 165-169.
BERGIN, C., REDMOND, T., NATHWANI, N., VERDON-ROE, G. M., CRABB, D. P., ANDERSON, R. S. & GARWAY-HEATH, D. F. 2011. The effect of induced intraocular straylight on perimetric tests. *Invest Ophthalmol Vis Sci,* 52**,** 3676-3682.
BERTUZZI, F., BENATTI, E., ESEMPIO, G., RULLI, E. & MIGLIOR, S. 2014. Evaluation of retinal nerve fiber layer thickness measurements for glaucoma detection: GDx ECC versus spectral-domain OCT. *J Glaucoma,* 23**,** 232-239.
BHARGAVA, S. K., LEIGHTON, D. A. & PHILLIPS, C. I. 1973. Early angle-closure glaucoma: distribution of iridotrabecular contact and response to pilocarpine. *Arch Ophthalmol,* 89**,** 369-372.
BOLAND, M. V., GUPTA, P., KO, F., ZHAO, D., GUALLAR, E. & FRIEDMAN, D. S. 2016. Evaluation of frequency-doubling technology perimetry as a means of screening for glaucoma and other eye diseases using the National Health and Nutrition Examination Survey. *JAMA Ophthalmol,* 134**,** 57-62.
BOSSUYT, P., DAVENPORT, C., DEEKS, J., HYDE, C., LEEFLANG, M. & SCHOLTEN, R. 2013. *Cochrane handbook for systematic reviews of diagnostic test accuracy* Chapter 11: interpreting results and drawing conclusions. The Cochrane Collaboration.
BOSSUYT, P. M., REITSMA, J. B., BRUNS, D. E., GATSONIS, C. A., GLASZIOU, P. P., IRWIG, L. M., MOHER, D., RENNIE, D., DE VET, H. C. & LIJMER, J. G. 2003. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med,* 138**,** W1-W12.

BOSWORTH, C. F., SAMPLE, P. A. & WEINREB, R. N. 1997. Motion perception thresholds in areas of glaucomatous visual field loss. *Vision Res,* 37**,** 355-364.

BOURNE, R. R. A., FLAXMAN, S. R., BRAITHWAITE, T., CICINELLI, M. V., DAS, A., JONAS, J. B., KEEFFE, J., KEMPEN, J. H., LEASHER, J., LIMBURG, H., NAIDOO, K., PESUDOVS, K., RESNIKOFF, S., SILVESTER, A., STEVENS, G. A., TAHHAN, N., WONG, T. Y., TAYLOR, H. R. & ZHENG, Y. 2017. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Glob Health,* 5**,** e888-e897.

BOURNE, R. R. A., JONAS, J. B., BRON, A. M., CICINELLI, M. V., DAS, A., FLAXMAN, S. R., FRIEDMAN, D. S., KEEFFE, J. E., KEMPEN, J. H., LEASHER, J., LIMBURG, H., NAIDOO, K., PESUDOVS, K., PETO, T., SAADINE, J., SILVESTER, A. J., TAHHAN, N., TAYLOR, H. R., VARMA, R., WONG, T. Y. & RESNIKOFF, S. 2018. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol,* 102**,** 575-585.

BOURNE, R. R. A., SUKUDOM, P., FOSTER, P. J., TANTISEVI, V., JITAPUNKUL, S., LEE, P. S., JOHNSON, G. J. & ROJANAPONGPUN, P. 2003. Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. *Br J Ophthalmol,* 87**,** 1069-1074.

BOURNE, R. R. A., TAYLOR, H. R., FLAXMAN, S. R., KEEFFE, J., LEASHER, J., NAIDOO, K., PESUDOVS, K., WHITE, R. A., WONG, T. Y., RESNIKOFF, S. & JONAS, J. B. 2016. Number of people blind or visually impaired by glaucoma worldwide and in world regions 1990 – 2010: a meta-analysis. *PLoS ONE,* 11**,** e0162229.

BOWLING, B., CHEN, S. & SALMON, J. 2005. Outcomes of referrals by community optometrists to a hospital glaucoma service. *Br J Ophthalmol,* 89**,** 1102-1104.

BRESSLER, N. M. 2004. Age-related macular degeneration is the leading cause of blindness. *JAMA,* 291**,** 1900-1901.

BROWN, K., SEWELL, J. M., TREMPE, C., PETO, T. & TRAVISON, T. G. 2013. Comparison of image-assisted versus traditional fundus examination. *Eye Brain,* 5**,** 1-8.

BRUSINI, P. & FILACORDA, S. 2006. Enhanced Glaucoma Staging System (GSS 2) for classifying functional damage in glaucoma. *J Glaucoma,* 15**,** 40-46.

BUDENZ, D. L., BARTON, K., WHITESIDE-DE VOS, J., SCHIFFMAN, J., BANDI, J., NOLAN, W., HERNDON, L., KIM, H., HAY-SMITH, G. & TIELSCH, J. M. 2013. Prevalence of glaucoma in an urban west African population: The Tema Eye Survey. *JAMA Ophthalmol,* 131**,** 651-658.

BUNCE, C., XING, W. & WORMALD, R. 2010. Causes of blind and partial sight certifications in England and Wales: April 2007–March 2008. *Eye,* 24**,** 1692.

BURR, J. M., MOWATT, G., HERNÁNDEZ, R., SIDDIQUI, M., COOK, J., LOURENCO, T., RAMSAY, C., VALE, L., FRASER, C. & AZUARA-BLANCO, A. 2007. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess,* 11**,** 1-190.

CAMPBELL, P., REDMOND, T., AGARWAL, R., MARSHALL, L. R. & EVANS, B. J. 2015. Repeatability and comparison of clinical techniques for anterior chamber angle assessment. *Ophthalmic Physiol Opt,* 35**,** 170-178.

CARTWRIGHT, M. J. & ANDERSON, D. R. 1988. Correlation of asymmetric damage with asymmetric intraocular pressure in normal-tension glaucoma (low-tension glaucoma). *Arch Ophthalmol,* 106**,** 898-900.

CASSON, R. J. & JAMES, B. 2006. Effect of cataract on frequency doubling perimetry in the screening mode. *J Glaucoma,* 15**,** 23-25.

CASTAÑEDA-DÍEZ, R., MAYORQUÍN-RUIZ, M., ESPONDA-LAMOGLIA, C. & ALBIS-DONADO, O. 2011. *Current diagnosis and management of angle-closure glaucoma* [Online]. IntechOpen. Available: https://www.intechopen.com/books/glaucoma-current-clinical-and-research-aspects/current-diagnosis-and-management-of-angle-closure-glaucoma [Accessed 27th March 2019].

CHAKRAVARTHY, U. 2006. Age related macular degeneration. *BMJ,* 333**,** 869-870.

CHAKRAVARTHY, U., WONG, T. Y., FLETCHER, A., PIAULT, E., EVANS, C., ZLATEVA, G., BUGGAGE, R., PLEIL, A. & MITCHELL, P. 2010. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol,* 10**,** 31.

CHAN, M. P. Y., BROADWAY, D. C., KHAWAJA, A. P., YIP, J. L. Y., GARWAY-HEATH, D. F., BURR, J. M., LUBEN, R., HAYAT, S., DALZELL, N., KHAW, K. T. & FOSTER, P. J. 2017. Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ,* 358**,** j3889.

CHAN, P. P., LI, E. Y. & THAM, C. C. 2014. Cost-effectiveness in the treatment of glaucoma. *US Ophthalmic Rev,* 7**,** 131–136.

CHANG, D. S., SAKATA, L. M., AUNG, T., HE, M. G., LAVANYA, R., KASHIWAGI, K. & FRIEDMAN, D. S. 2011. Single versus sequential testing with scanning peripheral anterior chamber depth analyser, IOLMaster and anterior segment optical coherence tomography for the detection of narrow angles. *Br J Ophthalmol,* 95**,** 1410-1414.

CHANSANGPETCH, S., ROJANAPONGPUN, P. & LIN, S. C. 2018. Anterior segment imaging for angle closure. *Am J Ophthalmol,* 188**,** 16-29.

CHE HAMZAH, J., DAKA, Q. & AZUARA-BLANCO, A. 2020. Home monitoring for glaucoma. *Eye,* 34**,** 155-160.

CHENG, J.-W., ZONG, Y., ZENG, Y.-Y. & WEI, R.-L. 2014. The prevalence of primary angle closure glaucoma in adult Asians: a systematic review and meta-analysis. *PLoS One,* 9**,** e103222.

CHONG, G. T. & LEE, R. K. 2012. Glaucoma versus red disease: imaging and glaucoma diagnosis. *Curr Opin Ophthalmol,* 23**,** 79-88.

CHOPRA, R., MULHOLLAND, P. J., TAILOR, V. K., ANDERSON, R. S. & KEANE, P. A. 2018. Use of a binocular optical coherence tomography system to evaluate strabismus in primary position. *JAMA Ophthalmol,* 136**,** 811-817.

CHYLACK, L. T., JR., WOLFE, J. K., SINGER, D. M., LESKE, M. C., BULLIMORE, M. A., BAILEY, I. L., FRIEND, J., MCCARTHY, D. & WU, S. Y. 1993. The Lens Opacities Classification System III. The longitudinal study of Cataract Study Group. *Arch Ophthalmol,* 111**,** 831-836.

CIOFFI, G. A., MANSBERGER, S., SPRY, P., JOHNSON, C. & VAN BUSKIRK, E. M. 2000. Frequency doubling perimetry and the detection of eye disease in the community. *Trans Am Ophthalmol Soc,* 98**,** 195-202.

CLEMMESEN, V. & ALSBIRK, P. H. 1971. Primary angle-closure glaucoma (a.c.g.) in Greenland. *Acta Ophthalmol (Copenh),* 49**,** 47-58.

COHEN, J. F., KOREVAAR, D. A., ALTMAN, D. G., BRUNS, D. E., GATSONIS, C. A., HOOFT, L., IRWIG, L., LEVINE, D., REITSMA, J. B., DE VET, H. C. & BOSSUYT, P. M. 2016. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open,* 6**,** e012799.

CONGDON, N., O'COLMAIN, B., KLAVER, C. C., KLEIN, R., MUNOZ, B., FRIEDMAN, D. S., KEMPEN, J., TAYLOR, H. R., MITCHELL, P. & EYE DISEASES PREVALENCE RESEARCH, G. 2004. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol,* 122**,** 477-485.

CONGDON, N. G., QUIGLEY, H. A., HUNG, P. T., WANG, T. H. & HO, T. C. 1996. Screening techniques for angle-closure glaucoma in rural Taiwan. *Acta Ophthalmol Scand,* 74**,** 113-119.

COO. 2015. *College of Optometrists. Optical Workforce Survey* [Online]. Available: https://www.college-optometrists.org/the-college/research/research-projects/optical-workforce-survey2.html [Accessed 06/08/2018].

COO. 2019. *College of Optometrists. Higher Qualifications* [Online]. College of Optometrists. Available: https://www.college-optometrists.org/cpd-and-cet/training-and-qualifications/higher-qualifications.html [Accessed 14/02/2019].

DABASIA, P., EDGAR, D. & LAWRENSON, J. 2014a. Methods of measurement of the anterior chamber angle part 3: screening for angle closure and angle closure glaucoma using advanced technologies. *Optom Pract,* 15**,** 11-19.

DABASIA, P. L. 2014. *A study of the role of advanced technologies in glaucoma case-finding.* Doctoral thesis, City, University of London.

DABASIA, P. L., EDGAR, D. F., GARWAY-HEATH, D. F. & LAWRENSON, J. G. 2014b. A survey of current and anticipated use of standard and specialist equipment by UK optometrists. *Ophthalmic Physiol Opt,* 34**,** 592-613.

DABASIA, P. L., EDGAR, D. F., MURDOCH, I. E. & LAWRENSON, J. G. 2015a. Non-contact screening methods for the detection of narrow anterior chamber angles. *Invest Ophthalmol Vis Sci,* 56**,** 3929-3935.

DABASIA, P. L., FIDALGO, B. R., EDGAR, D. F., GARWAY-HEATH, D. F. & LAWRENSON, J. G. 2015b. Diagnostic accuracy of technologies for glaucoma case-finding in a community setting. *Ophthalmology,* 122**,** 2407-2415.

DACEY, D. M. & PACKER, O. S. 2003. Colour coding in the primate retina: diverse cell types and cone-specific circuitry. *Curr Opin Neurobiol,* 13**,** 421-7.

DAVEY, C. J., GREEN, C. & ELLIOTT, D. B. 2011. Assessment of referrals to the hospital eye service by optometrists and GPs in Bradford and Airedale. *Ophthalmic Physiol Opt,* 31**,** 23-28.

DAVEY, C. J., SCALLY, A. J., GREEN, C., MITCHELL, E. S. & ELLIOTT, D. B. 2015. Factors influencing accuracy of referral and the likelihood of false positive referral by optometrists in Bradford, United Kingdom. *J Optom,* 9**,** 158-165.

DAY, A. C., BAIO, G., GAZZARD, G., BUNCE, C., AZUARA-BLANCO, A., MUNOZ, B., FRIEDMAN, D. S. & FOSTER, P. J. 2012. The prevalence of primary angle closure glaucoma in European derived populations: a systematic review. *Br J Ophthalmol,* 96**,** 1162-1167.

DE MORAES, C. G., HOOD, D. C., THENAPPAN, A., GIRKIN, C. A., MEDEIROS, F. A., WEINREB, R. N., ZANGWILL, L. M. & LIEBMANN, J. M. 2017. 24-2 visual fields miss central defects shown on 10-2 tests in glaucoma suspects, ocular hypertensives, and early glaucoma. *Ophthalmology,* 124**,** 1449-1456.

DEEKS, J. J. 2001. Systematic reviews of evaluations of diagnostic and screening tests. *BMJ,* 323**,** 157-162.

DEEKS, J. J. & MORRIS, J. M. 1996. Evaluating diagnostic tests. *Baillieres Clin Obstet Gynaecol,* 10**,** 613-630.

DELONG, E. R., DELONG, D. M. & CLARKE-PEARSON, D. L. 1988. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics,* 44**,** 837-845.

DETRY-MOREL, M., ZEYEN, T., KESTELYN, P., COLLIGNON, J. & GOETHALS, M. 2004. Screening for glaucoma in a general population with the non-mydriatic fundus camera and the frequency doubling perimeter. *Eur J Ophthalmol,* 14**,** 387-393.

DEVEREUX, J. G., FOSTER, P. J., BAASANHU, J., URANCHIMEG, D., LEE, P. S., ERDENBELEIG, T., MACHIN, D., JOHNSON, G. J. & ALSBIRK, P. H. 2000. Anterior chamber depth measurement as a screening tool for primary angle-closure glaucoma in an East Asian population. *Arch Ophthalmol,* 118**,** 257-263.

DOSHI, V., YING-LAI, M., AZEN, S. P., VARMA, R. & LOS ANGELES LATINO EYE STUDY, G. 2008. Sociodemographic, family history, and lifestyle risk factors for open-angle glaucoma and ocular hypertension. The Los Angeles Latino Eye Study. *Ophthalmology,* 115**,** 639-647 e2.

DRANCE, S. M. 1973. Angle closure glaucoma among Canadian Eskimos. *Can J Ophthalmol,* 8**,** 252-254.

EGS 2017. European glaucoma society terminology and guidelines for glaucoma, 4th Edition - Part 1. *Br J Ophthalmol,* 101**,** 1-72.

EMANUEL, M. E., PARRISH, R. K. & GEDDE, S. J. 2014. Evidence-based management of primary angle closure glaucoma. *Curr Opin Ophthalmol,* 25**,** 89-92.

ERVIN, A. M., BOLAND, M. V., MYROWITZ, E. H., PRINCE, J., HAWKINS, B., VOLLENWEIDER, D., WARD, D., SUAREZ-CUERVO, C. & ROBINSON, K. A. 2012. AHRQ Comparative Effectiveness Reviews. *Screening for Glaucoma: Comparative Effectiveness.* Rockville (MD). Agency for Healthcare Research and Quality (US).

EVANS, B. J. & ROWLANDS, G. 2004. Correctable visual impairment in older people: a major unmet need. *Ophthalmic Physiol Opt,* 24**,** 161-180.

EVANS, J. R. 2001. Risk factors for age-related macular degeneration. *Prog Retin Eye Res,* 20**,** 227-253.

FAN, X., WU, L. L., MA, Z. Z., XIAO, G. G. & LIU, F., JR. 2010. Usefulness of frequency-doubling technology for perimetrically normal eyes of open-angle glaucoma patients with unilateral field loss. *Ophthalmology,* 117**,** 1530-7.

FERRIS, F. L., 3RD, WILKINSON, C. P., BIRD, A., CHAKRAVARTHY, U., CHEW, E., CSAKY, K. & SADDA, S. R. 2013. Clinical classification of age-related macular degeneration. *Ophthalmology,* 120**,** 844-851.

FIDALGO, B. M., CRABB, D. P. & LAWRENSON, J. G. 2015. Methodology and reporting of diagnostic accuracy studies of automated perimetry in glaucoma: evaluation using a standardised approach. *Ophthalmic Physiol Opt,* 35**,** 315-323.

FIDALGO, B. R., DABASIA, P., JINDAL, A., EDGAR, D. F., CTORI, I., PETO, T. & LAWRENSON, J. G. 2019. Role of advanced technology in the detection of sight-threatening eye disease in a UK community setting. *BMJ Open Ophthalmol,* 4**,** e000347.

FIDALGO, B. R., JINDAL, A., TYLER, C. W., CTORI, I. & LAWRENSON, J. G. 2018. Development and validation of a new glaucoma screening test using temporally modulated flicker. *Ophthalmic Physiol Opt,* 38**,** 617-628.

FLAHAULT, A., CADILHAC, M. & THOMAS, G. 2005. Sample size calculation should be performed for design accuracy in diagnostic test studies. *J Clin Epidemiol,* 58**,** 859-862.

FLAXMAN, S. R., BOURNE, R. R. A., RESNIKOFF, S., ACKLAND, P., BRAITHWAITE, T., CICINELLI, M. V., DAS, A., JONAS, J. B., KEEFFE, J., KEMPEN, J. H., LEASHER, J., LIMBURG, H., NAIDOO, K., PESUDOVS, K., SILVESTER, A., STEVENS, G. A., TAHHAN, N., WONG, T. Y. & TAYLOR, H. R. 2017. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health,* 5**,** e1221-e1234.

FLEMING, C., WHITLOCK, E. P., BEIL, T., SMIT, B. & HARRIS, R. P. 2005. Screening for primary open-angle, glaucoma in the primary care setting: An update for the US Preventive Services Task Force. *Ann Fam Med,* 3**,** 167-170.

FORBES, M. 1966. Gonioscopy with corneal indentation: a method for distinguishing between appositional closure and synechial closure. *Arch Ophthalmol,* 76**,** 488-492.
FORTUNE, B., CULL, G., REYNAUD, J., WANG, L. & BURGOYNE, C. F. 2015. Relating retinal ganglion cell function and retinal nerve fiber layer (RNFL) retardance to progressive loss of RNFL thickness and optic nerve axons in experimental glaucoma. *Invest Ophthalmol Vis Sci,* 56**,** 3936-3944.
FOSTER, P. J., BAASANHU, J., ALSBIRK, P. H., MUNKHBAYAR, D., URANCHIMEG, D. & JOHNSON, G. J. 1996. Glaucoma in Mongolia: a population-based survey in Hövsgöl Province, Northern Mongolia. *Arch Ophthalmol,* 114**,** 1235-1241.
FOSTER, P. J., BUHRMANN, R., QUIGLEY, H. A. & JOHNSON, G. J. 2002. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol,* 86**,** 238-242.
FOSTER, P. J., DEVEREUX, J. G., ALSBIRK, P. H., LEE, P. S., URANCHIMEG, D., MACHIN, D., JOHNSON, G. J. & BAASANHU, J. 2000a. Detection of gonioscopically occludable angles and primary angle closure glaucoma by estimation of limbal chamber depth in Asians: modified grading scheme. *Br J Ophthalmol,* 84**,** 186-192.
FOSTER, P. J. & JOHNSON, G. J. 2001. Glaucoma in China: how big is the problem? *Br J Ophthalmol,* 85**,** 1277-1282.
FOSTER, P. J., OEN, F. T. S., MACHIN, D., NG, T.-P., DEVEREUX, J. G., JOHNSON, G. J., KHAW, P. T. & SEAH, S. K. L. 2000b. The prevalence of glaucoma in Chinese residents of Singapore: A cross-sectional population survey of the Tanjong pagar district. *JAMA Ophthalmol,* 118**,** 1105-1111.
FREEDMAN, L. S. 1987. Evaluating and comparing imaging techniques: a review and classification of study designs. *Br J Radiol,* 60**,** 1071-1081.
FRIEDMAN, D. S. 2007. Issues in screening for glaucoma. *Ophthalmic Epidemiol,* 14**,** 101-102.
FRIEDMAN, D. S. & HE, M. 2008. Anterior chamber angle assessment techniques. *Surv Ophthalmol,* 53**,** 250-273.
GARCIA-LAYANA, A., GARCIA-ARUMI, J., RUIZ-MORENO, J. M., ARIAS-BARQUET, L., CABRERA-LOPEZ, F. & FIGUEROA, M. S. 2015. A review of current management of vitreomacular traction and macular hole. *J Opthalmol,* 2015**,** 1-14.
GARUDADRI, C., SENTHIL, S., KHANNA, R. C., SANNAPANENI, K. & RAO, H. B. L. 2010. Prevalence and risk factors for primary glaucomas in adult urban and rural populations in the Andhra Pradesh Eye Disease Study. *Ophthalmology,* 117**,** 1352-1359.
GAZZARD, G., KONSTANTAKOPOULOU, E., GARWAY-HEATH, D., GARG, A., VICKERSTAFF, V., HUNTER, R., AMBLER, G., BUNCE, C., WORMALD, R., NATHWANI, N., BARTON, K., RUBIN, G. & BUSZEWICZ, M. 2019. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet,* 393**,** 1505-1516.
GEIMER, S. A. 2013. Glaucoma diagnostics. *Acta Ophthalmol,* 91**,** 1-32.
GOC. 2017. *Equality and diversity monitoring report 2016-2017* [Online]. General Optical Council. Available: http://www.optical.org/filemanager/root/site_assets/edi/2016-17_goc_edi_monitoring_report.pdf [Accessed 06/08/2018].
GONZALEZ-HERNANDEZ, M., GONZALEZ DE LA ROSA, M., RODRIGUEZ DE LA VEGA, R. & HERNANDEZ-VIDAL, A. 2007. Long-term fluctuation of standard automatic perimetry, pulsar perimetry and frequency-doubling technology in early glaucoma diagnosis. *Ophthalmic Res,* 39**,** 338-343.
GONZALEZ DE LA ROSA, M. 2011. Pulsar perimetry in the diagnosis of early glaucoma. *Am J Ophthalmol,* 152**,** 500-501.

GRACITELLI, C. P., LANDGREN, B., GRACIANI, F. B., SOUSA, A. K., PARANHOS, A., JR. & PRATA, T. S. 2014. Ability of non-ophthalmologist doctors to detect eyes with occludable angles using the flashlight test. *Int Ophthalmol,* 34**,** 557-561.

GREENFIELD, D. S. & WEINREB, R. N. 2008. Role of optic nerve imaging in glaucoma clinical practice and clinical trials. *Am J Ophthalmol,* 145**,** 598-603.e1.

GREWAL, D., BRAR, G., JAIN, R. & GREWAL, S. 2011. Comparison of scheimpflug imaging and spectral domain anterior segment optical coherence tomography for detection of narrow anterior chamber angles. *Eye,* 25**,** 603-611.

GRILLO, L. M., WANG, D. L., RAMACHANDRAN, R., EHRLICH, A. C., DE MORAES, C. G., RITCH, R. & HOOD, D. C. 2016. The 24-2 visual field test misses central macular damage confirmed by the 10-2 visual field test and optical coherence tomography. *Trans Vis Sci Tech,* 5**,** 1-7.

HADWIN, S. E., REDMOND, T., GARWAY-HEATH, D. F., LEMIJ, H. G., REUS, N. J., WARD, G. & ANDERSON, R. S. 2013. Assessment of optic disc photographs for glaucoma by UK optometrists: the Moorfields Optic Disc Assessment Study (MODAS). *Ophthalmic Physiol Opt,* 33**,** 618-624.

HAJIAN-TILAKI, K. 2014. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform,* 48**,** 193-204.

HARPER, R. A. & LAWRENSON, J. G. 2018. Rapid expansion of optometry student numbers in the UK: potential for significant risk. *Ophthalmic Physiol Opt,* 38**,** 471-473.

HARWERTH, R. S. & QUIGLEY, H. A. 2006. Visual field defects and retinal ganglion cell losses in human glaucoma patients. *Arch Ophthalmol,* 124**,** 853-859.

HAWLEY, C., ALBROW, H., STURT, J., MASON, L. 2011. *UK eye care services project. phase 1: systematic review of the organisation of UK eye care services* [Online]. College of Optometrists. Available: https://www.college-optometrists.org/uploads/assets/uploaded/67171c87-5b5f-4760-8dab4fd3489992ed.pdf [Accessed 1st August 2019].

HE, M., FOSTER, P. J., GE, J., HUANG, W., ZHENG, Y., FRIEDMAN, D. S., LEE, P. S. & KHAW, P. T. 2006a. Prevalence and clinical characteristics of glaucoma in adult Chinese: a population-based study in Liwan District, Guangzhou. *Invest Ophthalmol Vis Sci,* 47**,** 2782-2788.

HE, M., FOSTER, P. J., JOHNSON, G. J. & KHAW, P. T. 2006b. Angle-closure glaucoma in East Asian and European people. Different diseases? *Eye,* 20**,** 3-12.

HE, M., HUANG, W., FRIEDMAN, D. S., WU, C., ZHENG, Y. & FOSTER, P. J. 2007. Slit lamp–simulated oblique flashlight test in the detection of narrow angles in Chinese eyes: the Liwan Eye Study. *Invest Ophthalmol Vis Sci,* 48**,** 5459-5463.

HE, M., JIANG, Y., HUANG, S., CHANG, D. S., MUNOZ, B., AUNG, T., FOSTER, P. J. & FRIEDMAN, D. S. 2019. Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. *Lancet,* 393**,** 1609-1618.

HEIJL, A., LESKE, M. C., BENGTSSON, B. & HYMAN, L. 2002. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol,* 120**,** 1268.

HENSON, D. B., CHAUHAN, B. C. & HOBLEY, A. 1988. Screening for glaucomatous visual field defects: the relationship between sensitivity, specificity and the number of test locations. *Ophthalmic Physiol Opt,* 8**,** 123-127.

HENSON, D. B. & EMUH, T. 2010. Monitoring vigilance during perimetry by using pupillography. *Invest Ophthalmol Vis Sci,* 51**,** 3540-3543.

HERNÁNDEZ, R. A., BURR, J. M. & VALE, L. D. 2008. Economic evaluation of screening for open-angle glaucoma. *Int J Technol Assess Health Care,* 24**,** 203-211.
HIRASAWA, K., SHOJI, N., KASAHARA, M., MATSUMURA, K. & SHIMIZU, K. 2016. Comparison of size modulation and conventional standard automated perimetry with the 24-2 test protocol in glaucoma patients. *Sci Rep,* 6**,** 25563.
HODAPP, E., PARRISH, R. K. & ANDERSON, D. R. 1993. Clinical decisions in glaucoma. St Louis. Mosby 52-61.
HONG, S., YI, J. H., KANG, S. Y., SEONG, G. J. & KIM, C. Y. 2009. Detection of occludable angles with the Pentacam and the anterior segment optical coherence tomography. *Yonsei Med J,* 50**,** 525-8.
HORN, F. K., JONAS, J. B., KORTH, M., JUNEMANN, A. & GRUNDLER, A. 1997. The full-field flicker test in early diagnosis of chronic open-angle glaucoma. *Am J Ophthalmol,* 123**,** 313-319.
HORN, F. K., KREMERS, J., MARDIN, C. Y., JUNEMANN, A. G., ADLER, W. & TORNOW, R. P. 2015. Flicker-defined form perimetry in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol,* 253**,** 447-455.
HORN, F. K., SCHARCH, V., MARDIN, C. Y., LAMMER, R. & KREMERS, J. 2016. Comparison of frequency doubling and flicker defined form perimetry in early glaucoma. *Graefes Arch Clin Exp Ophthalmol,* 254**,** 937-946.
HORN, F. K., WAKILI, N., JÜNEMANN, A. M. & KORTH, M. 2002. Testing for glaucoma with frequency-doubling perimetry in normals, ocular hypertensives, and glaucoma patients. *Graefes Arch Clin Exp Ophthalmol,* 240**,** 658-665.
HORNBY, S. 2013. *Primary care ophthalmology* [Online]. Royal College of Ophthalmologists. Available: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013_PROF_234_Primary-Care-Ophthalmology-Care-June-2013_Final.pdf [Accessed 1st December 2016].
HUANG, D., SWANSON, E. A., LIN, C. P., SCHUMAN, J. S., STINSON, W. G., CHANG, W., HEE, M. R., FLOTTE, T., GREGORY, K., PULIAFITO, C. A. & ET AL. 1991. Optical coherence tomography. *Science,* 254**,** 1178-1781.
HUANG, J. Y., PEKMEZCI, M., MESIWALA, N., KAO, A. & LIN, S. 2011. Diagnostic power of optic disc morphology, peripapillary retinal nerve fiber layer thickness, and macular inner retinal layer thickness in glaucoma diagnosis with fourier-domain optical coherence tomography. *J Glaucoma,* 20**,** 87-94.
IWASE, A., TOMIDOKORO, A., ARAIE, M., SHIRATO, S., SHIMIZU, H. & KITAZAWA, Y. 2007. Performance of frequency-doubling technology perimetry in a population-based prevalence survey of glaucoma. *Ophthalmology,* 114**,** 27-32.
JAESCHKE, R., GUYATT, G. H., SACKETT, D. L., GUYATT, G., BASS, E., BRILL-EDWARDS, P., BROWMAN, G., COOK, D., FARKOUH, M. & GERSTEIN, H. 1994. Users' guides to the medical literature: III. How to use an article about a diagnostic test B. What are the results and will they help me in caring for my patients? *JAMA,* 271**,** 703-707.
JAGER, R. D., MIELER, W. F. & MILLER, J. W. 2008. Age-related macular degeneration. *N Engl J Med,* 358**,** 2606-2617.
JAMOUS, K. F., KALLONIATIS, M., HAYEN, A., MITCHELL, P., STAPLETON, F. J. & ZANGERL, B. 2014. Application of clinical techniques relevant for glaucoma assessment by optometrists: concordance with guidelines. *Ophthalmic Physiol Opt,* 34**,** 580-591.
JAMPEL, H. D., SINGH, K., LIN, S. C., CHEN, T. C., FRANCIS, B. A., HODAPP, E., SAMPLES, J. R., SMITH, S. D. & COLLINS, N. 2011. Assessment of visual function in glaucoma. A report by the American Academy of Ophthalmology. *Ophthalmology,* 118**,** 986-1002.

JAVITT, J. C. & AIELLO, L. 1996. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med,* 124**,** 164-169.

JEONG, S. Y., PARK, S. J., CHIN, H. S., KIM, S. H. & KIM, N. R. 2016. Spectral-domain optical coherence tomography features in open-angle glaucoma with diabetes mellitus and inadequate glycemic control OCT features in diabetic glaucomatous eyes. *Invest Ophthalmol Vis Sci,* 57**,** 3024-3031.

JINDAL, A., CTORI, I., FIDALGO, B., DABASIA, P., BALASKAS, K. & LAWRENSON, J. G. 2019. Impact of optical coherence tomography on diagnostic decision-making by UK community optometrists: a clinical vignette study. *Ophthalmic Physiol Opt,* 39**,** 205-215.

JINDAL, A., CTORI, I., VIRGILI, G., LUCENTEFORTE, E. & LAWRENSON, J. 2018. Non-contact methods for the detection of people at risk of primary angle closure glaucoma. *Cochrane Database Syst Rev*. DOI: 10.1002/14651858.CD012947.

JINDAL, A., MYINT, J., EDGAR, D. F., NOLAN, W. P. & LAWRENSON, J. G. 2015. Agreement among optometrists and ophthalmologists in estimating limbal anterior chamber depth using the van Herick method. *Ophthalmic Physiol Opt,* 35**,** 179-185.

JOHN, D. & PARIKH, R. 2018. Cost-effectiveness of community screening for glaucoma in rural India: a decision analytical model. *Public Health,* 155**,** 142-151.

JOHNSON, C. A. 1994. Selective versus nonselective losses in glaucoma. *J Glaucoma,* 3 Suppl 1**,** S32-44.

JOHNSON, C. A., CIOFFI, G. A. & VAN BUSKIRK, E. M. Evaluation of two screening tests for frequency doubling technology perimetry. Perimetry update, 1999. The Hague, Netherlands. Kugler Publications, 103-109.

JOHNSON, C. A., THAPA, S., KONG, Y. X. G. & ROBIN, A. L. 2017. Performance of an iPad application to detect moderate and advanced visual field Loss in Nepal. *Am J Ophthalmol,* 182**,** 147-154.

JOHNSON, M. W. 2005. Perifoveal vitreous detachment and its macular complications. *Trans Am Ophthalmol Soc,* 103**,** 537.

JOHNSON, T. V., RAMULU, P. Y., QUIGLEY, H. A. & SINGMAN, E. L. 2018. Low sensitivity of the van Herick method for detecting gonioscopic angle closure independent of observer expertise. *Am J Ophthalmol,* 195**,** 63-71.

JONES, P. R., SMITH, N. D., BI, W. & CRABB, D. P. 2019. Portable perimetry using eye-tracking on a tablet computer-a feasibility assessment. *Trans Vis Sci Tech,* 8**,** 17-17.

JONES, S. & EDWARDS, R. T. 2010. Diabetic retinopathy screening: a systematic review of the economic evidence. *Diabet Med,* 27**,** 249-256.

KANG, J. J., ALLEMANN, N., CRUZ JDE, L. & CORTINA, M. S. 2013. Serial analysis of anterior chamber depth and angle status using anterior segment optical coherence tomography after Boston keratoprosthesis. *Cornea,* 32**,** 1369-1374.

KANSKI, J. J. 2003. Clinical ophthalmology: a systematic approach. 5th edition ed. 202-203. Elsevier Health Sciences.

KAPETANAKIS, V. V., CHAN, M. P., FOSTER, P. J., COOK, D. G., OWEN, C. G. & RUDNICKA, A. R. 2016. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br J Ophthalmol,* 100**,** 86-93.

KASHANI, A. H., CHEN, C.-L., GAHM, J. K., ZHENG, F., RICHTER, G. M., ROSENFELD, P. J., SHI, Y. & WANG, R. K. 2017. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. *Prog Retin Eye Res,* 60**,** 66-100.

KASHIWAGI, K., KASHIWAGI, F., HIEJIMA, Y. & TSUKAHARA, S. 2006. Finding cases of angle-closure glaucoma in clinic setting using a newly developed instrument. *Eye,* 20**,** 319-324.

KASHIWAGI, K., KASHIWAGI, F., TODA, Y., OSADA, K., TSUMURA, T. & TSUKAHARA, S. 2004. A newly developed peripheral anterior chamber depth analysis system: principle, accuracy, and reproducibility. *Br J Ophthalmol,* 88**,** 1030-1035.

KATZ, J., TIELSCH, J. M., QUIGLEY, H. A., JAVITT, J., WITT, K. & SOMMER, A. 1993. Automated suprathreshold screening for glaucoma: The Baltimore Eye Survey. *Invest Ophthalmol Vis Sci,* 34**,** 3271-3277.

KAWASAKI, R., WANG, J. J., MITCHELL, P., AUNG, T., SAW, S.-M. & WONG, T. Y. 2008. Racial difference in the prevalence of epiretinal membrane between Caucasians and Asians. *Br J Ophthalmol,* 92**,** 1320-1324.

KEENAN, J., SHAHID, H., BOURNE, R. R., WHITE, A. J. & MARTIN, K. R. 2015. Cambridge community optometry glaucoma scheme. *Clin Exp Ophthalmol,* 43**,** 221-227.

KELLY, D. H. 1966. Frequency doubling in visual responses. *J Opt Soc Am,* 56**,** 1628-1633.

KELLY, S. P., WALLWORK, I., HAIDER, D. & QURESHI, K. 2011. Teleophthalmology with optical coherence tomography imaging in community optometry. Evaluation of a quality improvement for macular patients. *Clin Ophthalmol,* 5**,** 1673-1678.

KELTNER, J. L., JOHNSON, C. A., ANDERSON, D. R., LEVINE, R. A., FAN, J. J., CELLO, K. E., QUIGLEY, H. A., BUDENZ, D. L., PARRISH, R. K., KASS, M. A., GORDON, M. O., HYPERTENSION, O. & TREATMENT STUDY, G. 2006. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology,* 113**,** 1603-1612.

KELTNER, J. L., JOHNSON, C. A., CELLO, K. E., EDWARDS, M. A., BANDERMANN, S. E., KASS, M. A. & GORDON, M. O. 2003. Classification of visual field abnormalities in the ocular hypertension treatment study. *Arch Ophthalmol,* 121**,** 643-650.

KERRIGAN-BAUMRIND, L. A., QUIGLEY, H. A., PEASE, M. E., KERRIGAN, D. F. & MITCHELL, R. S. 2000. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. *Invest Ophthalmol Vis Sci,* 41**,** 741-748.

KERSEY, T., CLEMENT, C. I., BLOOM, P. & CORDEIRO, M. F. 2013. New trends in glaucoma risk, diagnosis & management. *Indian J Med Res,* 137**,** 659-668.

KHOR, W. B., SAKATA, L. M., FRIEDMAN, D. S., NARAYANASWAMY, A., LAVANYA, R., PERERA, S. A. & AUNG, T. 2010. Evaluation of scanning protocols for imaging the anterior chamber angle with anterior segment-optical coherence tomography. *J Glaucoma,* 19**,** 365-368.

KIELY, P. M., CAPPUCCIO, S. & MCINTYRE, E. 2017. Optometry Australia scope of practice survey 2015. *Clin Exp Optom,* 100**,** 260-269.

KIM, M., PARK, K. H., KIM, T.-W. & KIM, D. M. 2011. Changes in anterior chamber configuration after cataract surgery as measured by anterior segment optical coherence tomography. *Korean J Ophthalmol,* 25**,** 77-83.

KIM, N. R., HONG, S., KIM, J. H., RHO, S. S., SEONG, G. J. & KIM, C. Y. 2013. Comparison of macular ganglion cell complex thickness by Fourier-domain OCT in normal tension glaucoma and primary open-angle glaucoma. *J Glaucoma,* 22**,** 133-139.

KIM, T. W., ZANGWILL, L. M., BOWD, C., SAMPLE, P. A., SHAH, N. & WEINREB, R. N. 2007. Retinal nerve fiber layer damage as assessed by optical coherence tomography in eyes with a visual field defect detected by frequency doubling technology perimetry but not by standard automated perimetry. *Ophthalmology,* 114**,** 1053-1057.

KIM, Y. K., YOO, B. W., KIM, H. C., AUNG, T. & PARK, K. H. 2014. Relative lens vault in subjects with angle closure. *BMC Ophthalmol,* 14**,** 93.

KLEIN, B. E., KLEIN, R., SPONSEL, W. E., FRANKE, T., CANTOR, L. B., MARTONE, J. & MENAGE, M. J. 1992. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology,* 99**,** 1499-1504.

KO, Y. C., LIU, C. J., HSU, W. M., CHENG, C. Y., KUANG, T. M. & CHOU, P. 2015. Determinants and characteristics of angle-closure disease in an elderly Chinese population. *Ophthalmic Epidemiol,* 22**,** 109-115.

KONDO, Y., YAMAMOTO, T., SATO, Y., MATSUBARA, M. & KITAZAWA, Y. 1998. A frequency-doubling perimetric study in normal-tension glaucoma with hemifield defect. *J Glaucoma,* 7**,** 261-265.

KOPPLIN, L. J. & MANSBERGER, S. L. 2015. Predictive value of screening tests for visually significant eye disease. *Am J Ophthalmol,* 160**,** 538-546 e3.

KOSTANYAN, T., WOLLSTEIN, G. & SCHUMAN, J. S. 2015. New developments in optical coherence tomography. *Curr Opin Ophthalmol,* 26**,** 110-115.

KRUMHOLZ, D. M., JAANUS, S. D. & URQUIDI, R. L. 2001. Prescribing patterns of optometrists newly licensed in therapeutic drug use in New York state. *Optometry,* 72**,** 292-298.

KURITA, N., MAYAMA, C., TOMIDOKORO, A., AIHARA, M. & ARAIE, M. 2009. Potential of the pentacam in screening for primary angle closure and primary angle closure suspect. *J Glaucoma,* 18**,** 506-512.

LACHENMAYR, B. J. & DRANCE, S. M. 1992. The selective effects of elevated intraocular pressure on temporal resolution. *Ger J Ophthalmol,* 1**,** 26-31.

LACHENMAYR, B. J. & GLEISSNER, M. 1992. Flicker perimetry resists retinal image degradation. *Invest Ophthalmol Vis Sci,* 33**,** 3539-3542.

LAVANYA, R., FOSTER, P. J., SAKATA, L. M., FRIEDMAN, D. S., KASHIWAGI, K., WONG, T.-Y., AUNG, H. T., ALFRED, T., GAO, H., EE, A. G., SEAH, S. K. & AUNG, T. 2008. Screening of narrow angles in the Singapore population: Evaluation of new non-contact screening methods. *Ophthalmology,* 115**,** 1720-1727.

LAWRENSON, J. 2013. Glaucoma: the challenge of early case detection. *Ophthalmic Physiol Opt,* 33**,** 3-6.

LAWRENSON, J. G., GRAHAM-ROWE, E., LORENCATTO, F., BURR, J., BUNCE, C., FRANCIS, J. J., ALUKO, P., RICE, S., VALE, L., PETO, T., PRESSEAU, J., IVERS, N. & GRIMSHAW, J. M. 2018. Interventions to increase attendance for diabetic retinopathy screening. *Cochrane Database Syst Rev*. DOI: 10.1002/14651858.CD012054.pub2.

LEAL, J., LUENGO-FERNANDEZ, R., STRATTON, I. M., DALE, A., IVANOVA, K. & SCANLON, P. H. 2019. Cost-effectiveness of digital surveillance clinics with optical coherence tomography versus hospital eye service follow-up for patients with screen-positive maculopathy. *Eye,* 33**,** 640-647.

LEE, C. E., KIM, Y. K., JEOUNG, J. W., KIM, S. H., KIM, C. Y., KANG, S. W. & PARK, K. H. 2016. Topographic correlation between optic nerve head characteristics and retinal nerve fibre layer defect in primary open-angle glaucoma patients: Korea National Health and Nutrition Examination Survey. *Acta Ophthalmol,* 94**,** e98-e104.

LEE, P. P., WALT, J. G., DOYLE, J. J., KOTAK, S. V., EVANS, S. J., BUDENZ, D. L., CHEN, P. P., COLEMAN, A. L., FELDMAN, R. M., JAMPEL, H. D., KATZ, L. J., MILLS, R. P., MYERS, J. S., NOECKER, R. J., PILTZ-SEYMOUR, J. R., RITCH, R. R., SCHACKNOW, P. N., SERLE, J. B. & TRICK, G. L. 2006. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol,* 124**,** 12-19.

LEEPRECHANON, N., GIANGIACOMO, A., FONTANA, H., HOFFMAN, D. & CAPRIOLI, J. 2007. Frequency-doubling perimetry: comparison with standard automated perimetry to detect glaucoma. *Am J Ophthalmol,* 143**,** 263-271.

LEITGEB, R., HITZENBERGER, C. K. & FERCHER, A. F. 2003. Performance of fourier domain vs. time domain optical coherence tomography. *Opt Express,* 11**,** 889-894.
LEITGEB, R. A., WERKMEISTER, R. M., BLATTER, C. & SCHMETTERER, L. 2014. Doppler optical Coherence tomography. *Prog Retin Eye Res,* 41**,** 26-43.
LESKE, M. C., CONNELL, A. M., SCHACHAT, A. P. & HYMAN, L. 1994. The Barbados Eye Study. Prevalence of open angle glaucoma. *Arch Ophthalmol,* 112**,** 821-829.
LESKE, M. C., WU, S. Y., HENNIS, A., HONKANEN, R., NEMESURE, B. & GROUP, B. E. S. 2008. Risk factors for incident open-angle glaucoma: The Barbados Eye Studies. *Ophthalmology,* 115**,** 85-93.
LIANG, Y. B., FRIEDMAN, D. S., ZHOU, Q., YANG, X. H., SUN, L. P., GUO, L. X., CHANG, D. S., LIAN, L. Y., WANG, N. L., HANDAN EYE STUDY, G. & HANDAN EYE STUDY, G. 2011. Prevalence and characteristics of primary angle-closure diseases in a rural adult Chinese population: The Handan Eye Study. *Invest Ophthalmol Vis Sci,* 52**,** 8672-8679.
LIN, S. & HUANG, J.-Y. 2012. Clinical application of anterior segment optical coherence tomography for angle-closure related disease. *Taiwan J Ophthalmol,* 2**,** 77-80.
LIU, S., YU, M., WEINREB, R. N., LAI, G., LAM, D. S. & LEUNG, C. K. 2014. Frequency-doubling technology perimetry for detection of the development of visual field defects in glaucoma suspect eyes: a prospective study. *JAMA Ophthalmol,* 132**,** 77-83.
LORENZ, K., WOLFRAM, C., BREITSCHEIDEL, L., SHLAEN, M., VERBOVEN, Y. & PFEIFFER, N. 2013. Direct cost and predictive factors for treatment in patients with ocular hypertension or early, moderate and advanced primary open-angle glaucoma: The CoGIS Study in Germany. *Graefes Arch Clin Exp Ophthalmol,* 251**,** 2019-2028.
LOWE, R. F. 1970. Aetiology of the anatomical basis for primary angle-closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. *Br J Ophthalmol,* 54**,** 161-169.
LUCAS, M. 2006. *Gonioscopy* [Online]. Wikipedia. Available: https://commons.wikimedia.org/wiki/File:Gonio.png [Accessed 29th April 2019].
LY, A., NIVISON-SMITH, L., ZANGERL, B., ASSAAD, N. & KALLONIATIS, M. 2017. Self-reported optometric practise patterns in age-related macular degeneration: optometric practise patterns in AMD. *Clin Exp Optom,* 100**,** 718-728.
LY, A., NIVISON-SMITH, L., ZANGERL, B., ASSAAD, N. & KALLONIATIS, M. 2018. Advanced imaging for the diagnosis of age-related macular degeneration: a case vignettes study: imaging age-related macular degeneration *Clin Exp Optom,* 101**,** 243-254.
LY, A., NIVISON-SMITH, L., HENNESSY, M. P. & KALLONIATIS, M. 2016. Collaborative care of non-urgent macular disease: a study of inter-optometric referrals. *Ophthalmic Physiol Opt,* 36**,** 632-642.
MACASKILL, P., GATSONIS, C., DEEKS, J., HARBORD, R. & TAKWOINGI, Y. 2010. *Cochrane handbook for systematic reviews of diagnostic test accuracy* [Online]. The Cochrane Collaboration. London. Available: https://methods.cochrane.org/sdt/handbook-dta-reviews [Accessed 9th July 2019].
MALLETT, S., HALLIGAN, S., THOMPSON, M., COLLINS, G. S. & ALTMAN, D. G. 2012. Interpreting diagnostic accuracy studies for patient care. *BMJ,* 345**,** e3999.
MATSUMOTO, C., TAKADA, S., OKUYAMA, S., ARIMURA, E., HASHIMOTO, S. & SHIMOMURA, Y. 2006. Automated flicker perimetry in glaucoma using Octopus 311: a comparative study with the Humphrey Matrix. *Acta Ophthalmol Scand,* 84**,** 210-215.
MCCARTY, D. J., MUKESH, B. N., CHIKANI, V., WANG, J. J., MITCHELL, P., TAYLOR, H. R. & MCCARTY, C. A. 2005. Prevalence and associations of epiretinal membranes in the visual impairment project. *Am J Ophthalmol,* 140**,** 288-294.

MCKENDRICK, A. M. 2005. Recent developments in perimetry: test stimuli and procedures. *Clin Exp Optom,* 88**,** 73-80.

MEDEIROS, F. A., NG, D., ZANGWILL, L. M., SAMPLE, P. A., BOWD, C. & WEINREB, R. N. 2007. The effects of study design and spectrum bias on the evaluation of diagnostic accuracy of confocal scanning laser ophthalmoscopy in glaucoma. *Invest Ophthalmol Vis Sci,* 48**,** 214-222.

MEDEIROS, F. A., SAMPLE, P. A. & WEINREB, R. N. 2004. Frequency doubling technology perimetry abnormalities as predictors of glaucomatous visual field loss. *Am J Ophthalmol,* 137**,** 863-871.

MELESE, E. K., CHAN, J. D., BLIEDEN, L. S., CHUANG, A. Z., BAKER, L. A., BELL, N. P. & FELDMAN, R. M. 2016. Determination and validation of thresholds of anterior chamber parameters by dedicated anterior segment optical coherence tomography. *Am J Ophthalmol,* 169**,** 208-217.

MEUER, S. M., MYERS, C. E., BUITENDIJK, G. H. S., ROCHTCHINA, E., CHOUDHURY, F., DE JONG, P. T. V. M., MCKEAN-COWDIN, R., IYENGAR, S. K., GAO, X., LEE, K. E., VINGERLING, J. R., MITCHELL, P., KLAVER, C. C. W., WANG, J. J. & KLEIN, B. E. K. 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. *Ophthalmic Epidemiol,* 21**,** 14-23.

MICHELESSI, M., LUCENTEFORTE, E., ODDONE, F., BRAZZELLI, M., PARRAVANO, M., FRANCHI, S., NG, S. M. & VIRGILI, G. 2015. Optic nerve head and fibre layer imaging for diagnosing glaucoma. *Cochrane Database Syst Rev*. DOI: 10.1002/14651858.CD008803.pub2.

MIGLIOR, S., EUROPEAN GLAUCOMA PREVENTION, S. & EUROPEAN GLAUCOMA PREVENTION STUDY, G. 2007. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. *Ophthalmology,* 114**,** 3-9.

MILLETT, C. & DODHIA, H. 2006. Diabetes retinopathy screening: audit of equity in participation and selected outcomes in South East London. *J Med Screen,* 13**,** 152-155.

MINASSIAN, D. & REIDY, A. 2009. *Future sight loss UK 2: An epidemiological and economic model for sight loss in the decade 2010-2020* [Online]. London, UK: RNIB. Available: https://www.rnib.org.uk/knowledge-and-research-hub/research-reports/general-research/future-sight-loss-uk-2 [Accessed 1st August 2019].

MITCHELL, P., LIEW, G., GOPINATH, B. & WONG, T. Y. 2018. Age-related macular degeneration. *Lancet,* 392**,** 1147-1159.

MITCHELL, P., SMITH, W., ATTEBO, K. & HEALEY, P. R. 1996. Prevalence of open-angle glaucoma in Australia: The Blue Mountains Eye Study. *Ophthalmology,* 103**,** 1661-1669.

MITCHELL, P., SMITH, W., CHEY, T., WANG, J. J. & CHANG, A. 1997. Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study, Australia. *Ophthalmology,* 104**,** 1033-1040.

MIYAZAKI, M., NAKAMURA, H., KUBO, M., KIYOHARA, Y., IIDA, M., ISHIBASHI, T. & NOSE, Y. 2003. Prevalence and risk factors for epiretinal membranes in a Japanese population: The Hisayama Study. *Graefes Arch Clin Exp Ophthalmol,* 241**,** 642-646.

MORGAN, J. E. 1994. Selective cell death in glaucoma: does it really occur? *Br J Ophthalmol,* 78**,** 875-880.

MORGAN, J. E. 2002. Retinal ganglion cell shrinkage in glaucoma. *J Glaucoma,* 11**,** 365-370.

MOWATT, G., BURR, J. M., COOK, J. A., SIDDIQUI, M. A., RAMSAY, C., FRASER, C., AZUARA-BLANCO, A. & DEEKS, J. J. 2008. Screening tests for detecting open-angle glaucoma: systematic review and meta-analysis. *Invest Ophthalmol Vis Sci,* 49**,** 5373-5385.

MREJEN, S. & SPAIDE, R. F. 2013. Optical coherence tomography: imaging of the choroid and beyond. *Surv Ophthalmol,* 58**,** 387-429.

MUEN, W. J. & HEWICK, S. A. 2011. Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study. *JRSM Short Rep,* 2**,** 64.

MÜSKENS, R. P., HEEG, G. P. & JANSONIUS, N. M. 2004. An evaluation of algorithms designed to classify the results from frequency doubling perimetry. *Ophthalmic Physiol Opt,* 24**,** 498-503.

MYINT, J. 2013. *A study of case finding for chronic open angle glaucoma by UK community optometrists.* Doctoral thesis, City, University of London.

MYINT, J., EDGAR, D. F., KOTECHA, A., MURDOCH, I. E. & LAWRENSON, J. G. 2011. A national survey of diagnostic tests reported by UK community optometrists for the detection of chronic open angle glaucoma. *Ophthalmic Physiol Opt,* 31**,** 353-359.

MYINT, J., EDGAR, D. F., MURDOCH, I. E. & LAWRENSON, J. 2014. The impact of postgraduate training on UK optometrists' clinical decision-making in glaucoma. *Ophthalmic Physiol Opt,* 34**,** 376-384.

NA, J. H., SUNG, K. R., BAEK, S., KIM, Y. J., DURBIN, M. K., LEE, H. J., KIM, H. K. & SOHN, Y. H. 2012. Detection of glaucoma progression by assessment of segmented macular thickness data obtained using spectral domain optical coherence tomography segmented macular layer thinning in glaucoma. *Invest Ophthalmol Vis Sci,* 53**,** 3817-3826.

NARAYANASWAMY, A., SAKATA, L. M., HE, M.-G., FRIEDMAN, D. S., CHAN, Y.-H., LAVANYA, R., BASKARAN, M., FOSTER, P. J. & AUNG, T. 2010. Diagnostic performance of anterior chamber angle measurements for detecting eyes with narrow angles: an anterior segment OCT study. *Arch Ophthalmol,* 128**,** 1321-1327.

NEEDLE, J. J., PETCHEY, R. & LAWRENSON, J. G. 2008. A survey of the scope of therapeutic practice by UK optometrists and their attitudes to an extended prescribing role. *Ophthalmic Physiol Opt,* 28**,** 193-203.

NEELY, D. C., BRAY, K. J., HUISINGH, C. E., CLARK, M. E., MCGWIN, G. & OWSLEY, C. 2017. Prevalence of undiagnosed age-related macular degeneration in primary eye care. *JAMA Ophthalmol,* 135**,** 570-575.

NEWMAN-CASEY, P. A., VERKADE, A. J., OREN, G. & ROBIN, A. L. 2014. Gaps in glaucoma care: a systematic review of monoscopic disc photos to screen for glaucoma. *Expert Rev Ophthalmol,* 9**,** 467-474.

NGUYEN, A. T., LIU, T. & LIU, J. 2016. Applications of Scheimpflug imaging in glaucoma management: current and potential applications. *J Ophthalmol,* 2016**,** 3062381.

NICE. 2017. *Glaucoma: diagnosis and management* [Online]. National Institute of Health and Clinical Excellence. Available: https://www.nice.org.uk/guidance/ng81/evidence/full-guideline-pdf-4660991389 [Accessed 8th July 2019].

NICE. 2018. *Age-related macular degeneration* [Online]. National Institute of Health and Clinical Excellence. Available: https://www.nice.org.uk/guidance/ng82 [Accessed 1st August 2019].

NICHOLAS, S. P. & WERNER, E. B. 1980. Location of early glaucomatous visual field defects. *Can J Ophthalmol,* 15**,** 131-133.

NOLAN, W., BAASANHU, J., UNDRAA, A., URANCHIMEG, D., GANZORIG, S. & JOHNSON, G. 2003. Screening for primary angle closure in Mongolia: a randomised controlled trial to determine whether screening and prophylactic treatment will reduce the incidence of primary angle closure glaucoma in an east Asian population. *Br J Ophthalmol,* 87**,** 271-274.

NOLAN, W. P., AUNG, T., MACHIN, D., KHAW, P. T., JOHNSON, G. J., SEAH, S. K. & FOSTER, P. J. 2006. Detection of narrow angles and established angle closure in Chinese residents of Singapore: potential screening tests. *Am J Ophthalmol,* 141**,** 896-901.

NOLAN, W. P., SEE, J. L., CHEW, P. T., FRIEDMAN, D. S., SMITH, S. D., RADHAKRISHNAN, S., ZHENG, C., FOSTER, P. J. & AUNG, T. 2007. Detection of primary angle closure using anterior segment optical coherence tomography in Asian eyes. *Ophthalmology,* 114**,** 33-39.

NONGPIUR, M. E. M. D., HE, M. M. D. P., AMERASINGHE, N. M., FRIEDMAN, D. S. M. D. P., TAY, W.-T. B., BASKARAN, M. M. S., SMITH, S. D. M. D. M. P. H., WONG, T. Y. M. D. P. & AUNG, T. F. P. 2011. Lens vault, thickness, and position in Chinese subjects with angle closure. *Ophthalmology,* 118**,** 474-479.

NOURI-MAHDAVI, K., NASSIRI, N., GIANGIACOMO, A. & CAPRIOLI, J. 2011. Detection of visual field progression in glaucoma with standard achromatic perimetry: a review and practical implications. *Graefes Arch Clin Exp Ophthalmol,* 249**,** 1593-1616.

NSC. 2016. *Screening in the UK: making effective recommendations* [Online]. UK National Screening Committee. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/538524/Screening_in_the_UK___making_effective_recommendations_2015_to_2016_180716_final.pdf [Accessed 8th July 2019].

O'CONNOR, P. M., HARPER, C. A., BRUNTON, C. L., CLEWS, S. J., HAYMES, S. A. & KEEFFE, J. E. 2012. Shared care for chronic eye diseases: perspectives of ophthalmologists, optometrists and patients. *Med J Aust,* 196**,** 646-650.

ODDONE, F., LUCENTEFORTE, E., MICHELESSI, M., RIZZO, S., DONATI, S., PARRAVANO, M. & VIRGILI, G. 2016. Macular versus retinal nerve fiber layer parameters for diagnosing manifest glaucoma: a systematic review of diagnostic accuracy studies. *Ophthalmology,* 123**,** 939-949.

OKABE, I., TOMITA, G., SUGIYAMA, K. & TANIGUCHI, T. 1991. An epidemiological study on the prevalence of the narrow chamber angle in Japanese. *Nippon Ganka Gakkai Zasshi,* 95**,** 279-287.

OLSON, J., SHARP, P., GOATMAN, K., PRESCOTT, G., SCOTLAND, G., FLEMING, A., PHILIP, S., SANTIAGO, C., BOROOAH, S., BROADBENT, D., CHONG, V., DODSON, P., HARDING, S., LEESE, G., STYLES, C., SWA, K. & WHARTON, H. 2013. Improving the economic value of photographic screening for optical coherence tomography-detectable macular oedema: a prospective, multicentre, UK study. *Health Technol Assess,* 17**,** 1-142.

ONG, E. L., ZHENG, Y., AUNG, T., TAN, L., CHENG, C. Y., WONG, T. Y. & HOW, A. 2014. Performance of the Moorfields motion displacement test for identifying eyes with glaucoma. *Ophthalmology,* 121**,** 88-92.

ONTARIO, H. Q. 2009. Optical coherence tomography for age-related macular degeneration and diabetic macular edema: an evidence-based analysis. *Ont Health Technol Assess Ser,* 9**,** 1.

OPTOVUE 2010. Model iVue100; User's manual (version 1.4).

OSBORNE, N. N., WOOD, J. P., CHIDLOW, G., BAE, J. H., MELENA, J. & NASH, M. S. 1999. Ganglion cell death in glaucoma: what do we really know? *Br J Ophthalmol,* 83**,** 980-986.

OUYANG, Y., HEUSSEN, F. M., KEANE, P. A., SADDA, S. R. & WALSH, A. C. 2013. The retinal disease screening study: retrospective comparison of nonmydriatic fundus photography and three-dimensional optical coherence tomography for detection of retinal irregularities. *Invest Ophthalmol Vis Sci,* 54**,** 5694-5700.

OWEN, C., FLETCHER, A., DONOGHUE, M. & RUDNICKA, A. 2003. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? *Br J Ophthalmol,* 87**,** 312-317.

OWEN, C. G., JARRAR, Z., WORMALD, R., COOK, D. G., FLETCHER, A. E. & RUDNICKA, A. R. 2012. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol,* 96**,** 752-756.

PARK, S. B., SUNG, K. R., KANG, S. Y., JO, J. W., LEE, K. S. & KOOK, M. S. 2011. Assessment of narrow angles by gonioscopy, Van Herick method and anterior segment optical coherence tomography. *Jpn J Ophthalmol,* 55**,** 343-350.

PARKINS, D. J., BENWELL, M. J., EDGAR, D. F. & EVANS, B. J. W. 2018. The relationship between unwarranted variation in optometric referrals and time since qualification. *Ophthalmic Physiol Opt,* 38**,** 550-561.

PATEL, A., WOLLSTEIN, G., ISHIKAWA, H. & SCHUMAN, J. S. 2007. Comparison of visual field defects using matrix perimetry and standard achromatic perimetry. *Ophthalmology,* 114**,** 480-487.

PAZ, S. H., VARMA, R., KLEIN, R., WU, J., AZEN, S. P., LOS ANGELES LATINO EYE STUDY, G. & LOS ANGELES LATINO EYE STUDY, G. 2006. Noncompliance with vision care guidelines in Latinos with type 2 diabetes mellitus - The Los Angeles Latino Eye Study. *Ophthalmology,* 113**,** 1372-1377.

PEABODY, J. W., LUCK, J., GLASSMAN, P., DRESSELHAUS, T. R. & LEE, M. 2000. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. *JAMA,* 283**,** 1715-1722.

PEABODY, J. W., LUCK, J., GLASSMAN, P., JAIN, S., HANSEN, J., SPELL, M. & LEE, M. 2004. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med,* 141**,** 771-780.

PEZZULLO, L., STREATFEILD, J., SIMKISS, P. & SHICKLE, D. 2018. The economic impact of sight loss and blindness in the UK adult population. *BMC Health Serv Res,* 18**,** 63.

PORPORATO, N., BASKARAN, M. & AUNG, T. 2018. Role of anterior segment optical coherence tomography in angle-closure disease: a review: Anterior segment optical coherence tomography. *Clin Exp Ophthalmol,* 46**,** 147-157.

POTSAID, B., BAUMANN, B., HUANG, D., BARRY, S., CABLE, A. E., SCHUMAN, J. S., DUKER, J. S. & FUJIMOTO, J. G. 2010. Ultra high speed 1050nm swept source/fourier domain OCT retinal and anterior segment imaging at 100,000 to 400,000 axial scans per second. *Opt Express,* 18**,** 20029-20048.

PROKOSCH, V. & ETER, N. 2014. Correlation between early retinal nerve fiber layer loss and visual field loss determined by three different perimetric strategies: white-on-white, frequency-doubling, or flicker-defined form perimetry. *Graefes Arch Clin Exp Ophthalmol,* 252**,** 1599-1606.

PRUM, B. E., ROSENBERG, L. F., GEDDE, S. J., MANSBERGER, S. L., STEIN, J. D., MOROI, S. E., HERNDON, L. W., LIM, M. C. & WILLIAMS, R. D. 2016. Primary open-angle glaucoma preferred practice pattern guidelines. *Ophthalmology,* 123**,** 41-111.

QUEK, D. T., NONGPIUR, M. E., PERERA, S. A. & AUNG, T. 2011. Angle imaging: advances and challenges. *Indian J Ophthalmol,* 59 Suppl**,** S69-75.

QUIGLEY, H. A. 1996. Number of people with glaucoma worldwide. *Br J Ophthalmol,* 80**,** 389-393.

QUIGLEY, H. A. 1998. Identification of glaucoma-related visual field abnormality with the screening protocol of frequency doubling technology. *Am J Ophthalmol,* 125**,** 819-829.

QUIGLEY, H. A. & BROMAN, A. T. 2006. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol,* 90**,** 262-267.

QUIGLEY, H. A., DUNKELBERGER, G. R. & GREEN, W. R. 1989. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol,* 107**,** 453-464.

QUIGLEY, H. A., KATZ, J., DERICK, R. J., GILBERT, D. & SOMMER, A. 1992. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. *Ophthalmology,* 99**,** 19-28.

QUIGLEY, H. A., MILLER, N. R. & GEORGE, T. 1980. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. *Arch Ophthalmol,* 98**,** 1564-1571.

QUIGLEY, H. A., SANCHEZ, R. M., DUNKELBERGER, G. R., L'HERNAULT, N. L. & BAGINSKI, T. A. 1987. Chronic glaucoma selectively damages large optic nerve fibers. *Invest Ophthalmol Vis Sci,* 28**,** 913-920.

QUIGLEY, H. A. & VITALE, S. 1997. Models of open-angle glaucoma prevalence and incidence in the United States. *Invest Ophthalmol Vis Sci,* 38**,** 83-91.

RADHAKRISHNAN, S., GOLDSMITH, J., HUANG, D., WESTPHAL, V., DUEKER, D. K., ROLLINS, A. M., IZATT, J. A. & SMITH, S. D. 2005. Comparison of optical coherence tomography and ultrasound biomicroscopy for detection of narrow anterior chamber angles. *Arch Ophthalmol,* 123**,** 1053-1059.

RAMAKRISHNAN, R., NIRMALAN, P. K., KRISHNADAS, R., THULASIRAJ, R. D., TIESLCH, J. M., KATZ, J., FRIEDMAN, D. S. & ROBIN, A. L. 2003. Glaucoma in a rural population of southern India - The Aravind Comprehensive Eye Survey. *Ophthalmology,* 110**,** 1484-1490.

RAMULU, P. Y., WEST, S. K., MUNOZ, B., JAMPEL, H. D. & FRIEDMAN, D. S. 2009a. Driving cessation and driving limitation in glaucoma: The Salisbury Eye Evaluation Project. *Ophthalmology,* 116**,** 1846-1853.

RAMULU, P. Y., WEST, S. K., MUNOZ, B., JAMPEL, H. D. & FRIEDMAN, D. S. 2009b. Glaucoma and reading speed: The Salisbury Eye Evaluation Project. *Arch Ophthalmol,* 127**,** 82-87.

RAO, H. L., KUMBAR, T., ADDEPALLI, U. K., BHARTI, N., SENTHIL, S., CHOUDHARI, N. S. & GARUDADRI, C. S. 2012. Effect of spectrum bias on the diagnostic accuracy of spectral-domain optical coherence tomography in glaucoma. *Invest Ophthalmol Vis Sci,* 53**,** 1058-1065.

RATNARAJAN, G., KEAN, J., FRENCH, K., PARKER, M. & BOURNE, R. 2015. The false negative rate and the role for virtual review in a nationally evaluated glaucoma referral refinement scheme. *Ophthalmic Physiol Opt,* 35**,** 577-581.

RCGP. 2016. *Impact of the eye health clinical priority* [Online]. Royal College of General Practioners. Available: http://www.rcgp.org.uk/eyehealth [Accessed 15th March 2018].

RCO. 2017a. *The way forward. Age-related macular degeneration and diabetic retinopathy* [Online]. Royal College of Ophthalmologists. Available: https://www.rcophth.ac.uk/wp-content/uploads/2015/10/RCOphth-The-Way-Forward-AMD-300117.pdf [Accessed 31st July 2019].

RCO. 2017b. *The way forward. Glaucoma* [Online]. Royal College of Ophthalmologists. Available: https://www.rcophth.ac.uk/wp-content/uploads/2015/10/RCOphth-The-Way-Forward-Glaucoma-300117.pdf [Accessed 31st July 2019].

REDMOND, T., O'LEARY, N., HUTCHISON, D. M., NICOLELA, M. T., ARTES, P. H. & CHAUHAN, B. C. 2013. Visual field progression with frequency-doubling matrix perimetry and

standard automated perimetry in patients with glaucoma and in healthy controls. *JAMA Ophthalmol,* 131**,** 1565-1572.

REES, A., ZEKITE, A., BUNCE, C. & PATEL, P. J. 2014. How many people in England and Wales are registered partially sighted or blind because of age-related macular degeneration? *Eye,* 28**,** 832-837.

RESNIKOFF, S., PASCOLINI, D., ETYA'ALE, D., KOCUR, I., PARARAJASEGARAM, R., POKHAREL, G. P. & MARIOTTI, S. P. 2004. Global data on visual impairment in the year 2002. *Bull World Health Organ,* 82**,** 844-851.

REVMAN 2015. Review Manager 5.3.5. Copenhagen: The Nordic Cochrane Centre: Cochrane Collaboration.

REZNICEK, L., LAMPARTER, J., VOGEL, M., KAMPIK, A. & HIRNEIß, C. 2015. Flicker defined form perimetry in glaucoma suspects with normal achromatic visual fields. *Cure Eye Res,* 40**,** 683-689.

RNIB. 2009. *Future Sight Loss UK 1: The economic impact of partial sight and blindness in the UK adult population* [Online]. RNIB. Available: https://www.rnib.org.uk/sites/default/files/FSUK_Report_0.doc [Accessed 8th July 2019].

ROBIN, T. A., MÜLLER, A., RAIT, J., KEEFFE, J. E., TAYLOR, H. R. & MUKESH, B. N. 2005. Performance of community-based glaucoma screening using frequency doubling technology and heidelberg retinal tomography. *Ophthalmic Epidemiol,* 12**,** 167-178.

ROGERS, S., MCINTOSH, R. L., CHEUNG, N., LIM, L., WANG, J. J., MITCHELL, P., KOWALSKI, J. W., NGUYEN, H. & WONG, T. Y. 2010. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology,* 117**,** 313-319.e1.

ROSSI, G., SCUDELLER, L., DELFINO, A., RAIMONDI, M., PEZZOTTA, S., MACCARONE, M., ANTONIAZZI, E., PASINETTI, G. M. & BIANCHI, P. E. 2012. Pentacam sensitivity and specificity in detecting occludable angles. *Eur J Ophthalmol,* 22**,** 701-708.

ROTCHFORD, A. P. & JOHNSON, G. J. 2002. Glaucoma in Zulus: A population-based cross-sectional survey in a rural district in South Africa. *Arch Ophthalmol,* 120**,** 471-478.

ROTCHFORD, A. P., KIRWAN, J. F., MULLER, M. A., JOHNSON, G. J. & ROUX, P. 2003. Temba Glaucoma Study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology,* 110**,** 376-382.

ROTH, M. 2007. Optometry in Australia is a therapeutic profession. *Clin Exp Optom,* 90**,** 67-69.

RUDNICKA, A. R., JARRAR, Z., WORMALD, R., COOK, D. G., FLETCHER, A. & OWEN, C. G. 2012. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology,* 119**,** 571-580.

RUTHERFORD, T. 2012. *Population ageing: statistics* [Online]. House of Commons Library. Available: https://researchbriefings.files.parliament.uk/documents/SN03228/SN03228.pdf [Accessed 1st August 2019].

SAADINE, J. B., FONG, D. S. & YAO, J. 2008. Factors associated with follow-up eye examinations among persons with diabetes. *Retina,* 28**,** 195-200.

SACKETT, D., HAYNES, R., GUYATT, G. & TUGWELL, P. 1991. Clinical epidemiology:a basic science for clinical medicine. 2nd ed. Boston Little, Brown, 59-138.

SAKATA, L. M., LAVANYA, R., FRIEDMAN, D. S., AUNG, H. T., GAO, H., KUMAR, R. S., FOSTER, P. J. & AUNG, T. 2008. Comparison of gonioscopy and anterior segment ocular coherence tomography in detecting angle closure in different quadrants of the anterior chamber angle. *Ophthalmology,* 115**,** 769-774.

SAKATA, L. M., WONG, T. T., WONG, H. T., KUMAR, R. S., HTOON, H. M., AUNG, H. T., HE, M. & AUNG, T. 2010. Comparison of Visante and slit-lamp anterior segment optical coherence tomography in imaging the anterior chamber angle. *Eye,* 24**,** 578-587.

SAMPLE, P. A., BOSWORTH, C. F., BLUMENTHAL, E. Z., GIRKIN, C. & WEINREB, R. N. 2000. Visual function-specific perimetry for indirect comparison of different ganglion cell populations in glaucoma. *Invest Ophthalmol Vis Sci,* 41**,** 1783-1790.

SANTINA, L. & OU, Y. 2017. Who's lost first? Susceptibility of retinal ganglion cell types in experimental glaucoma. *Exp Eye Res,* 158**,** 43-50.

SARTORI, M. T., BARBAR, S., DONÀ, A., PIERMAROCCHI, S., PILOTTO, E., SAGGIORATO, G. & PRANDONI, P. 2013. Risk factors, antithrombotic treatment and outcome in retinal vein occlusion: an age-related prospective cohort study. *Eur J Haematol,* 90**,** 426-433.

SAUNDERS, L. J., RUSSELL, R. A., KIRWAN, J. F., MCNAUGHT, A. I. & CRABB, D. P. 2014. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. *Invest Ophthalmol Vis Sci,* 55**,** 102-109.

SAWAGUCHI, S., SAKAI, H., IWASE, A., YAMAMOTO, T., ABE, H., TOMITA, G., TOMIDOKORO, A. & ARAIE, M. 2012. Prevalence of primary angle closure and primary angle-closure glaucoma in a southwestern rural population of Japan: the Kumejima Study. *Ophthalmology,* 119**,** 1134-1142.

SCHEIE, H. G. 1957. Width and pigmentation of the angle of the anterior chamber: a system of grading by gonioscopy. *AMA Arch Ophthalmol,* 58**,** 510-512.

SCHULZ, A. M., GRAHAM, E. C., YOU, Y., KLISTORNER, A. & GRAHAM, S. L. 2018. Performance of iPad-based threshold perimetry in glaucoma and controls: performance of iPad-based perimetry. *Clin Exp Ophthalmol,* 46**,** 346-355.

SCHULZER, M., ALWARD, W. L., FELDMAN, F., CASHWELL, L. F., WILENSKY, J., GEIJSSEN, H. C., GREEVE, E., QUIGLEY, H., SKUTA, G., LICHTER, P. R., BLONDEAU, P., ANDERSON, D. R., GRAJEWSKI, A., HODAPP, E., BALAZSI, G., AMYOT, M., LEVENE, R. Z., MINCKLER, D., HEUER, D., DRANCE, S. M., MIKELBERG, F., DOUGLAS, G., JOHNSTONE, M., TROPE, G., HOSKINS, H. D., POLLACK, I. P., MILLS, R., KASNER, O. P., SCHWARTZ, A., LIEBMANN, L., RITCH, R., COHEN, J., TUULONEN, A., AIRAKSINEN, P. J. & NEN, A. 1998. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol,* 126**,** 487-497.

SEKHAR, G. C., NADUVILATH, T. J., LAKKAI, M., JAYAKUMAR, A. J., PANDI, G. T., MANDAL, A. K. & HONAVAR, S. G. 2000. Sensitivity of Swedish interactive threshold algorithm compared with standard full threshold algorithm in Humphrey visual field testing. *Ophthalmology,* 107**,** 1303-1308.

SEONG, M., SUNG, K. R., CHOI, E. H., KANG, S. Y., CHO, J. W., UM, T. W., KIM, Y. J., PARK, S. B., HONG, H. E. & KOOK, M. S. 2010. Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. *Invest Ophthalmol Vis Sci,* 51**,** 1446-52.

SEVIM, M. S., BUTTANRI, B., ACAR, B. T., KAHYA, A., VURAL, E. T. & ACAR, S. 2013. Ability of fourier-domain optical coherence tomography to detect retinal ganglion cell complex atrophy in glaucoma patients. *J Glaucoma,* 22**,** 542-549.

SHAFFER, R. N. 1960. Primary glaucomas. Gonioscopy, ophthalmoscopy and perimetry. *Trans Am Acad Ophthalmol Otolaryngol,* 64**,** 112-127.

SHAH, N. N., BOWD, C., MEDEIROS, F. A., WEINREB, R. N., SAMPLE, P. A., HOFFMANN, E. M. & ZANGWILL, L. M. 2006. Combining structural and functional testing for detection of glaucoma. *Ophthalmology,* 113**,** 1593-1602.

SHAH, R., EDGAR, D. F., SPRY, P. G., HARPER, R. A., KOTECHA, A., RUGHANI, S. & EVANS, B. J. W. 2009. Glaucoma detection: the content of optometric eye examinations for a presbyopic patient of African racial descent. *Br J Ophthalmol,* 93**,** 492-496.

SHEEHY, A. M., COURSIN, D. B. & GABBAY, R. A. 2009. Back to Wilson and Jungner: 10 good reasons to screen for type 2 diabetes mellitus. *Mayo Clin Proc,* 84**,** 38-42.

SHINOJ, V., HONG, X. J. J., MURUKESHAN, V., BASKARAN, M. & TIN, A. 2016. Progress in anterior chamber angle imaging for glaucoma risk prediction. A review on clinical equipment, practice and research. *Med Eng Phys,* 38**,** 1383-1391.

SIGN. 2015. *144: Glaucoma referral and safe discharge: A National Clinical Guideline* [Online]. Scottish Intercollegiate Guidelines Network. Available: https://www.sign.ac.uk/assets/sign144.pdf [Accessed 8th July 2019].

ŠIMUNDIĆ, A.-M. 2009. Measures of Diagnostic Accuracy: Basic Definitions. *EJIFCC,* 19**,** 203-211.

SMITH, S. D., SINGH, K., LIN, S. C., CHEN, P. P., CHEN, T. C., FRANCIS, B. A. & JAMPEL, H. D. 2013. Evaluation of the anterior chamber angle in glaucoma: a report by the American Academy of Ophthalmology. *Ophthalmology,* 120**,** 1985-1997.

SOMMER, A., KATZ, J., QUIGLEY, H. A. & ET AL. 1991. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol,* 109**,** 77-83.

SPAETH, G. L. 1971. The normal development of the human anterior chamber angle: a new system of descriptive grading. *Trans Ophthalmol Soc U K,* 91**,** 709-739.

SPRY, P. G., HUSSIN, H. M. & SPARROW, J. M. 2005. Clinical evaluation of frequency doubling technology perimetry using the Humphrey Matrix 24-2 threshold strategy. *Br J Ophthalmol,* 89**,** 1031-1035.

STEIN, J. D., KIM, D. D., PECK, W. W., GIANNETTI, S. M. & HUTTON, D. W. 2012. Cost-effectiveness of medications compared with laser trabeculoplasty in patients with newly diagnosed open-angle glaucoma. *Arch Ophthalmol,* 130**,** 497-505.

STOUTENBEEK, R., HEEG, G. P. & JANSONIUS, N. M. 2004. Frequency doubling perimetry screening mode compared to the full-threshold mode. *Ophthalmic Physiol Opt,* 24**,** 493-497.

SUN, X., DAI, Y., CHEN, Y., CHEN, J., YU, D.-Y., CRINGLE, S. J., KONG, X., WANG, X. & JIANG, C. 2017. Primary angle closure glaucoma: What we know and what we don't know. *Prog Retin Eye Res,* 57**,** 26-45.

SWANSON, W. H., DUL, M. W. & FISCHER, S. E. 2005. Quantifying effects of retinal illuminance on frequency doubling perimetry. *Invest Ophthalmol Vis Sci,* 46**,** 235-240.

SWETS, J. & PICKETT, R. 1982. Evaluation of diagnostic systems: methods from signal detection theory. Medical Physics, 266-267.

TAKAHASHI, N., HIRASAWA, K., HOSHINA, M., KASAHARA, M., MATSUMURA, K. & SHOJI, N. 2017. Diagnostic ability and repeatability of a new supra-threshold glaucoma screening program in standard automated perimetry. *Trans Vis Sci Tech,* 6**,** 1-9.

TAKWOINGI, Y., LEEFLANG, M. M. & DEEKS, J. J. 2013. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. *Ann Intern Med,* 158**,** 544-554.

TALKS, J., KOSHY, Z. & CHATZINIKOLAS, K. 2007. Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration. *Br J Ophthalmol,* 91**,** 600-601.

TAN, G. S., HE, M., ZHAO, W., SAKATA, L. M., LI, J., NONGPIUR, M. E., LAVANYA, R., FRIEDMAN, D. S. & AUNG, T. 2012. Determinants of lens vault and association with narrow angles in patients from Singapore. *Am J Ophthalmol,* 154**,** 39-46.

TAN, O., CHOPRA, V., LU, A. T.-H., SCHUMAN, J. S., ISHIKAWA, H., WOLLSTEIN, G., VARMA, R. & HUANG, D. 2009. Detection of macular ganglion cell loss in glaucoma by fourier-domain optical coherence tomography. *Ophthalmology,* 116**,** 2305-2314.e2.

TANG, J., LIANG, Y., O'NEILL, C., KEE, F., JIANG, J. & CONGDON, N. 2019. Cost-effectiveness and cost-utility of population-based glaucoma screening in China: a decision-analytic Markov model. *Lancet Glob Health,* 7**,** e968-e978.

TANNA, A. P., ABRAHAM, C., LAI, J. & SHEN, J. 2004. Impact of cataract on the results of frequency-doubling technology perimetry. *Ophthalmology,* 111**,** 1504-1507.

TAY, E. L., YONG, V. K., LIM, B. A., SIA, S., WONG, E. P. & YIP, L. W. 2015. Agreement of angle closure assessments between gonioscopy, anterior segment optical coherence tomography and spectral domain optical coherence tomography. *Int J Ophthalmol,* 8**,** 342-346.

THAM, Y.-C., LI, X., WONG, T. Y., QUIGLEY, H. A., AUNG, T. & CHENG, C.-Y. 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology,* 121**,** 2081-2090.

THAPA, S. S., PAUDYAL, I., KHANAL, S., TWYANA, S. N., PAUDYAL, G., GURUNG, R., RUIT, S. & RENS, V. G. H. M. B. 2012. A population-based survey of the prevalence and types of glaucoma in Nepal: The Bhaktapur Glaucoma Study. *Ophthalmology,* 119**,** 759-764.

THEODOSSIADES, J., MYINT, J., MURDOCH, I. E., EDGAR, D. F. & LAWRENSON, J. G. 2012. Does optometrists' self-reported practice in glaucoma detection predict actual practice as determined by standardised patients? Can self-reporting predict clinical practice in glaucoma detection? *Ophthalmic Physiol Opt,* 32**,** 234-241.

THOMAS, R., GEORGE, R., PARIKH, R., MULIYIL, J. & JACOB, A. 2003. Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. *Br J Ophthalmol,* 87**,** 450-454.

THOMAS, R., GEORGE, T., BRAGANZA, A. & MULIYIL, J. 1996. The flashlight test and van Herick's test are poor predictors for occludable angles. *Aust N Z J Ophthalmol,* 24**,** 251-256.

TIELSCH, J. M., KATZ, J., SINGH, K., QUIGLEY, H. A., GOTTSCH, J. D., JAVITT, J. & SOMMER, A. 1991a. A population-based evaluation of glaucoma screening: The Baltimore Eye Survey. *Am J Epidemiol,* 134**,** 1102-1110.

TIELSCH, J. M., SOMMER, A., KATZ, J., ROYALL, R. M., QUIGLEY, H. A. & JAVITT, J. 1991b. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA,* 266**,** 369-374.

TING, D. S. W., PASQUALE, L. R., PENG, L., CAMPBELL, J. P., LEE, A. Y., RAMAN, R., TAN, G. S. W., SCHMETTERER, L., KEANE, P. A. & WONG, T. Y. 2019. Artificial intelligence and deep learning in ophthalmology. *Br J Ophthalmol,* 103**,** 167.

TRAVERSO, C. E., WALT, J. G., KELLY, S. P., HOMMER, A. H., BRON, A. M., DENIS, P., NORDMANN, J. P., RENARD, J. P., BAYER, A., GREHN, F., PFEIFFER, N., CEDRONE, C., GANDOLFI, S., ORZALESI, N., NUCCI, C., ROSSETTI, L. & AZUARA-BLANCO, A. 2005. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol,* 89**,** 1245-1249.

TRIBLE, J. R., SCHULTZ, R. O., ROBINSON, J. C. & ROTHE, T. L. 2000. Accuracy of glaucoma detection with frequency-doubling perimetry. *Am J Ophthalmol,* 129**,** 740-745.

TUN, T. A., BASKARAN, M., TAN, S. S., PERERA, S. A., AUNG, T. & HUSAIN, R. 2017. Evaluation of the anterior segment angle-to-angle scan of Cirrus high-definition optical coherence tomography and comparison with gonioscopy and with the Visante OCT. *Invest Ophthalmol Vis Sci,* 58**,** 59-64.

TYLER, C. W. 1981. Specific deficits of flicker sensitivity in glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci,* 20**,** 204-212.
TYLER, C. W. 1991. Analysis of normal flicker sensitivity and its variability in the visuogram test. *Invest Ophthalmol Vis Sci,* 32**,** 2552-2560.
TYLER, C. W., HARDAGE, L. & STAMPER, R. L. 1994. The temporal visuogram in ocular hypertension and its progression to glaucoma. *J Glaucoma,* 3 Suppl 1**,** S65-S72.
UN. 2015. *World population ageing report* [Online]. United Nations. Available: http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf [Accessed 30th August 2018].
UN. 2019. *World population prospects 2019: highlights* [Online]. United Nations. Available: https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf [Accessed 1st August 2019].
VAAHTORANTA-LEHTONEN, H., TUULONEN, A., ARONEN, P., SINTONEN, H., SUORANTA, L., KOVANEN, N., LINNA, M., LAARA, E. & MALMIVAARA, A. 2007. Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta Ophthalmol Scand,* 85**,** 508-518.
VAN HERICK, W., SHAFFER, R. N. & SCHWARTZ, A. 1969. Estimation of width of angle of anterior chamber. Incidence and significance of the narrow angle. *Am J Ophthalmol,* 68**,** 626-629.
VARGAS, E. & DRANCE, S. M. 1973. Anterior chamber depth in angle-closure glaucoma: clinical methods of depth determination in people with and without the disease. *Arch Ophthalmol,* 90**,** 438-439.
VARMA, R., YING-LAI, M., FRANCIS, B. A., NGUYEN, B. B. T., DENEEN, J., WILSON, M. R. & AZEN, S. P. 2004. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: The Los Angeles Latino Eye Study. *Ophthalmology,* 111**,** 1439-1448.
VELOSKI, J., TAI, S., EVANS, A. S. & NASH, D. B. 2005. Clinical vignette-based surveys: a tool for assessing physician practice variation. *Am J Med Qual,* 20**,** 151-157.
VIJAYA, L., GEORGE, R., BASKARAN, M., ARVIND, H., RAJU, P., RAMESH, S. V., KUMARAMANICKAVEL, G. & MCCARTY, C. 2008. Prevalence of primary open angle glaucoma in an urban south Indian population and comparison with a rural population: The Chennai Glaucoma Study. *Ophthalmology,* 115**,** 648-654.
VINGRYS, A. J., HEALEY, J. K., LIEW, S., SAHARINEN, V., TRAN, M., WU, W. & KONG, G. Y. 2016. Validation of a tablet as a tangent perimeter. *Trans Vis Sci Tech,* 5**,** 1-13.
VIRGILI, G., MENCHINI, F., CASAZZA, G., HOGG, R., DAS, R. R., WANG, X. & MICHELESSI, M. 2015. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev*. 10.1002/14651858.CD008081.pub3.
VIRGILI, G., MICHELESSI, M., COOK, J., BOACHIE, C., BURR, J., BANISTER, K., GARWAY-HEATH, D. F., BOURNE, R. R. A., ASOREY GARCIA, A., RAMSAY, C. R. & AZUARA-BLANCO, A. 2018. Diagnostic accuracy of optical coherence tomography for diagnosing glaucoma: secondary analyses of the GATE study. *Br J Ophthalmol,* 102**,** 604.
VIRGILI, G., MICHELESSI, M., MIELE, A., ODDONE, F., CRESCIOLI, G., FAMELI, V. & LUCENTEFORTE, E. 2017. STARD 2015 was reproducible in a large set of studies on glaucoma. *PLoS One,* 12**,** e0186209.
WANG, B., NEVINS, J. E., NADLER, Z., WOLLSTEIN, G., ISHIKAWA, H., BILONICK, R. A., KAGEMANN, L., SIGAL, I. A., GRULKOWSKI, I. & LIU, J. J. 2014. Reproducibility of in-vivo OCT measured three-dimensional human lamina cribrosa microarchitecture. *PLoS One,* 9**,** e95526.

WANG, L., HUANG, W., HUANG, S., ZHANG, J., GUO, X., FRIEDMAN, D. S., FOSTER, P. J. & HE, M. 2019. Ten-year incidence of primary angle closure in elderly Chinese: the Liwan Eye Study. *Br J Ophthalmol,* 103**,** 355-360.

WANG, Y. F. & HENSON, D. B. 2013. Diagnostic performance of visual field test using subsets of the 24-2 test pattern for early glaucomatous field loss. *Invest Ophthalmol Vis Sci,* 54**,** 756-761.

WCO. 2018. World Council of Optometry. Available: https://worldcouncilofoptometry.info/ [Accessed 14th August 2018].

WEBER, J. & KLIMASCHKA, T. 1995. Test time and efficiency of the dynamic strategy in glaucoma perimetry. *Ger J Ophthalmol,* 4**,** 25-31.

WEIH, L. M., NANJAN, M., MCCARTY, C. A. & TAYLOR, H. R. 2001. Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. *Ophthalmology,* 108**,** 1966-1972.

WEINREB, R. N. Angle closure and angle closure glaucoma. 3rd Global AIGS Consensus Meeting on angle closure glaucoma, 2006. The Hague, Netherlands. Kugler Publications.

WEINREB, R. N., AUNG, T. & MEDEIROS, F. A. 2014. The pathophysiology and treatment of glaucoma: a review. *JAMA,* 311**,** 1901-1911.

WESTCOTT, M. C., FITZKE, F. W., CRABB, D. P. & HITCHINGS, R. A. 1999. Characteristics of frequency-of-seeing curves for a motion stimulus in glaucoma eyes, glaucoma suspect eyes, and normal eyes. *Vision Res,* 39**,** 631-639.

WHITE, A. J., SUN, H., SWANSON, W. H. & LEE, B. B. 2002a. An examination of physiological mechanisms underlying the frequency-doubling illusion. *Invest Ophthalmol Vis Sci,* 43**,** 3590-3599.

WHITE, A. J. R., SUN, H., SWANSON, W. H. & LEE, B. B. 2002b. An examination of physiological mechanisms underlying the frequency-doubling illusion. *Invest Ophthalmol Vis Sci,* 43**,** 3590-3599.

WHITING, P., RUTJES, A. W., REITSMA, J. B., BOSSUYT, P. M. & KLEIJNEN, J. 2003. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol,* 3**,** 1.

WHITING, P. F., RUTJES, A. S., WESTWOOD, M. E. & ET AL. 2011. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med,* 155**,** 529-536.

WILENSKY, J. T., KAUFMAN, P. L., FROHLICHSTEIN, D., GIESER, D. K., KASS, M. A., RITCH, R. & ANDERSON, R. 1993. Follow-up of angle-closure glaucoma suspects. *Am J Ophthalmol,* 115**,** 338-346.

WILSON, J. M. G. & JUNGNER, G. 1968. Principles and practice of screening for disease. *Public Health Papers,* 34.

WIRBELAUER, C., KARANDISH, A., HÄBERLE, H. & PHAM, D. T. 2005. Non-contact goniometry with optical coherence tomography. *Arch Ophthalmol,* 123**,** 179-185.

WOJCIECHOWSKI, R., CONGDON, N., ANNINGER, W. & BROMAN, A. T. 2003. Age, gender, biometry, refractive error and the anterior chamber angle among Alaskan Eskimos. *Ophthalmology,* 110**,** 365-375.

WOLFS, R. C., KLAVER, C. C., RAMRATTAN, R. S., VAN DUIJN, C. M., HOFMAN, A. & DE JONG, P. T. 1998. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. *Arch Ophthalmol,* 116**,** 1640-1645.

WONG, H.-T., CHUA, J. L. L., SAKATA, L. M., WONG, M. H. Y., AUNG, H. T. & AUNG, T. 2009a. Comparison of slitlamp optical coherence tomography and scanning peripheral anterior chamber depth analyzer to evaluate angle closure in Asian eyes. *Arch Ophthalmol,* 127**,** 599-603.

WONG, H.-T., LIM, M. C., SAKATA, L. M., AUNG, H. T., AMERASINGHE, N., FRIEDMAN, D. S. & AUNG, T. 2009b. High-definition optical coherence tomography imaging of the iridocorneal angle of the eye. *Arch Ophthalmol,* 127**,** 256-260.

WONG, S. H. & PLANT, G. T. 2015. How to interpret visual fields. *Pract Neurol,* 15**,** 374-381.

WONG, W. L., SU, X., LI, X., CHEUNG, C. M. G., KLEIN, R., CHENG, C.-Y. & WONG, T. Y. 2014. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health,* 2**,** e106-e116.

WORMALD, R. P. L., BASAURI, E., WRIGHT, L. A. & EVANS, J. R. 1994. The African Caribbean Eye Survey: risk factors for glaucoma in a sample of African Caribbean people living in London. *Eye,* 8**,** 315-320.

WU, R.-Y., NONGPIUR, M. E., HE, M.-G., SAKATA, L. M., FRIEDMAN, D. S., CHAN, Y.-H., LAVANYA, R., WONG, T.-Y. & AUNG, T. 2011. Association of narrow angles with anterior chamber area and volume measured with anterior-segment optical coherence tomography. *Arch Ophthalmol,* 129**,** 569-574.

WU, Z. & MEDEIROS, F. A. 2017. Recent developments in visual field testing for glaucoma. *Curr Opin Ophthalmol,* 29**,** 141-146.

WYSZECKI, G. & STILES, W. S. 1982. Color science: concepts and methods, quantitative data and formulae. 2nd ed. Chichester;New York;. Wiley, 83-116.

YAMAMOTO, T., IWASE, A., ARAIE, M., SUZUKI, Y., ABE, H., SHIRATO, S., KUWAYAMA, Y., MISHIMA, H. K., SHIMIZU, H. & TOMITA, G. 2005. The Tajimi Study Report 2: prevalence of primary angle closure and secondary glaucoma in a Japanese population. *Ophthalmology,* 112**,** 1661-1669.

YE, T., YU, Q., PENG, S., WANG, N. & CHEN, X. 1998. Six year follow-up of suspects of primary angle-closure glaucoma. *Zhonghua Yan Ke Za Zhi,* 34**,** 167-169.

YIP, J. L., FOSTER, P. J., GILBERT, C. E., URANCHIMEG, D., BASSANHUU, J., LEE, P. S., KHAW, P. T., JOHNSON, G. J. & NOLAN, W. 2008. Incidence of occludable angles in a high-risk Mongolian population. *Br J Ophthalmol,* 92**,** 30-33.

YOSHIOKA, N., WONG, E., KALLONIATIS, M., YAPP, M., HENNESSY, M. P., AGAR, A., HEALEY, P. R., HAYEN, A. & ZANGERL, B. 2015. Influence of education and diagnostic modes on glaucoma assessment by optometrists. *Ophthalmic Physiol Opt,* 35**,** 682-698.

YOSHIYAMA, K. K. & JOHNSON, C. A. 1997. Which method of flicker perimetry is most effective for detection of glaucomatous visual field loss? *Invest Ophthalmol Vis Sci,* 38**,** 2270-2277.

YU, Q., XU, J., ZHU, S. & LIU, Q. 1995. A role of oblique flashlight test in screening for primary angle closure glaucoma. *Yan Ke Xue Bao,* 11**,** 177-179.

ZEPPIERI, M., DEMIREL, S., KENT, F. K. & JOHNSON, C. A. 2008. Perceived spatial frequency of sinusoidal gratings. *Optom Vis Sci,* 85**,** 318-329.

ZHANG, Y., LI, S. Z., LI, L., THOMAS, R. & WANG, N. L. 2014. The Handan Eye Study: comparison of screening methods for primary angle closure suspects in a rural Chinese population. *Ophthalmic Epidemiol,* 21**,** 268-275.

ZHOU, X.-H., MCCLISH, D. K. & OBUCHOWSKI, N. A. 2009. Statistical methods in diagnostic medicine. New York. John Wiley & Sons.

Appendices

Non-contact methods for the detection of people at risk of primary angle closure glaucoma.

Appendix 1a. Characteristics of study extraction table.

Study identification	First author, year of publication.
Clinical features and settings	Previous testing and clinical setting including country where the study was conducted. Presentation at recruitment, prior treatment that would affect the ACD (i.e. peripheral iridotomy, iridoplasty, etc.)
Participants	Sample size, age, sex, ethnicity and country
Study design	Whether the sample was selected as a single group (consecutive series) or as separate groups with and without the target condition (case-control). Whether participants were consecutively enrolled in the study and were identified retrospectively or prospectively. Training involved for index tests, both eyes included in the study
Target condition	A narrow angle as a referable condition, which includes PACS, PAC and PACG
Reference standard	The reference standard test used: gonioscopy for diagnosing a narrow angle; this is acceptable if this is the only target condition in large-scale screening or primary-care settings. Gonioscopy combined with tonometry, visual fields investigation and optic disc assessment for distinguishing the relative subgroup of participants with a narrow angle PACS/PAC/PACG
Index tests	- Flashlight technique: grade recorded - LACD using the van Herick technique: van Herick grade, or percentage, or both - SPAC: numerical or categorical grade, or both - Scheimpflug photography: ACA, ACV and ACD - AS-OCT: model of OCT device, manufacturer and any technical characteristics (e.g. software analyses). TISA, ARA, AOD 500 microns and 750 microns for each parameter
Follow up	Numbers of participants lost to follow-up or who had uninterpretable test results
Notes	Source of funding, anything else of relevance

Appendix 1b. Characteristics of the included studies.

Alonso 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Cohort study. Methods of patient sampling and recruitment were not reported. Both eyes were used for analysis
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 112 eyes (38 eyes narrow angle and 74 open angle) Age: mean (SD), 51±12, range 21-72 years. Sex: 32 (53.3%) female Setting: secondary care Country: Brazil Ethnicity: not reported Exclusions: not reported
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	**Scheimpflug photography**: HR Pentacam, Oculus Inc, Germany, nasal and temporal angles were studied in the horizontal meridian, cut off values were derived from the study data for ACA, ACD and ACV.

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Could the conduct or interpretation of the index test have introduced bias?	

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Static gonioscopy was performed, a narrow-angle was classified using a Shaffer grade of 1 (the number of quadrants/degrees occluded were not reported).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	It was not reported if there were any uninterpretable results or any excluded patients. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided.

Andrews 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Case-control study. Cases were primary angle-closure suspects (PACS), controls were participants with open-angles who did not meet the PACS criteria. Data from the right eye was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 442 eyes (370 narrow angle and 72 open angle) Age: mean (SD), 59.8±4.9 years (narrow angle 59.7±5.2; controls 60.2±3.2). Sex: 345 (78.0%) female Setting: secondary care Country: China Ethnicity: Chinese Exclusions: prior intraocular surgery, excessively high risk of acute angle-closure attack	
Are there concerns that the included patients and setting do not match the review question?		High concern

Index Test

Index tests	**LACD:** graded as a percentage fraction of adjacent corneal thickness at the temporal limbus: >100%, 75%, 40%, 25%, 15%, 5%, and 0%, cut off value used ≤ 25%. **SPAC**: measurements ranged from 1 to 12, with 1 representing the shallowest anterior chamber depth, cut off value used ≤ 6.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	PACS: participants with pigmented trabecular meshwork not visible in at least two quadrants (≥ 180 degrees) on gonioscopy (without PAS, glaucomatous optic neuropathy or elevated IOP).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable test results reported and no patients were excluded. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: Dr Kashiwagi has a Japanese patent on the SPAC (Japanese patent No. 3878164).

Ashaye 2003

Patient Selection

A. Risk of Bias	
Patient Sampling	Cohort study. Cases were newly diagnosed patients with primary glaucoma, with both cases and open angle controls were recruited from a secondary care setting from 1996 to 1998. Data from one eye was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 490 eyes (40 narrow angle and 450 open angle) Age: mean (SD) 56.8±11.1 years, (glaucoma 57.8±11.5; non-glaucoma 55.8±10.7) Sex: 214 (43.7%) female Setting: secondary care Country: Nigeria Ethnicity: African Exclusions: not reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD**: If the peripheral anterior chamber depth was equal to or greater than the corneal thickness it was recorded as grade 4; half corneal thickness was grade 3; quarter thickness of cornea was noted as grade 2, less than a quarter as grade 1 and no distance between the iris and cornea as grade 0. A cut off value of ≤ 25% was used at the temporal limbus.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as an angle in which the pigmented trabecular meshwork was not seen in ≥ 270 degrees of the angle circumference by static gonioscopy.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable or exclusions reported. The index test and reference standard conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	From the 450 participants with an open angle, 214 patients had POAG and 236 had no glaucoma. Conflict of interest: no conflict of interest statement provided.

Baskaran 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	Cohort study, adult subjects were recruited from glaucoma and general ophthalmology clinics. Consecutive subjects were enrolled with either narrow or open angles. Data from one eye was selected randomly for analysis if both eyes were eligible.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 120 eyes (53 narrow angle and 67 open angle) Age: mean (SD) 62.1±11.3, range 30-90 years Sex: 68 (56.7%) female Setting: secondary care Country: Singapore Ethnicity: 87 (72.5%) Chinese, 25 (20.8%) Indian, 8 Malay (6.7%) Exclusions: Subjects with corneal disorders and uveitis were excluded in the control group. Patients with a history of laser or intraocular surgery were excluded in the narrow angle group.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD**: determined at the temporal limbus and graded as % categories: 0%, 5%, 15%, 25% , 40%, 75% and ≥ 100%. Cut off values analysed were 0%, ≤ 5%, ≤ 15%, ≤ 25% and ≤ 40%. **SPAC:** SPAC categorical grades used for risk of angle closure: S (suspect angle closure), P (potential angle closure). Thresholds used were S, P and a combination of S & P.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as the presence of a Shaffer grade of up to 1 (10 degree iridotrabecular angle) for at least 180 degrees on gonioscopy with or without PAS.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no reported uninterpretable test results or excluded patients. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Dr Kashiwagi has a Japanese patent on SPAC (Japanese patent application no: 2003-111322).

Baskaran 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Subjects above the age of 40 years were recruited from a glaucoma clinic at a Singapore hospital. One eye from each patient was chosen randomly if both eyes were suitable.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 98 eyes (39 narrow angle and 59 open angle) Age: mean (SD) 60.7±12.6 years Sex: 49 (50%) female Setting: secondary care Country: Singapore Ethnicity: 69 (70%) Chinese Exclusions: prior intraocular surgery or penetrating eye injury, corneal disorders such as corneal endothelial dystrophy, pterygium or corneal scars that may preclude satisfactory imaging or those on medications that act on the pupil.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain, Visante; Carl Zeiss Meditec, Dublin, CA, USA. Three ASOCT images of each eye were obtained in dark conditions: one image scanning the angle at the nasal and temporal positions, one scanning the superior angle and one scanning the inferior angle. The cut off value was a closed angle in two or more quadrants which was defined as contact between the iris and angle wall anterior to the scleral spur.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	The ACA was considered 'closed' in that quadrant if the posterior pigmented trabecular meshwork (TM) could not be seen in the primary position without indentation on gonioscopy (Scheie grade 3 or 4). The eye was classified as having angle closure if there were two or more quadrants (180 degrees) closed.
Is the reference standards likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	98 participants entered the study, 1 was excluded, reason not specified. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Aung has received research support, travel support and honoraria from Carl Zeiss Meditec, Dublin, CA USA, as well as an instrument loan. Patients who underwent peripheral iridotomy were not excluded

Campbell 2015

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Subjects aged ≥ 40 years with glaucoma or suspect glaucoma were recruited from two community optometry practices. One eye from each subject was selected at random if both eyes were eligible for the study.
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 80 eyes (12 narrow angle and 68 open angle) Age: mean (SD) 58.9±10.0, range 40-80 years Sex: 53 (66%) female Setting: Primary

	Country: United Kingdom Ethnicity: 70 (87.5%) Caucasian, 6 (7.5%) African, 4 (5%) Indian Exclusions: corneal disorders, recent eye infection, ocular inflammation (within the previous 6 months), previous refractive surgery, peripheral iridotomy or intra-ocular surgery.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**LACD**: original van Herick grading scheme used (grade 1-4) performed at the the nasal and temporal angle. Grade 1 was used as the cut off (<25%) at either nasal or the temporal angle. **AS-OCT:** Spectral Domain, Topcon OCT-2000 (Topcon Europe Medical B.V). Laser wavelength of 840nm using anterior segment mode via a 3 mm line scan size with the scan count at 32. If any iris contact was visible anterior to the position of the scleral spur for either the nasal or temporal image or both, this was qualitatively classified as 'occludable'.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	If posterior trabecular meshwork was not visible for >90 degrees, or in other words, if one or more quadrants was graded 0–1 on the Shaffer grading scheme.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	84 subjects were recruited and 83 subjects attended for both visits. 4 subjects were unable to tolerate gonioscopy, 80 eyes were included in the final analysis for LACD. In 4 cases, the AS-OCT images were un-gradable and 76 eyes were analysed for AS-OCT.The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Chang 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study, asymptomatic subjects aged over 50 years were identified by systematic sampling from a community polyclinic in Singapore, completing a comprehensive ophthalmic examination at the same visit between December 2005 and June 2006. Data from the right eye was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 2047 eyes (395 narrow angle and 1652 open angle) Age: mean (SD), 63.2 ± 8.0 years, (narrow angle 65.1±7.8; controls 62.7±8.0) Sex: 1077 (52.6%), female Setting: primary care Country: Singapore Ethnicity: Chinese Exclusions: patients with glaucoma, intraocular surgery or corneal disorders preventing anterior-chamber imaging.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**SPAC**: measurements ranged from 1 to 12, with 1 representing the shallowest anterior chamber depth. Cut off values used were a numerical value of 4 and ≤ 5. **AS-OCT:** Time domain, Visante, Carl Zeiss Meditec AG. Scans were centred on the pupil and taken along the horizontal (nasal-temporal) and vertical meridians (superior-inferior) to the peripheral angle. A quadrant was classified as closed when the iris was in contact with the angle wall. Cut off values; qualitative;when two or more quadrants were observed as closed, quantitative cut offs were derived from the study data using AOD750.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An eye was defined as narrow if it had a Shaffer score of 0 or 1 on non-indentation gonioscopy for at least two quadrants (180 degrees), with or without PAS.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2102 participants originally studied, 55 could not complete all the tests and were excluded from the analysis due to: alignment errors (n=12), inability to follow instructions (n=16), refused gonioscopy (n=4), other reasons (n=18), 2047 eyes were included in the final analysis. There was quantitative AS-OCT data missing from 579 of the eyes analysed (28%) and SPAC data were not available on 41 eyes (2%). The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: KK has a Japanese patent on the SPAC (Japanese patent no. 3878164). TA has received funding, travel support and honoraria from Carl Zeiss Meditec.

Congdon 1996

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross sectional study. Residents of Jin Shan Township, Taiwan, aged 40 years and above were invited for screening. Both eyes were included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 562 subjects Age: mean (SD) 59.2±11.8 years Sex: 312 (55.6%) female Setting: Primary Country: Taiwan Ethnicity: East Asian Exclusions: none reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD:** modified van Herick grading method used; Grades 3 or 4 termed 'deep', Grade 2 'narrow'; Grade 1'critically narrow'. Cut off values were <25% and >25% to ≤ 50%. **Flashlight**: oblique handlight illumination using three grades: critically narrow (nasal shadow > 1/2 the distance from limbus to pupillary axis); narrow (1/4 to 1/2); or deep (<1/4). Cut off values used were critically narrow (grade 1) and narrow (grade 2).

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Flashlight

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	The anterior chamber angle was graded by Zeiss 4-mirror dynamic gonioscopy. If no trabecular meshwork was seen in 1 or more quadrants (≥ 90 degrees), an overall grade of 'narrow' was given. A grade of 'critically narrow' was given to eyes that were 'closed' in two or more quadrants (≥ 180 degrees). The authors defined PACG as 'one or both eyes graded as narrow or critically narrow by gonioscopy who had one or more of the following: intraocular pressure (IOP) greater than 18 mmHg, a rise in IOP greater than or equal to 8 mmHg on dark-prone provocative testing, or past acute attack with an iridectomy already performed. The optic disc and visual field could be normal or abnormal.'
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	562 participants were recruited, 503 participants were included in the analysis for LACD and 352 for the flashlight test. For the flashlight, the numbers were smaller than the LACD as handlight testing of all subjects was started one month after the study had begun.The index test and reference standard were conducted on the same occasion. It was not reported how many participants had uninterpretable results or were excluded.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Unclear

Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided. The study definition of PACG does not conform to the International Society Geographical & Epidemiological Ophthalmology (ISGEO) standard since the optic disc and visual field could be normal or abnormal. Van Herick Grade 2 is a modified version of the original van Herick grade. For both van Herick and flashlight grade 1 and grade 2 was compared to a critical narrow and narrow angle respectively on gonioscopy.

Dabasia 2015

Patient Selection

A. Risk of Bias		
Patient Sampling	Case-control study. Adult subjects were recruited from glaucoma and general ophthalmology clinics. Cases comprised subjects with suspected or confirmed PAC The open angle control group had no current or previous history of ocular disease, or were diagnosed with eye conditions not affecting angle configuration. Data from the right eye was included in the analysis (left eye was used if the right eye was not eligible for inclusion).	
Was a consecutive or random sample of patients enrolled?		No
Was a case-control design avoided?		No
Did the study avoid inappropriate exclusions?		No
Could the selection of patients have introduced bias?		High risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 78 eyes (42 narrow angle and 36 open angle) Age: median 66 IQR (53-79), range 30-83 years Sex: 44 (56.4%) female Setting: secondary care Country: United Kingdom Ethnicity: 44 (56%) White, 27 (35%) South Asian Exclusions: subjects receiving systemic or topical medications known to affect the ACA configuration (e.g., miotics), anomalies of the anterior segment that affect ACA configuration.	
Are there concerns that the included patients and setting do not match the review question?		High concern

Index Test

Index tests	**LACD**: determined at the temporal limbus. Graded as a percentage fraction of adjacent corneal thickness at the temporal limbus: >100%, 75%, 40%, 25%, 15%, 5%, and 0%, cut off value used ≤ 25%. **Scheimpflug photography**: Oculus Pentacam (software version 1.19r11). ACA estimates were obtained along the nasal-temporal meridian using Scheimpflug horizontal image segment 16 (184 to 4 degrees). Cut off values were derived from the study data for ACA, ACD and ACV. **AS-OCT:** Time domain, Visante, Carl Zeiss Meditec AG (software version 2.0.1.88). An 'anterior segment single' mode using wide-field scanning optics was used to provide a cross-section of the nasal and temporal angles in a single, 16 x 6 mm image frame between the 3 and 9 o'clock positions. Optimal cut off were defined using the study data for ACA and ACD.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as the posterior trabecular meshwork not visible for ≥ 270 degrees on non-indentation gonioscopy and with the eye in the primary position
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable test results reported and no patients were excluded. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Cut off values were obtained by contacting the author for 0%, ≤ 5% and ≤ 15%. Conflict of interest: the authors declare no conflicts of interest.

Foster 2000

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study. Conducted in two phases, subjects aged 40 years and older were selected for examination in 1995 using a combination of multistage, clustered, simple random, and systematic sampling.The second phase was conducted in 1997 in which local government census data were used to select subjects aged 40 years and older evenly

	distributed between each decade age group. Both eyes were included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size:1717 subjects analysed, a gonioscopically narrow angle was found in at least one eye of 140 subjects. 35 eyes were classified as having PAC, and a further 28 as PACG. Age: mean age not reported, range 40-93 years Sex: 974 (56.7%) female Setting: primary care Country: Mongolia Ethnicity: not reported Exclusions: if it was not possible to allocate a LACD grade for either eye the subject was excluded from the analysis.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD:** determined at the temporal limbus and graded as % categories: 0%, 5%, 15%, 25%, 40%, 75% and ≥ 100%. Cuts off reported for 0%, ≤ 5%, ≤ 15%, ≤ 25% and ≤ 40%.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as an angle in which the trabecular meshwork was not seen in ≥ 270 degrees of the angle circumference by gonioscopy. PAC was diagnosed in subjects with an occludable angle and either raised IOP and/or PAS. PACG was diagnosed in cases with an occludable angle combined with glaucomatous optic neuropathy.

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	1800 subjects were originally recruited, with 1717 subjects analysed. Uninterpretable results were reported for 17 subjects for reference standard and 76 for index test. Index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Gracitelli 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Patients with glaucoma or who were glaucoma suspects were enrolled when attending an outpatient clinic. One eye was randomly selected for analysis
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 45 eyes (9 narrow angle and 36 open angle) Age: mean (SD), 47.1±16.4, range 19-85 years. Sex: 30 (67.7%) female Setting: secondary care Country: Brazil Ethnicity: not reported Exclusions: conditions precluding clear visualization of the AC (e.g., pterygium, corneal opacity), congenital anterior segment, abnormalities, eyelid alterations, ocular trauma and intraocular surgery (incisional or laser procedures).
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Flashlight**: A flashlight beam was directed parallel to the iris from the temporal side. Eyes identified as having a narrow anterior chamber were those in which a nasal iris shadow, formed between the limbus and the pupillary edge, was visualized (grade 1). Eyes identified as having a deep anterior chamber were those in which a nasal light reflex, formed between the limbus and the pupillary edge was visualized. (grade 4). Cut off value grade 1 was used for the analysis.

Flashlight

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy was performed in a dark room. Angles were graded as occludable where the posterior trabecular meshwork was not visible in 2 or more quadrants without indentation (180 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Eyes which were excluded or had uninterpretable test results were not reported.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Grewal 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Patients aged ≥ 40 years were recruited from an ophthalmology clinic. Data from the right eye was analysed if both eyes were eligible.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 265 eyes (28 narrow angle and 237 open angle) Age: mean (SD), 55.3 ± 5.1 years, (narrow angle 56.2±6.5; controls 58.3±5.7) Sex: 136 (51.3%) female Setting: secondary care Country: India Ethnicity: Indian Exclusions: history of glaucoma, intraocular surgery, laser treatment, penetrating trauma, and corneal disorders that precluded SD-ASOCT or Scheimpflug imaging.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** spectral domain, RTVue 100 (Optovue Inc., Fremont, CA, USA, software version 4.0). Anterior segment morphology was assessed with the corneal adaptor module long (CAM-L), using the angle scan protocol, which captured 1 1024 A-scans in 0.04s in the nasal and temporal quadrants. Optimal cut off values were derived from the study data at AOD500 and TISA 500. **Scheimpflug photography:** Pentacam (Oculus, software version 1.11). Optimal cut off values were derived from the study data using ACD and ACV.

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Static gonioscopy, Shaffer grading system was used and a narrow angle was defined as Shaffer grade 1 or less in all four quadrants (360 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	300 participants were recruited; 35 subjects were excluded because of an undetectable scleral spur on AS-OCT.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: the authors declare no conflict of interest

He 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	Case control study, subjects aged 50 and older were enrolled from Liwan District, Guangzhou, using cluster random sampling. Data from the right eye was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 295 eyes (186 narrow angle and 109 open angle) Age: mean (SD), 67.8±9.5 years, (narrow angle 70.0±8.7; controls 64.0±9.6) Sex: 186 (63.0%) female Setting: primary care Country: China Ethnicity: Chinese Exclusions: subjects with abnormalities precluding clear visualization of the anterior chamber (e.g., pterygium, corneal opacity, iris abnormalities) and subjects who underwent surgery that changes the configuration of the anterior segment (e.g., cataract, glaucoma, laser peripheral iridotomy).

Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**Flashlight**: flashlight beam was set parallel to the iris plane from the temporal side when the subjects looked straight ahead. Grading was in reference to the area occupied by the iris shadow on the nasal iris between the limbus and the pupil margin, as follows: shallow, iris shadow reaching the pupil margin;medium, iris shadow reaching middle of the nasal iris; deep, almost no shadow. The cut of value of 'shallow' was used (Grade 1).

Flashlight

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	All subjects identified as having "occludable" angles were defined as posterior and usually pigmented trabecular meshwork not visible in two or more quadrants (≥ 180 degrees) using static gonioscopy.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	602 subjects entered the study, excluded cases were eyes with aphakia/pseudophakia (n=44) and angle closure suspects (n=236) for the right eye, presence of pterygium and cornea abnormalities (n=22) and gonioscopy data missing (n=5). 295 eyes were included in the final analysis. There were no uninterpretable results reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Hong 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	Case-control study. One eye from each subject was randomly chosen for the analysis
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 73 eyes (41 narrow angle and 32 open angle) Age: mean (SD), 65.2±10.0 years, (narrow angle 67.5 ± 8.0; controls 62.2 ± 11.5) Sex: 50 (68.5%), female Setting: secondary care Country: South Korea Ethnicity: Korean Exclusions: history of previous ocular trauma or intraocular disease/surgery
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**AS-OCT:** SL-OCT, Heidelberg Engineering,GmbH, Germany. Angle images were captured using the horizontal linear scan protocol (from 3-o'clock to 9-o'clock direction). ACA was measured automatically by the angle at ARA500. **Scheimpflug photography:** Oculus Inc., Wetzlar, Germany.Angle images were captured using the horizontal linear scan protocol (from 3-o'clock to 9-o'clock direction). Optimal cut off values were derived from the study data for both index tests for ACA and ACD

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as an angle where the trabecular meshwork could not be seen ≥ 270 degrees of the angle circumference by static gonioscopy.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uninterpreatable results or excluded participants were not reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Unclear
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Conflict of interest: the authors report no conflict of interest

Khor 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross sectional study. Participants aged 50 years or older were recruited from a non-ophthalmic community clinic. Data from the right eye was analysed
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 1853 eyes (380 narrow angle and 1473 open angle) Age: mean (SD), 63.4±8.1, range 50-93 years Sex: 1103 (52.4%), female Setting: primary care Country: Singapore Ethnicity: 1883 (89.5%) Chinese, 44 (2.1%) Malay, 154 (7.3%) Indian and 23 (1.1%) other. Exclusions: history of intraocular surgery or penetrating trauma, previous anterior segment laser treatment, or a history of glaucoma.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time-domain, Visante, Carl Zeiss Meditec, Dublin, CA. All four quadrants were examined, a closed angle was defined by contact between the iris and angle wall anterior to the scleral spur in any quadrant.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Static gonioscopy; posterior trabecular meshwork not be seen in the primary position without indentation (Scheie grade 3 or 4) in one or more quadrants (≥ 90 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2104 participants originally studied; 251(11.9%) eyes were uninterpretable as at least one of the quadrants could not be classified due to poor image quality on the AS-OCT images. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes

Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Carl Zeiss Meditec loaned the anterior segment optical coherence tomography for the study and provided technical support. Dr Aung has received financial support and honoraria for travel to conferences from Carl Zeiss Meditec. Patient characteristics: Reported ethnicity and gender demographics was based on original 2104 subjects recruited. Data reported compared a range of closed angles observed on gonioscopy and AS-OCT. Data extracted for the review; narrow angle defined on gonioscopy at ≥ 90 degrees and an closed angle observed on AS-OCT in one quadrant or more.

Kim 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Case control study. Study participants were identified by retrospective medical review and then examined between January 2010 and August 2013 at an University Hospital in glaucoma and cataract clinics. One eye was randomly selected for analysis if both eyes were eligible.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 202 eyes, (101 narrow angle and 101 open angle) Age: mean (SD) for all participants, 64.5±6.2 years. Sex: 110 (54.4%) female Setting: secondary care Country: Korea Ethnicity: Korean Exclusions: prior intraocular surgery	
Are there concerns that the included patients and setting do not match the review question?		High concern

Index Test

Index tests	**AS-OCT:** time domain, Visante, Carl Zeiss Meditec, Dublin, CA. Mode to capture; one cross-sectional horizontal scan. Cut off values were derived from the study data at examining lens vault and ACD.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Static gonioscopy; were the pigmented posterior trabecular meshwork was not visible for 180 degrees or more in the primary position, with peripheral anterior synechiae and/or raised intraocular pressure (IOP).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 124 narrow angles and 112 age matched controls; 12 narrow angle participants and 11 controls had poor image quality (uninterpretable results), a further 11 narrow angles were excluded to match the number of controls. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: the authors declare no conflict of interest

Ko 2015

Patient Selection

A. Risk of Bias		
Patient Sampling	Prospective cross-sectional study, subjects were recruited from participants of the first Shihpai Eye Study visit in 1999, a community-based,cross-sectional survey of vision and eye diseases aged 65 years and older in Shihpai, Taipei, Taiwan. Only one eye of each subject was included in the analysis.	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 374 eyes (199 narrow angle and 175 open angle) Age: mean (SD), 77.4±3.8 years, (narrow angle 77.6±4.1; controls 77.2±3.5) Sex: 122 (32.6%) female Setting: primary care Country: Taiwan Ethnicity: Chinese Exclusions: subjects with secondary angle-closure or visual field defects caused by other causes were excluded. Subjects were also excluded if the eye was pseudophakic.	
Are there concerns that the included patients and setting do not match the review question?		Low concern

Index Test

Index tests	**LACD**: modified van Herick, Grade 0 Iridocorneal contact, Grade 1 ≤ 1/4, Grade 2 >1/4 to ≤ 1/2, Grade 3 >1/2 to ≤ 3/4, Grade 4 >3/4 but ≤ 3/4 corneal thickness and Grade 5 > corneal thickness. Cut off values of >25% to ≤ 50% were used.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as an angle in which the trabecular meshwork was not seen in ≥ 270 degrees of the angle circumference by gonioscopy. PAC was diagnosed in subjects with an occludable angle and either raised IOP and/or PAS. PACG was diagnosed in cases with an occludable angle combined with glaucomatous optic neuropathy.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	460 subjects were initially recruited, 86 excluded due to: gonioscopy not performed (n=15), exclusion criteria not met (n= 62) bilateral pseudophakia, (n= 3) pseudophakic PACG, (n= 6) Laser peripheral iridotomy. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Kurita 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study, subjects were referred and consecutively recruited for a detailed examination of the ACA with gonioscopy to confirm a diagnosis in the outpatient clinic of the University Hospital of the University of Tokyo Graduate School of Medicine between April 1, 2006 and September 31, 2006. Both eyes were included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 39 subjects (72 eyes), a gonioscopically narrow angle was found in 42 eyes in subjects with either PACS or PAC, 16 eyes of 9 patients with open angle glaucoma and 14 open angle eyes in normal eyes Age: mean (SD), 58.4±15.3, range 27-83 years Sex: not reported Setting: secondary care Country: Tokyo, Japan Ethnicity: Japanese Exclusions: pathological changes or history of diseases in the cornea, anterior chamber, iris, or ocular tissues which would affect anterior chamber angle, history of acute PAC in either eye, history of ocular surgery that would affect anterior chamber or evidence of broad PAS on gonioscopy.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Scheimpflug photography:** Pentacam, Oculus Inc, Wetzlar, Germany, cut off value was derived from the study data for ACD.

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Using gonioscopy, an eye having an ACA width of Shaffer's Grade 2 or less in 3 or more quadrants (≥ 270 degrees) was considered to be narrow.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	47 subjects (83 eyes) entered the study, four eyes with broad PAS, 3 eyes with nodules in the ACA, 2 eyes with suspected ACA recession suggesting a history of ocular injury, and 2 eyes with significant ocular nystagmus were excluded, 39 subjects (72 eyes) were analysed. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Lavanya 2008

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study. Subjects aged 50 years were recruited from a community polyclinic, they were systematically sampled (every fifth patient registered at the polyclinic) and examined between December of 2005 to June of 2006. Both eyes were included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes

Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 2052 subjects (422 subjects at least 1 eye had a narrow angle and 1630 subjects had an open angle in both eyes) Age: mean (SD), 63.3 ±8.0 years, (narrow angle 65.5±8.2; controls 62.8±7.9) Sex: 1085 (52.9%) female Setting: primary care Country: Singapore Ethnicity: 1840 (89.7%) Chinese, 43 Malay (2.1%), 146 Indian (7.1%), others (1.1%) Exclusions: history of glaucoma, previous intraocular surgery or penetrating eye injury, and corneal disorders, such as corneal endothelial dystrophy, corneal opacity, or pterygium, preventing ACD measurement.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**SPAC**: The range of peripheral ACD values was divided into 12 groups, each representing an equal increment in ACD and categorical grades. Cut off values used were a numerical grade of ≤ 5, P or S, combination of grade ≤ 5 and/or S or P. **AS-OCT**: Time Domain, Visante, Carl Zeiss Meditec, Dublin, CA, Scans were centered on the pupil and taken along the horizontal (nasal-temporal angles at 0–180 degrees) and vertical meridians (superior–inferior angles 90–270 degrees). A closed angle on AS-OCT was defined by contact between the iris and any part of angle wall anterior to the scleral spur in ≥ 2 quadrants.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No

Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An eye was defined as having narrow angle by gonioscopy, if the posterior pigmented trabecular meshwork was not visible on non-indentation gonioscopy for ≥ 180 degrees, with or without PAS.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2114 participants originally studied, Twelve subjects were ineligible because they were pseudophakic in both eyes or were known to have glaucoma , 50 subjects could not complete the tests for various reasons: alignment errors (12); inability to follow instructions (16) or focus on the fixation light (4); refused gonioscopy (4); or other reasons (14). Data from 2052 was included in the final analysis. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Dr Kashiwagi has a Japanese patent on the SPAC (Japanese patent No. 3878164). Dr Friedman has been a paid consultant to Carl Zeiss-Meditec.Dr Foster has received honoraria and travel support from Carl Zeiss Meditec. Dr Aung has received research funding and travel support from Carl Zeiss Meditec.

Melese 2016

Patient Selection

A. Risk of Bias	
Patient Sampling	Case-control study. Subjects were recruited across 3 sites. When both eyes qualified, 1 eye was randomly selected for the study.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 189 subjects recruited, however 69 eyes were used for analysis (31 narrow angle and 38 open angle) Age: mean (SD), 54.0±14.1 years, (narrow angle 60.9±9.2; controls 49.1±14.9) of the 189 subjects reported Sex: 132 (70%), female Setting: secondary care Country: USA Ethnicity: 94 (50%) Caucasian, 44 (23%) African origin, 27 (14%) Hispanic, and 24 (13%) Asian Exclusions: anterior segment abnormalities that could affect the angle parameters, such as significant corneal opacity, lid obstruction or eye movement artefact that could not properly be imaged, medication that may have affected angle anatomy within a month before imaging.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**AS-OCT:** Swept source CASIA SS-1000 (Tomey Corporation, Nagoya, Japan). For 3D image reconstruction, the CASIA SS-1000 obtains a series of 128 cross-sectional images (512 A-scans each) across the whole anterior chamber. Cut off values were derived from the study data

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Using the Spaeth grading system on gonioscopy, eyes were considered to have open angles if anything beyond the scleral spur was visible (grade D or E); all other eyes were graded as narrow (A or B) based on the deepest structure visible in one quadrant (90 degrees). For angles graded as C where the scleral spur was partially visualized, the classification as narrow or open was based on the clinical decision of whether treatment was required.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 189 participants recruited, 120 eyes were used for training, therefore 69 were analysed for the study. Eyes which were excluded or had uninterpretable test results were not reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Demographics reported on whole set but not separately for the test set. Open angle eyes included normals, POAG and suspect POAG Conflict of interest: reported financial disclosures considered not to raise any conflict of interest for the study

Narayanaswamy 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study. Subjects aged 50 years or older were recruited from a community polyclinic, they were systematically sampled (every fifth patient registered at the polyclinic) and examined from December of 2005 to June of 2006. Both eyes were included in the analysis
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 1465 subjects (315 narrow angle and 1150 open angle) Age: mean (SD), 62.7±7.7, range 50-93 years. Sex: 793 (54.1%), female Setting: primary care Country: Singapore Ethnicity: 1318 (90.0%) Chinese, 27 (1.8%) Malay, 102 (7.0%), Indian and 8 (1.2%) others Exclusions: history of intraocular surgery, evidence of aphakia/pseudophakia, or penetrating trauma in the eye; previous anterior segment laser treatment; history of glaucoma; or corneal disorders such as corneal endothelial dystrophy, corneal opacity, or pterygium,
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain, Visante; Carl Zeiss Meditec Inc. Single-scan-mode protocol: one image scanning the angle at the 3- and 9-o'clock positions followed by one scanning the superior angle at 12 o'clock and one scanning the inferior angle at 6 o'clock. Cut off values were derived from the study data for several parameters.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An eye was defined as having a narrow angle if the posterior pigmented trabecular meshwork was not visible for at least 180 degrees on non-indentation gonioscopy with the eye in the primary position.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2047 participants originally studied, 582 were excluded due to; inability to locate the scleral spur (515), poor image quality (28), or software delineation errors (39). Data from 1465 participants was included in the final analysis. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Dr Friedman reports having been as a paid consultant to Carl Zeiss Meditec Inc, Dr Foster reports receiving honoraria and travel support from Carl Zeiss Meditec Inc, and Dr Aung reports receiving research funding, honoraria, and travel support from Carl Zeiss Meditec Inc.

Nolan 2006

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study, recruited from the electoral register of Tanjong Pagar district residing in 50 area clusters defined by street name, using a disproportionate, stratified, clustered, random sampling procedure. Subjects were drawn from each of four age strata (40 to 49, 50 to 59, 60 to 69, and 70 to 79 years). Only data from the right eye was analysed.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 1090 eyes (71 narrow angle and 1019 open angle) Age: range 40-81 years Sex: 593 (54.4%) female Setting: secondary care Country: Singapore Ethnicity: Chinese Exclusions: none reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD**: Determined at the temporal limbus and graded as percentage categories: 0%, 5%, 15%, 25%, 40%, 75% and ≥ 100%. Cut off values used were 0%, ≤ 5%, ≤ 15% and ≤ 25%.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Angles were classified narrow on gonioscopy if the posterior (usually pigmented) trabecular meshwork could be seen for less than 90 degrees (not visible ≥ 270 degrees) of the angle circumference.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable test results reported and no patients were excluded. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest

Nolan 2007

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective case-control study. Subjects 40 years old or older were recruited from glaucoma clinics at an eye hospital. Both eyes were used in the analysis.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 200 subjects (99 narrow angle and 101 open angle) Age: median age 62.5, range 40-86 years Sex: 123 (60.6%) female Setting: secondary care Country: Singapore Ethnicity: 174 (85.7%) Chinese, 9 (4.4%) Malay, 12 (5.9%) Indian and 8 (3.9%) were of other ethnic origins. Exclusions: eyes of patients with pseudophakia or had previous glaucoma surgery.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**AS-OCT:** prototype anterior segment OCT (Carl Zeiss Meditec, Dublin, CA). Images of the temporal, inferior, and nasal quadrants were analysed qualitatively. The cut off values used to as define angle closure on AS-OCT was contact between the peripheral iris and any part of the angle wall anterior to the scleral spur in one or more quadrants.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An angle quadrant (90 degrees) was classified as closed on gonioscopy if the iris was in contact with the posterior (usually pigmented) trabecular meshwork (Spaeth grade, 0 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	203 participants were recruited. In 3 subjects, it was not possible to obtain either gonioscopic grading or AS-OCT images. Data from 200 subjects were included in the final analysis.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: technical support and loan of AS-OCT from Carl Zeiss Meditec, Dublin, California. Demographics: ethnicity and age were reported from the original 203 subjects entering the study, open angle cohort included normals and those with POAG. Study participants included patients who had undergone peripheral iridotomy.

Nongpiur 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Case-control study. Angle closure subjects were recruited were those attending a glaucoma clinic and control subjects were recruited from an ongoing population-based study. Only data from the right eye was analysed.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 278 eyes (102 narrow angle and 176 open angle) Age: mean (SD), 58.3±9.9 years, (65.3±9.1; controls 54.2±7.9) Sex: 150 (54.0%) female Setting: secondary care Country: Singapore Ethnicity: Chinese Exclusions: secondary angle closure, corneal abnormalities that would affect imaging, laser iridoplasty or an history of intraocular surgery history. Controls;

	family history of glaucoma.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**AS-OCT**: time Domain, Visante, Carl Zeiss Meditec, Dublin, CA, Scans were centered on the pupil and were obtained along the horizontal axis (0°–180°) using the standard anterior segment single-scan protocol. The optimal threshold was derived from the study data examining lens vault.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Presence of appositional angle closure for 180 degrees or more with peripheral anterior synechiae on gonioscopy, raised intraocular pressure, or both, but with or without glaucomatous optic neuropathy. Those with previous acute primary angle closure were defined as the presence of at least 2 of the following symptoms: ocular or periocular pain, nausea or vomiting or both, and an antecedent history of intermittent blurring of vision with haloes; a presenting intraocular pressure of more than 28 mmHg on Goldmann applanation tonometry; and the presence of at least 3 of the following signs: conjunctival injection, corneal epithelial edema, mid-dilated un-reactive pupil, and shallow anterior chamber.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Eyes which were excluded or had uninterpretable test results were not reported.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	All cases diagnosed with angle closure previously had LPI Conflict of interest: Tin Aung and Tien Yin Wong received financial Support from Carl Zeiss Meditec

Okabe 1991

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross sectional study, recruited from a glaucoma screening programme in the Gifu prefecture, Japan. Participants were selected randomly between 1988-1989. Both eyes were included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 585 subjects (1169 eyes) Age: mean, male 59.1; female 58.4 years. SD was not reported Sex: 380 (65.0%), female Setting: primary care Country: Japan Ethnicity: Japanese Exclusions: history of glaucoma or trauma and ophthalmic diseases that could influence the angle
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD:** original van Herick grading used with a cut off value of <25%.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined on gonioscopy as the mean grade from all four quadrants ≤ 2 using the Shaffer grading system
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable or excluded results reported. Not reported when the reference test was conducted with respect to the the index test.
Was there an appropriate interval between index test and reference standard?	Unclear
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided

Park 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study, consecutively recruited from the glaucoma service at the Asian Medical Center from May 2008 to January 2009. Data from one eye (randomly selected) was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 148 eyes (93 narrow angle and 55 open angle) Age: mean (SD), 65.1±12.0 years, (narrow angle 66.0±10.1; controls 63.5±14.6) Sex: 72 (48.6%) female Setting: secondary care Country: Republic of Korea Ethnicity: not reported Exclusions: ages of <40 or >80 years, refractive errors >3.00DS, pseudophakia/aphakia, corneal disorders, a history of glaucoma, previous intraocular surgery or penetrating eye injury. Plateau iris configuration and eyes with PAS were also excluded.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD:** determined at the nasal and temporal limbus. Original van Herick grading (Grade 4 ≥ 100%, Grade 3 50%, Grade 2 .25%. Grade 1 <25%). Grade 0 was defined as no space visible between the corneal slit image and the slit image on the iris. A cut off value of <25% was used at the temporal limbus. **AS-OCT:** Time domain, Visante, Carl Zeiss Meditec, Dublin, CA. Enhanced anterior segment single" protocol (scan length 16 mm; 256 A-scans, with only only nasal and temporal angle images obtained. Angle closure was defined as contact between the peripheral iris and the angle wall anterior to the scleral spur. The cut off value used was at the temporal angle image.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy, a narrow angle was determined when the posterior pigmented trabecular meshwork was not visible on non-indentation gonioscopy for at ≥ 60 degrees (two-thirds of quadrant) both with and without PAS at either the nasal or temporal quadrant.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable test results reported and no patients were excluded. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided.

Radhakrishnan 2005

Patient Selection

A. Risk of Bias		
Patient Sampling	Case control study. Subjects were recruited from an secondary care setting. Both eyes were used in the analysis	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		No
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		High risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 31 eyes (24 subjects) (8 eyes narrow angle and 23 open angle) Age: mean (SD), 42.9 years, SD not reported Sex: 15 (62.5%), female Setting: secondary care Country: USA Ethnicity: 14 (58.3%) Caucasian Exclusions: not reported	
Are there concerns that the included patients and setting do not match the review question?		High concern

Index Test

Index tests	**AS-OCT:** prototype anterior segment OCT (Carl Zeiss Meditec, Dublin, CA). Temporal and nasal AC angles were recorded in lateral gaze. Optimal thresholds were derived from study data on AOD 500, ARA 500, ARA 750, TISA 500 AND TISA 750

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A narrow angle was defined as Shaffer grade 1 or lower in all quadrants (360 degrees) on gonioscopy
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uninterpretable or excluded results were not reported. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	The number of the reported ethnicity of subjects do not match the number analysed Conflict of interest: Dr Huang has provided research support to Carl Zeiss Meditec Inc, Dublin, Calif, and has received a patent royalty for optical coherence tomography.

Rossi 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Case-control study. Cases ≥ 40 years and controls ≥ 18 years were both recruited from an ophthalmology clinic. Both eyes were used in the analysis.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 64 eyes (28 narrow angle and 36 open angle) Age: mean (SD), 66.7±10.5 years, (66.1±13.2; controls 66.2±7.9) Sex: 23 (67.7%), female Setting: secondary care Country: Italy Ethnicity: Caucasian Exclusions: no previous laser treatment, no previous filtering surgery or other ocular surgery.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**Scheimpflug photography:** Oculus Pentacam HR, optimal cut off's were derived from the study data for the following parameters; ACA, ACD (central-superior-inferior-nasal-temporal); ACV and central ACD.

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Narrow angle was defined by the presence of Shaffer grade 0-1 in at least 2 quadrants (≥ 180 degrees) on gonioscopy and no evidence of glaucomatous optic neuropathy or visual field defect.
Is the reference standards likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uninterpretable or excluded participants were not reported.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: the authors declared no conflict of interest

Sakata 2010

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Patients were recruited from a Glaucoma Clinic at a Singapore hospital from January to June 2007. One eye per patient was randomly selected for analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 101 eyes (30 narrow angle and 71 open angle) Age: mean (SD), 62.4±9.6, range 41-89 years Sex: 57 (58%) female Setting: secondary care Country: Singapore Ethnicity: 88 (87%) Chinese, 2 Malay (2%), 7 Indian (7%), 4 others (4%) Exclusions: history of previous intraocular surgery or penetrating trauma, or

	any cornea opacities or abnormalities that precluded AS-OCT imaging
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain,Visante; (model 1000,software version 1.0, Carl Zeiss Meditec) **AS-OCT:** time domain, SL-OCT device (software version 1.1, Heildelberg Engineering) Scans for both devices examined the ACA of each eye were obtained at the 3 and 9 o' clock positions (horizontal), and at the 6 and 12 o'clock positions (vertical). The ACA was considered 'closed' on both devices if there was any contact between the iris and angle wall anterior to the scleral spur in at least one quadrant.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An ACA quadrant was considered 'closed' using gonioscopy if the posterior trabecular meshwork could not be seen in the primary position without indentation (Scheie grade 3 or 4) in 90 degrees or more.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 101 participants originally studied, there were 18 participants excluded where ACA could not be assessed in four quadrants with both AS-OCT devices. Data from 83 eyes where used in the final analysis. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	All cases diagnosed with angle closure previously had LPI Demographics reported are of those recruited and not number analysed. Conflict of interest: Carl Zeiss Meditec and Heidelberg Engineering loaned the respective anterior segment OCTs. Dr Aung has received research support and honoraria for travel to conferences from Carl Zeiss Meditec. Dr HT Wong has received financial support and honoraria for travel to conferences from Carl Zeiss Meditec and Heidelberg Engineering.

Tan 2012

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study. Subjects aged 50 years were recruited from a community polyclinic, they were systematically sampled (every fifth patient registered at the polyclinic) and examined between December of 2005 to July of 2006. Only data from the right eye was analsyed
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 1465 eyes (315 narrow angle and 1150 open angle) Age: mean (SD), 62.7 ±7.7 years Sex: 793 (54.1%) female Setting: primary care Country: Singapore Ethnicity: 1317 (90%) Chinese, 27 Malay (1.8%), 102 Indian (7.0%), others (1.2%) Exclusions: history of glaucoma, previous intraocular surgery or laser treatment, penetrating eye injury or corneal disorders preventing anterior chamber assessment

Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain,Visante; Visante, Carl Zeiss Meditec, Dublin, California, USA). Scans were centered on the pupil and taken along the horizontal axis,using the standard anterior segment single-scan protocol. Optimal thresholds were derived from study's data on ACV. LV, ACA

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An narrow angle was defined if the posterior trabecular meshwork was not visible for at least 180 degrees on non-indentation gonioscopy with the eye in the primary position.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2047 participants originally studied, 582 subjects were excluded for the following reasons:11 subjects could not undergo gonioscopy; 62 subjects did not complete AS-OCT examination or had poor quality AS-OCT images;42 subjects showed software delineation errors;and the scleral spur was not clearly visible on AS-OCT images in 467 subjects. Data from 1465 eyes where used in the final analysis

	The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Dr Aung has received research support and honoraria for travel to conferences from Carl Zeiss Meditec.

Thomas 1996

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study, patients were consecutively recruited when they attended an outpatient clinic. Data from one eye (randomly selected) was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 96 eyes (21 narrow angle and 75 open angle) Age: mean (SD), 45.5±14.9, range 14-74 years Sex: 46 (47.9%) female Setting: secondary care Country: India Ethnicity: Indian Exclusions: acute conditions
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**LACD**: original van Herick grading used Grade 4 ≥ 100%, Grade 3 50%, Grade 2 .25%. Grade 1 <25%. Cut off used LACD <25% **Flashlight**: The flashlight beam was directed parallel to the iris from the temporal side. The crescent iris shadow thus formed was graded according to the area between the limbus and the pupillary edge that it occupied. Grade 1 was defined as more than half, Grade 2 as half to one-third; Grade 3 minimal; and Grade 4 as no shadow. Grade 1 and 2 were used as the cut offs.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Flashlight

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	No
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Dynamic gonioscopy was performed with the clinician deciding whether the angle was 'gonioscopically occludable. A Scheie grade 3 or less was considered to be narrow (middle third of the trabecular meshwork visible)
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	100 patients recruited, 4 patients were excluded as they had acute conditions: phacolytic glaucoma (n=1), phacomorphic glaucoma (n=2) and a corneal ulcer (n=1). There were no uninterpretable test results. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided

Tun 2017

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. 202 phakic subjects were recruited from a glaucoma clinic of the Singapore National Eye Center. Data from one eye was in the analysed.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 202 eyes (50 narrow angle and 152 open angle) Age: mean (SD), 62.3 ±9.7 years Sex: 113 (55.9%) female Setting: secondary care Country: Singapore Ethnicity: 170 (84.2%) Chinese Exclusions: history of intraocular surgery or any corneal abnormalities that would preclude OCT imaging
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** spectral domain, HD-OCT Cirrus-OCT, model 5000; Carl Zeiss Meditec Dublin, California, USA). Any contact of the iris to cornea anterior to the scleral spur (SS) defined as a closed angle in that quadrant. If the SS was not visible but the TM was, any contact between the trabecular meshwork and the iris was also diagnosed as a closed angle in that quadrant where two or more quadrants were defined as closure.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	A eye was considered closed if the posterior trabecular meshwork could not be seen in the primary position without indentation (the Scheie grade 3 or 4) in 2 quadrants (180 degrees) on gonioscopy. .
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 202 subjects recruited, and there 10 images excluded from AS-OCT as the examiner was unable to determinate the trabecular meshowork and SS locations. It is not reported whether this participants were from the open or narrow angle group. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes

Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	From the 152 participants with an open angle, 70 patients had POAG and 64 had no glaucoma. Of the original angle closure eyes, 18 had open angles after LPI and were included also in the open angle group. Dr Aung has received research support and honoraria for travel to conferences from Carl Zeiss Meditec.

Wirbelauer 2005

Patient Selection

A. Risk of Bias		
Patient Sampling	Prospective cohort study, both eyes were included in the analysis.	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclear risk

B. Concerns regarding applicability		
Patient characteristics and setting	Sample size: 109 subjects (138 eyes) Age: mean (SD), 66±15 years, range 23-90 years Sex: 66 (60.1%) female Setting: not reported Country: Germany Ethnicity: not reported Exclusions: not reported	
Are there concerns that the included patients and setting do not match the review question?		Unclear concern

Index Test

Index tests	**LACD**: determined at the temporal limbus using the original van Herick grading Grade 4 ≥ 100%, Grade 3 50%, Grade 2 .25%, Grade 1 <25%). Cut off used a temporal LACD ≤ 25% **AS OCT:** slit lamp-adapted OCT system (4Optics AG, Lübeck, Germany), measurements were performed perpendicularly to the ocular surface with the slitlamp aligned at a 45 degree angle. The nasal and temporal angles were studied. Optimal thresholds were extrapolated from the study data for ACA and AOD500.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy; ACA of ≤ 20 degrees, the angle was considered narrow in the nasal and/or temporal angle.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uninterpretable test results and exclusions were not reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided. AS-OCT analysis; study combined both AS-OCT nasal and temporal quadrant data for both eyes. LACD analysis; study compared the temporal LACD to the reference temporal ACA for both eyes.

Wong 2009

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study, participants recruited from a glaucoma clinic at a Singapore hospital from January 1 to July 31, 2007. One eye of each subject was included in the analysis.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 188 eyes Age: mean (SD), 63.3±10.5, range 37-99 years. Sex: 107 (57.0%), female Setting: secondary care Country: Singapore Ethnicity: 162 (86.2%) Chinese, 8 (4.3%) Malay, 12 (6.4%) Indian and other 6 (3.2%). Exclusions: patients who had undergone any prior intraocular procedures or had any penetrating eye injuries or corneal disorders, such as corneal endothelial dystrophy, pterygium, or a corneal scar, that may preclude satisfactory imaging.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**SPAC**: numerical scale ranged from 1 to 12, with 12 representing the deepest ACD. The categorical grading indicates the risk for angle closure: S, suspect angle closure; P, potential angle closure; and no suffix (for open angle results). Cut off values used: optimal thresholds were derived from study data using either separate or combined categorical and numerical grading. **AS-OCT**: SL-OCT (Heidelberg Engineering, Heidelberg, Germany), image acquisition with the SL-OCT required imaging of the entire cross-section of the anterior segment in 1 single-image frame. The ACA was considered closed on SL-OCT imaging if there was contact between the iris and angle wall anterior to the scleral spur in two quadrants or more.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy, the ACA was considered closed if the posterior trabecular meshwork could not be seen in the primary position without indentation (Scheie grade 3 or 4) in 2 or more quadrants (≥ 180 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes

Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	188 participants recruited, 35 were excluded due; failure in obtaining SL-OCT images due to obstructions or motion artefacts (n=14), SL-OCT images could not be graded owing to poor definition of the scleral spur (n=21), leaving 153 participants for final analysis. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Ethnicity reported on original participants entering the study and not the analysed subjects. Defined ACA closure for AS-OCT and gonioscopy was reported in one or more quadrants, data entry for this review was considered for only 2 quadrants identified as closed for both the reference and index test. Conflict of interest: no conflict of interest reported

Wong 2009a

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cohort study. Recruited from a glaucoma clinic at a Singapore hospital. One eye per patient was selected for analysis; this was the right eye if both eyes fulfilled the inclusion criteria.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 45 eyes (17 narrow angle and 28 open angle) Age: mean (SD), 62.5±9.1 years Sex: 28 (62.2%) female Setting: secondary care Country: Singapore Ethnicity: 41 (91.1%) Chinese Exclusions: history of previous intraocular surgery or penetrating trauma or any cornea opacities or abnormalities that precluded angle imaging.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain,Visante; Carl Zeiss Meditec **HD-OCT:** spectral domain, Cirrus-OCT; Carl Zeiss Meditec Dublin, California Cut off values used for both devices was if there was any contact between the iris and angle wall anterior to the scleral spur was noted in one quadrant.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy, an angle quadrant (90 degrees) was considered "closed" if the posterior trabecular meshwork could not be seen in the primary position without indentation (Scheie grade 3 or 4).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Eyes which were excluded or had uninterpretable results were not reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest:Dr Wong has received financial support and honoraria for travel to conferences from Carl Zeiss Meditec and Heidelberg Engineering. Dr Friedman has received an instrument loan and has been a consultant for Carl Zeiss Meditec. Dr T. Aung has received grant funding as well as financial support and honoraria for travel to conferences from Carl Zeiss Meditec. Patients who had undergone peripheral iridotomy were not excluded

Wu 2011

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross-sectional study. Subjects aged 50 years who did not have any ophthalmic symptoms were recruited from a government-run community polyclinic, they were systematically sampled (every fifth patient registered at the polyclinic) and examined between December of 2005 to June of 2006. Only data from the right eye was analysed.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 1922 eyes (317 narrow angle and 1605 open angle) Age: mean (SD), 63.0±7.9 years Sex: 1007 (52.4%) female Setting: primary care Country: Singapore Ethnicity: 1717 (89.3%) Chinese, 39 Malay (2%), 142 Indian (7.4%), 24 others (1.2%)

	Exclusions: history of glaucoma, previous intraocular surgery, previous laser treatment, penetrating eye injury, or corneal disorders preventing anterior chamber assessment were excluded.
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**AS-OCT:** time domain,Visante; Carl Zeiss Meditec, California. Scans were centered on the pupil and were obtained along the horizontal axis (0°–180°) using the standard anterior segment single-scan protocol. The optimal thresholds was derived from the study data examining ACA and ACV.

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	An eye was considered to have narrow angles if the posterior pigmented trabecular meshwork was not visible for at least 180 degrees on non-indentation gonioscopy with the eye in the primary position
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 2047 participants originally studied, 125 (6.1%) were excluded from analysis for the following reasons: 5 subjects (0.2%) could not undergo gonioscopy, 63 subjects (3.1%) could not complete AS-OCT examination or had poor-quality AS-OCT images, and 57 subjects (2.8%) had Zhongshan Angle Assessment Program software delineation errors.The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: Dr Aung has received research funding, travel support, and honoraria from Carl Zeiss Meditec. Dr Friedman has received an instrument loan from Carl Zeiss Meditec.

Yu 1995

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross sectional study, 20% random sample taken from a population over 50 years old from the Doumen county of the Guangdong province in November 1995. Both eyes were included in the analysis
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 390 eyes (72 narrow angle and 318 open angle) Age: not reported Sex: not reported Setting: primary care Country: China Ethnicity: Chinese Exclusions: not reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	**Flashlight:** flashlight beam was shown from the temporal side, a cut off using 1/4 (grade 2) or <1/4 (grade 1) nasal iris light band ratio were used.

Flashlight

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Gonioscopy using Shaffer's chamber angle grading ≤ grade 2 was considered as narrow in the temporal quadrant (90 degrees).
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were no uninterpretable or excluded results reported. The index test and reference standard were conducted on the same occasion
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflict of interest: no conflict of interest statement provided

Zhang 2014

Patient Selection

A. Risk of Bias	
Patient Sampling	Prospective cross sectional study. All Handan eye study subjects aged 40 years or older participated in a 5-year follow-up examination between August and December 2012. Gonioscopy was performed on subjects with a LACD ≤ 40% as well as 1:10 subjects registered per day. Data from the right eye was analysed.
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	Sample size: 425 eyes (126 narrow angle and 299 open angle) Age: mean (SD), 56.9±10.1 years, (narrow angle 60.7±8.1; open angle 55.4±10.4) Sex: 270 (63.5%) female Setting: primary care Country: China Ethnicity: Chinese Exclusions: cases that could confound the results of the ACA examinations, and broad PAS (>3 clock hours) that could influence the ACA configuration. Also if there was pre-existing ocular surface pathology, history of eye trauma, contact lens wear, previous ocular surgery, use of drops that could influence ACA, inability to fixate on the target, or general physical or mental impairments that precluded participation.
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	**LACD**: determined at the temporal limbus and graded as % categories: 0%, 5%, 15%, 25%, 40%, 75% and ≥ 100%. Cut off values used : ≤ 15%, ≤ 25% and ≤ 40%. **SPAC**: measurements ranged from 1 to 12, with 1 representing the shallowest anterior chamber depth. Cut off values used: ≤ 5 and/or S or P; ≤ 6 and/or S or P and ACD. **AS-OCT:** Time domain, Visante, Carl Zeiss Meditec AG (software version 1.0). A closed angle on AS-OCT was defined by contact between the iris and any part of the angle wall anterior to the scleral spur in 2 quadrants. **Scheimpflug photography:** Pentacam, Oculus Inc, Wetzlar, Germany, optimal cut off values were derived form the study data for ACD, ACA and ACV.

LACD

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Scheimpflug photography

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

AS-OCT

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

SPAC

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Dynamic gonioscopic examination was carried with PACS diagnosed as ≥ 180 degrees of the posterior trabecular meshwork was not visible on static gonioscopy.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	There were 431 participants originally studied, 6 participants were excluded due to inability to follow instructions or focus on the fixation light, or unwillingness to undergo gonioscopy. 425 eyes were included in the analysis. There were no uninterpretable results reported. The index test and reference standard were conducted on the same occasion.
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Conflicts of interest: the authors declare no conflicts of interest Gonioscopy was performed on those with an LACD ≤ 40% and for 1 in 10 subjects (number 1, 11, 21, etc) registered per day when seen in clinic

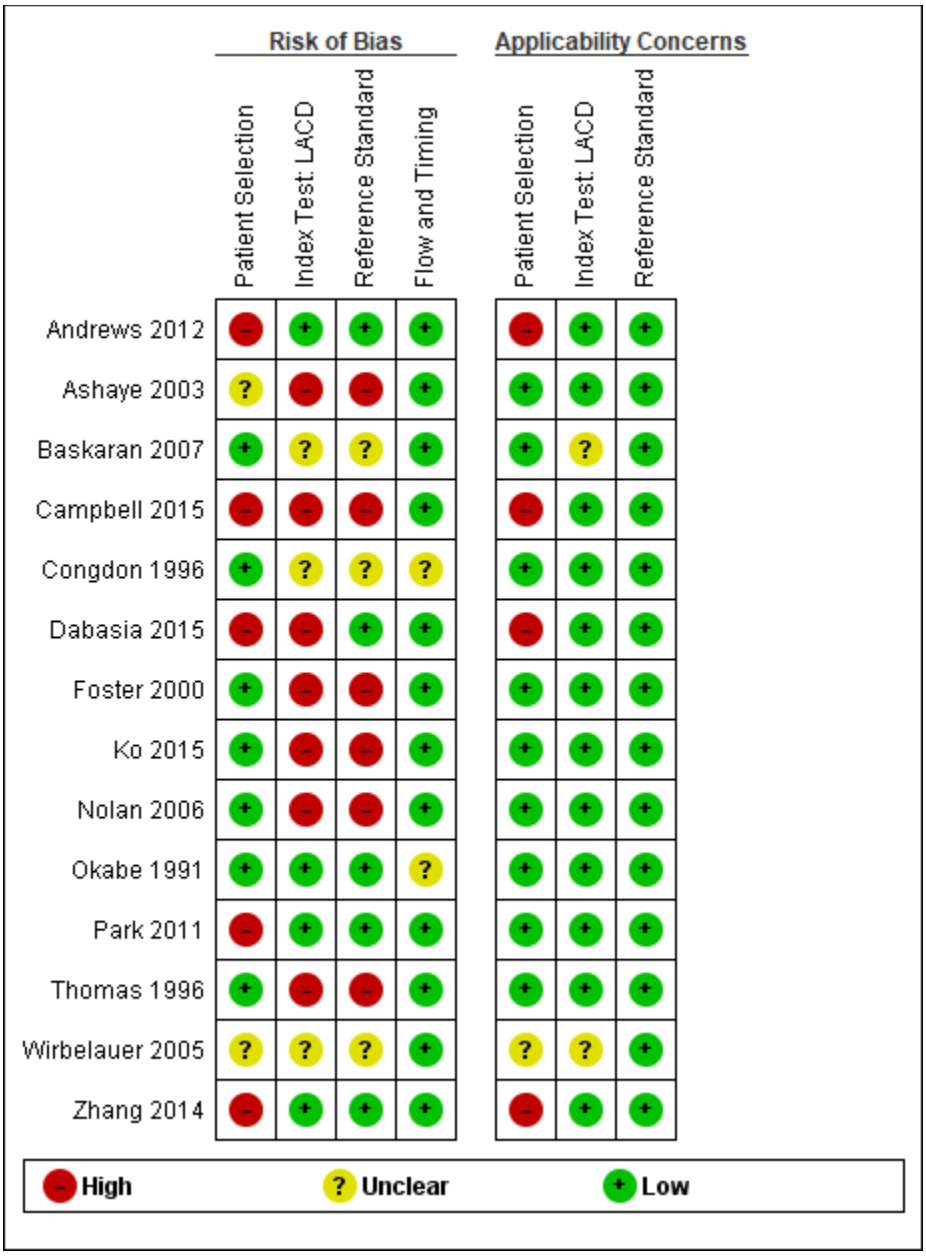
Appendix 1c. Study demographics. No. cases refer to the number of eyes/subjects with a narrow angle.

Study Identification	No. Eyes Analysed	No. Cases (Eyes)	No. Subjects Analysed	No. Cases (Subjects)	Unit of Analysis	Age Mean (SD)	Female No. (%)	Ethnicity
Alonso 2010	112	38	60	NR	Both eyes	51±12	32 (53.3)	NR
Andrews 2012	442	370	442	370	One eye	59.8±4.9	345 (78.0)	100% Chinese
Ashaye 2003	490	40	490	40	One eye	56.8±11.1	214 (43.7)	100% African
Baskaran 2007	120	53	120	53	One eye	62.1±11.3	68 (56.7)	72.5% Chinese
Baskaran 2012	97	39	97	39	One eye	60.7±12.6	49 (50.0)	70% Chinese
Campbell 2015	80	12	80	12	One eye	58.9±10.0	53 (66.0)	87.5% Caucasian
Chang 2011	2047	395	2047	395	One eye	63.2±8.0	1077 (52.6)	100% Chinese
Congdon 1996	NR	NR	503 LACD 362 flashlight	17	Both eyes	59.2+11.8	312 (55.6)	100% East Asian
Dabasia 2015	78	42	78	42	One eye	NR (Median 66)	44 (56.4)	56% Caucasian
Foster 2000	NR	NR	1717	140	Both eyes	NR (Age range 40-93)	974 (56.7)	NR
Gracitelli 2014	45	9	45	9	One eye	47.1±16.4	30 (67.7)	NR
Grewal 2011	265	28	265	28	One eye	55.3±5.1	136 (51.3)	100% Indian
He 2007	295	186	295	186	One eye	67.8±9.5	186 (63.0)	100% Chinese
Hong 2009	73	41	73	41	One eye	65.2±10.0	50 (68.5)	100% Korean
Khor 2010	1853	380	1853	380	One eye	63.4±8.1	1103 (52.4)	89.5% Chinese
Kim 2014	202	101	202	101	One eye	64.5±6.2	110 (54.4)	100% Korean
Ko 2015	374	199	374	199	One eye	77.4±3.8	122 (32.6)	100% Chinese
Kurita 2009	72	42	39	NR	Both eyes	58.4±15.3	NR	100% Japanese
Lavanya 2008	NR	NR	2052	422	Both eyes	63.3±8.0	1085 (52.9)	89.7% Chinese
Melese 2016	69	31	69	31	One eye	54.0±14.1	132 (70.0)	50% Caucasian

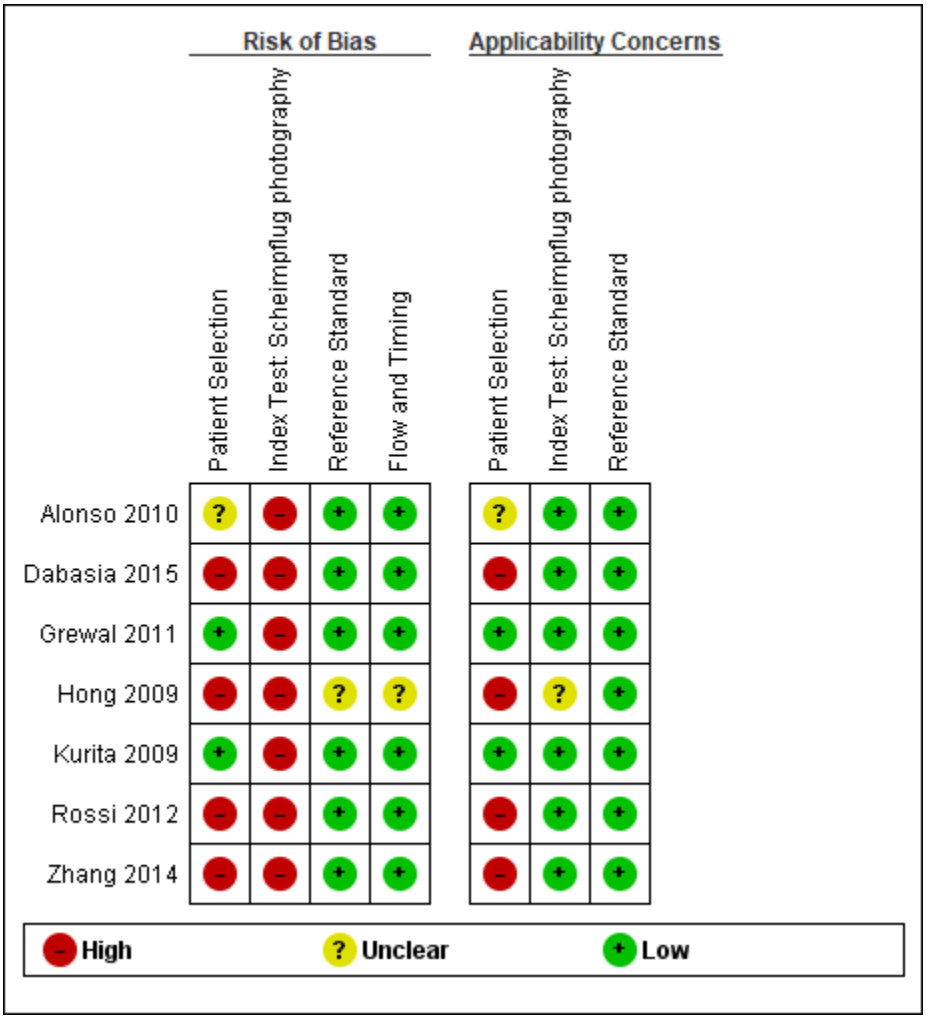
Study Identification	No. Eyes Analysed	No. Cases (Eyes)	No. Subjects Analysed	No. Cases (Subjects)	Unit of Analysis	Age Mean (SD)	Female No. (%)	Ethnicity
Narayanaswamy 2010	NR	NR	1465	315	Both eyes	62.7±7.7	793 (54.1)	90.0% Chinese
Nolan 2006	1090	71	1090	71	One eye	NR Age range (40-81)	593 (54.4)	100% Chinese
Nolan 2007	342	152	200	99	Both eyes	NR (Median 62.5)	123 (60.6)	85.7% Chinese
Nongpiur 2011	278	102	278	102	One eye	58.3±9.9	150 (54.0)	100% Chinese
Okabe 1991	1169	94	585	NR	Both eyes	59.1 (SD NR)	380 (65.0)	100% Japanese
Park 2011	148	93	148	93	One eye	65.1±12.0	72 (48.6)	NR
Radhakrishnan 2005	31	8	24	NR	Both eyes	42.9 (SD NR)	15 (62.5)	58.3% Caucasian
Rossi 2012	64	28	34	28	Both eyes	66.7±10.5	23 (67.7)	100% Caucasian
Sakata 2010	83	30	83	30	One eye	62.4±9.6	57 (58.0)	87% Chinese
Tan 2012	1465	315	1465	315	One eye	62.7±7.7	793 (54.1)	90.0% Chinese
Thomas 1996	96	21	96	21	One eye	45.5±14.9	46 (47.9)	100% Indian
Tun 2017	202	50	202	50	One eye	62.3±9.7	113 (55.9)	84.2% Chinese
Wirbelauer 2005	138	64 LACD 122 AS-OCT	109	NR	Both eyes	66±15	66 (60.1)	NR
Wong 2009a	153	51	153	51	One eye	63.3±10.5	107 (57.0)	86.2% Chinese
Wong 2009b	45	17	45	17	One eye	62.5±9.1	28 (62.2)	91.1% Chinese
Wu 2011	1922	317	1922	317	One eye	63.0±7.9	1007 (52.4)	89.3% Chinese
Yu 1995	390	72	200	NR	Both eyes	NR	NR	100% Chinese
Zhang 2014	425	126	425	126	One eye	56.9±10.1	270 (63.5)	100% Chinese

Appendix 1d. Risk of bias and applicability graphs per index test.

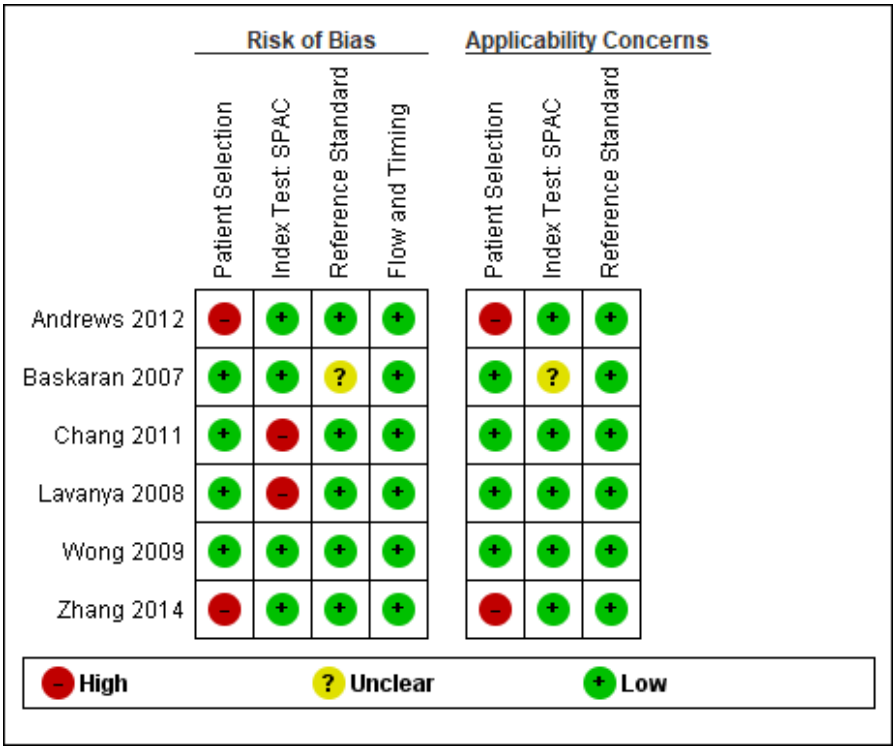
LACD



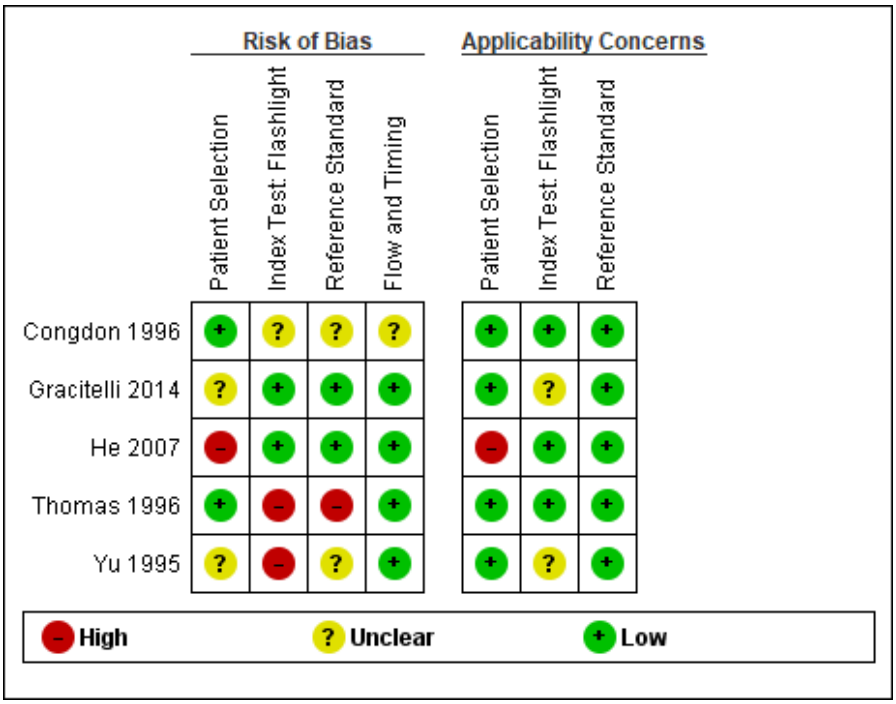
Scheimpflug photography



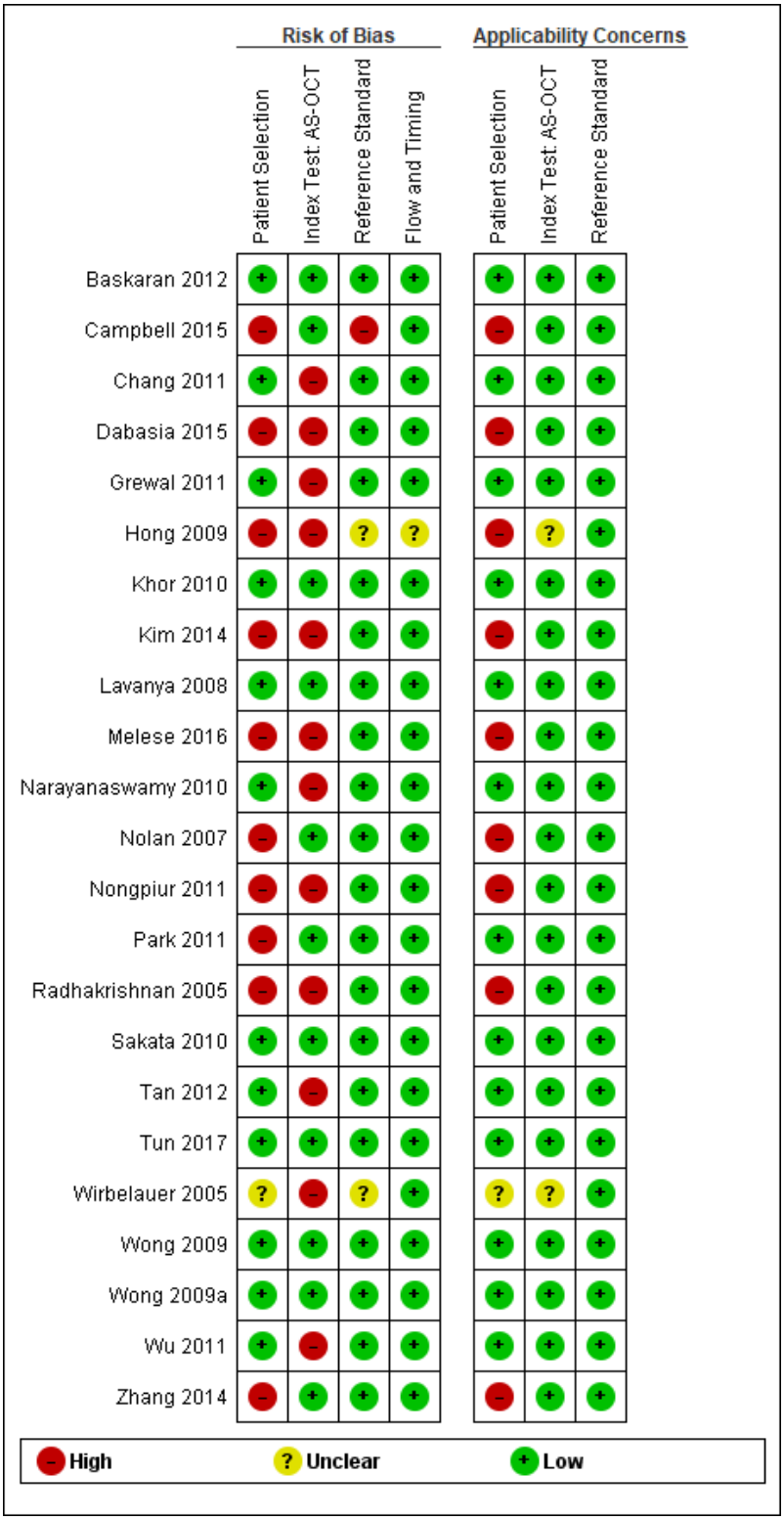
SPAC



Flashlight



AS-OCT


Risk of Bias
Applicability Concerns
Patient Selection
Index Test: AS-OCT
Reference Standard
Flow and Timing
Patient Selection
Index Test: AS-OCT
Reference Standard
Baskaran 2012
Campbell 2015
Chang 2011
Dabasia 2015
Grewal 2011
Hong 2009
Khor 2010
Kim 2014
Lavanya 2008
Melese 2016
Narayanaswamy 2010
Nolan 2007
Nongpiur 2011
Park 2011
Radhakrishnan 2005
Sakata 2010
Tan 2012
Tun 2017
Wirbelauer 2005
Wong 2009
Wong 2009a
Wu 2011
Zhang 2014
High
Unclear
Low

Appendix 1e. Number of eyes/subjects excluded from the final analysis.

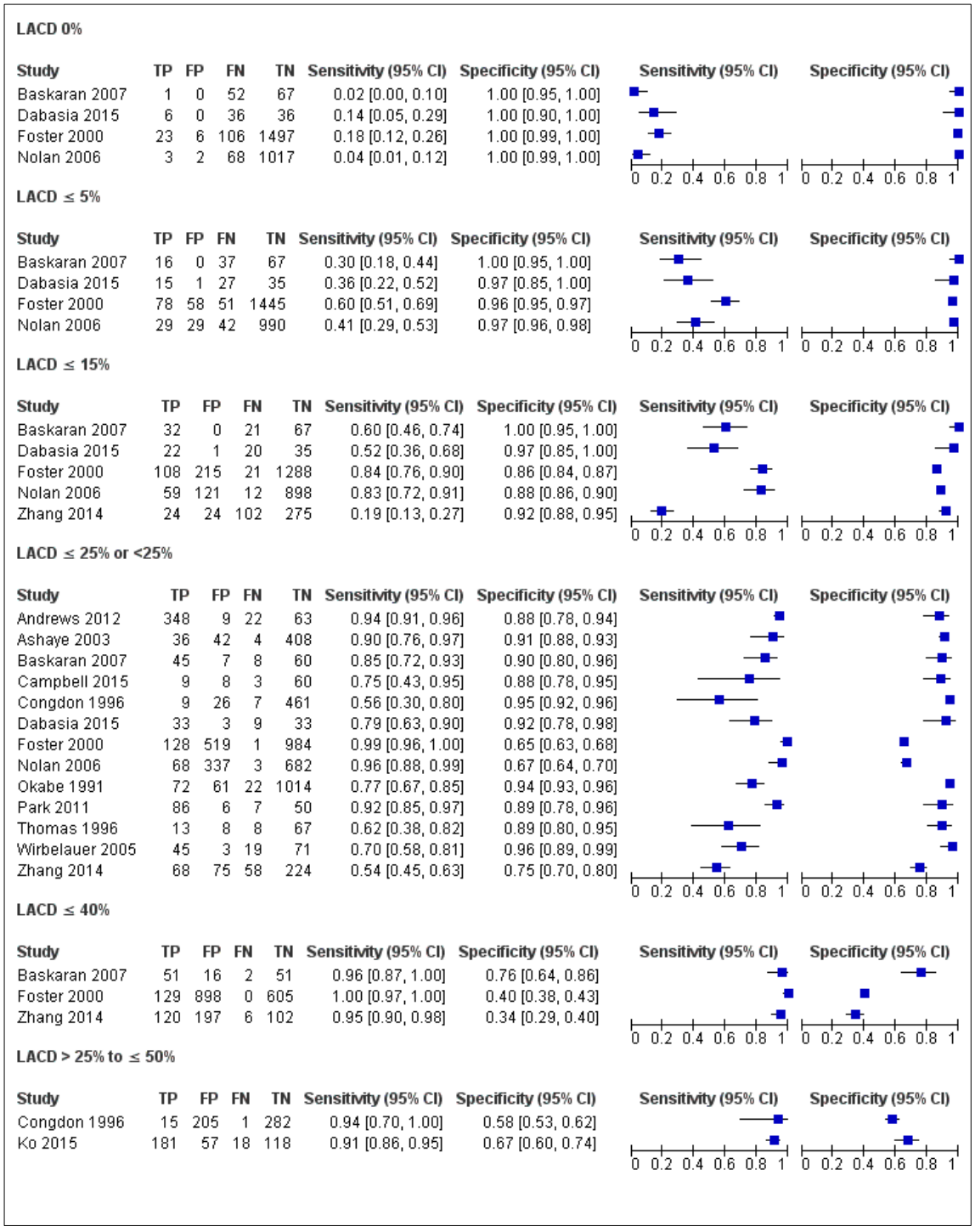
Study Identification	Index Test(s)	Recruited No. Eyes; subjects	Excluded No. Eyes; subjects	Excluded No. Eyes (index test)	Excluded No. Eyes (gonioscopy)	Exclusion Comment
Alonso 2010	Scheimpflug photography	112;60	0	0	0	None
Andrews 2012	LACD and SPAC	442	0	0	0	None
Ashaye 2003	LACD	490	0	0	0	None
Baskaran 2007	LACD and SPAC	120	0	0	0	None
Baskaran 2012	AS-OCT	98	1	NR	NR	Reason not specified (n=1)
Campbell 2015	LACD and AS-OCT	84	4	0	4	Gonioscopy not tolerated (n=4)
Chang 2011	SPAC and AS-OCT	2102	579 AS-OCT 41 SPAC	See comment	0	Quantitative data missing AS-OCT (n=579), couldn't complete all tests (n=55)
Congdon 1996	LACD and flashlight	NR;562	NR	NR	NR	Flashlight sample smaller than LACD as study recruitment was delayed
Dabasia 2015	LACD, AS-OCT and Scheimpflug photography	78	0	0	0	None
Foster 2000	LACD	NR;1800	NR;83	See comment	See comment	Subjects: LACD ungradable (n=76), gonioscopy ungradable (n=17)
Gracitelli 2014	Flashlight	45	0	0	0	None
Grewal 2011	AS-OCT and Scheimpflug photography	300	35	35	0	AS-OCT Undetectable scleral spur (n=35)
He 2007	Flashlight	602	307	22	5	Angle closure suspects (n=236), aphakic/pseudophakic (n=44), corneal defects (n=22), gonioscopy data missing (n=5)
Hong 2009	AS-OCT and Scheimpflug photography	73	0	0	0	None

Study Identification	Index Test(s)	Recruited No. Eyes; subjects	Excluded No. Eyes; subjects	Excluded No. Eyes (index test)	Excluded No. Eyes (gonioscopy)	Exclusion Comment
Khor 2010	AS-OCT	2104	251	251	0	Poor AS-OCT image quality (n=251)
Kim 2014	AS-OCT	236	34	23	0	Poor AS-OCT image quality (n=23), cases excluded to match control no (n=11)
Ko 2015	LACD	460	86	0	15	Pseudophakia (n=65), gonioscopy not performed (n=15), LPI (n=6)
Kurita 2009	Scheimpflug photography	83;47	11;8	0	0	Eyes: ACA abnormalities (n=9), nystagmus (n=2)
Lavanya 2008	SPAC and AS-OCT	NR;2114	NR;62	See comment	See comment	Subjects: Couldn't complete tests (n=50), pseudophakic/glaucoma (n=12)
Melese 2016	AS-OCT	189	120	0	0	Eyes used for training (n=120)
Narayanaswamy 2010	AS-OCT	NR;2047	NR;582	See comment	See comment	Subjects: AS-OCT data not interpretable (n=582); scleral spur undetected (n=515)
Nolan 2006	LACD	1090	0	0	0	None
Nolan 2007	AS-OCT	346;203	4;3	See comment	See comment	Subjects: Either gonioscopy or AS-OCT not possible (n=3)
Nongpiur 2011	AS-OCT	278	0	0	0	None
Okabe 1991	LACD	1169;585	0	0	0	None
Park 2011	LACD and AS-OCT	148	0	0	0	None
Radhakrishnan 2005	AS-OCT	31;24	0	0	0	None
Rossi 2012	Scheimpflug photography	64;34	0	0	0	None
Sakata 2010	AS-OCT	101	18	18	0	AS-OCT data not interpretable (n=18)
Tan 2012	AS-OCT	2047	582	571	11	AS-OCT not interpretable (n=571); scleral spur undetected (n=467), gonioscopy not possible (n=11)

Study Identification	Index Test(s)	Recruited No. Eyes; subjects	Excluded No. Eyes; subjects	Excluded No. Eyes (index test)	Excluded No. Eyes (gonioscopy)	Exclusion Comment
Thomas 1996	LACD and flashlight	100	4	0	0	Acute ocular co-morbidities (n=4)
Tun 2017	AS-OCT	202	10	10	0	AS-OCT not interpretable (n=10)
Wirbelauer 2005	LACD and AS-OCT	138;109	0	0	0	None
Wong 2009a	SPAC and AS-OCT	188	35	35	0	AS-OCT data not interpretable (n=35); scleral spur undetected (n=21)
Wong 2009b	AS-OCT	45	0	0	0	None
Wu 2011	AS-OCT	2047	125	120	5	AS-OCT data not interpretable (n=120), gonioscopy not possible (n=5)
Yu 1995	Flashlight	390;200	0	0	0	None
Zhang 2014	LACD, SPAC, AS-OCT and Scheimpflug photography	431	6	See comment	See comment	Could not fixate on index or gonioscopy refused (n=6)

Appendix 1f. Forest plots for all reported thresholds per index test.

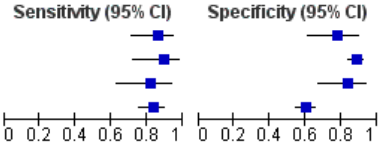
LACD



Scheimpflug photography

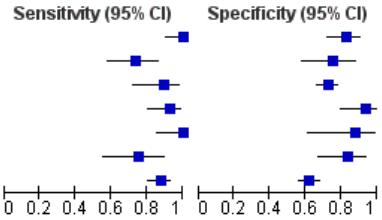
Scheimpflug photography ACV

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dabasia 2015	36	8	6	28	0.86 [0.71, 0.95]	0.78 [0.61, 0.90]
Grewal 2011	25	28	3	209	0.89 [0.72, 0.98]	0.88 [0.83, 0.92]
Rossi 2012	23	6	5	30	0.82 [0.63, 0.94]	0.83 [0.67, 0.94]
Zhang 2014	105	119	21	180	0.83 [0.76, 0.89]	0.60 [0.54, 0.66]



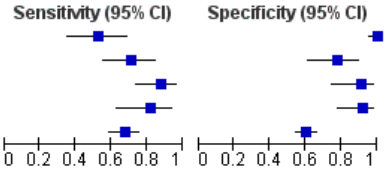
Scheimpflug photography ACD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alonso 2010	38	13	0	61	1.00 [0.91, 1.00]	0.82 [0.72, 0.90]
Dabasia 2015	31	9	11	27	0.74 [0.58, 0.86]	0.75 [0.58, 0.88]
Grewal 2011	25	65	3	172	0.89 [0.72, 0.98]	0.73 [0.66, 0.78]
Hong 2009	38	2	3	30	0.93 [0.80, 0.98]	0.94 [0.79, 0.99]
Kurita 2009	23	2	0	14	1.00 [0.85, 1.00]	0.88 [0.62, 0.98]
Rossi 2012	21	6	7	30	0.75 [0.55, 0.89]	0.83 [0.67, 0.94]
Zhang 2014	110	113	16	186	0.87 [0.80, 0.93]	0.62 [0.56, 0.68]



Scheimpflug photography ACA

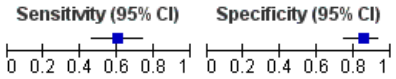
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alonso 2010	20	0	18	74	0.53 [0.36, 0.69]	1.00 [0.95, 1.00]
Dabasia 2015	30	8	12	28	0.71 [0.55, 0.84]	0.78 [0.61, 0.90]
Hong 2009	36	3	5	29	0.88 [0.74, 0.96]	0.91 [0.75, 0.98]
Rossi 2012	23	3	5	33	0.82 [0.63, 0.94]	0.92 [0.78, 0.98]
Zhang 2014	85	118	41	181	0.67 [0.59, 0.76]	0.61 [0.55, 0.66]



SPAC

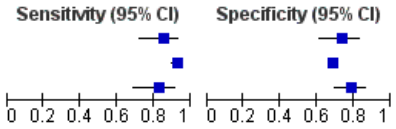
SPAC S

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baskaran 2007	32	10	21	57	0.60 [0.46, 0.74]	0.85 [0.74, 0.93]



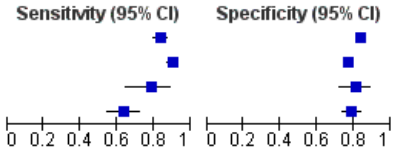
SPAC S or P

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baskaran 2007	45	18	8	49	0.85 [0.72, 0.93]	0.73 [0.61, 0.83]
Lavanya 2008	390	517	32	1113	0.92 [0.89, 0.95]	0.68 [0.66, 0.71]
Wong 2009	42	22	9	80	0.82 [0.69, 0.92]	0.78 [0.69, 0.86]



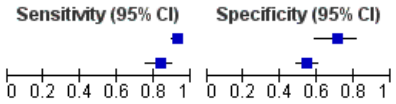
SPAC ≤ 5 and or S or P

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chang 2011	330	269	65	1383	0.84 [0.80, 0.87]	0.84 [0.82, 0.85]
Lavanya 2008	380	381	42	1249	0.90 [0.87, 0.93]	0.77 [0.74, 0.79]
Wong 2009	40	19	11	83	0.78 [0.65, 0.89]	0.81 [0.72, 0.88]
Zhang 2014	80	63	46	236	0.63 [0.54, 0.72]	0.79 [0.74, 0.83]



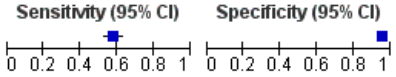
SPAC ≤ 6 and or S or P

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andrews 2012	344	21	26	51	0.93 [0.90, 0.95]	0.71 [0.59, 0.81]
Zhang 2014	105	136	21	163	0.83 [0.76, 0.89]	0.55 [0.49, 0.60]



SPAC ≤ 4

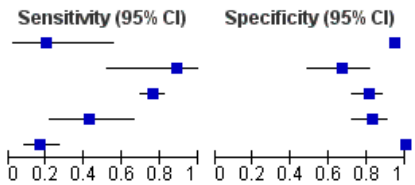
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chang 2011	228	83	167	1569	0.58 [0.53, 0.63]	0.95 [0.94, 0.96]



Flashlight

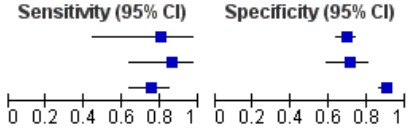
Flashlight grade 1

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Congdon 1996	2	19	8	333	0.20 [0.03, 0.56]	0.95 [0.92, 0.97]
Gracitelli 2014	8	12	1	24	0.89 [0.52, 1.00]	0.67 [0.49, 0.81]
He 2007	142	21	44	88	0.76 [0.70, 0.82]	0.81 [0.72, 0.88]
Thomas 1996	9	13	12	62	0.43 [0.22, 0.66]	0.83 [0.72, 0.90]
Yu 1995	12	0	60	318	0.17 [0.09, 0.27]	1.00 [0.99, 1.00]



Flashlight grade 2

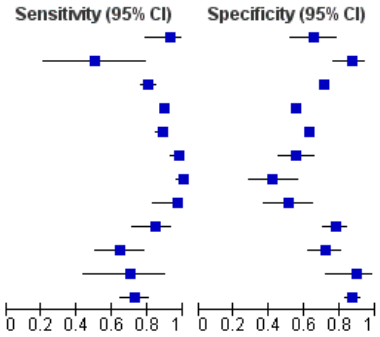
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Congdon 1996	8	109	2	243	0.80 [0.44, 0.97]	0.69 [0.64, 0.74]
Thomas 1996	18	22	3	53	0.86 [0.64, 0.97]	0.71 [0.59, 0.81]
Yu 1995	54	32	18	286	0.75 [0.63, 0.84]	0.90 [0.86, 0.93]



AS-OCT

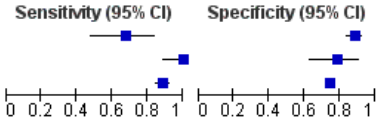
AS-OCT (subjective judgement)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baskaran 2012	36	20	3	38	0.92 [0.79, 0.98]	0.66 [0.52, 0.78]
Campbell 2015	6	9	6	59	0.50 [0.21, 0.79]	0.87 [0.76, 0.94]
Chang 2011	318	472	77	1180	0.81 [0.76, 0.84]	0.71 [0.69, 0.74]
Khor 2010	468	592	54	739	0.90 [0.87, 0.92]	0.56 [0.53, 0.58]
Lavanya 2008	373	605	49	1025	0.88 [0.85, 0.91]	0.63 [0.60, 0.65]
Nolan 2007	97	45	2	56	0.98 [0.93, 1.00]	0.55 [0.45, 0.65]
Park 2011	93	32	0	23	1.00 [0.96, 1.00]	0.42 [0.29, 0.56]
Sakata 2010	29	26	1	27	0.97 [0.83, 1.00]	0.51 [0.37, 0.65]
Tun 2017	42	34	8	118	0.84 [0.71, 0.93]	0.78 [0.70, 0.84]
Wong 2009	33	29	18	73	0.65 [0.50, 0.78]	0.72 [0.62, 0.80]
Wong 2009a	12	3	5	25	0.71 [0.44, 0.90]	0.89 [0.72, 0.98]
Zhang 2014	92	38	34	261	0.73 [0.64, 0.81]	0.87 [0.83, 0.91]



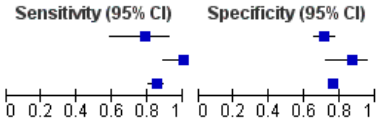
AS-OCT AOD 500 temporal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	19	28	9	209	0.68 [0.48, 0.84]	0.88 [0.83, 0.92]
Melese 2016	31	8	0	30	1.00 [0.89, 1.00]	0.79 [0.63, 0.90]
Narayanaswamy 2010	280	292	35	858	0.89 [0.85, 0.92]	0.75 [0.72, 0.77]



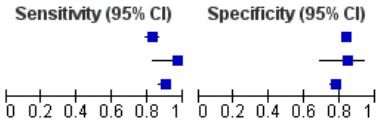
AS-OCT AOD 500 nasal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	22	68	6	169	0.79 [0.59, 0.92]	0.71 [0.65, 0.77]
Melese 2016	31	5	0	33	1.00 [0.89, 1.00]	0.87 [0.72, 0.96]
Narayanaswamy 2010	268	275	47	875	0.85 [0.81, 0.89]	0.76 [0.74, 0.79]



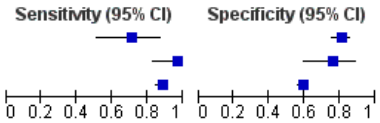
AS-OCT AOD 750 temporal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chang 2011	327	276	68	1376	0.83 [0.79, 0.86]	0.83 [0.81, 0.85]
Melese 2016	30	6	1	32	0.97 [0.83, 1.00]	0.84 [0.69, 0.94]
Narayanaswamy 2010	284	260	31	890	0.90 [0.86, 0.93]	0.77 [0.75, 0.80]



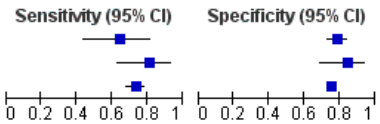
AS-OCT TISA 500 temporal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	20	45	8	192	0.71 [0.51, 0.87]	0.81 [0.75, 0.86]
Melese 2016	30	9	1	29	0.97 [0.83, 1.00]	0.76 [0.60, 0.89]
Narayanaswamy 2010	278	470	37	680	0.88 [0.84, 0.92]	0.59 [0.56, 0.62]



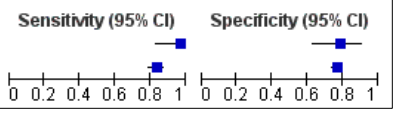
AS-OCT TISA 500 nasal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	18	50	10	187	0.64 [0.44, 0.81]	0.79 [0.73, 0.84]
Melese 2016	25	6	6	32	0.81 [0.63, 0.93]	0.84 [0.69, 0.94]
Narayanaswamy 2010	231	285	84	865	0.73 [0.68, 0.78]	0.75 [0.73, 0.78]



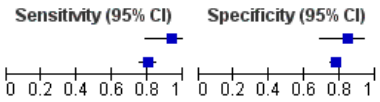
AS-OCT TISA 750 temporal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melese 2016	30	8	1	30	0.97 [0.83, 1.00]	0.79 [0.63, 0.90]
Narayanaswamy 2010	263	268	52	882	0.83 [0.79, 0.87]	0.77 [0.74, 0.79]



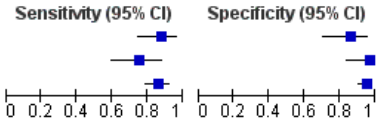
AS-OCT TISA 750 nasal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melese 2016	29	6	2	32	0.94 [0.79, 0.99]	0.84 [0.69, 0.94]
Narayanaswamy 2010	253	259	62	891	0.80 [0.75, 0.85]	0.77 [0.75, 0.80]



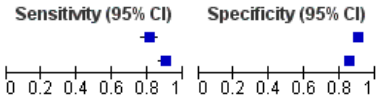
AS-OCT ACA angle

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dabasia 2015	37	5	5	31	0.88 [0.74, 0.96]	0.86 [0.71, 0.95]
Hong 2009	31	1	10	31	0.76 [0.60, 0.88]	0.97 [0.84, 1.00]
Wirbelauer 2005	105	8	17	146	0.86 [0.79, 0.92]	0.95 [0.90, 0.98]



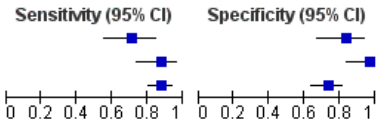
AS-OCT ACA area

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tan 2012	255	144	60	1321	0.81 [0.76, 0.85]	0.90 [0.89, 0.92]
Wu 2011	285	233	32	1372	0.90 [0.86, 0.93]	0.85 [0.84, 0.87]



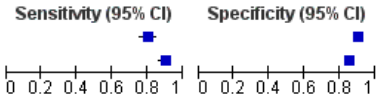
AS-OCT ACD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dabasia 2015	30	6	12	30	0.71 [0.55, 0.84]	0.83 [0.67, 0.94]
Hong 2009	36	1	5	31	0.88 [0.74, 0.96]	0.97 [0.84, 1.00]
Kim 2014	89	27	12	74	0.88 [0.80, 0.94]	0.73 [0.64, 0.82]



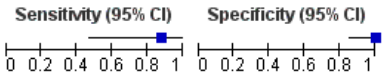
AS-OCT ACV

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tan 2012	253	142	62	1323	0.80 [0.75, 0.85]	0.90 [0.89, 0.92]
Wu 2011	286	239	31	1366	0.90 [0.86, 0.93]	0.85 [0.83, 0.87]



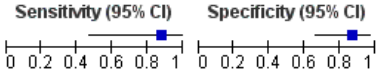
AS-OCT ARA 500 average

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Radhakrishnan 2005	7	0	1	23	0.88 [0.47, 1.00]	1.00 [0.85, 1.00]



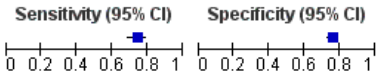
AS-OCT ARA 750 average

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Radhakrishnan 2005	7	3	1	20	0.88 [0.47, 1.00]	0.87 [0.66, 0.97]



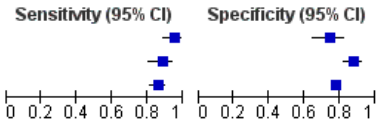
AS-OCT ARA 750 nasal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Narayanaswamy 2010	233	278	82	872	0.74 [0.69, 0.79]	0.76 [0.73, 0.78]



AS-OCT LV

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2014	96	26	5	75	0.95 [0.89, 0.98]	0.74 [0.65, 0.82]
Nongpiur 2011	90	21	12	155	0.88 [0.80, 0.94]	0.88 [0.82, 0.92]
Tan 2012	270	330	45	1135	0.86 [0.81, 0.89]	0.77 [0.75, 0.80]



Appendix 2.

Diagnostic accuracy of a new thresholding glaucoma programme using temporally modulated flicker.

User acceptability survey of diagnostic technology.

Questionnaire of user acceptability of diagnostic equipment

Date of Examination……Subject ID VFF……..

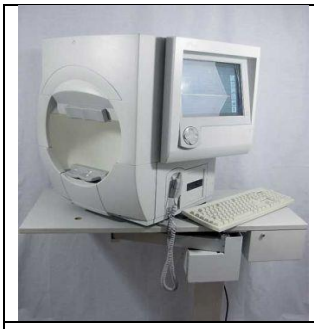
Unless otherwise stated, please fill one circle for each question using black or blue ink.

For questions 1-4, 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.

Example: The test was uncomfortable

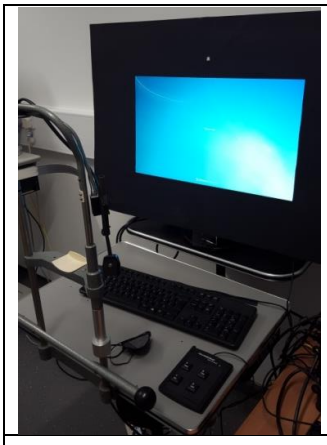
Disagree Agree							
○	○	○	○	○	○	●	○

Q1) **Humphrey visual fields** (Location DAIR 2) –Responding to white flashes on a screen

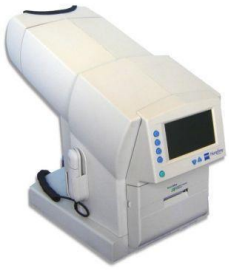


	Disagree						Agree
a) The test was uncomfortable	○	○	○	○	○	○	○
b) Test was too long	○	○	○	○	○	○	○
c) The test was difficult to undertake	○	○	○	○	○	○	○

Q2) A4FTp test (Location DAIR 2) –Pressing the numbers on the keypad and flicker (On large monitor/screen)

							
	Disagree						Agree
a) The test was uncomfortable	◯	◯	◯	◯	◯	◯	◯
b) Test was too long	◯	◯	◯	◯	◯	◯	◯
c) The test was difficult to undertake	◯	◯	◯	◯	◯	◯	◯

Q3) FDT (Location DAIR 2) –Seeing flicker bars flicker (looking down at a display)

							
	Disagree						Agree
a) The test was uncomfortable	◯	◯	◯	◯	◯	◯	◯
b) Test was too long	◯	◯	◯	◯	◯	◯	◯
c) The test was difficult to undertake	◯	◯	◯	◯	◯	◯	◯

Q4) **iVue OCT** (Location DAIR 2)- Instrument capturing image of the back of the eye

	Disagree						Agree
a) The test was uncomfortable	◯	◯	◯	◯	◯	◯	◯
b) Test was too long	◯	◯	◯	◯	◯	◯	◯
c) The test was difficult to undertake	◯	◯	◯	◯	◯	◯	◯

Demographics

How would you best describe your ethnicity? (Your answer will help us analyse the results of the tests that you have undertaken today)

◯	White/Caucasian	◯	Black African/Caribbean
◯	Asian Indian/Pakistani/ Bangladeshi/Sri Lankan)	◯	Asian Chinese
◯	Mixed	◯	Arab
◯	Other Ethnic group, please describe:		

If you have any further comments on the usability of the tests today or any other aspect of the study, please write them in the box below.

Thank you for your time.

Appendix 3.

Impact of optical coherence tomography on diagnostic decision-making by UK community optometrists.

Eligibility survey for participants working status.

A comparative study of the diagnostic accuracy of fundus photography alone and in combination with optical coherence tomography (OCT) for detection of abnormalities of the optic disc and retina.

Name:

Email Address:

The following questionnaire will ask about your mode of practice and training with respect to imaging, which is relevant to our study. This survey will take approximately 5 minutes and your responses will remain confidential.

Questionnaire

1. Are you currently practicing as a community optometrist?
   -Yes (Includes optometrists who work in the HES/ Academia but undertake part-time work in community practice)
   -No

2. Have you ever participated in any age-related macular degeneration shared care scheme or worked in a medical retina or glaucoma secondary care clinic?
   - Yes/No
   - If yes, please provide details

3. Which of the following is your principal mode of community practice?
   - Independent
   - Multiple/Group
   - Locum
   - Other

4. Please indicate the proportion of your working time as (%) spent working in practice specified in Q3
   i. Division of time (percentage) ___%

5. During the last working month how many days per week did you spend working in the practice specified in Q3?
   - <1
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7

6. Do you work in secondary care (HES/ophthalmology triage, etc)?
   i. If no, go to question 9.
   ii. Please indicate the proportion of your working time as (%) spent working in HES? - Division of time (percentage) ___%

7. During the last working month how many days in the week did you spend working in the HES?
   - <1
   - 1
   - 2
   - 3
   - 4
   - 5
   - 6
   - 7

9. Do you use OCT routinely in your work in community and/or hospital clinics?

   - Yes/No

10. Do you use fundus imaging routinely in your work community and/or hospital clinics?

- Yes/No

11. Have you completed any postgraduate qualifications specific to glaucoma or medical retina?

   -No

   - Yes, please provide details

12. Have you received any training specific to OCT interpretation?

   -No

   - Yes, please provide details of the training you have received

13. In which year did you register with the GOC?

14. Are you:

    i. Male
    ii. Female
    iii. Prefer not to say
    iv. Other

List of publications and presentations

Conference presentations: published abstracts

Jindal A, Ctori I, Lawrenson JG. The impact of optical coherence tomography on clinical decisions by community optometrists. Presentation: City, University of London, Annual Doctoral Research Conference, 2019 (London).

Jindal A, Ctori I, Lawrenson JG. The impact of optical coherence tomography on clinical decisions by community optometrists. Poster presented at: European Academy of Optometry and Optics, 2019 (Rome).

Jindal A, Ctori I, Lawrenson JG. The impact of optical coherence tomography on clinical decision making in primary eye care. Poster presented at: The Association for Research in Vision and Ophthalmology, 2019 (Vancouver).

Jindal A, Fidalgo B, Ctori I, Tyler CW, Lawrenson JG. Diagnostic accuracy of a new thresholding glaucoma screening programme using temporally modulated flicker. Presentation: United Kingdom Eire Glaucoma Society, 2018 (London).

Jindal A, Fidalgo B, Ctori I, Tyler CW, Lawrenson JG. Diagnostic accuracy of a new thresholding glaucoma screening programme using temporally modulated flicker. Presentation: European Association for Vision and Eye Research, 2018 (Nice).

Jindal A, Ctori I, Lawrenson JG. Optical coherence tomography: Impact on diagnostic competence and confidence. Presentation: British Congress of Optometry and Vision Science, 2018 (Cambridge).

Jindal A, Fidalgo B, Ctori I, Tyler CW, Lawrenson JG. Diagnostic accuracy of a new thresholding glaucoma screening programme using temporally modulated flicker. Poster presented at: City, University of London, Annual Doctoral Research Conference, 2018 (London).

Jindal A, Fidalgo B, Ctori I, Tyler CW, Lawrenson JG. Diagnostic accuracy of a new thresholding glaucoma screening programme using temporally modulated flicker. Poster presented at: The College of Optometrists, 2018 Research symposium; Optometry Tomorrow (Birmingham).

Jindal A, Ctori I, Virgili G, Lucenteforte E, Lawrenson JG. A systematic review of the accuracy of non-contact methods for the detection of narrow drainage angles in people at risk of angle closure glaucoma. Poster presented at: City, University of London, Annual Doctoral Research Conference, 2017 (London).

Other presentations

Jindal A, Ctori I, Lawrenson JG. Diagnostic accuracy of structural imaging and visual function tests to detect age-related eye disease: City, University of London, MPhil upgrade, Nov 2017 (London).

Jindal A, Ctori I, Lawrenson JG. Diagnostic accuracy of tests to detect age-related eye disease: City, University of London, Crabb Lab research meeting, Feb 2017 (London).

Published papers

Jindal A, Ctori I, Fidalgo B, Dabasia P, Balaskas K, Lawrenson JG. Impact of optical coherence tomography on diagnostic decision-making by UK community optometrists: a clinical vignette study. Ophthalmic Physiol Opt. 2019; 39: 205-215.

Fidalgo B, Jindal A, Ctori I, Tyler CW, Lawrenson JG. Development and validation of a new glaucoma screening test using temporally modulated flicker. Ophthalmic Physiol Opt. 2018; 38: 617-628.

Jindal A, Ctori I, Virgili G, Lucenteforte E, Lawrenson JG. Non-contact methods for the detection of people at risk of primary angle closure glaucoma (Protocol). Cochrane Database of Systematic Reviews (2). 2018. DOI: 10.1002/14651858.