Anterior Segment Morphology in Angle Closure

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<td>Anterior Closure or Angle Closure Glaucoma</td>
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<td>Anterior chamber Angle</td>
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<td>EPR</td>
<td>Electronic Patient Record</td>
</tr>
<tr>
<td>FD</td>
<td>Fourier Domain</td>
</tr>
<tr>
<td>FD-OCT</td>
<td>Fourier Domain Optical Coherence Tomography</td>
</tr>
<tr>
<td>FM</td>
<td>Farnsworth Munsell</td>
</tr>
<tr>
<td>GON</td>
<td>Glaucomatous optic neuropathy</td>
</tr>
<tr>
<td>ICPD</td>
<td>Iris Ciliary Process Distance</td>
</tr>
<tr>
<td>IER</td>
<td>Institute for Eye Research</td>
</tr>
<tr>
<td>IOP</td>
<td>Intra-ocular Pressure</td>
</tr>
<tr>
<td>ISGEO</td>
<td>International Society Geographical &amp; Epidemiological Ophthalmology</td>
</tr>
<tr>
<td>IT</td>
<td>Iris thickness</td>
</tr>
<tr>
<td>ITC</td>
<td>Irido trabecular contact</td>
</tr>
<tr>
<td>IZD</td>
<td>Irido – zonular distance</td>
</tr>
<tr>
<td>LAF</td>
<td>Lens to axial length factor</td>
</tr>
<tr>
<td>LAL</td>
<td>Longitudinal axial length</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>LOA</td>
<td>Limits of Agreement</td>
</tr>
<tr>
<td>LPI</td>
<td>Laser peripheral iridotomy</td>
</tr>
<tr>
<td>LV</td>
<td>Lens vault</td>
</tr>
<tr>
<td>MC-D</td>
<td>McMonnies Chapman-Davies scale</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega hertz</td>
</tr>
<tr>
<td>MIP</td>
<td>Medical Image Perception</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>NA</td>
<td>Narrow Angle</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>NN</td>
<td>Neural networks</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
</tr>
<tr>
<td>ONH</td>
<td>Optic nerve head</td>
</tr>
<tr>
<td>PAC</td>
<td>Primary Angle Closure</td>
</tr>
<tr>
<td>PAC(G)</td>
<td>Primary Angle Closure or Primary Angle Closure Glaucoma</td>
</tr>
<tr>
<td>PACD</td>
<td>Primary angle closure disease</td>
</tr>
<tr>
<td>PACG</td>
<td>Primary Angle Closure Glaucoma</td>
</tr>
<tr>
<td>PAS</td>
<td>Peripheral Anterior Synechiae</td>
</tr>
<tr>
<td>POAG</td>
<td>Primary Open Angle Glaucoma</td>
</tr>
<tr>
<td>PROM’s</td>
<td>Patient Reported Outcome Measure</td>
</tr>
<tr>
<td>PVDF</td>
<td>Polyvinylidene Fluoride</td>
</tr>
<tr>
<td>PVDF-TrFE</td>
<td>Polyvinylidene Fluoride trifluoro ethylene</td>
</tr>
<tr>
<td>PZT</td>
<td>Piezoelectric transducer</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
</tr>
<tr>
<td>RLP</td>
<td>Relative Lens Position</td>
</tr>
<tr>
<td>S</td>
<td>Sclera</td>
</tr>
<tr>
<td>SCPA</td>
<td>Scleral Ciliary process area</td>
</tr>
<tr>
<td>SGGS</td>
<td>Spaeth Gonioscopy Grading Scale</td>
</tr>
<tr>
<td>SL</td>
<td>Schwalbe’s Line</td>
</tr>
<tr>
<td>SL-OCT</td>
<td>Slit lamp Optical Coherence Tomography</td>
</tr>
<tr>
<td>SLD</td>
<td>Super Luminescent Diode</td>
</tr>
<tr>
<td>SS</td>
<td>Scleral Spur</td>
</tr>
<tr>
<td>TCPD</td>
<td>Trabecular ciliary process distance</td>
</tr>
<tr>
<td>TD-OCT</td>
<td>Time domain Optical Coherence Tomography</td>
</tr>
<tr>
<td>TICL</td>
<td>Trabecular irido-contact length</td>
</tr>
<tr>
<td>TISA</td>
<td>Trabecular–iris space area</td>
</tr>
<tr>
<td>TM</td>
<td>Trabecular Meshwork</td>
</tr>
<tr>
<td>UBM</td>
<td>Ultrasound Biomicroscopy</td>
</tr>
<tr>
<td>VBR</td>
<td>Validated Bulbar Redness</td>
</tr>
<tr>
<td>VDS</td>
<td>Verbal descriptor scale</td>
</tr>
<tr>
<td>YAG</td>
<td>Yttrium Aluminium Garnet</td>
</tr>
<tr>
<td>ZAP</td>
<td>Zhongshan Angle closure Prevention</td>
</tr>
</tbody>
</table>
Abstract

Primary Angle Closure Glaucoma (PACG) is a worldwide leading cause of irreversible blindness much more prevalent in Asia than in European-derived populations. Patterns of ethnic differences may account for prevalence variation of the disease. Recent papers have reported a predicted rise in European-derived populations. Ocular risks associated with PAC(G) include an axially small, hypermetropic eye with a large lens. Potentially, there are patients in the UK with ‘at risk’ ocular biometrics predisposing them to PAC(G). Biometric disparities between ethnicities infer morphological variation of PAC(G).

The morphology of PAC(G) can be evaluated using ultrasound biomicroscopy (UBM) and the development of a novel linear probe has enhanced its clinical utility. UBM allows quantitative analysis of the anterior chamber, however, there are inherent difficulties in identifying the landmark scleral spur. Qualitative image analyses are urgently required to assess the morphology of closure. Clinical grading scales (CGS) have been successful in other areas within ophthalmology; their application to PAC(G) is investigated within this thesis.

The specific aims of the thesis are to: a) examine biometric differences between Caucasian & Chinese patients with PAC(G); b) describe the development of a series of CGS for PAC(G) and c) validate the CGS.

Biometric differences between Chinese and Caucasian sample populations exist. The Caucasian cohort exhibit typical biometric findings associated with PAC(G): significantly smaller eyes, shallower anterior chambers, larger lenses, and a significantly shorter vitreous depth, when compared to Chinese counterparts. Biometric differences lend support to variation of PAC(G) mechanisms between ethnicities.

A series of clinical CGS were developed using a ‘consensus’ based approach. The results: utilize psychometric techniques to evaluate inter-observer error; analyse intra-observer agreement by visualizing concordance; target pruning to eliminate inter-observer confusion when constructing the CGS. A new custom-made software was developed to evaluate the performance of the CGS. The results show good intra- and inter- observer repeatability to characterize the morphology of closure.

This is the first study describing a comprehensive method to construct and validate CGS in PAC(G). These can be used to evaluate the morphology of closure and in the future assess the fidelity of PAC(G) management.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Dedicated to Mum, Dad & Aila
Acknowledgements

First, I offer my sincerest gratitude to my supervisor, Professor David Henson, who has supported me throughout my thesis with great patience. Without his encouragement, this thesis would be twice this size. I simply could not wish for a better or friendlier supervisor. I have been fortunate enough to work with Miss Winifred Nolan. I am grateful for her believing in my work; spending the time to develop a clinical protocol and ethical approval; giving me the networking opportunities at Moorfields’ Eye Hospital; involving me with UK Angle Closure Network; and involving me with collaborative studies with Professor Tin Aung’s group at the Singapore National Eye Centre. Without Professor Henson and Miss Winifred Nolan obtaining my NIHR Clinical Doctorate Research Fellowship would not have been possible.

With nearly fifteen years of ocular ultrasound experience, in 2008 I started to teach myself how to use the novel linear UBM technology. After spending two months: reviewing the literature; learning about PAC(G); I applied the previous work of others to devise a clinical protocol to examine patients with PAC(G). The glaucoma team at BMEC are certainly more aware of the morphology of PAC(G). The UBM service has grown to be a super-regional service. Birmingham & Midland Eye Centre has a library of older journals and books. It has been fascinating reviewing the works of Priestly Smith and Torququist. It is interesting how the answers we search for often lie in the past.

I also gratefully acknowledge the support given by the Birmingham & Midland Eye Centre in developing my interests, provided me with the clinical support and without whom I wouldn’t have an office to work in. My ‘study buddy’ Richard Stanton has been a sounding board throughout this PhD and has read many ‘snippets’ of this thesis and has probably read this thesis several times in the process. I am fortunate enough to have been blessed with many pleasant colleagues at BMEC & MREH, many of who have been observers in one study. A special thanks to Manos Tsamis for playing the role of IT services

I have been blessed with very many friends in particular: Dr Waheeda Illahi, Dr Jawaher Alsalem and Ghosya have all been encouraging me throughout and provided support for my family. Tanveer Tariq has supported me tremendously as an ‘Agony Aunt’ throughout the many challenges of the last few years – I would not have soldiered on with him.

My parents receive my deepest gratitude and love for their dedication and the many years of support they have always provided. We all miss my mum, and I can’t thank my father enough for playing both parental roles to Aila as well as myself. Thank you Abu-jaan for: always being there, for your support and for everything we share. Thank you Aila for being patient with your mummy.
Chapter 1 Introduction

1 Rationale of the Study

Primary Angle Closure (PAC) is reported to be the most common type of diagnosed glaucoma in Asia (Foster, 2002) whilst Primary Open Angle Glaucoma (POAG) is more prevalent in African-Caribbean and Caucasian eyes (Congdon et al., 1997) and is more likely to result in irreversible blindness if not treated properly. Quigley et al. (2006) projected that by 2020 PACG will affect 20 million people worldwide, and 5.3 million will be blind. In the UK, PAC(G) affects between 50,000 and 100,000 people with an estimated 1000 cases of irreversible blindness every year, (Azuara-Blanco, 2008) and many more cases of visual impairment and reduced quality of life.

Primary Angle Closure Glaucoma (PACG) and PAC (collectively termed as PAC(G)) is primarily a disease of the anterior segment, which can lead to structural changes at the optic nerve head. Early detection of the anterior segment morphology can prevent structural changes to the optic nerve head (ONH). The anterior chamber angle is viewed with the aid of a gonioscopy lens, however, the complex nature of gonioscopy and its dependency upon skill set and experience make the identification and quantification of anterior segment morphology a difficult task. Results are difficult to compare clinically as they are dependent on experience, technique, skill and documentation, all of which vary between clinicians.

The early works of Smith (1891) and the advent of ultrasound biometry have helped identify the ocular risk factors associated with PAC(G). While good prevalence data on Caucasian populations are lacking, Day et al. (2012) have recently reported a rise in PAC(G) in Caucasian populations. With recent data from EPIC-Norfolk Eye Study (European Prospective Investigation of Cancer) it seems that there are potential Caucasian patients, which fell into the “at risk” category for PAC(G) (Foster et al., 2010; Lowe, 1977b). Chapter 2 evaluates the biometric differences between Singaporean Chinese and UK Caucasian patients with PAC(G).

In recognition of the need to standardize and quantify the anterior segment, Pavlin developed a number of indices (Pavlin et al., 1992a; Pavlin et al., 1992b; Pavlin et al., 1991; Wand et al., 1993) using the scleral spur (SS) as a key anatomical landmark. For the purpose of PAC(G) research, algorithms and software have been developed to quantify geometric angle width and iris thickness as well as the anatomic relationship between the iris and the ciliary body in UBM images (Sakata et al., 2008b). Although UBM allows quantitative measurements of the anterior segment to be made, these quantitative parameters alone may not be sufficient to fully describe the features associated with PAC(G).
Quantitative measures are theoretically useful for comparing anterior segment indices, however, accurate identification of the scleral spur remains a significant problem for image analysis. According to Sakata et al. (2008b) the scleral spur is not identifiable in 28% of patients with narrow angles (NA). The inter-observer variability in quantifying these indices varies. There is 50% variation in measurements of the angle area and 10% variation in linear measurements (Console et al., 2008). The semi-automated nature of quantitative assessment for PAC(G) may compromise its reproducibility and limit its value in clinical practice. Therefore, with currently available technology, UBM is used for qualitative observation in most instances (Nolan, 2008; Sakata et al., 2008b) playing an important role in identifying retro-iris pathophysiology (Gazzard et al., 2001; Gazzard et al., 2003a).

The qualitative evaluation of images using clinical grading scales (CGS) has been successful in other areas within ophthalmology (Bailey et al., 1991; Bencic et al., 2005; Cantor et al., 2003; Chong et al., 2000; Efron, 1998; Efron et al., 2001; Pine et al., 2012; Schulze et al., 2007). The use of CGS has the potential to overcome problems associated with the identification of the SS and the cumbersome nature of measuring anterior segment indices in the clinical setting. This thesis reports on the development of a CGS for PAC(G) in Chapter 3.

Chapter 4 tests the performance of the CGS using custom software, which I have written. Measures of inter- and intra-observer repeatability were obtained from ophthalmologists based in 3 different centres. The CGS were found to be reliable, repeatable and precise. It is hoped that further development and adoption of such scales will lead to a better understanding of the mechanisms of PAC(G) and how the eye responds to treatment.

Chapter 5 concludes the findings of this thesis and discusses future areas of work.
2 Glaucoma

Glaucoma is the commonest cause of irreversible blindness worldwide (Quigley, 1996). It is a heterogeneous disease in which the axons of the retinal ganglion cells within the optic nerve head become damaged, leading to irreversible visual loss with or without an elevated IOP. Quigley (1996) estimated that 66.8 million people would be affected by primary glaucoma and another 6 million by secondary glaucoma by 2002. In a later paper Quigley et al (2006) they revised their predictions and provided further breakdowns of type, gender and blindness.

“60.5 million people will have OAG and ACG in 2010, increasing to 79.6 million by 2020, and of these, 74% will have OAG. Women will comprise 55% of OAG, 70% of PACG, and 59% of all glaucoma in 2010. Asians will represent 47% (nearly 29.8 million) of those with glaucoma and 87% of those with ACG. Bilateral blindness will be present in 4.5 million people with OAG and 3.9 million people with ACG in 2010, rising to 5.9 and 5.3 million people in 2020, respectively.” Quigley et al (2006).

NICE guidelines, in the UK, reported over one million glaucoma-related outpatient visits were seen in the NHS annually (Freeman, 2009; Nice, 2009), however, exact numbers affected by PAC(G) are unknown.

2.1 Classification of Glaucoma

Glaucoma may be classified in several ways, for example, on the basis of the structure of the anterior chamber angle (ACA), aetiology (primary or secondary), age of onset (juvenile, congenital), intra-ocular pressure (IOP), and stage (acute or chronic).

2.1.1 Structure of the Anterior Chamber Angle

Glaucoma may be classified according to the appearance of the anterior chamber angle (ACA), the angle between the iris and the cornea (Dellaporta, 1975). If the iris is close to the posterior surface of the cornea and impedes the flow of aqueous humour to the trabecular meshwork (TM) the condition is called angle closure glaucoma (ACG). If the angle is open then it is called open angle glaucoma (OAG), see figure 2.1.

Figure 2.1 Demonstrates an open angle (left) and a closed angle (right) (Youmaran, 2005)
2.1.2 Aetiology

Both ACG and OAG may be primary or secondary. In primary glaucoma there is no pre-existing ocular pathology that has given rise to glaucoma. In secondary glaucoma there is a pre-existing ocular pathology that has triggered glaucoma, e.g. uveitis, trauma.

The focus of this thesis is PAC(G), therefore, OAG will not be further discussed in this thesis.

3 Primary Angle Closure

In the normal eye, aqueous humour is produced by the ciliary body, behind the iris, and flows through the pupil to drain into the TM, which lies within the ACA (see figure 3.1). PAC(G) is caused by factors that either pull or push the iris up into the angle (i.e. junction of the iris and cornea at the periphery of the anterior chamber), physically blocking drainage of aqueous, which leads to high IOP. The iris can become apposed to the trabecular meshwork leading to impaired and/ or permanent reduction in outflow with a rise in IOP. The mechanistic theory of PAC(G) is discussed in section 3.4.

![Image](image_url)  
Figure 3.1 Anatomy of the ACA showing the flow of aqueous humor in blue (with kind permission of National Eye Institute, National Institutes of Health (NEI/NIH)).

3.1 Prevalence of AC(G)

Although the prevalence and pattern of disease varies across various parts of the world, the majority of those with PAC(G) are East Asian. The number of people with PAC(G) is predicted to increase substantially over the next few years as the result of: an ageing population (Quigley, 1996) and raised awareness of narrow angle pathologies (Foster et al., 2002).
3.1.1 International Prevalence

The reported prevalence of PAC(G) ranges from 0.09% in Wales to 2.87% in China (Rudnicka et al., 2007). 47.5% of the World PAC(G) occurs in China, followed by 23.7% India (Day et al., 2012; Nolan et al., 2007a). These and other prevalence figures have been applied to the projected global populations for 2010 to estimate the absolute numbers of individuals with glaucoma worldwide (table 3.1).

Table 3.1 Prevalence estimates in various regions in participants over 40 years old (Nolan et al., 2007a).

<table>
<thead>
<tr>
<th>Region</th>
<th>Author</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States, Europe &amp; Australia</td>
<td>Baltimore (Caucasians)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Beaver Dam</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Melbourne</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Wales</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Egna-Neumarkt, Italy</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Proyecto, VER (Hispanic)</td>
<td>0.1</td>
</tr>
<tr>
<td>Asia (South)</td>
<td>Andra-Pradesh</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Aravind</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Chennai</td>
<td>0.07</td>
</tr>
<tr>
<td>Asian (East)</td>
<td>Beijing, China</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Guangzou, China</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Tajimi, Japan</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Mongolia</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Singapore</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Thailand</td>
<td>0.9</td>
</tr>
<tr>
<td>Africa</td>
<td>Tanzania</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Temba, South Africa</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Cape coloreds, South Africa</td>
<td>2.3</td>
</tr>
</tbody>
</table>

3.1.2 Prevalence of PAC(G) in Europeans

In the UK, PAC(G) has been estimated to affect between 50,000 and 100,000 people but it is estimated to cause 1000 cases of irreversible blindness every year, (Azuara-Blanco, 2008; Azuara-Blanco et al., 2011) and many more live with a visual impairment and reduced quality of life. PAC(G) is not a common condition in Europeans, and typically has a prevalence rate of around 0.1% in the population aged over 40 years of age (Congdon et al., 1997; Day et al., 2012) or 0.25% (Quigley, 1996). A recent population-based study in northern Italy has found a somewhat higher prevalence of 0.6% (Azuara-Blanco et al., 2011; Bonomi et al., 2000)

Due to the uncertainty surrounding the prevalence of PAC(G) in European derived populations, Day et al. (2012) systematically reviewed and modeled PAC(G) prevalence data from seven population studies. In their study, PAC(G) was defined according to the
ISGEO definition and prevalence estimates were applied to the 2010 United Nations projected population figures to estimate future case numbers. Day’s meta-analysis concluded that 0.4% of the population over 40 years of age have PACG. Three-quarters of cases occur in female subjects. Day et al. (2012) report PACG is 2-4 times more common than previous estimates.

Table 3.2 Estimated population with PACG (thousands) by region (& 95% CI), the table shows that by the year 2050 percentage increase in PAC(G) will increase by 50.7 % in the UK, 30 % in Europe and 67.4 % in the USA compared to 2010 (Day et al., 2012).

<table>
<thead>
<tr>
<th></th>
<th>Number of PACG cases (thousands) 40 years old+</th>
<th>% Increase in PACG cases relative to 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>Europe</td>
</tr>
<tr>
<td>2010</td>
<td>130 (71–211)</td>
<td>1600 (873–2604)</td>
</tr>
<tr>
<td>2015</td>
<td>141 (77–229)</td>
<td>1663 (902–2713)</td>
</tr>
<tr>
<td>2020</td>
<td>154 (85–248)</td>
<td>1743 (953–2837)</td>
</tr>
<tr>
<td>2025</td>
<td>160 (89–258)</td>
<td>1831 (1012–2967)</td>
</tr>
<tr>
<td>2030</td>
<td>165 (93–265)</td>
<td>1934 (1082–3115)</td>
</tr>
<tr>
<td>2040</td>
<td>188 (108–302)</td>
<td>2102 (1198–3344)</td>
</tr>
<tr>
<td>2050</td>
<td>195 (112–309)</td>
<td>2080 (1208–3285)</td>
</tr>
</tbody>
</table>

After accounting for the projected demographic changes in these areas, cases are predicted to increase by 19% in the UK, 9% in Europe and 18% in the USA within the next decade (Day et al., 2012). The authors did not take account ethnic variations within the different populations (in the UK 86% of the 2011 population were Caucasian (Consensus, 2012)). Table 3.2 gives the projected percentage increase in PACG up to 2050. By 2020 the number of cases are projected to increase by 19% in the UK, 9% in Europe 18% in Europe.

3.2 Nomenclature & Terminology

Temporal changes in disease, epidemiology, management and comparisons across different ethnic groups are made more challenging by variations in terminology. The term “glaucoma” has been used loosely throughout the literature. Since the ISGEO working group met in 1998, the term glaucoma is reserved for eyes with established, visually significant end organ (optic nerve) damage (Foster et al., 2002).

There are several terms used interchangeably to describe the anatomical predisposition to “closure.” Arkell et al. (1987) described the term “occludable angle” as an angle in which the trabecular meshwork was not visible throughout three-quarters or more of the angle circumference in the primary position without manipulation or indentation. George et al. (2003) defined occludable angle where less than 180 degrees of the filtering TM was visible before indentation. The terminologies “occludable” and “Narrow Angle” (NA) and irido-trabecular contact (ITC) are often used synonymously. In epidemiological research ITC has
been defined as an angle in which ≥270° of the posterior TM cannot be seen, however, with imaging devices it is often defined on the basis of the iris touching any part of the TM. The variability of the definition of PAC(G) in prevalence surveys makes it difficult to compare the data between studies (Foster et al., 2002; Nolan, 2007). According to Foster et al., (2002) these definitions have not been validated, this is “too stringent a term and can be used inappropriately.”

3.3 Classification of PAC(G)

There are many ways to classify PAC(G) according to the type of PAC(G), disease staging or anatomical mechanisms. All of which are all discussed below.

3.3.1 Disease staging

The current International Society Geographical & Epidemiological Ophthalmology (ISGEO) scheme is based upon the natural history of PAC and the spectrum of PAC(G). Each stage, as seen in table 3.3, indicates an increment in tissue damage likely to influence a patient’s visual function (Foster et al., 2002; He et al., 2006b; Yip et al., 2006).

Table 3.3 ISGEO classification of PAC(G) along with a description of each item (Foster et al., 2002)

<table>
<thead>
<tr>
<th>Classification terms</th>
<th>Description of term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Angle Closure Suspect (PACS)</td>
<td>Eyes with an anatomical predisposition toward PAC - where appositional contact between the peripheral iris and posterior TM is considered</td>
</tr>
<tr>
<td>Primary Angle Closure (PAC)</td>
<td>Eyes in which there has been significant closure of the angle that is associated with tissue damage (peripheral anterior synechia, iris ischaemia or “glaukomfleken” lens opacities). The optic disc and visual field are normal.</td>
</tr>
<tr>
<td>Primary Angle Closure Glaucoma (PAGC)</td>
<td>GON combined with PAC (Kim et al., 1997a).</td>
</tr>
</tbody>
</table>

It is still unclear which ‘occludable’ angles or suspects go on to develop PAC or PAC(G). There are few longitudinal studies, which have evaluated the natural history of PAC(G) and literature that predates ISGEO classification, may use other ways of classifying PAC(G). More recently the term primary angle closure disease (PACD) encompasses the spectrum of PAC suspect, PAC and PAC(G) (Thomas et al., 2012; Walland et al., 2011).

3.3.2 Subtypes according to Chronicity

Traditionally, subtypes of PAC(G) are classified according to the chronicity: sub acute (Sihota et al., 2000); latent, acute; chronic; and absolute (Lowe, 1988). Latent or chronic stages suggest there are anatomical predispositions present. Chronic stages refer to the situation where there is an insidious, progressive closing off of the trabecular meshwork, resulting in a gradual rise in IOP. In sub-acute there may be mild symptomatic episodes,
which suggest incomplete PAC(G). Acute describes a symptomatic PAC(G), which is severe. Clinically, the sub-acute and acute closure stages may merge. The absolute stage is the end stage of untreated PACG when irreversible blindness results. These can be seen along with their descriptions in table 3.4.

Table 3.4 shows the various stages of Angle Closure, (tabulated descriptions from (Ming et al., 2004)

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent</td>
<td>angle-closure inducible</td>
</tr>
<tr>
<td>Chronic</td>
<td>high IOP, no symptoms</td>
</tr>
<tr>
<td>Intermittent or sub-acute</td>
<td>remitting symptoms</td>
</tr>
<tr>
<td>Acute</td>
<td>severe symptoms</td>
</tr>
<tr>
<td>Absolute</td>
<td>end stage of disease</td>
</tr>
</tbody>
</table>

It has been reported that acute symptomatic episodes are more common in Caucasians while a chronic asymptomatic form is more common in Asian (He et al., 2006b), South East Asians and Africans (Alper et al., 1968; Clemmesen et al., 1976; Tomlinson et al., 1973). The considerable overlap between stages of this classification system to has been superseded by the ISGEO classification (Kim et al., 1997b).

3.3.3 Anatomical causes of PAC(G)

Similar to the classification described by Benedikt (1978). Ritch et al. (1996) popularised a classification system based upon the anatomical level of TM obstruction. This included four distinct causes of closure: pupil-block; plateau iris; lens-related and retro-lenticular, representing progressively more posterior sites of obstruction to aqueous flow.

The use of anatomical causes of closure is complicated when multiple mechanisms co-exist and this classification deals only with the level of block and excludes other structural mechanisms, e.g. the iris, ciliary body may contribute to closure. These descriptions give details of the level of TM obstruction but do not give details of visual loss in PAC(G) (Gazzard et al., 2002).

3.3.4 Alternative Classification

According to Yip et al. (2006), the two schemes (disease staging and anatomical mechanism) should be used in parallel in order to account for the stage of disease as well as the mechanism of closure (see table 3.5).

Yip et al. (2006) proposed that this approach may be useful in the clinical setting when the patient is symptomatic and when identifying the anatomical mechanism of closure. This may help to provide a combined classification encompassing visual function and prognosis.
Table 3.5 Classification of PAC(G) using parallel schemes specifying disease stage & mechanism of closure (Yip et al., 2006).

<table>
<thead>
<tr>
<th>Disease staging</th>
<th>ISGEO</th>
<th>Combined ‘stage &amp; mechanism’</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1. Primary Angle-Closure Suspect (PACS)</strong></td>
<td>Narrow drainage angle – An anatomical predisposition to closure, but no signs of tissue damage or dysfunction: normal IOP, disc and visual field. No peripheral anterior synechiae</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2. Primary Angle-Closure (PAC)</strong></td>
<td>Partially or totally closed angle with synechiae and/or raised IOP. The disc and visual field show no signs of glaucomatous optic neuropathy</td>
<td></td>
</tr>
<tr>
<td>a. non-ischemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. ischemic – With tissue injury e.g. iris whorling or stromal atrophy, symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage 3. Primary Angle-closure with glaucomatous optic neuropathy (PACG)</strong></td>
<td>Structural changes consistent with glaucoma in the RNFL, neuro-retinal rim and/ or visual field</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism of closure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Pupil-block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Anterior non-pupil-block, including plateau iris and peripheral iris crowding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lens-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Factors behind the lens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6 compares the level of information provided by the traditional ISGEO scheme to that proposed by Yip.

Table 3.6 Comparison of traditional and combined staging and mechanism classification of angle-closure glaucoma (Yip et al., 2006)

<table>
<thead>
<tr>
<th>Classification</th>
<th>ISGEO</th>
<th>Combined ‘stage &amp; mechanism’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosological basis</td>
<td>Site-specific tissue damage &amp; dysfunction</td>
<td>Site-specific tissue damage &amp; dysfunction</td>
</tr>
<tr>
<td></td>
<td>Symptoms</td>
<td>Presumed mechanism causing closure</td>
</tr>
<tr>
<td>Specifies visual dysfunction?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indicates prognosis?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Guides targeted intervention?</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

3.4 Mechanistic theory of Primary Angle Closure

The prerequisite for PAC is the apposition of the peripheral iris to the trabecular meshwork (TM). This apposition or ITC can be constant or intermittent. It can lead to trabecular dysfunction, peripheral anterior synechiae (PAS), elevated intraocular pressure (IOP), optic neuropathy, functional loss and visual impairment. The resistance of the aqueous outflow causes a pressure differential between the posterior and anterior chamber is created. Curran (1920) suggested that aqueous was impeded when moving through the pupil “on account of the iris hugging the lens.
3.4.1 Pupillary Block Mechanism

Lowe (1966) suggested that pupillary block was the result of excessive iris-lens contact (at the pupillary margin) known as iris bombe and prevents the aqueous flowing from the posterior to the anterior chamber. Pressure from the continued secretion of aqueous into the posterior chamber by the ciliary body pushes the peripheral iris anteriorly (causing a forward-bowing iris).

According to Mapstone (1968), using vector force analysis, pupillary block results from a "pupil-blocking force (PBF)" the sum of posterior forces exerted by iris muscles and material stretch that holds the iris tip near the anterior lens surface despite a counteracting pressure difference. He concluded that there was a major contribution from the sphincter muscle (S, figure 3.2) pulling in a direction perpendicular to the anterior-posterior lens axis, $S \cos \alpha$ (Mapstone, 1981). This centripetal pulling force causes irido-lenticular contact (or iris bombe).

Mapstone’s model predicts that the PBF would increase if the lens is more anteriorly positioned. As seen in the equation below, vector force analysis takes into account the magnitude and direction of a force, which will vary with anatomical relationships, such as the position of the iris root.

Mapstone (1968) described

$$PBF = (D + E) \cos a + S \cos b$$

where PBF is the pupil blocking force, D is the pupil dilating force, E is the iris stretching force, S is the Sphincter Contraction Force, a is the angle between D & E, b is the angle between S and the irido-lenticular apposition to the centre of the lens.

In 1978 (Friedland) developed the first hydrodynamic model of AH flow in the posterior and anterior chambers. This model assumed axial symmetry and neglected time dependence, the pupillary rough, the dynamic iris (rollup) and AH convection currents. The geometry of the eye was simplified in this model so that a solution to the Stokes’ equations (fluid flow where inertial forces are small compared with viscous forces) could be obtained in the
anterior and posterior chambers. To understand how the iris takes on its typically convex shape (bowed forward slightly toward the cornea), he concluded that the forward curvature of the iris increases with more anterior lens position and with a mid-dilated pupil.

Tiedeman (1991) analysed the positions of the iris, cornea, and lens using a model, which treated the iris as a pressure relief valve where the edges of the iris were fixed. Tension was placed on the iris at the inner radius and there was uniform pressure acting on the lower surface. The model assumed that iris is infinitely thin, whose properties did not change, and neglected aqueous flow.

Heys et al. (2001) presented a mathematical model evaluating a coupled AH-iris system that accounts for the contribution of aqueous flow and passive iris deformability to the iris contour. The AH was modelled as a Newtonian fluid and the iris is modelled as linear elastic solid. This model supported the hypothesis that passive iris deformation can produce the iris contours observed using UBM.

Silver (2004) modelled aqueous flow through the “iris-lens channel” driven by the pressure differential between the two chambers. Viscous forces within the aqueous govern flow resistance and the pressure differential. AH was modelled as a three-dimensional viscous, homogeneous, isotropic fluid. The critical geometry associated with this flow was taken to be the iris-lens channel. This channel is posterior to the iris and just peripheral to the pupil margin. Its posterior limit, taken to be in the shape of a sector of a sphere, is the anterior surface of the lens, which is defined by its radius of curvature, R. Its anterior limit, also taken to be in the shape of a sector of a sphere, is the posterior surface of the iris. The geometry and dimensions of a specific iris-lens channel determine whether the pressure differential is of clinical significance.

After initially using computer simulations of interactions between the aqueous and “active iris.” Huang et al. (2004) performed steady-state simulations of the AH–iris fluid–solid system. Their model outputs compared favourably with Mapstone’s analysis. The study evaluated anatomical risk factors and quantified their contributions to pupillary block and PAC(G) showing that the greater anterior lens curvature and shorter irido-zonular distance contribute significantly to pupillary block. However, blocking the steady flow of aqueous did not explain the increased anterior bowing when the pupil dilates. Amini et al. (2012) conducted an in vivo human study, an ex vivo porcine experiment and an in silico computational model. Their findings confirmed that the posterior location of the dilator muscle could cause bowing of the anterior iris during dilation.
Zheng et al (2012) also used vector force analysis in conjunction with pupil state to obtain results that compared favourably with Mapstone’s pupil block analysis. Again, they implicated both iris-lens interactions and iris property differences.

Historically the pupil block mechanism has received much attention. However, it is not unusual for patients to experience recurrent PAC(G) attacks after iridectomy (Wand et al., 1977) suggesting that there are non-pupil block mechanisms in PAC(G).

### 3.4.2 Non-Pupil Block Mechanisms

The occurrence of NA’s in eyes with relatively normal ACD and a relatively flat iris plane had been noted by Gradle et al. (1940). Barkan (1954) noted that 20% of eyes with congestive NA glaucoma had normal ACD, minimal pupil block and little iris bombe. Chandler et al. (1965) also presented a case which continued to have NA glaucoma post iridectomy and that this was most likely to occur in younger patients (Wand et al., 1977). The termed “Plateau Iris” was coined by (Tornquist, 1958b) describing a flat iris and a narrow angle secondary to an abrupt angulation at the root of the iris.

Non-pupil block mechanisms were further sub classified by Wand et al. (1977) into plateau iris configuration (PIC) and plateau iris syndrome (PIS). Plateau iris was further divided into complete and incomplete forms. Complete plateau iris has a high plateau and covers the ACA after dilation while incomplete syndrome only partially covers the ACA. The IOP may or may not elevate after dilating the pupil. However, peripheral anterior synchiae (PAS) may develop over time Wand et al. (1977). Terminology of incomplete plateau syndrome and plateau iris configuration is used interchangeably in the clinical setting. Figure 3.3 shows complete Plateau Iris occludes the ACA at the level of A.

![Diagram of Plateau Iris Syndrome](image)

*Figure 3.3 Schematic representation of plateau iris syndrome. A. Complete plateau iris syndrome. Iris will occlude the trabecular meshwork up to Schwalbe’s line and intraocular pressure will rise. B and C. Incomplete plateau iris syndrome. Iris will occlude the angle to the level of mid-meshwork. The lower the plateau relative to the trabecular meshwork, the less likely a rise in intraocular pressure. D. Low plateau (Ritch et al., 1996).*
In the incomplete form the level of the plateau is below Schwalbe’s line occluding the angle to the level of mid-meshwork (B and C). D shows a low-lying plateau. In plateau iris syndrome, the physical presence of an anteriorly placed ciliary body forces the peripheral iris into the ACA. However, this model assumes that the iris inserts at the ciliary face.

The downside of these theoretical modelling for non-pupil block and pupil block mechanisms is that multiple mechanisms can co-exist to generate a complex PAC(G). The pathogenesis of PAC(G) and theoretical mechanisms are discussed further in section 5. Whilst pupil block is still considered to be the main mechanism of PAC(G) non-pupil block mechanisms like plateau iris, lenticular mechanisms, the role of the iris etcetera are discussed in this chapter. It is unclear which morphologies go on to cause structural damage.

### 3.5 Anterior Segment Damage in PAC(G)

PAC(G) may cause structural damage in many ways: corneal endothelial cell loss occurs after ‘symptomatic’ acute angle closure. With high IOP’s the iris may suffer ischaemic damage to the iris musculature resulting in ‘iris whorling’ (distortion of the radial orientated fibres) and a dilated unresponsive pupil. The lens epithelium may suffer focal necrosis causing ‘glaucomaflecken’. The TM can become damaged by the formation of PAS or as a result of longstanding ITC or appositional closure (Sihota, 2011). Optic neuropathy in PAC(G) can present in one of two ways 1) after an acute attack or 2) as an excavated disc with a visual field defect. Appositional closure can be prolonged or intermittent and can be accompanied by PAS. Appositional closure and PAS most commonly form in the superior angle causing pigmentation of the TM and, in the angle, a blotchy pigmented appearance (Desjardins et al., 1985; Ritch, 2001).

### 3.6 Risk factors for PAC(G)

#### 3.6.1 Demographic factors

Prevalence and incidence data show PAC(G) is more common among women (Lowe, 1972b), people of East Asian origin and in the elderly (Foster et al., 2001). Some of these factors can be explained by trends in ocular biometry (Lowe, 1970b).

#### 3.6.2 Ocular Risks

The advent of ocular ultrasound in the 1960’s allowed the examination of the eye and orbit in vivo (Byrne et al., 2002). Lowe (1967) identified several biometric traits for PAC(G). Compared with unaffected eyes the PAC(G) eye has a smaller corneal diameter, short axial length, thick lens, shallow anterior chamber, smaller anterior or posterior corneal curvature, smaller radius of anterior surface of lens and more anteriorly placed crystalline lens. The
importance of biometry and the ocular risks are discussed in more detail in section 4 along with anatomical and physiological mechanism of disease.

3.7 Anterior Segment Examinations for PAC(G)

The diagnosis of PAC(G) is traditionally made by 1) slit lamp biomicroscopy 2) tonometry (measurement of Intra-ocular pressure 3) gonioscopy (assessment of the anterior chamber angles) along with 4) assessment of visual function by visual field testing and 5) imaging of the optic disc.

3.7.1 Gonioscopy

Gonioscopy is the “reference standard” for diagnosing PAC(G), and remains an essential component of the complete ocular examination (Dellaporta, 1975; Palmberg, 1996; Spaeth, 1978; Spaeth et al., 1995), figure 3.4. Under normal conditions the ACA is not visible with a slit lamp as total internal reflection occurs at the cornea – air surface, when the angle of incident light exceeds the critical angle.

Figure 3.4 demonstrates an open angle on gonioscopy (Ming et al., 2004).

The purpose of gonioscopy is primarily to determine if there is any pathology of the ACA – whether it is closed and if there are any abnormalities that may cause glaucoma. More specifically it helps to establish the level of iris insertion, the shape and profile of the peripheral iris, estimate the width of the angle, determine the degree of trabecular pigmentation and detect irido-trabecular apposition or peripheral anterior synechiae (EGS, 2008). According to European Glaucoma Society (EGS) guidelines gonioscopy should be performed in a dark room, using the thinnest beam, taking care to avoid shining the light through the pupil (EGS, 2008).

3.7.1.1 Grading gonioscopy findings

There are several grading systems of the ACA and all aim to standardize the recording of gonioscopy findings (Shaffer et al., 1957). There are three main grading systems Scheie, Shaffer and Spaeth (Lowe, 1995a) - each with its own strengths and weaknesses.
3.7.1.2 Scheie System

In 1957, Scheie proposed a descriptive grading system in which Roman numerals represent the degree of closure based upon the visualization of the ACA’s structures. Scheie’s descriptive five stage (or point) grading system describes the “openness of the angle” according to the structures visible by gonioscopy see figure 3.5. Scheie also described angle pigmentation on a scale from 0 (no pigmentation) to IV (heavy pigmentation). An important weakness of this system is that the number of structures seen can vary considerably depending on the direction of gaze and the orientation of the gonioscope lens.

![Figure 3.5 Scheie Classification illustrating a 5-point system of angle depth based on openness of angle & structures visualized higher numbers signify a narrower angle, with “IV” representing a closed angle (Longmuir, 2010).](image)

3.7.1.3 Shaffer System

In 1960, Shaffer devised a 5-point descriptive grading system, which included estimates of the width of the peripheral iris insertion (i.e. the point of insertion of the iris to the internal lining of the eye) at the trabecular meshwork (Shaffer et al., 1957). It describes the geometric width of the irido-corneal angle as seen in figure 3.6. Description of grades and an approximation of angle width are listed in Table 3.7.

Table 3.7 Showing the 5-point Shaffer Grading System describing ACA width and description of ACA & corresponding grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Angle width</th>
<th>Description of angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4</td>
<td>45°- 35° angle</td>
<td>Wide open</td>
</tr>
<tr>
<td>Grade 3</td>
<td>35°- 20° angle</td>
<td>Wide open</td>
</tr>
<tr>
<td>Grade 2</td>
<td>20° angle</td>
<td>Narrow</td>
</tr>
<tr>
<td>Grade 1</td>
<td>&lt; 10° angle</td>
<td>Extremely narrow</td>
</tr>
<tr>
<td>Slit</td>
<td>0° angle</td>
<td>Narrowed to slit</td>
</tr>
</tbody>
</table>
3.7.1.4 Spaeth-Modified Grading System

In 1971, Spaeth proposed the Spaeth’s gonioscopic grading system (SGGS) see table 3.8. Grading of the iris insertion, angular approach, peripheral iris and pigmentation are given in order to document the level and involvement of closure.

Table 3.8 Spaeth Gonioscopic Grading System evaluating iris insertion, angular approach, peripheral iris configuration & degree of TM pigmentation. SL – Schwalbe’s Line; SS – scleral spur; CB –ciliary body

<table>
<thead>
<tr>
<th>Iris Insertion</th>
<th>Angular Approach</th>
<th>Peripheral Iris</th>
<th>Pigment Meshwork</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Anterior to SL</td>
<td>0 to 50</td>
<td>r regular</td>
<td>0 no pigment</td>
</tr>
<tr>
<td>B Between SL &amp; SS</td>
<td>50 to 100</td>
<td>f flat</td>
<td>1+ minimal</td>
</tr>
<tr>
<td>C SS visible</td>
<td>100 to 180</td>
<td>B bowed anteriorly</td>
<td>2+ mild</td>
</tr>
<tr>
<td>D deep with CB visible</td>
<td>180 to 280</td>
<td>p plateau iris</td>
<td>3+ moderate</td>
</tr>
<tr>
<td>E &gt; 1 mm CB visible</td>
<td>280 to 450</td>
<td>q queer</td>
<td>4+ intense</td>
</tr>
</tbody>
</table>

The SGGS allows the most detailed recording of angle characteristics including the geometric width of the irido-trabecular angle, the iris profile, as well as the true and apparent levels of insertion.
3.7.1.5 Drawbacks of Gonioscopy

Although gonioscopy is the reference standard in assessing the ACA it has many disadvantages. It is a highly subjective technique, requiring great skill to determine mechanisms of closure (Ritch et al., 1992). Gonioscopy is, unfortunately, not widely performed in routine clinical practice because:

**Training, practice required.** Gonioscopy is a skill that requires training and practice to master where recognizing angle landmarks can be difficult.

**Subjective assessment.** Gonioscopy provides qualitative information, and the use of different grading schemes and types of gonioscopic lenses leads to variability in angle assessment. Quantitative analysis of the ACA cannot be made.

**Technical confounders.** The light of the slit lamp causes pupillary constriction, drawing the iris away from the angle. With inadvertent pressure from the goniolens this can artificially open the angle. Intermittent closure can be missed and not until the disease has become chronic with PAS may it be seen. It is not possible to see how the iris and ACA change during dynamic pupillary changes.

**Corneal contact.** The goniolens requires topical anaesthesia, corneal contact and causes discomfort to the patient.

**Limitations of gonioscopy technique.** There is an inability to visualize structure and such as the ciliary body, lens and zonules as well as possible causes of PAC(G) such as iridociliary cysts, masses and plateau iris syndrome, e.g. relationship of iris to anterior surface of lens, position of ciliary body etc. (modified from Asrani et al., 2011).

3.7.2 Limbal Chamber Depth

The slit lamp grading of the limbal chamber depth (LCD) gives an indication of the width of the ACA. LCD can be assessed by the technique described by Van Herick et al. (1969), where a narrow slit of light is projected onto the peripheral cornea at an angle of 60° as near as possible to the limbus. This results in a slit image as seen in figure 3.8.

![Figure 3.8](image)

Figure 3.8 Schematic diagram of the slit lamp image in the Van Herick method, where: SC= Slit on cornea; ACA = anterior chamber angle; SI – slit on iris (EGS, 2008).

If the distance between the posterior surface of the cornea and the iris has at least the same width as the slit projected onto the cornea, the ACA is wide open and therefore PAC(G) is unlikely. Van Herick’s test is a five-point grading scheme where Grade 4 of Van Herick’s classification depicts a wide-open ACA (see table 3.9). If there is no space between the corneal and iris slit image the ACA is closed and PAC(G) is likely.
Table 3.9 Summary the grading of Van Herick’s technique. The grading is numerical grade representing the relationship between the corneal slit & ACD. The interpretation is also given in terms of likelihood of angle closure and the approximate size of the ACA (EGS, 2003). Where PAC – angle closure; ACD – anterior chamber depth; SC – cornea slit image

<table>
<thead>
<tr>
<th>Grade</th>
<th>Relation between SC &amp; ACD</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1:1 or higher</td>
<td>AC unlikely; ACA approx. 35°-45°</td>
</tr>
<tr>
<td>3</td>
<td>1:1/2</td>
<td>AC unlikely; ACA 20° - 35°</td>
</tr>
<tr>
<td>2</td>
<td>1: 1/4</td>
<td>AC possible, ACA 20°</td>
</tr>
<tr>
<td>1</td>
<td>1:&lt; 1/4</td>
<td>AC likely, ACA 10°</td>
</tr>
<tr>
<td>0</td>
<td>closed</td>
<td>AC, ACA 0°</td>
</tr>
</tbody>
</table>

Foster et al. (2000b) devised a modified limbal grading scale which graded LCD as a percentage fraction of the thickness of the adjacent cornea in a 7-point scale: 0%, 5%, 15%, 25%, 40%, 75% and 100%. Despite the uneven scale increments, the modified scheme gives enhanced performance (area under ROC curve) in detection of established PACG (0.955 compared to 0.888 for Van Herick’s test). The 5% grade gave greatest sensitivity (91%) and specificity (93%) for the detection of PACG. Assessment of the LCD is useful in cases where gonioscopy is not available (Congdon et al., 1999)

### 3.7.3 Provocation testing

Provocative testing involves changing the normal structure of the eye (e.g. pupil dilation) in a way that is likely to induce an increase in IOP in eyes with an occludable angle (Lowe, 1967). Many provocative tests have been suggested and evaluated over time (Hung et al., 1979; Ishikawa et al., 1999; Kim et al., 2007; Leung et al., 2007; Mingying et al., 1997; Pavlin et al., 1999; Pavlin et al., 1995b; Sihota et al., 2007). The principle of a provocation test (or dilation) either: 1) increases the relative pupil block mechanism or 2) the iris folds into the ACA and occludes TM. The following sections describe the main types of provocative tests.

#### 3.7.3.1 Mydriatic Test

The use of a mydriatic as a provocative test has been proposed many times. Such tests are not physiological, have frequent false negatives, are time consuming and often require the patient to wait for reversal of the mydriasis before they can leave (Lowe, 1967). Severe damage has been seen to follow phenylephrine provocative tests in about 10% of eyes (Pavlin et al., 1999).

#### 3.7.3.2 Dark Room Provocation Test

Placing patient in the dark, where pupil dilation can trigger an attack of PAC(G), has been widely reported on (Leung et al., 2007; Mingying et al., 1997; Sakata et al., 2008a; See et al., 2007; Sihota et al., 2007; Woo et al., 1999). It forms a part of a routine clinical protocol
when examining patients with PAC(G) at BMEC where a positive outcome (raised IOP) can identify patients at risk of PAC(G). Li et al. (2012) found that there was little additional change in the angle configuration after three minutes of dark adaptation (DA).

3.7.3.3 Prone Provocation Test

Prone provocation testing requires the patient to be supine, face down with eyes open for one hour (Hung, 1990; Hung et al., 1979; Lowe, 1967). An IOP increase of approximately 8mmHg is considered positive along with gonioscopy closure. However, the anterior movement of the lens diaphragm can induce a closed angle attack. Interestingly, the most common head posture for vitreo-retinal patients may induce an attack in at risk patients (Sutter et al., 2003).

3.7.4 Anterior Segment Imaging

In addition to gonioscopy, anterior segment imaging technologies are useful to elucidate the mechanism of PAC(G) offering the possibility of non-contact cross-sectional imaging of the cornea and whole anterior segment (Pavlin et al., 1991); (Nolan et al., 2007b). Approaches such as rotating Scheimpflug imaging and anterior segment optical coherence tomography (AS-OCT) provide sharp and crisp images from the anterior corneal surface through to the posterior crystalline lens. UBM has also been instrumental in understanding the mechanisms of PAC(G). UBM is only briefly discussed below, a more extensive discussion can be found in the following chapter.

3.7.4.1 Ultrasound Biomicroscopy

UBM is an imaging modality that uses high-frequency ultrasound (usually 50 MHz) to give cross-sectional in vivo images of anterior chamber, the cornea, iris, lens zonules and ciliary body. The cornea, sclera, iris and ciliary body are highly reflective and can be seen easily, see figure 3.9. UBM differs from traditional ocular ultrasound imaging by the use of higher frequency transducers which provide a higher resolution but with lower penetration (Pavlin, 1995).
The development of UBM has revolutionised the understanding of the anatomy, pathophysiology and mechanisms of AC(G) (Pavlin et al., 1991; Pavlin et al., 1994; Pavlin et al., 1996; Pavlin et al., 1995c; Pavlin et al., 1992c). UBM provides real-time imaging of the various anterior segment structures (Pavlin, 1995; Pavlin et al., 1992a) and can document the effects of illumination, pharmacological and surgical interventions. (Macken et al., 1995; Pavlin, 1995; Pavlin et al., 1997a; Pavlin et al., 1995b; Pavlin et al., 1997b). UBM, unlike AS-OCT, enables visualization of retro-iris structures.

3.7.4.2 Anterior Segment Optical Coherence Tomography

OCT is a non-contact form of imaging that can provide cross-sectional images of living tissue. The method was first described by Huang et al. (1991) and was based on measuring the delay of light (mainly infrared) reflected from tissues. A light beam is directed onto biological tissue and the intensity and time delay of reflections returning from the tissue are compared with light that has travelled a known reference path. Early OCT axial resolution was 10\(\mu\)m using a wavelength of 800nm.

A time-domain (TD)-OCT system operating at a wavelength of 1310 nm and a line rate of 2 kHz has been commercialized for ocular anterior segment imaging (Visante OCT; Carl Zeiss Meditec, Dublin, California). However, high-speed Fourier Domain-OCT (FD-OCT) systems operating with swept source FD-OCT have higher axial and lateral resolutions. A comparison between TD-OCT and FD-OCT systems can be seen in table 3.10. Despite the high-resolution, some FD-OCT modalities are susceptible to asymmetric overlapping artefacts, referred to as the ‘complex conjugate’ artefacts that can corrupt the FD-OCT image.

Table 3.10 Shows the different properties of various time domain (TD) and Fourier domain (FD) OCT where SLD = Super luminescent Light Diode.

<table>
<thead>
<tr>
<th>TD-OCT</th>
<th>FD-OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visante</td>
<td>Slit lamp</td>
</tr>
<tr>
<td>Beam Width</td>
<td>1310 (SLD)</td>
</tr>
<tr>
<td>Resolution Axial ((\mu)m)</td>
<td>18</td>
</tr>
<tr>
<td>Lateral ((\mu)m)</td>
<td>60</td>
</tr>
<tr>
<td>Scan size Depth</td>
<td>6</td>
</tr>
<tr>
<td>Width</td>
<td>16</td>
</tr>
<tr>
<td>Frames/ sec</td>
<td>2000</td>
</tr>
</tbody>
</table>

AS-OCT has many advantages, such as its non-contact nature, convenience, high resolution and wide field. Although imaging depths are not as deep as with traditional UBM, the
resolution of OCT is much higher (10-100X) than standard clinical ultrasound. However, OCT is unable to penetrate pigmented tissues, such as the iris pigment epithelium, and provide images of the ciliary body. Although FD-OCT is a new and exciting technology, there have been advancements in UBM probe technology, which improve its utility in the clinical setting. The following chapter discusses the development of ophthalmic ultrasound biometry.

3.8 Treatment

Management of PAC(G) is aimed at modifying the anterior segment configuration before irreversible trabecular dysfunction and GON occurs (Friedman et al., 2012). Ritch et al. (1998) have proposed that the anterior forces that contribute to closure are eliminated first. This is line with the opinion that a peripheral iridotomy should be performed to eliminate the pupil block forces (Kumar et al., 2008b; Kumar et al., 2009). Ritch et al. (1998) suggested the phenotypic classification of the level of block leads to TM obstruction and this may be useful in the selection of treatment, see table 3.11. This mechanistic management is also described in EGS guidelines (EGS, 2008). However, this decision tree still requires further definition.

Table 3.11 Ritch et al. (1998) treatment protocol when identifying the level of block

<table>
<thead>
<tr>
<th>Level of block leading to TM obstruction</th>
<th>Example of mechanism</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iris</td>
<td>Pupil Block</td>
<td>Iridotomy</td>
</tr>
<tr>
<td>Lens</td>
<td>Phacomorphic</td>
<td>Lens Extraction</td>
</tr>
<tr>
<td>Ciliary Body</td>
<td>Plateau Iris</td>
<td>Iridoplasty</td>
</tr>
<tr>
<td>Posterior Forces</td>
<td>Aqueous Misdirection, Uveal or supra-choroidal effusion</td>
<td>Vitrectomy/ Steroids</td>
</tr>
</tbody>
</table>

If, for example, a patient presents with narrow angles and high IOP due to a non-pupil mechanisms and/or a basal iris insertion then LPI will not always open the ACA. The residual mechanism post LPI may also require evaluation.

3.8.1 Medical Treatment

Topical medications act by either decreasing the rate of aqueous production or increasing the rate of outflow, e.g. prostaglandins increase outflow and beta-blocker decrease production. Miotic agents such as pilocarpine may also be used to constrict the pupil and pull the peripheral iris away from the TM thereby opening the angle and increasing the outflow. Long-term use of pilocarpine can result in the development of posterior synechiae and pupil miosis and can make future cataract surgery technically difficult. Miotics are widely available and can be used in a low dose form for PAC(G) patients with plateau iris syndrome and residual appositional closure following iridotomy and iridoplasty.
3.8.2 Laser Peripheral Iridotomy

Laser peripheral iridotomy (LPI) alleviates pupillary block by allowing aqueous to bypass the pupil eliminating the pressure differential between the two chambers. The iris loses its convex configuration and falls away from the TM, resulting in the partial or complete opening of the angle. LPI eliminates appositional closure due to pupillary block and removes the principal causal mechanism underlying PAS development (Ritch et al., 1995). LPI lowers existing raised IOP, or prevents future IOP elevation, which can lead to optic neuropathy.

LPI is the treatment of choice for all PAC(G), it replaced surgical iridectomy as first line treatment of PAC(G) in the late 1970's with the advent of argon and then Nd:YAG laser technology. LPI is an effective treatment for light-coloured irides, however, African, Asian and Chinese irides are often thicker and more heavily pigmented and the YAG laser is less effective (Ho et al., 1994). de Silva et al. (2007) described a combined argon–YAG laser as an effective technique for dark irides of African and Asian patients. While there is general consensus that nearly all cases with PAC should have LPI, there is less agreement on its profilative use (Thomas et al., 2012). LPI relieves the contribution of pupillary block component to the angle narrowing, but not closure related to the abnormal ciliary body position.

3.8.3 Argon Laser Peripheral Iridoplasty

Argon Laser Peripheral Iridoplasty (ALPI) is a method of opening an appositionally closed angle in situations in which ALP either cannot be performed or where non-pupillary block mechanisms exist. The procedure consists of placing contraction burns in the extreme iris periphery to shrink the iris stroma between the site of the burn and angle, shrinking and pulling the peripheral iris tissue away from the meshwork. It is useful in managing an attack of APAC, either as a primary measure or when medications fail to control IOP. A Cochrane review for ALPI found there were no randomised control trials for its use in PACG in non-acute situations when compared with any other intervention. ALPI for PAC(G) is currently registered on UK Database of Uncertainties about the Effects of Treatments (UK DUETs, (Ng et al., 2008a).

3.8.4 Surgical Treatment

3.8.4.1 Goniosynechialysis

When PAS exists, LPI may not succeed in reopening the ACA. Goniosynechialysis (GSL) is a procedure for removing adhesions that have formed between the iris and the meshwork. GSL is commonly performed at the same time as cataract extraction (phaco-GSL) in order to prevent PAS reformation (Teekhasaenee et al., 1999).
3.8.4.2 Trabeculectomy & Lens Extraction

If first line treatments (LPI) fail to control the IOP, glaucoma filtration surgery (trabeculectomy) and lens extraction may be undertaken (Nolan, 2006). Removing the lens creates more space in the anterior chamber and widens the ACA, which may be enough to achieve IOP control, "killing two birds with one stone" (Chan et al., 2012). While the decision to remove the lens in the presence of a cataract is easy, clear lens extraction has been the source of debate for many years (Azuara-Blanco et al., 2011; Chan et al., 2012; Nolan, 2006; Smith, 1891; Thomas et al., 2011b; Walland et al., 2011).

The standard care for PAC(G) at Birmingham & Midland Eye Centre (BMEC) is a stepped approach of a combination of surgery (laser or incisional) and medical management. Initially LPI is used to open the drainage angle. Hypotensive medication may be added to further reduce the IOP. If the drainage pathway is still closed after LPI, alternative laser treatment is an option. These approaches to PACG management have been noted to have variable success (Nolan, 2006).

The mechanism of PAC(G) is rarely established in individual cases (Gazzard et al., 2003a; Marchini et al., 1998) and there is a concern that early management may not always be optimal (Thomas et al., 2012; Thomas et al., 2011a).

3.9 PAC(G) Studies & Trials

High quality evidence from longitudinal studies and RCT’s are lacking although there have been a large number of small studies. In the Liwan Eye study those with PACS showed an increase in ACA width after an LPI (He et al., 2007), however, some ITC was found in 59% of eyes with a patent LPI. This was associated with smaller ACA dimensions, thicker anterior iris and an anterior ciliary body – all of which may play a causative role in maintaining angle closure after LPI. Aung et al. (2004) found that several years after the initial attack of APAC in Asian subjects, 17.8% were blind in the affected eye and half had blindness caused by advanced glaucoma demonstrating that there is still a risk of further glaucomatous damage post a patent LPI particularly in phakic eyes.

In a small longitudinal study 22% of the normal patients with narrow angles developed synechial (64%) or appositional (36%) closure over a period of 5 years (Thomas et al., 2003). Of 28 subjects who were identified as having PPAC, eight progressed to PACG within 5 years. Only one of the nine participants who underwent (LPI) progressed compared with seven of 19 subjects who refused the LPI.

The EAGLE (Effectiveness, in Angle Closure Glaucoma of Lens Extraction) study is evaluating the effectiveness of early lens extraction (and IOL implantation) as a first line
treatment of PAC(G) (Azuara-Blanco, 2008). EAGLE involves 22 centres in UK and eight centres in East Asia. Over 400 patients with either PACG or PAC with elevated IOP have been enrolled. This study is designed to determine the cost effectiveness of lens extraction compared to LPI. The inclusion criteria for this study include age>50 years and IOP>30 mmHg (Azuara-Blanco, 2008).

The Zhongshan Angle Prevention (ZAP) trial is a RCT of bilateral PACS patients who undergo an LPI in one eye. This study has recruited ~ 900 patients and has a 36-month follow up stage (Friedman et al., 2012; Jiang et al., 2010a).

There are many gaps in our understanding of PAC(G) some of which may well be answered by the results from EAGLE (Azuara-Blanco et al., 2011) and ZAP (He et al., 2007). What is becoming more apparent to PAC(G) researchers is that while pupil block is a significant mechanism in the pathogenesis of PAC(G) it is not the only one. This has major implications for treatment, as laser iridotomy is designed specifically to relieve pupil block and may not be effective in all people with the disease. Eliciting the morphology of closure may help to focus early treatment on the underlying disease mechanism – particularly when multiple mechanisms co-exist.

The following chapter discusses ophthalmic ultrasound, the technology of higher frequency imaging, and its use in eliciting the mechanism of closure.
4 Ophthalmic Ultrasound

Medical ultrasound is an imaging modality widely used for many clinical applications. Ultrasound images are obtained by transmitting high frequency sound waves into the body and then capturing and processing the reflected signals (Pavlin, 1995). It provides a cross-section image of the soft-tissue volume under investigation, however, it cannot be used to image bone and gas. It has the advantage of being a real-time modality that does not use any ionizing radiation and can provide quantitative measurements of different structures. This chapter discusses the history of ultrasound and the basic physics of ultrasound imaging and its application to ophthalmology.

4.1 The acoustic spectrum

Ultrasound is an acoustic wave that consists of an oscillation of particles in a medium. Ultrasonic waves, by definition, have frequencies greater than 20KHz and are inaudible to human ears. Generally, medical applications in ultrasound extend from 1 to 10 MHz (see figure 4.1). As the frequency increases, wave penetration is reduced, since it undergoes stronger attenuation in the body, while resolution improves.

![Figure 4.1 The acoustic spectrum indicating the medical applications of ultrasound of varying frequency. Above image adapted from (Pavlin et al., 1995a)](image)

Frequencies between 3 and 5 MHz are used to image large body parts at a depth of 15 to 20 cm. Frequencies between 7 and 10MHz can be used to image smaller parts of the body such as the eye where only 4-5cm of penetration is needed. High frequency ultrasound, between 10 and 50MHz, is used to image the skin (Foster et al., 2000a; Pavlin et al., 1991), the gastrointestinal tract and blood vessels. Frequencies used in ophthalmology range from 8 to 50MHz. The eye presents an ideal clinical application for UBM because of its anatomical position at the body surface.
4.2 The physics of ultrasound

Ultrasound consists of waves of compression and rarefaction propagating through a medium. Wavelength and frequency are defined by the equation:

\[ c = \nu \lambda, \]

Where \( c \) is speed-of-sound, \( \lambda \) is wavelength, and \( \nu \) is frequency. Speed-of-sound is related to the medium’s composition (or density) and temperature, but is largely independent of frequency. Acoustic reflection occurs at interfaces between regions of different acoustic impedance (AI) (where \( AI = \text{density} \times \text{speed-of-sound} \)). Attenuation of ultrasound occurs as it propagates through tissue as a consequence of reflection, scattering and absorption (Byrne et al., 2002).

The ultrasound probe itself contains a piezoelectric transducer (PZT), which expands or contracts when an electrical voltage is applied. Ultrasound is focused by placing an acoustic lens over the surface of the PZT or by forming the piezoelectric material into a curved surface of suitable radius. After emitting an acoustic pulse, the PZT waits passively for echoes to return before it emits another pulse. Echoes interact with the piezoelectric element and the resulting voltages are then amplified and processed to a series of one-dimensional lines (A-scan). Multiple A-scans can be further processed to form images (B scan). The range to a reflector can be computed from the speed-of-sound, \( c \), and the time interval, \( t \), between pulse emission and echo return, specifically, range = \( ct/2 \).

The piezoelectric element of a conventional 10MHz transducer is usually a ceramic material, lead zirconate. Use of this material for frequencies above 15–20MHz is impracticable where the brittle nature cannot be made thin enough to generate high frequencies. Consequently, UBM devices could not be constructed until an alternative material became available. Polyvinylidene fluoride (PVDF) is a piezopolymer that, unlike PZT, is highly flexible and readily available in thin sheets. A 9 mm thick PVDF membrane, for instance, can be used to form the piezoelectric element of a 50MHz probe. Foster et al. (2000a) reported on the use of PVDF to fabricate a UBM transducer. Currently, the co-polymer polyvinylidene fluoride trifluoroethylene (PVDF-TrFE) has largely replaced PVDF because of its greater sensitivity (Pavlin et al., 1992a; Pavlin et al., 1991). The characteristics of a typical 10 and 50MHz are given in table 4.1.

Table 4.1 Comparative properties of typical 10 MHz ophthalmic B-scanner & traditional UBM system.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>B-Scan</th>
<th>UBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (MHz)</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Aperture (mm)</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Focal length (mm)</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>F-ratio</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Axial resolution (µm)</td>
<td>150</td>
<td>30</td>
</tr>
<tr>
<td>Lateral resolution (µm)</td>
<td>450</td>
<td>60</td>
</tr>
<tr>
<td>Depth of field (mm)</td>
<td>9.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Attenuation in water (dB/mm)</td>
<td>0.02</td>
<td>0.55</td>
</tr>
</tbody>
</table>

### 4.3 Applications of Ultrasound in Ophthalmology

The first applications of ultrasound in ophthalmology were by Mundt in 1956 (Byrne et al., 2002) while Ossoinig (1974) developed standardized methods to interpret one-dimensional ultrasound images “A-mode”. Baum (1956), Coleman (1977) and many others helped to develop the two dimension or “B-mode” ultrasound imaging (Byrne et al., 2002).

Figure 4.2 illustrates an ocular imaging system where a transducer generates a pulse in response to an electrical simulation, which travels through the coupling medium at the speed of sound. At each boundary between different tissues in the eye, a fraction of the pulse is reflected back to the transducer while the remainder continues through the medium see figure 4.2(a). The first reflection is seen at the boundary between the coupling medium and the cornea, the second between the lens and the vitreous humour, and the third at the fovea. The received echoes, as seen in Figure 4.2(b), are then converted to radio frequency electrical signals by the transducer, amplified and demodulated.

#### 4.3.1 A scan

Amplitude scan or ‘A –scan’ ultrasound is a one-dimensional display where the echoes are represented as vertical spikes from a baseline (figure 4.2c). The spacing between spikes is dependent on the time taken for the beam to reach the object and the echo to return to the probe. The height of the spike represents the amplitude or strength of the echoes. A-scan ultrasound operates at a frequency of 8 to 10 MHz, with a sound velocity of 1,532 m/sec for phakic eyes. The examination can be performed by either the contact or immersion technique. The contact technique, the probe is in applanated with centre of the cornea. The immersion technique, utilizes the probe is used in a standoff water bath. The immersion technique is generally believed to be more precise (Ossoinig, 1979) as direct contact may induce some degree of corneal distortion (Shammas, 1984). The axial length (AL) measured by immersion is reportedly 0.14 to 0.36 mm longer than that obtained by the contact technique (Olsen et al., 1989; Shammas, 1984).

#### 4.3.2 B Scan

If the ultrasound probe is rotated about a fixed axis a two-dimensional acoustic section, known as B or brightness scan, can be generated. Ophthalmic B-scans can be generated 10-20 times a second resulting in a real-time image of the eye. B-scan is gaining in popularity for biometry – known as B-biometry, where it can provide more information in difficult cases, such as in neonates and high myopia with a posterior staphyloma. Immersion
B–biometry can provide an A-scan output and allows better identification of the ocular interfaces including the posterior lens capsule (Olsen, 1992).

Figure 4.2 Schematic diagram of ultrasound system displaying A & B scan formation (Pavlin et al., 1995a).

4.4 Development of High Frequency Ultrasound

In 1989, Charles and Foster at the Princess Margaret Hospital in Toronto, Canada developed the first UBM machine, see figure 4.3 (Pavlin et al., 1995a).

Figure 4.3 Shows (right) the first clinical UBM & (left) the cumbersome examination technique to image the anterior segment (Pavlin et al., 1995a).
Three probes operating at 50, 80 and 100MHz were used to image different structures in the eye (Foster et al., 2000a). The 50MHz transducer provided the best compromise between depth and resolution. In 1991 the first commercial UBM machine was produced with a probe operating at 50MHz. The main components and characteristics of the UBM are discussed in more detail below.

4.4.1 Scanner

The operating frequency of UBM is higher than a B probe, The achievement of real-time B-mode imaging at high frequencies required the development of new transducers, high-frequency signal analysis and precise motion control. The transducer moves linearly over the imaging field (5mm) undertaking 512 equally spaced scans with a distance of 8µm between each scan (Pavlin, 1995). Using time-gain compensation techniques, the backscattered ultrasound is received by the same transducer and amplified. Afterwards, the signal is non-linearly processed and demodulated to produce the A-scan, which is converted to digital format and displayed as brightness on a video monitor. B-mode imaging is performed at 5 to 10 frames per second.

4.5 Examination of the anterior segment with UBM

4.5.1 Patient preparation

For the examination procedure, an eyecup filled with saline solution acts as a fluid-coupling medium, see fig 4.4 (Pavlin et al, 1995). The patient is placed in a supine position and the eyecup inserted under the lids of the anaesthetized eye.

Figure 4.4 Left: Eyecup placed in between the eyelids (taken from Deepak (2002). Middle: The patient is supine, anaesthetized cornea, water immersion technique using an eye bath (Pavlin et al., 1995a). Right: Early commercial UBM, the probe is fixed and mounted on a gantry arm (Pavlin et al., 1995a).
4.5.2 Probe technique

The UBM probe is carefully manipulated with reference to the screen image as seen in figure 4.5. Early versions used a moving probe without a covering membrane since, at that time, the latter attenuated the wave, and moved the transducer further from the test region.

![Image](image1)

Figure 4.5 Demonstrates the UBM examination of the eye (Pavlin et al., 1995a)

4.5.3 Producing optimal images

The ultrasound beam should be directed perpendicular to the structures being examined. This produces a sectoral image of the area being examined, see figure 4.6.

![Image](image2)

Figure 4.6 UBM image of the irido-corneal angle – the landmark scleral spur is marked by the black arrow. The cornea, iris and sclera are all seen as hyper-reflective areas marked c= cornea, i=iris, s=sclera (Pavlin et al., 1995a).

The corneo-scleral junction and scleral spur (SS) are important in maintaining orientation within the angle region. The sclera is generally thickest in the region of the SS (black arrow...
head seen in figure 4.6), which is often used as a landmark for various indices that have been developed (Ishikawa et al., 2000; Pavlin et al., 1992a; Pavlin et al., 1992b). The importance of the SS is discussed in section 5.10.1.

4.6 Linear array UBM

The development of a linear probe (linear UBM, AVISO; Quantel Medical, Clermont-Ferrand, France) has enabled imaging of the entire AC, see figure 4.7. The linear UBM provides a lateral resolution of 60µm and an axial resolution of 35µm (earlier probes had a resolutions of 50 and 25µm respectively). The linear UBM probe also has an increased depth of focus, 12 versus 5mm. The linear scanning gives a better signal intensity as the probe is always perpendicular with the tissue interface of interest. See Table 4.2 for a comparison of the specifications between linear and sectoral probe arrays.

![Image of linear UBM](image)

Figure 4.7 Shows a cross-section of the anterior chamber (top left) obtained using Linear UBM (top right). The probe moves in a linear fashion to sweep and image the anterior segment (Bottom left). The patient is examined with a fluid coupling method (the cornea is anaesthetised and methyl cellulose is used as a coupling medium, photograph of myself performing UBM on Winifred Nolan (Bottom Right). Images on top left and bottom left courtesy of Quantel Medical, Clermont-Ferrand, France.)
Table 4.2 Comparing the physical attributes of traditional sectoral and linear UBM

<table>
<thead>
<tr>
<th>UBM Type</th>
<th>Sectoral (Paradigm)</th>
<th>Lin 50 (Quantel Medical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe Array</td>
<td>Sector</td>
<td>Linear</td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial</td>
<td>25 µm</td>
<td>35 µm</td>
</tr>
<tr>
<td>Lateral</td>
<td>50 µm</td>
<td>60 µm</td>
</tr>
<tr>
<td>Focus (mm)</td>
<td>4-5</td>
<td>9 -11</td>
</tr>
</tbody>
</table>

4.6.1 Advantages of linear UBM

One of the advantages of UBM technology over that of the OCT is that it is capable of imaging retro-iris structures such as the ciliary body and lens zonules. The linear scanning probe houses a self-contained water bath, which has no restrictions when angling. It’s ease of use and portability provides good infection control, comfortable examination (including paediatrics) and examinations under anaesthetic. Linear UBM has enabled the routine use in clinical practice at BMEC. However, standardization of reporting UBM findings is lacking.

The ability to evaluate the morphology of PAC(G) in vivo has developed since the advent of gonioscopy and ophthalmic ultrasound. The following chapter describes pathophysiology in terms of biometric measures and anterior segment imaging in PAC(G).
5 Pathophysiology of PAC(G)

The association between a small eye with a shallow anterior chamber and “acute glaucoma” was first recognised in the 19th century by von Graefe (Lowe, 1995b). After many years studying enucleated eyes Smith (1891) concluded that:

- a shallow anterior chamber predisposed the eye to ‘primary glaucoma’;
- the aging lens was larger (as measured by width and weight of lens);
- smaller eyes were more likely to have smaller lenses;
- when the filtration angle was closed, the iris base was close to the cornea and these signs of anterior compression could also be seen when the angle was nearly closed.

Priestly Smith found that there were “predisposing physiological causes that lead to ‘primary glaucoma’ which are connected with the growth of the lens and variations of the size of the globe: these factors induce crowding of the structures that surround the filtration angle and vary with race.” In the late 19th Century post-mortem data supported the proposition that primary glaucoma was not a single disease entity (Smith, 1891). With the evolving definition of glaucoma these early findings have been increasingly relevant in PAC(G).

Tornquist et al. (1958) recognised that the disproportion of the eye may be causing PAC(G), for example an increased size of the lens in proportion to the corneo-scleral capsule. Similarly (Tello et al., 2002) have described PAC(G) as a spectrum of disease “characterized by abnormalities of the relative or absolute sizes or positions of anterior segment structures and forces that alter the anatomy of the anterior segment in such a way as to cause narrowing of the irido-corneal angle. This alteration in anterior segment anatomy can be caused by changes in the relative or absolute sizes or positions of anterior segment structures, which then create vector forces directed anteriorly at the iris root.”

The advent of ultrasound biometry and gonioscopy has improved our understanding of glaucoma, PAC(G), the role of ocular risk factors, gender differences (Lowe, 1969) and the risk of PAS (Gazzard et al., 2003b; Lowe, 1969).

5.1 Ocular Biometry

Typically PAC(G) is associated with a thin cornea, smaller radius of anterior corneal curvature, smaller radius of posterior corneal curvature, shallow ACD, thick lens, smaller radius of anterior lens curvature, anterior lens position and shorter axial length.

5.1.1 Axial length of the globe

Historically, PAC(G) has been associated with short axial lengths (Lowe, 1970b; Tornquist, 1956). Patients with a shallow anterior chamber and shorter axial lengths were often found to be hypermetropic.
In a study of Chinese people, Sun et al. (1994) found those suffering “acute” attacks had shorter axial lengths than those with asymptomatic PAC(G), both groups having shorter axial lengths than controls. A further study in Taiwan compared ocular dimensions in 80 people suffering “acute” angle closure and 60 unaffected people (Lin et al., 1997). Those with symptomatic PAC had an axial length of 22.25mm, while normal people had a globe length of 23.26mm. It was not clear whether the subjects were matched for age and gender. Similarly, in India, a study of the ocular dimensions in groups of people with acute, sub-acute and chronic angle closure found that all groups of people with angle closure had shorter axial lengths than age and gender-matched controls (Sihota et al., 2005). Measurements of axial length have shown that PACG is not restricted to short axial lengths and hypermetropia (Barkana et al., 2006; Chhipa, 2009).

5.1.2 Cornea
Alsbirk (1976) reported that the predisposition to PAC(G) in Eskimos could be related to their smaller corneal diameters. Alsbirk (1976) proposed that the shallow AC, bringing the vascularized, warm iris in close proximity to the cornea, which was typical of Greenlandic Inuit eyes, may be a thermoregulatory adaptation to resist corneal freezing. Anatomical factors mitigating against it would have a selection advantage.

5.1.3 Anterior Chamber Depth
A shallow central AC is a well-established early risk factor for PAC(G) (Congdon et al., 1997; Lowe, 1969; Tornquist, 1956). The demographic risk factors (increasing age, female gender and Chinese ethnicity) are all associated with shallower anterior chambers (He et al., 2008a). The “true” ACD is the distance between the posterior surface of the cornea and the anterior surface of the lens along the visual axis. The relative resistance to flow of the aqueous humour from the posterior chamber into the anterior chamber increases when the iris-lens channel meniscus decreases (Quigley, 2009a). This in turn encourages the iris to rest close to the lens where it further impedes flow.

Törnquist quantified the risk of PAC(G) in Europeans for various ACDs. He found risk increased as ACD reduced (Tornquist, 1956). In a review by Lowe (1970b) mean ACD in normal eyes was found to be 3.03-3.15mm while that for PACG eyes was 2.31-2.38mm. Congdon et al. (1997) found Caucasians, seen as part of the Baltimore Eye Study, had mean ACD of 3.07mm (men) and 2.99mm (women). Lowe (1969) found a threshold for risk of ACD started at 2.5mm, and increased below this level. In the EPIC-Norfolk cohort, 7.3% of women and 6.5% of men fell into this “at risk” category (Foster et al., 2010).

Similar associations between shallower ACD and high risk of PAC have been documented in Inuit and Mongolian populations, (Alsbirk, 1975; Alsbirk, 1982) as well as Indian cohorts (George et al., 2003) and a predominantly Caucasian group in Australia (Lowe, 1969).
However, while the prevalence of PAC(G) is high in Chinese patients there is no associated increase in the prevalence of shallow anterior chambers in comparison to other ethnicities, (see figure 5.1)

Figure 5.1 The distributions of anterior chamber depth in 3 major ethnicities, from population based data (from Quigley, 2009). There is no greater proportion of Chinese patients with shallower chamber depth compared to two other ethnicities. Thus anatomic differences do not appear to explain the greater prevalence of angle closure among Chinese population in fact highlights the spectrum of PAC(G) mechanisms (Congdon et al., 1997).

In Southern China, it was found that ACD was shallower in people with an acute, symptomatic presentation of PAC than in cases with an asymptomatic presentation (Wang et al., 1994). A summary of previous studies examining the biometric differences between normal can be seen in table 5.1.

Table 5.1 Mean values (with standard deviations) for biometry measurements in patients with PAC(G) compared with unaffected control group.

<table>
<thead>
<tr>
<th>Biometric Parameter</th>
<th>Control</th>
<th>PAC(G)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACD + Corneal thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal thickness</td>
<td>3.00 (0.30)</td>
<td>2.63 (0.22)</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>3.08</td>
<td>2.31</td>
<td>(Leighton et al., 1973)</td>
</tr>
<tr>
<td><strong>Lens thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.30 (0.31)</td>
<td>4.23 (0.69)</td>
<td>(George et al., 2003)</td>
<td></td>
</tr>
<tr>
<td>4.50 (0.34)</td>
<td>5.09 (0.34)</td>
<td>(Lowe, 1970a)</td>
<td></td>
</tr>
<tr>
<td>4.46 (0.42)</td>
<td>5.43 (0.46)</td>
<td>(Delmarcelle et al., 1976)</td>
<td></td>
</tr>
<tr>
<td>4.67</td>
<td>5.23</td>
<td>(Leighton et al., 1973)</td>
<td></td>
</tr>
<tr>
<td><strong>Axial Length</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.10 (0.82)</td>
<td>22.01 (1.06)</td>
<td>(Lowe, 1970a)</td>
<td></td>
</tr>
<tr>
<td>22.58 (0.78)</td>
<td>22.07 (0.69)</td>
<td>(George et al., 2003)</td>
<td></td>
</tr>
<tr>
<td>22.76 (0.78)</td>
<td>21.92 (0.70)</td>
<td>(Leighton et al., 1973)</td>
<td></td>
</tr>
<tr>
<td><strong>Relative Lens Position</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Calculated by me)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0.22 (0.02)</td>
<td>0.2 (0.013)</td>
<td>(Lowe, 1970a)</td>
<td></td>
</tr>
<tr>
<td>0.24</td>
<td>0.224</td>
<td>Tomlinson &amp; Leighton</td>
<td></td>
</tr>
<tr>
<td>0.23</td>
<td>0.21</td>
<td>(George et al., 2003)</td>
<td></td>
</tr>
<tr>
<td><strong>LAF (Calculated by me)</strong></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>0.19</td>
<td>0.20</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td>0.19</td>
<td>0.23</td>
<td>(Lowe, 1970a)</td>
<td></td>
</tr>
<tr>
<td><strong>ALP (Calculated by me)</strong></td>
<td>5.15</td>
<td>4.73</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>5.05</td>
<td>4.35</td>
<td>(Lowe, 1970a)</td>
</tr>
</tbody>
</table>
However, it is known that ACD may be deep centrally and the peripheral ACD should be considered.

### 5.1.4 Lens position and thickness

The crystalline lens has a pivotal role in PAC(G), both in the pathogenesis of pupil block (Nolan, 2006) and by exacerbating the effect of non-pupil block mechanisms such as peripheral iris crowding. Eyes with PAC(G) tend to have thick, anteriorly positioned lenses when compared with normal eyes. Removal of the lens increases ACD and widens the ACA.

The early work of Smith (1891) was on cadavers, where the lens was measured by its weight and horizontal diameter. Smith established that continued growth of the lens during adulthood results in, progressively thicker lens, forward movement of the anterior lens surface and a decrease in anterior chamber depth and volume that increased crowding of the anterior chamber. Lowe et al. (1969) concluded that 35% of the ACD variation was attributable to lens thickness and 65% was due to an anteriorly placed lens. Another anatomic trait thought to be associated with PAC is curvature of the anterior lens surface, the lens becoming more steeply curved with advancing age. In Europeans, there is a close correlation between lens thickness and its anterior curvature, and an inverse correlation between axial length of the globe and lens curvature (Lowe, 1972a). Analysis of the age related changes have shown a pattern of lens growth where thickness increases at an accelerated rate between the fourth and sixth decades. Growth then stabilises for about a decade, and finally increasing again, but at a slower pace. The ACD, however, appeared to continue decreasing at a constant rate. This suggests that forward movement of the lens, probably secondary to loosening of the zonules, may also play a role in the reducing ACD (Markowitz et al., 1985).

In Congdon’s landmark ocular biometry study, the lens thickness was not evaluated when looking for biometric differences between Caucasians, Chinese and Afro-Caribbean’s (Congdon et al., 1997). Their study evaluated the difference between ACD, Axial length, hyperopia >2.DS and corneal radius of curvature. Their study did not acknowledge that the position and thickness of the lens might alter the ACD.

### 5.1.5 Lens Parameters

In recognition of the possible role of lens parameters upon PAC(G), researchers have developed a series of parameters that define the size, shape and position of the lens.

#### 5.1.5.1 Absolute lens position

The Absolute Lens Position (ALP) describes the equatorial position of the lens. In PAC(G), the AC is shallow and the lens is thought to be more anterior. Demarcelle et al found (quoted...
by Cennamo et al., 1987) that the equatorial position of the lens is closer to the apex of the cornea and the limbus in PACG (Cennamo et al., 1987; Lim et al., 2006).

\[
\text{ALP} = \text{ACD} + \frac{\text{LT}}{2}
\]

### 5.1.5.2 Relative Lens Position

The relative lens position (RLP) is the ratio of the central lens position expressed as a ratio of axial length (Lan et al., 2007; Lowe, 1970b).

\[
\text{RLP} = \frac{\left(\frac{\text{ACD} + \frac{\text{LT}}{2}}{\text{AXL}}\right)}{}
\]

Eyes with PAC generally have a more anterior RLP than normal eyes (Lan et al., 2007; Lowe, 1970b). The RLP is determined not only by the thickness of the lens but also by the position of the ciliary processes and the configuration of the zonules. Anteriorly situated ciliary processes are thought to play a role in PAC(G) (Lan et al., 2007). In their study, the RLP helps differentiate between APAC eyes and uninvolved fellow eyes suggesting that, anteriorly situated ciliary processes or zonule relaxation may predispose the eye to an acute attack. However all eyes were post PI which deepens the ACD and alters the RLP.

### 5.1.5.3 Lens to axial length factor

The relative size of the lens is represented by the lens to axial length factor (LAF). Markowitz et al. (1985) defined the ratio as a representative and unifying unit for biometric assessment of the eye. This factor helps define the relationship between the lens, iris, and cornea and thus the status of the angle. LAF values were found to be age dependent and were greater than normal for most age groups with PAC(G). The mean normal value was 1.91 ± 0.44; the mean values for patients in different age groups with PAC(G) ranged from 1.87 ± 0.11 to 2.39 ± 0.17 (Markowitz et al., 1985).

Oh et al. (1994) used the LAF index for assessing PAC(G) in Chinese eyes. A LAF value of 2.00 best discriminated between PAC(G) and normal eyes (i.e., lens thickness equals to 1/5 of axial length). This suggests that a disproportionately thick lens, especially when located in an eye with a shorter AL, predisposes an eye to an attack of PACG (Nongpiur et al., 2011a).

The importance of lens parameters, ALP and RLP and LAF, has not been established conclusively (Lowe, 1970b; Marchini et al., 1998). There are inconsistent reports on the association of PAC(G) with a more anteriorly placed lens (Nongpiur et al., 2011a). A possible reason for the discrepancy is that lens position is calculated from two variables (lens thickness and ACD) that could be interdependent.
5.1.6 Differences between Ethnicities

Congdon et al. (1997) evaluated the biometric differences of PAC(G) between three ethnic groups: Caucasian (n=531), Chinese (n=170) and Afro-Caribbean (n=188). Chinese patients were recruited from Taiwan, Afro-Caribbean and Caucasian patients were recruited from Baltimore (Congdon et al., 1997). Significant differences in axial lengths were not found (p=0.98) between Chinese (23.35 ± 1.38mm) and Caucasian patients (23.32 ± 1.07 mm). Similarly, no significant differences (p=0.24) were seen when comparing Afro-Caribbean (23.14 ± 0.87mm) and Chinese (23.35 ± 1.38mm) patients. Table 5.2 shows details of the ethnical differences of the ocular parameters found in this study.

Table 5.2 Ocular Parameter (mean ± sd) by ethnicity and sex (Data from RE only), where: * p value comparing Caucasian & Chinese 0.09, p value comparing AFC & Chinese 0.49; ♦ p value comparing Caucasians & Chinese 0.98, p value comparing AFC & Chinese 0.24; ♠ p value comparing Caucasians & Chinese 0.01, p value comparing AFC & Chinese 0.001; ♣ p value comparing Caucasians & Chinese 0.03, p value comparing AFC & Chinese 0.08. Table adapted from (Congdon et al., 1997).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Anterior Chamber Depth, mm *</th>
<th>Axial Length, mm&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.07 ± 0.29</td>
<td>2.99 ± 0.31</td>
</tr>
<tr>
<td>AFC</td>
<td>3.14 ± 0.28</td>
<td>2.96 ± 0.28</td>
</tr>
<tr>
<td>Chinese</td>
<td>3.09 ± 0.32</td>
<td>2.98 ± 0.34</td>
</tr>
</tbody>
</table>

Caucasian subjects had a significantly higher prevalence of hyperopia >2 D than did Chinese (p=0.01) and corneal radius of corneal curvature was significantly shorter in Chinese eyes (p=0.03). Later, using biometric gonioscopy, Congdon et al. (2002) found that there was no significant difference in the overall biometric gonioscopic measurements between black, white and Chinese populations. However, at younger ages, Chinese eyes had deeper angles than white or black people, whereas the angles of older Chinese were significantly narrower, a fact that may relate to near-task-induced axial myopia in younger Chinese (a cohort effect rather than an age-related effect).

Subjects with PAC(G) have shorter axial lengths (Lowe, 1969) (George et al., 2003; Lin et al., 1997). In addition, eyes suffering from “acute” angle closure have shorter axial lengths than those affected by the “chronic” asymptomatic angle closure (Sihota et al., 2000).

A hospital-based study comparing angle configuration in healthy East Asians, Afro-American, and Caucasians in the US, using the Spaeth gonioscopic grading scheme, gives
another perspective (Oh et al., 1994). Iris insertion was found to be more anterior in Asian Americans compared with Caucasian and black subjects, although the recruited Asian individuals tended to be younger and more myopic. Hence, there is likely to be complex age–related interaction between genes and the environment, which affects the angle anatomy. High iris insertion was assumed to increase the risk of PAS formation in Asian eyes (Oh et al., 1994).

5.1.7 Importance of biometry

Ocular biometry may play a role in determining:

• Which eyes have small axial length containing a thick lens;
• Which eyes which have shallow ACD as a result of thick or anterior lenses;
• The relationship with refractive error, which has shown to be valuable in the evaluation of PAS risk and may have the potential to determine ethnic variation in biometry.

Biometry can quantify dimensions and relationships between the eyes component parts such as LAF, RLP and ALP (Foster et al., 1996; Lowe, 1977b; Markowitz et al., 1984; Markowitz et al., 1985; Wong et al., 2001). Many researchers have explored the use of biometry with age, gender, ethnicity (Au Eong et al., 1993; Panek et al., 1990; Salmon et al., 1994; Wojciechowski et al., 2003) and with pathology (Sihota et al., 2000).

ACD is an inheritable trait, which is affected by variables such as age and gender and it, is influenced by lens position and lens thickness (Casson, 2008). The relationship between ACD and ITC cannot be explained by ocular biometry alone and there is clearly more to ITC than a shallow AC (Lowe, 1977b). Anterior segment imaging has provided much insight into the mechanism of PAC(G) and, according to (Friedman et al., 2012), anterior segment imaging may help to shape the management of PAC(G).

5.2 Mechanisms of PAC(G) with anterior segment imaging

Anterior segment imaging can be used to identify and document the mechanism of PAC(G). In the field of glaucoma, the most important advancements have been made in the description of plateau iris, pigment dispersion syndrome and malignant glaucoma (Pavlin, 1994; Pavlin et al., 1993; Pavlin et al., 1992a; Pavlin et al., 1992b; Pavlin et al., 1991; Pavlin et al., 1992c; Wand et al., 1993). Pavlin et al. (1995a) were the first to present techniques of quantifying the angle of the anterior chamber (Pavlin et al., 1992a; Pavlin et al., 1992b). Mechanisms of damage to the AC in PAC(G) may be structural or physiological. These are explained with the use of AS-OCT or UBM images in the following sections.

5.2.1 Structural Mechanisms of PAC(G)

In PAC(G) obstruction of the TM may be caused by forces acting at one or more of four separate anatomical sites, each more posterior to the other:
1. the iris (most commonly pupillary block);
2. the ciliary body (most commonly plateau iris);
3. the lens (“lenticular glaucoma”);
4. forces posterior to the lens (Kim et al., 1997a).

This classification, popularised by Ritch (2003), helps describe the various mechanisms responsible for PAC(G). The identification of PAC(G) morphology has become increasingly important where LPI has not been successful (Wand 1977).

5.2.1.1 Pupillary Block Mechanism

As already discussed, according to Mapstone (1968) pupillary block accounts for most cases of PAC(G) and may be precipitated by mid-dilation of the pupil and predisposed in patients with narrow anterior chambers, age-related lens thickening and hyperopia, see figure 5.2.

Figure 5.2 UBM image of an eye with pupillary block a) in scotopic conditions where the angle is narrow and crowded (black arrow). a) The arrow shows peripheral iris convexity with a region of irido-lenticular contact (white arrows) in photopic conditions and b) under scotopic conditions. Note the reduced irido-lenticular contact in b) in scotopic conditions where the angle (black arrow) has closed completely secondary to iris thickening and iris convexity.

The alleviation of pupil block force (the convexed peripheral iris) by LPI may be observed with axial and sectoral UBM imaging. Figure 5.3 shows pupil block profile and the same eye after LPI.
Figure 5.3 Shows linear UBM images: a) a pupil block profile, white arrow indicates peripheral iris convexity; b) after LPI the pupil block is eliminated leaving a flat iris profile where the iris root (shown by yellow arrow) is still in close proximity to the inner side of the cornea; c) shows an axial view of the same eye with irido-lenticular contact which is alleviated after LPI in figure d; and d) shows an axial view with the remaining lenticular (or vesuvian) profile. Post LPI images show non-pupil block mechanisms also co-exist.

The pupil block is eliminated leaving a flat iris profile where the iris root is still in close proximity to the inner side of the cornea. Figure 5.3 c) shows an axial view of the same eye with a “double hump” sign which is alleviated after LPI in figure 5.3 d. Post LPI images highlight that non-pupil block mechanisms can co-exist.

5.2.1.2 Plateau iris Configuration

Plateau iris was first described by Tornquist (1958) and is an important non-pupil block mechanism in PAC(G) (Pavlin et al., 1999). It is defined (Pavlin et al., 1992c; Quigley et al., 2003; Ritch et al., 2007; Tornquist, 1958a) as an occludable angle on gonioscopy, with a flat iris plane and a relatively deep AC. Figure 5.4 shows a case of plateau iris where the ciliary body is tucked underneath the iris and the ciliary sulcus is only just visible see figure 5.4.

Figure 5.4 Showing UBM image of quadrant with plateau iris syndrome. The black arrows indicate an angular apposition with the TM. The iris profile is flat and the ciliary body is anterior. NB the ciliary sulcus is just visible (Pavlin et al., 1999). S-sclera, CB-ciliary body, C-cornea, AC- anterior chamber.

Figure 5.5 shows a plateau iris with an angular iris insertion under a) photopic conditions and b) scotopic conditions where the ACA is compromised.
Figure 5.6 Sectoral UBM images showing a) flat iris plane, deep central PAC, angular iris root in photopic conditions and b) the angular iris root causing ITC. UBM image performed by self (with consent to use image from patient).

A recent study by Kumar et al (2008a) found that plateau iris syndrome is common mechanism for PAC(G) in Chinese eyes. Their findings show that 38% of PAC(G) was due to plateau iris syndrome, while 54% had a mixed mechanism. The Liwan Eye Study from southern China reported the UBM findings in 72 PACS eyes that underwent LPI (He et al., 2007). About 60% had some persistence of appositional closure in at least 1 quadrant after LPI. Although the Liwan study reported that anteriorly rotated ciliary processes seem to predispose to closure, the authors did not attempt to classify eyes as having plateau iris. The Liwan Eye Study also reported that although 33.3% of eyes had a plateau iris before LPI (diagnosed with gonioscopy), 65% of these converted to a regular profile after LPI, and the author suggested that plateau iris might be relieved by LPI (He et al., 2006a; He et al., 2006b; He et al., 2007).

5.2.1.3 Lenticular Mechanism

A forward position of the anterior lens surface, creating a shallow ACD and increasing the risk of PAC(G), was first described by Smith (1891). Figure 5.6 demonstrates a Vesuvian iris appearance, which follows the contour of the anterior lens surface. An anterior lens position may also increase the amount pupil block.

Figure 5.6 The iris bows forward following the contour of the anterior lens surface. UBM image performed by self (with consent to use image from patient).
Fig 5.7 shows a pupil block profile characterized by a convex profile (an anterior movement of the peripheral iris towards the TM) due to the thickening and anterior bowing of the iris. Following a LPI, there is a flattening of the iris plane, ideally causing it to fall away posteriorly from the TM, resulting in a widening of the angle and in this case a lenticular profile where the iris follows the shape of the anterior surface of the lens.

![Figure 5.7: Pupil Block Profile and Lenticular Profile](image)

Figure 5.7 shows sectorial imaging can differentiate between pupil block and lenticular profiles a) a pupil block profile characterized by a convexed profile and b) a lenticular profile where the iris follows the shape of the anterior surface of the lens. UBM image performed by self (with consent to use image from patient).

Nongpiur et al. (2011a) hypothesized the amount of lens located anterior to the plane of the angles that plays a role in the pathogenesis of PAC(G). This is described as the perpendicular distance between the anterior pole of the crystalline lens and a horizontal line (extending spur to spur) termed the lens vault (LV), see figure 5.8. Nongpiur et al. (2011a) found that the amount of irido-lenticular contact increased with the extent of LV and that LV had the highest diagnostic value (AUC; 0.94) when compared to other lens parameters (AUC range, 0.58–0.66) or previously used screening parameters such as ACD (AUC, 0.75) and AL (AUC, 0.74). However, this may not be useful in plateau configurations. A forward lens position may also exist due to weak lens zonules.

![Figure 5.8: Lens Vault and Anterior Chamber Width](image)

Figure 5.8 Anterior segment optical coherence topography illustrating the measurements of lens vault (LV) and anterior chamber width (ACW) in the Zhongshan Angle Assessment program (Nongpiur et al., 2011b).
5.2.1.4 Aqueous Misdirection

An increase in retro-lenticular pressure can push the lens-iris diaphragm forwards and block the angle. Shaffer et al. (1978) described the aqueous misdirection as either as secretion of aqueous into or around the vitreous pushing the hyaloid face forward and blocking the passage of aqueous into the trabecular meshwork.

5.2.1.5 The ciliary body in PAC(G)

There are relatively few studies, which have evaluated the role of the ciliary body in PAC(G). The ciliary body thickness was studied using UBM in eighteen eyes of eighteen Japanese subjects with PAC(G) (Gohdo et al., 2000). Ciliary Body Thickness (CBT) was measured at two locations posterior to the SS (see figure 5.9).

![Figure 5.9 Schematic illustration and ultrasound biomicroscopy image of the measurement of ciliary body thickness measured perpendicular to the inner surface of the sclera at 1 mm (CBT1, arrows) and 2 mm (CBT2, arrows) posterior to the scleral spur (S, arrow).](image)

Gohdo et al. (2000) demonstrated a correlation between the ciliary body thickness, lens thickness and ACD. The size of the ciliary body and the anterior nature of the ciliary body were described throughout the literature however the ‘anterior’ position was not quantified. In PAC(G) it has been found that forward rotation of the ciliary process swings the zonules and lens forward causing a reduction of the ACD (Pavlin et al., 1992c), see figure 5.10.

![Figure 5.10 Shows UBM images of A: Closed superior angle with irido-corneal contact (arrowhead) anterior to scleral spur (black arrow) B; the ciliary processes (CP) the white arrow. Shows the direction of the CP is anterior (Barkana et al., 2006).](image)
5.2.1.6 Iris Lens Channel

Silver et al proposed that the forward convexity of the iris is generated by the difference in pressure between the posterior and anterior chambers and that a critical component was the flow through the iris-lens channel, see figure 5.11 (Silver et al., 2004).

![Figure 5.11 Illustrating the three-dimensional schematic of the iris-lens channel and the adjoining structures from (Silver et al., 2004).](image)

5.2.1.7 Iris parameters

Several studies have suggested that the iris may play a role in the pathogenesis of angle closure (Quigley, 2009a; Quigley et al., 2009). Wang et al. (2011) assessed the relationship between iris parameters and the presence of NA in a large community based population in Singapore. They found that larger iris curvature, iris area and iris thickness were independently associated with NA. The authors propose that a thicker peripheral iris could crowd the angle, especially in eyes with associated morphological characteristics, such as shallow ACD.

The iris moves toward the cornea when there is a significant posterior-to-anterior pressure differential. Whether this leads to PAC(G) may depend upon: 1) iris insertion; 2) iris stiffness; 3) the size of the pressure differential; and 4) iris-lens channel resistance. When the pupil dilates the peripheral iris can fold or there can be a ‘prominent roll.’ The iris insertion relative to meshwork varies (Wang et al., 2013) but how the iris behaves dynamically may also contribute to morphology of closure (Quigley, 2009a).

5.2.1.8 Iris insertion

There have been several attempts to classify the iris insertion and then to measure the importance of this structure in PAC(G). Sakuma et al. (1997) described two types of appositional angle closure based on the topology of the iris root, see figure 5.12. The B-type root starts near the SS with the iris root inserted more toward the base of the ACA. The S-type starts near Schwalbe’s line, with the iris inserted more toward the apex of the ciliary body. Dorairaj et al. (2007) reported that in the B type, the peripheral iris and iris root move evenly toward the TM while in the S type, peripheral iris moves independently of the iris root.
toward the TM. He hypothesized that the asymmetry was caused by a) a difference in the iris insertion distance or b) an asymmetry of plateau iris configuration.

Figure 5.12 Shows Dorairaj et al. (2007) description of B type (A [light illumination] and B [dark illumination]) and S-type (C [light illumination] and D [dark illumination]). Arrows indicate areas of appositional closure.

Using UBM the iris root was classified into 3 types by Jiang et al. (2010b), see figure 5.13.

Figure 5.13 Locations of iris insertion: (1) basal, (starting at the base of the CB (2) middle, or (3) apical (the apex of the ciliary body).

However, both classifications of the iris insertion do not include insertions that are anterior to the spur.
5.2.2 Physiological Mechanisms of PAC(G)

More recently altered physiology or dynamic factors have been highlighted as factors for PAC(G) including: a) changes in the volume of the iris upon dilation and b) Choroid/ uveal expansion/ effusion theories (Nongpiir et al., 2011b).

5.2.2.1 The iris is a sponge

Quigley (2009a) evaluated the changes in iris cross-sectional area measured with AS-OCT in 65 glaucoma patients, including OAG and ACG. They reported a 4% loss in iris volume per 1mm increase in pupil size, with peak loss complete in 5 seconds. Patients with AC(G) lost less iris volume compared with controls during dilation (P < 0.008). The authors proposed that the iris acts like a sponge losing volume when it dilates.

5.2.2.2 Choroidal Expansion

Choroidal effusion (also known as uveal effusion) is an abnormal accumulation of fluid in the supra-choroidal space (Quigley, 2009a; Quigley et al., 2003). Quigley suggested, that under normal circumstances, an increase in choroidal volume would not normally affect flow or result in a shift in the lens or iris position. However, in some cases, compression of the vitreous and its limited capacity to transmit fluid could raise the posterior chamber pressure and produce forward movement of the iris and lens, see figure 5.14 (Quigley, 2009a; Quigley et al., 2003).

Figure 5.14 Schematic descriptions of ocular fluid movement: 4.13(a) An eye with posteriorly detached vitreous is shown indicating that fluid normally moves through the vitreous gel and exits the anterior chamber (AC) through the trabecular meshwork and uveoscleral pathways. 4.13(b) The black shaded area represents choroidal expansion, which immediately increases intraocular pressure. As aqueous humor exits the AC, the pressure differential from the posterior vitreous fluid compartment (P2) to the AC (P1) is responsible for a net movement of fluid anteriorly. This would be associated with some forward movement (toward the cornea) of the lens, intensifying resistance at the iris-lens channel (relative pupil block). In this manner, choroidal expansion could contribute to producing angle-closure in predisposed eyes. 4.13c Choroidal expansion leads to differential pressure across the vitreous gel, as in top right figure, but in an eye with poor vitreous fluid conductivity, the pressure difference is not adequately equilibrated, as the vitreous compresses and moves forward, causing both iris and lens to flatten the AC in typical malignant glaucoma. From (Quigley, 2009a).
A shallow anterior chamber due to choroidal effusion has also been reported as a postoperative condition (Gazzard *et al.*, 2001; Quigley, 2009a; Quigley, 2009b; Quigley *et al.*, 2003). A high prevalence of uveal effusion in the acute stage of Vogt–Koyanagi–Harada syndrome has been described (Maruyama *et al.*, 1998). They showed the frequency of a shallow anterior chamber to be 33% and suggested that this corresponded to the height of ciliary detachment. In addition to a reduction of ACD, secondary ACG has been reported to be associated with uveal effusion (Fourman, 1989; Kishi *et al*., 1996; Phelps, 1974).

Gazzard *et al.* (2001) hypothesized that choroidal expansion was another mechanism for PAC(G) and may precede and precipitate an acute attack of PAC(G). Sakai *et al.* (2005) investigated the prevalence of choroidal effusion using UBM in 501 UK subjects with PAC(G). This included 70 eyes with APAC, 70 fellow PAC eyes and 357 Chronic PAC eyes (including 39 eyes with history of sub acute attack and 35 with a previous history of acute attack). Gazzard *et al.* (2001) found that 9% of cases with chronic PAC had choroidal effusion, 58% with acute and 23% of fellow eyes with acute PAC. It is unclear whether choroidal effusion was detected in each quadrant. There is no statistical difference in demographic characteristics, axial length, history of acute attack, or therapeutic modalities between eyes with uveal effusion and eyes without effusion. However, in phakic eyes (384 eyes), the average ACD in eyes with uveal effusion was significantly shallower than that in eyes without uveal effusion, but there was no statistical difference in age or gender. Figure 5.15 shows choroidal effusion described by Sakai *et al.* (2005).

![Figure 5.15 Radial (A) and transverse (B) sections of ultrasound biomicroscopic findings of a 44-year-old female’s eye with acute primary-angle glaucoma. IOP was 44 mmHg at initial examination, and was successfully reduced to 12 mmHg on the next day. Grade 3 uveal effusion (*) was evident as a hypoechographic area between the sclera (S) and the pars plana of the ciliary body (CB) on the next day. Note that the angle was still closed. C=cornea; I=iris; L=lens. Taken from (Sakai *et al*., 2005).](image)

The authors do not mention that this UBM shows a closed angle, the iris has a flat profile and there may well be angular apposition in other quadrants. The ciliary body appears to be anterior. Is this a phenomena found in PAC(G) with a plateau iris syndrome.
Uveal effusion in nanophthalmic eyes is well known (Brockhurst, 1974). Brockhurst reported that shorter axial length was not a distinctive characteristic of uveal effusion in his chronic PAC group. However, in PAC(G) eyes the axial length is usually shorter (Lowe, 1970a; Lowe, 1977a) and was significantly shorter than in the open-angle eyes in this study. The anatomical characteristic of a small PAC(G) eye may be associated with idiopathic uveal effusion in chronic PAC. In addition, central ACD in phakic eyes with uveal effusion was significantly shallower than that in phakic eyes without effusion. Although it is unclear which comes first, uveal effusion may contribute to the progression of anterior chamber shallowing in PAC eyes.

Kumar et al. (2008b) performed a prospective observational case series study of 74 consecutive patients diagnosed with PACG, 28 were newly diagnosed untreated eyes and forty six were eyes with a previous iridotomy (LI) (Kumar et al., 2008a). Twenty normal eyes served as controls. Newly diagnosed PACG underwent UBM before and after LPI, while control and treated PACG eyes underwent UBM at the time of enrolment. Overall, choroidal effusion was found in 11/74 PACG eyes and in none in the controls. Choroidal effusion was found in 4/28 eyes with newly diagnosed PACG before LI. However, only two eyes had effusion after LI. 7/46 had effusion in previously treated PAC. Their results confirmed the findings of Sakai et al. (2005) that the presence of uveal effusion is similar in untreated and previously treated PACG.

These results along with that of Sakai et al. (2005) open up new questions about the significance of choroidal effusion in PAC(G). Shorter axial length was not a distinctive characteristic of choroidal effusion in the chronic PAC group in this study. Detection of choroidal effusion in different axial length eyes also warrants further study, although Sakai et al did not demonstrate a significant difference in eyes with or without choroidal effusion.

Quigley (2009a) suggested that the mechanisms of PAC(G) seen in the different entities are component causes that can be dominant in some patients and contributory in others (Quigley, 2009a). PAC(G) could occur in an eye that was small and had high resistance in the iris-lens channel alone. PAC(G) may have contributions from iris volume retention on dilation, plateau configuration, choroidal expansion, and vitreous collapse. There is a plethora of PAC(G) literature that describes biometric data and mechanism of disease. The spectrum of PAC(G) is described through the publications of many groups however the issue of managing the spectrum of PAC(G) in relation to the mechanistic cause needs further research.
5.3 Imaging the mechanism of PAC(G)

According to Dorairaj et al. (2007) early PAC is detected in the superior irido-corneal angle by AS-OCT and UBM. However, the AS-OCT is particularly awkward in imaging the superior angle, examination of all four quadrants and ciliary body visualization, (See, 2009). Figure 5.16 shows the AS-OCT images in various types of PAC(G).

![AS-OCT images in different mechanisms of PAC(G)](image)

Figure 5.16 (Right) Shows AS-OCT images in different mechanisms of PAC(G). AS-OCT images of the whole anterior chamber. (a) Pupillary block is the commonest mechanism encountered, characterized by convexity and bowing of the peripheral iris. (b) In non-pupil block mechanisms the iris convexity is not prominent and the anterior chamber depth also tends to be deeper than the other forms of angle-closure. (c) Plateau iris is one form of non-pupil block angle-closure, whereby there is a flat central iris plane, a relatively deep anterior chamber and a sharp angulation of the peripheral iris where it inserts into the iris root. (c) Lenticular mechanisms has a typical ‘vesuvian’ iris profile and central lens opacities can be seen. (e) Retro-lenticular mechanisms) may be induced by pharmacological agents or intra-operative surgery. AS-OCT, anterior segment optical coherence tomography (courtesy of Sancy Low, Glaucoma research fellow, Moorfields’ Eye Hospital).
Figure 5.17 demonstrates linear UBM images for various types of PAC(G). The linear UBM is able to identify post-iris mechanisms. In the phacomorphic case the whole of the lens is imaged and the highly reflective lens opacities seen. In a case of plateau iris the angular nature to the iris root may be seen as well as the anterior ciliary body (which is tucked underneath the peripheral iris).

Limitations of the UBM include the requirement of a coupling medium and supine position, which might lead the iris diaphragm to fall back and change the depth of the anterior chamber and the angle opening. Ishikawa et al. (2004) demonstrated that inadvertent
pressure on the eyecup, while scanning, can also influence the angle configuration. However, novel linear UBM probes, which house the water bath, have largely overcome this problem. Compared with OCT, UBM requires a more highly skilled operator. However, these limitations are outweighed by the benefit of UBM for visualizing the ciliary body, zonules and posterior chamber. UBM accuracy and ability to visualize behind a clouded cornea makes it very useful in presence of pathology. UBM can be used to perform a darkroom provocative test, and is superior to OCT when diagnosing anterior supra-choroidal effusions.

### 5.3.1 Landmarks of imaging

Once an image is captured, accurate quantification can be achieved after identifying the SS Pavlin et al. (1992a). The SS represents an anatomical landmark for the TM, which is located approximately 250 to 500µm anterior to the SS along the angle wall. The SS has been described in several ways (Pavlin, 1995; Pavlin et al., 1992a; Pavlin et al., 1992b):

1. the peaked outline which has a greater contrast than the ciliary body;
2. the projection into the anterior chamber from the posterior chamber to the TM;
3. the inward protrusion with a change in internal scleral structure or curvature;
4. the internal line which separates the ciliary muscle and the sclera.

Seager et al. (2014) recently compared three methods to identify the SS. These are seen in figure 5.18 and include:

1. the intersection of the ciliary muscle with the inner corneal margin (CM Method);
2. the bump like structure on the inner corneal meshwork (the Bump Method)
3. location of Schwalbe’s Line in relation to the SS (the SL Method).

![Image of UBM landmarks](attachment:figure5_18.png)

**Figure 5.18** Visante OCT images of the ACA showing three methods to identify the SS a) CM method b) Bump Method c) Schwalbe’s Line Methods described by Seager et al. (2014), where s is the sclera, i is the iris and c is the cornea.
Using a combination of all three methods, Seager et al. (2014) reported that the SS could be identified in 98% of eyes. However, two observers participated in this study: neither found the bump method useful and only horizontal scans (nasal-temporal meridian) were evaluated. They also found that the SS was more likely to be detected in open angle eyes that in those with PAC(G).

5.3.2 Quantitative Parameters

Pavlin developed a number of biometric indices using the SS as landmark (Pavlin et al., 1992a; Pavlin et al., 1992b; Pavlin et al., 1991; Wand et al., 1993). Anatomically 500µm microns from the SS should fall on the anterior TM therefore suggesting clinical importance particularly in PAC(G).

The angle opening distance (AOD) figure 5.19. This consisted of identifying the SS, drawing a line from the SS to the point on the corneal endothelial surface 500µm away and then drawing a perpendicular to the corneal endothelium down to the iris surface (Pavlin et al., 1992a).

The trabecular iris angle (TIA) figure 5.19. The angle opposite the AOD 500 at the iris apex. Both AOD and TIA assume the iris surface is flat and do not account for variation of the iris configuration (plateau iris), the type of iris insertion or the convexity of the peripheral iris.

![Schematic drawing of early angle indices. Angle Opening Distance (AOD500) is the length of the perpendicular from the trabecular meshwork (TM) to the iris from a point 500µm from the scleral spur (SS). The trabecular iris angle (TIA) is measured from the apex in the iris sulcus – boundaries pass through 500µm from the scleral spur (SS) and where the AOD500 meets the iris. Image from (Mansouri et al., 2009).](image)

The trabecular-ciliary process distance (TCPD) figure 5.20. The iris-ciliary process distance (ICPD) estimates the size of the posterior chamber and the iris thickness (or distance, ID), at three different locations. This gives a measure of angle congestion (Figure 5.20).

Ishikawa et al. (2000) defined the angle recess area (ARA), figure 5.21. which is the triangular area formed by the AOD 500 (the base), the iris surface, and the inner corneo-
scleral wall (sides of triangle). ARA, takes into account the whole contour of the iris surface (Radhakrishnan et al., 2005).

Figure 5.20 Shows a schematic diagram of the anterior chamber angle and indices as described by Pavlin and others. Where: \( \theta \) = Angle; IT (1-3) - Iris Thickness; ICPD – irido-ciliary process distance; TCPD – trabecular–ciliary process distance; IZD – iris zonular distance; line BC – AOD500; line DE- AOD750 (Friedman et al., 2008).

**The trabecular-iris area (TISA), figure 5.21.** TISA is defined as the trapezoidal area with boundaries shown in figure 5. (Radhakrishnan et al., 2005). This parameter represents the filtering area.

Figure 5.21 Showing AS-OCT measurements of angle indices: AOD- Angle opening distance TISA trabecular–iris space area; ARA – angle recess area (courtesy of Miss Winifred Nolan).

TISA, AOD 500 and AOD 750 all have good discriminatory power for detecting narrow angles (AUC 0.97; (Radhakrishnan et al., 2005). However, the ARA 750 and the TISA 750 also provided excellent discrimination (AUC = 0.96) for detecting NA’s. However, their study included a small sample of cases (n=17 normal patients and 7 with NA’s). Furthermore, their analyses included horizontal quadrants only.

These techniques are often labour intensive, as they were observer dependent and relied upon the identification of the SS (Nolan, 2008). Sakata et al. (2008b) reported the SS could not be detected in 30 % of eyes with PAC(G) using the Visante OCT. However, they found that 90% of images could be qualitatively assessed for the presence or absence of closure..
Console et al. (2008) estimated that there was 50% variation in angle-area (TISA and ARA) measures and 10% in linear measurements (AOD). Both studies suggest improvements in image quality may help to overcome the problems associated with SS identification. In a study by Cumba et al. (2012), using swept source OCT, SS was identified in all (31 eyes) where 90% of all quadrants the SS was placed within 80µm, 88% in narrow angle eyes, and 92% in open-angle eyes.

Many factors contribute to the reproducibility of the indices/and the location of the SS including:

1) the quadrant being examined (Sakata et al., 2008);
2) the nature of the PAC(G) (Sakata et al., 2008),
3) the colour of the iris (Seager et al., 2014),
4) image quality (Radhakrishnan et al., 2007)
5) older eye (Seager et al., 2014), with the shallow ACD and short axial length (Liu et al., 2011).

The UBM images seen in the figure 5.22 are examples of patients with PAC(G). All of these sectoral images are typical cases seen at BMEC where the SS cannot be identified.

Figure 5.22 The UBM images are examples of patients with PAC(G). All of these sectoral images are typical cases that seen at Birmingham and Midland Eye Centre (BMEC) where the scleral spur cannot be identified in order to perform quantitative analysis. Images a & b are examples of basal iris insertion;
c is a basal iris insertion in conjunction with a pupil block mechanism; d, and e are examples of iris insertions which appear to be anterior to the scleral spur.

These images indicate that techniques that are based on location of the SS are limited as the SS cannot be located in a proportion of eyes.

5.4 Combined biometry and UBM findings

Clinically linear UBM enables the mechanism of PAC(G) to be more easily recognised. However, in figures 5.23/ 24 we can see the advantages of a combined UBM biometry approach that gives axial length, lens thickness and detailed imaging of the AC.

Figure 5.23 Shows B biometry & UBM in patient with ACG a) B biometry ACD=2.63 mm, LT 5.22 mm VCD= 15.03 mm AXL=22.88 mm, b) axial linear UBM shows a pupil block profile (with the double hump sign) combined with a lens vault of LV from 0.90 mm; c) sectoral UBM of 3 o’clock showing peripheral iris convexity occluding the SS d) axial linear UBM post PI showing a vesuvian profile LV of 1.09mm (one year post PI); e) post LPI the iris is flat with a basal iris insertion occluded the SS.
Figure 5.24 Shows biometry and UBM on a 56 year old male with PAC a) shows B biometry where ACD=2.11 mm, LT = 5.79 mm, AXL=22.71 mm; b) shows pre-LPI axial linear UBM showing vesuvian Iris profile with true ACD=1.11 & marked LV= 1.80 mm. c) is a sectoral UBM of 9 o’clock where the thick basal iris is a convex shape which d) occludes in DRPT.

Where quantitative analyses is possible, the danger of reducing these highly complex images to a relatively small number of indices can hide important information regarding the morphology of disease such as whether there is angular configuration of the iris or peripheral bowing (convex shape) of the iris. A qualitative assessment to classify size and rotation of the ciliary body, iris insertion, iris convexity, iris thickness, and iris angulation (Jiang et al., 2010b) is much needed. The interpretation of these features may benefit from the development of clinical grading scales (CGS) enabling the clinician to describe the morphology of the anterior segment. The following chapter discusses the use of CGS in ophthalmology in an attempt to establish a standardized methodology to construct CGS for UBM images.
6 Clinical Decision Making

Clinical decision-making is often binary, e.g. the presence or absence of a pathological finding. Since the assessment of clinical conditions and the management of patients are in part concerned with the detection of change, binary decision-making may not always be sufficient. Clinical grading scales (CGS) are often used to categorize the severity or advancement of clinical conditions. Before the introduction of CGS, the assessment and recording of ocular signs was often based on the use of descriptive (qualitative) terms such as ‘absent’, ‘normal’, ‘slight’, ‘mild’, ‘moderate’ or ‘severe’. The use of descriptive terms allows flexibility for practitioners in the assessment of clinical presentations; however, they often lack precise definitions and are often clinician-dependent. The clinician may also use symbols such as +, ++, +++ - for emphasis i.e. lens opacity NS+, NS ++.

6.1 Clinical Grading Scales

CGS possess high discrimination and reliability and are quick and easy to use (Bailey et al., 1991). CGS employs grades that are systematically assigned to terms or illustrations in order to "enable the quantification of the severity of a condition with reference to a set of standardized descriptions or illustrations. Particularly in the field of contact lens research and practice where the detection of small changes is required so that possible treatment may be initiated" (Efron, 1998).

The CGS require a given ocular feature to be gauged relative to a chosen reference that represents different degrees of the condition of interest on an ordinal scale. These can be verbal and illustrative or continuous CGS. Table 6.1 lists definitions of various CGS.

Table 6.1 Definitions of various types of grading scales(Efron, 1999; Efron et al., 2001).

<table>
<thead>
<tr>
<th>Type of CGS</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal, descriptive or Verbal descriptor</td>
<td>Written description of CGS</td>
</tr>
<tr>
<td>Illustrative</td>
<td>Pictoral or photographing CGS</td>
</tr>
<tr>
<td>Grading Morphs or Continuous</td>
<td>A movie sequenced CGS</td>
</tr>
</tbody>
</table>

6.1.1 Descriptive Scales

A number of descriptive CGS have been created to record and compare the anatomy and pathology of the ACA’s, such as SGGS, and Shaffer Grading system (sections 3.7.1) and Van Herick’s Test (section 3.7.2). These descriptive CGS, require the observer to estimate the level of severity of a condition, with reference to a series of printed statements, typically on a 5-step scale from 0 (normal) to 4 (severe).
6.1.2 Illustrative grading Scales

Illustrative CGS may be hand drawn or photographic. The Efron (1998) formulated contact lens illustrative CGS was produced by the British medical artist Terry R Tarrant and included 8 scales for epithelium staining, epithelial microcysts, stromal oedema, neovascularisation, endothelial polymegathism, endothelial blebs, conjunctival hyperaemia and papillary conjunctivitis.

![Grading Scales](image)

Figure 6.1 An example of Efron's grading scale for contact lens complication. Top: grading scale for papillary conjunctivitis. Bottom: grading scale for conjunctival redness. With the grading scale clinicians score the patients complications with one of the above in the appropriate scale 0 is normal increasing in severity to 4.

An example of an illustrative grading scale can be seen in figure 6.1 showing a five step grading scale for conjunctival redness and papillary conjunctivitis. Although the drawings were not ‘real’ they allowed for better standardization of eye size, illumination, magnitude etc. Later CGS utilised photographic images.

Van Herick technique is not an illustrative CGS, however, figure 6.2 shows the potential use of figures to provide a CGS depicting the degree of closure (Adapted from (EGS, 2008).

![Schematic Diagram](image)

Figure 6.2 Schematic diagram of the slit lamp in the Van Herick grading system ranging from Grade 4 (right) to grade 0 (left). Adapted from (EGS, 2008).

6.1.3 Continuous Scales

An alternative to illustrative CGS is the use grading morphs (Efron et al., 2002). Morphing is a computer-based technique that involves electronic linkage of key elements in a sequence of fixed images of a given condition, which are depicted in increasing levels of severity (Chong et al., 2000). This involves user manipulation of a movie sequence to match to the severity of the condition being observed. Computer-based morphs may have considerable utility in clinical practice. Efron et al. (2002) published a grading morph computer program.
that demonstrated eight complications of contact lens wear. A screen shot of Efron’s grading morphs can be seen in the figure 6.3.

![Efron Grading Morphs](image)

Figure 6.3 Showing a screenshot of Efron Grading Morphs (Efron, 1999; Efron et al., 2002) where a video loop for complication can be played to determine a matching reference a corresponding grading score.

The authors subsequently upgraded this to a more sophisticated morphing program showing 16 complications (Efron et al., 2001b). These morphing programs were derived from paintings. A photographic-based grading morph computer program has also been described (Chong et al., 2000) to investigate the repeatability of three anterior segment clinical grading scales: 1) verbal descriptors scale (VDS), 2) photographic matching scale (PS), and 3) continuous matching scale (CS) for bulbar redness. Continuous grading techniques have not been widely used in clinical practice, printed grading scales have the advantage of being inexpensive, portable and simple to administer in non-EPR systems.

For a CGS to be widely used it needs to be simple, accurate and reliable in risk-stratification (medico-legal reasons) and not require extensive specialist training. The ideal scale should be easy to teach, fine enough to detect clinically significant change and have good test-retest repeatability (Bailey et al., 1991).

There is currently no ‘gold standard’ to qualitatively assess the morphology of ACA via the UBM despite their potential to facilitate decision-making and allows comparison of clinical studies and quality of care (Efron et al., 2003a).
6.2 Research on CGS

Research on CGS has largely focused on evaluating their application in clinical practice or a research setting, and has addressed a number of factors that may affect their performance and repeatability (Bailey et al., 1991; Efron, 1998; Efron, 1987; Efron et al., 1988; Efron et al., 2007a; Efron et al., 2007b; Efron et al., 2003a; Efron et al., 2003b; Efron et al., 2002; Schulze et al., 2007; Woods, 1989). The inter- and intra-observer repeatability has received the most attention and is affected by factors such as the number of scale steps (Bailey et al., 1991; Miller, 1994; Schulze et al., 2007) or the fineness/coarseness of the scales (Bailey et al., 1991; Miller, 1994; Schulze et al., 2007).

6.2.1 Selection of Reference Images

The selection of reference images are usually based on clinical experience or subjective judgments using a “best clinician approach” (Chong et al., 2000; Chylack et al., 1993a; Chylack et al., 1993b; Jiang et al., 2010b; Schulze et al., 2007; Sparrow et al., 1986). This may lead to unevenly spaced reference scales (Bailey et al., 1991) and may not represent the full range of pathology (Bailey et al., 1991). There are a number of publications validating various CGS—however there is little information regarding the method of constructing the scale.

In a UBM study grading the characteristics of PAC(G), Jiang et al. (2010b) attempted to classify the anatomic features related to the anterior chamber angles by a qualitative assessment system based on UBM images. They constructed a 3-point (3 pictures) CGS for iris thickness, iris insertion, iris convexity, iris angulation, ciliary body size and ciliary process position (Jiang et al., 2010b). Examples of their three point scales can be seen in figure 6.4.

![Figure 6.4](image_url)

Figure 6.4 Referring to the iris thickness: 1) thin overall iris thickness, 2) medium overall iris thickness, 3) thick overall iris thickness, 4) thin basal iris thickness, 5) medium basal iris thickness and 6) basal iris thickness (Jiang et al., 2010b).

However, details regarding the construction of the scales are lacking: ‘two observers reviewed the UBM database and selected the representative 3 images as standard
One of the observers selecting the images was also one of two observers validating the scale– inducing an observer bias, see table 6.2.

Table 6.2 \( \kappa \)-Values of the Inter-observer & Intra-observer Reproducibility Tests for the UBM features assessed by (Jiang et al., 2010b). Note that only two observers were used to evaluate reproducibility.

<table>
<thead>
<tr>
<th>Assessed Feature</th>
<th>value of Reproducibility Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter-observer</td>
</tr>
<tr>
<td>Basal iris thickness</td>
<td>0.609</td>
</tr>
<tr>
<td>Overall iris thickness</td>
<td>0.878</td>
</tr>
<tr>
<td>Iris Convexity</td>
<td>0.751</td>
</tr>
<tr>
<td>Iris Insertion</td>
<td>0.878</td>
</tr>
<tr>
<td>Iris Angulation</td>
<td>0.657</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>0.654</td>
</tr>
<tr>
<td>Ciliary Body Size</td>
<td>0.654</td>
</tr>
</tbody>
</table>

Jiang et al’s intra-observer and inter-observer reproducibility ranged between 0.61-0.89 and 0.66-0.94 respectively. Intra-observer reproducibility was generally higher than inter-observer reproducibility. Inter-observer reproducibility of the grading of overall iris thickness and iris insertion were higher (both 0.878) than those of other features. The limited number of steps within Jiang’s scales (3) provides a limited forced choice, which can escalate the reliability indices. There appears to be a lack of standardised reference scale criteria- the impact of this can be seen in the inter- and intra-observer \( \kappa \)-statistics in several studies (Chong et al., 2000; Jiang et al., 2010b).

The Validated Bulbar Redness (VBR) scale used a combination of psychophysical and physical method to constructing the scale. Nine observers were asked to position the 25 photographs on a 1.5 metre scale according to level of redness (Schulze et al., 2007). Subjects were required to place each image within a designated 1.5m range so that the separation reflected the observer’s perception of redness. Using inter-observer agreement, ten pictures were selected from the original set of 25 images (each 4 x 3 cm in size) to construct a “VBR 10 Scale.” Two other versions of the new grading scale prototype were also constructed, five images (“VBR 5 Scale”) and a continuous scale. VBR 5 and VBR 10 scales can be seen in the figures 6.5 and 6.6 where the scales increase in severity of redness (Schulze et al., 2007).
The VBR methodology has been adopted by Pine to develop CGS for prosthetic research (Pine et al., 2012) in order to displaying deposits on prosthetic eyes. Their study aimed to develop and confirm reliability of three photographic grading scales to aid prosthetic eye research. The study included consultation with experienced ophthalmologists and optometrists and used perceptual and physical attributes when developing the scales similar to that described by Schulze et al. (2007).

6.2.2 Number of scale steps

A scale is made up of a series of graduations, which are labelled at regular intervals. According to Bailey et al. (1991) there are difficulties in dividing a scale into steps (categories or graduations) that are determined by observer impression (Bailey et al., 1991). The nature of the steps depends on the intended use of the scales, finer scales being more appropriate for monitoring change. Steps may be unequal across the range of the scale therefore parameters that are being evaluated need to provide information that is useful in clinical decision-making (Bailey et al., 1991).

Five to seven reference steps have been recommended as an optimum number for clinical grading scales (Chong et al., 2000; McMonnies et al., 1987; Miller, 1994; Schulze et al., 2007; Woods, 1989) - this is supported by ‘the magical number seven, plus or minus two’ described in clinical psychology (Miller, 1994). Most of the grading scales for bulbar redness are based on this design, with five reference images for the Efron scale (Efron, 1998) and six for the McMonnies–David scale (MC-D) (McMonnies et al., 1987). Schulze et al. (2007) tested two scales, a 5-point (VBR 5) and a 10-point (VBR 10) scale. Users preferred the 5-point scale. The overall repeatability of both scales were identical for all observers where
Pearson’s r = 0.997, see Table 6.3 (Schulze et al., 2007). However, Pearson’s r will be closer to 1 amongst all sub-groups.

Studies such as Jiang et al. (2010b) did not consider consistency in their selection of reference pictures, i.e. reference steps vary between 3 and 6– justification for these step numbers were not discussed. According to Bailey et al. (1991) there are difficulties in dividing a scale into incremental steps that are determined by subjective impression (Bailey et al., 1991).

Table 6.3 Modified from (Schulze et al., 2007) showing Pearson’s r for 2 different scales: VBR 10 (10-picture) & VBR 5 (5-picture scales).

<table>
<thead>
<tr>
<th>Pearson’s r</th>
<th>VBR 10</th>
<th>VBR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All observers</td>
<td>0.997</td>
<td>0.997</td>
</tr>
<tr>
<td>Clinical researchers</td>
<td>0.990</td>
<td>0.993</td>
</tr>
<tr>
<td>Students</td>
<td>0.986</td>
<td>0.991</td>
</tr>
<tr>
<td>Administrative Staff</td>
<td>0.989</td>
<td>0.989</td>
</tr>
</tbody>
</table>

6.2.3 Use of incremental scale sub-divisions

The scale increment is the difference between two adjacent images/figures. Increments may be unequal or too coarse. The performance and repeatability of scales are not only dependent on the number of reference steps provided but also upon whether graders use subdivisions of the increments. e.g. by dividing each increment into 0.1 steps, or by using integers for 100-point scales such as the VBR scale (Schulze et al., 2007). It has been shown that the repeatability and concordance of assessments are closely connected to the number of incremental subdivisions used, with a fine line between how coarse a scale should be to provide acceptable sensitivity to detect change and the concordance between repeated assessments (Bailey et al., 1991). To estimate the sensitivity of scales, Bailey et al. (1991) proposed criteria that relate to the size of the scale increments. Coarse scales may be more appropriately used in studies where inter-observer concordance is important while fine incremental steps were suggested for studies for which all assessments are made by a single observer only, and for the detection of very small changes (Bailey et al., 1991).

6.3 Criticism related to CGS

The development of CGS and the use of illustrations to improve the scales have contributed to a better standardization of clinical assessments. Despite these advances inter- and intra-observer variability still represents a major challenge. Aside from subjectivity being a factor for the variability of the assessments, the CGS themselves have been a focus of criticism, which included unequal distribution of scale steps or differences in the scale range.
(pathology range). Inspection of figure 6.7 shows how differences in bulbar redness is graded in four different CGS i.e. in the MC-D, Institute for Eye Research (IER) Efron, and VBR scales (Schulze et al., 2007). Each of the scales is likely to be dependent upon the clinical range of patients these authors are exposed to in their own clinics leading to discrepancies in the selection of end-points. An obvious potential cause of unequal intervals is the “end-point” problem.

![Figure 6.7 Comparing four different bulbar redness scales: VBR, IER, Efron, MC-D (Schulze et al., 2007).](image)

Figure 6.8 depicts how hypothetical perceived values for three stimuli can produce overt ratings according to four different observers' judgment criterion scales (Brown et al., 1990). The perceived values for the three stimuli are assumed to be identical for all observers, and are indicated by the three horizontal lines that pass from the “perceived value” axis through the four different judgment criterion scales.

When referred to the judgment criterion scale of observer A, the perceived value of stimulus 1 is sufficient to meet the criterion for the eighth category, but not high enough to reach the ninth category, so the observer would assign a rating of 8 to the stimulus. Similarly, the same stimulus would be assigned a rating of 10 according to observer C’s judgment criterion scale, and only a 6 according to observer D’s judgment criterion scale. Relationships between ratings of different stimuli by the same observer(s) are used to infer perceptions. The scenario in figure 6.8 is an example of where the end-points are not fixed leading the variation in scale construction. This figure may explain the end-point problem seen when comparing the bulbar CGS. When considering the development of a clinical grading scale one must fix the end-points to eliminate the effect illustrated in figure 6.8 (Brown et al., 1990) and shown by Schulze in figure 6.7.
Knowledge of appearances of anatomical structures (ability to recognize abnormalities or pathologies) play a vital role in medical image interpretation. However, in the clinical setting the 'clinical set' varies between various allied health professionals in ophthalmology who are involved in performing imaging. Semi-quantitative analysis relies on the identification of landmarks like the SS and neuro-retinal rim in HRT. Whilst subjectivity will always be a source of error, inter-observer variability may be used to develop consensus-based decisions. However, inter-observer error can be assessed using psychometric techniques. The following chapter explores psychometric techniques already established within Ophthalmology, the method of which is applied in Project 2.
7 Psychometric Tests in Ophthalmology

In the quest to analyse the grading of UBM images, similar to the methods described by Schulze et al. (2007), the techniques employed in colour vision testing may be appropriate. In colour vision tests samples are arranged by similarity in a colour series. Table 7.1 describes several colour tests and the test strategy employed to test colour vision.

Table 7.1 Shows colour arrangement tests have different test strategies. FM is Farnsworth Munsell.

<table>
<thead>
<tr>
<th>Test type</th>
<th>Test Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM-100</td>
<td>hue discrimination</td>
</tr>
<tr>
<td>D-15</td>
<td>colour confusion</td>
</tr>
<tr>
<td>Desaturated D-15</td>
<td>colour confusion</td>
</tr>
<tr>
<td>Lanthony</td>
<td>New colour confusion &amp; colour test neutral zones</td>
</tr>
</tbody>
</table>

7.1 Psychometric scaling

The psychometric scaling technique of the Farnsworth Munsell (FM) 100 hue test is used to assess colour discrimination where a series of coloured pots are ranked in colour order. The test consists of four cases with 93 colour caps in which colours are mounted. Each case consists of two fixed end-points, which enclose a quarter of eighty-five numbered removable colour caps. The scoring sheets contain four rows of numbers corresponding to the numbers on the backs of the removable colour caps in the four cases, along with a scoring diagram, and spaces for recording other data, see figure 7.1.

One of the most popular methods for obtaining reactions from observers in a psychological measurement context uses rating scales, e.g. Likert scales. The procedure requires observers to assign ratings to objects to indicate their attitude about some statement or object, or their perception of some property of the preferred object. Here the observer places a relatively small set of objects (rarely more than 10) in order from lowest (least preferred) to highest (most preferred). Psychometric scaling techniques (Pine et al., 2012; Schulze et al., 2007) are a promising method for the development of novel scales for PAC(G). The inter-observer analysis of psychometric scaling experiments can be done in several ways— the FM test is based on error score calculation. Details of the FM100 calculation of an error score are described in 7.2.
A standard error of measurement is an estimate of the average standard error of measurement for all observers. The standard error of measurement may also be defined (for the whole sample or multiple observers) as the standard deviation of the inconsistency errors or the standard deviation of the differences between raw scores and the corresponding true scores. With this last definition, computation of a standard error of measurement can be made - which includes instability errors over a given task. The use of standard error of measurement can be seen when scoring the FM data (Donaldson, 1975; Farnsworth, 1957).

Figure 7.1 Farnsworth Munsell scoring sheet

7.2 Standard error of measurement
7.3 Scoring FM data

The test is scored by noting the numbers \(d_n\) of the coloured disks that are placed at each of the 85 locations \(n\). The size of the error score \(\varepsilon_n\) is an indication of how well the disk at \(n\) is ordered with respect to its immediate neighbours, rather than a measure of how far from its correct location it has been placed. The score of the FM cap is the sum of the differences between the number of that cap and the numbers of the caps adjacent to it. That is,

\[
\varepsilon_n = |d_n - d_{n+1}| + |d_n - d_{n-1}|
\]

The minimum value of \(\varepsilon_n\), corresponding to correct order, is 2.

Subtotal error scores

\[S_n = \sum \text{box}(\varepsilon_n - 2)\]

Total error scores

\[T_n = \sum \text{all boxes } S_n\]

An example of its calculation can be seen in table 8.2 (Farnsworth, 1957).

Table 7.2 Shows the calculation of error for the series of caps seen in the top row.

<table>
<thead>
<tr>
<th>Observer cap arrangement</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>13</th>
<th>11</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calc for (\varepsilon_n)</td>
<td>(1+1)</td>
<td>(1+1)</td>
<td>(1+5)</td>
<td>(5+2)</td>
<td>(2+2)</td>
<td>(2+1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error Score (\varepsilon_n)</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The error scores are calculated and recorded on the FM sheet figure 7.2.

![Figure 7.2](image.png)

Figure 7.2 Section of a subject’s profile illustrating how error scores are plotted. Taken from (Farnsworth, 1957)
The line of numbers on the score sheet is printed only for the clinician’s convenience when there are a few or no errors. In scoring an irregular series, only the subject’s order is required for scoring. The inner circle of numbers corresponds to the number of caps. The first (inside/lowest possible) dotted line has a score of two. The error score for each cap is marked on the radial line carrying its number. Figure 8.2 illustrates a section of the subject’s profile illustrating error score plotting. The total error score is obtained by summing the errors on each radial line counting the inner circle as zero (this has the effect of subtracting two from each individual score. The error scores, reading clockwise are: 0, 0, 4, 5, 2, 6, 6, 6, 4, 7, 6, 6, 5, 3, 3, 3, 3, 4, 2, 0, 1, 1, 1, 1, 1, 0, 0. The total errors score is 76, midpoint 38 that falls nearest cap 16. This sum of errors methodology can be employed to analyse the results for the UBM grading scales for PAC(G).

These methods will be applied to determine inter-observer error scores will be used to identify areas of inter-observer disagreement or confusion within the developed CGS for UBM images.

7.4 Designing clinical grading scales for PAC(G)

There have been a number of publications validating various CGS. With the exception of Schulze’s psychometric scaling work (Schulze et al., 2007) there is little information regarding the method used to construct these scales. In many ophthalmic CGS the design of the scaling process is not described. However, the design process of scaling is well described in the field of psychometrics with suggestions for sample selection, observers, task instructions and presenting and viewing the samples. Engeldrum (2001) provides practical guidance to scaling leading to improved efficiency of any scaling study.

When analysing UBM’s qualitatively there is no gold standard of interpretation. Similarly, there is no gold standard to develop a medical image CGS. In fact, most CGS have been defined using a “best person” or “best clinician” technique. The development of a reference scale set needs to be constructed by a ‘consensus’ approach. In order for the scale to be effective there needs to be a ‘scaling plan’ (Engeldrum, 2001).

In most applications scaling utilises either image quality, or perceptual characteristics (or "nesses"). Engeldrum’s process of developing the scale values for a consists of seven basic steps (Engeldrum, 2001):

1) Select the samples;
2) Prepare the samples for observer judgment;
3) Select observers;
4) Determine observer judgment task or question;
5) Present samples to observers for their judgment or preference;
6) Collect and record observer responses;
7) Analyse observer response data to generate the scale values

Selection of samples is governed by the objective of the scaling study. Sample selection is, practically, one of the most labour intensive parts of the scaling study. Engeldrum (2001) suggested four key factors, which need to be addressed during sample selection (generation phase) of the scaling plan:

1) What categories should the samples represent?
2) What range should the sample set contain?
3) What image size should be used?
4) What image content or elements should the samples contain?

Engeldrum describes ‘categorization’ (5 samples of imagery and their basic properties) as an organized way to make a rational sample selection that also identifies exclusion criteria (Engeldrum, 2001).

Purposeful sampling can be extremely useful during product design. Often the prototype produces some unexpected characteristics and raises the question, "What level of the (unwanted) characteristics of features is acceptable?" A set of sample images that exhibit various levels of the features in question would comprise the sample set in a scaling study. Incidental sampling uses a "reference" set, supposedly representing product performance requirements. These images then become the "gold standards." Experienced observers often select these reference images. However, the inclusion and exclusion criteria of the images also need defining when generating reference images.
8 Neural Networks and Pruning

There is an expectation that high resolution imaging will not only portray anatomical structures and give a clear representation of the morphology of disease, but will also perform the preliminary analysis of the image. Directing the clinician’s attention to those features, which may carry the most vital information for the diagnosis is vital. Researchers have been developing various algorithms for the automatic interpretation of medical images. However, there is a growing demand for better techniques of analysis, classification and recognition. Pattern recognition of medical images is the ability to recognise normal anatomy and physiology. Clinicians’ interpretation is the key underlying component. They are able to analyse visual scenes with very little effort distinguishing features among a remarkable variety of objects, actions and interactions in complex, cluttered visual scenes. Clinicians learn by training from past experience data and this learning process has been modelled in artificial neural networks (ANN). Knowledge or feature extraction is the process of extracting valuable information from trained neural networks in the form a set of ‘if-then’ rules. The extracted rules describe the knowledge acquired by neural networks. Clinicians do not analyze medical images for isolated facts; they try to describe them in terms of patterns of related facts. Sometimes these relations are implicit because they all refer to the same object.

In neuroscience, synaptic pruning refers to neurological regulatory processes, which facilitate changes in neural structure by reducing the overall number of neurons and synapses, leaving more efficient synaptic configurations. Pruning is influenced by environmental factors and is widely thought to represent learning. Similarly, pruning ANN in medicine results in a less complex ANN while improving its function. Once the pruning is complete, the ANN is trained with the same dataset to ensure that the recall accuracy of the ANN has not diminished. Algorithms from unsupervised learning require pruning in order to remove redundant, irrelevant features or to eliminate areas of inter-observer confusion.

The next chapter explores the biometric and refractive differences between two cohorts of PAC(G) of different ethnicity. The use of UBM and anterior segment OCT has been used to document changes in anterior segment morphology in PAC(G), however, the area of qualitative assessment of the anterior segment lacks standardisation. The areas of clinical grading scales, psychometric testing and pruning are used to generate clinical grading scales for UBM features of PAC(G).
Chapter 2 : Project One

9 To compare biometry & refractive error in Caucasian & Chinese patients with PAC(G)

9.1 Contributions

Table 9.1 detailing role of each author in this publication Y denotes significant contribution.

<table>
<thead>
<tr>
<th></th>
<th>Concept/ Design</th>
<th>Recruitment</th>
<th>Acquisition of Data</th>
<th>Analysis</th>
<th>Supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqi, R</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Henson, DBH</td>
<td>Y</td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Aung, T</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nolan, W</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Nongpiur, M</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.2 Abstract

**Purpose:** To compare biometric dimensions between eyes of Singaporean Chinese and UK Caucasian patients with PAC(G).

**Methods:** 172 patients were assessed from two glaucoma centres. Eighty-six Chinese and 86 Caucasians, all with a PAC(G) or with a history of an acute attack. The groups were age and sex-matched. One eye of each subject was randomly selected for biometry. Measurements including: axial length, anterior chamber depth, lens thickness, vitreous chamber depth and ratio's such as lens: axial length factor, absolute lens position, relative lens position were compared between the groups using a paired t test.

**Results:** The male/female ratio was 26:60. The mean axial length and anterior chamber depth were significantly shorter in Caucasian eyes (p<0.0001). Lens thickness, relative lens position and absolute lens position were also significantly larger in Caucasian eyes (p<0.0001).

**Conclusions:** In this study the Caucasian cohort exhibit biometric findings typically associated with PAC(G). The Caucasians had significantly shorter eyes, shallower anterior chambers, larger lenses with a LAF >0.20, and a significantly shorter vitreous depth, when compared to their Chinese counterparts. Biometric differences lend support to variation of PAC(G) mechanisms between ethnicities.
10 Introduction

The understanding of PAC(G) is largely based on evidence from East Asia (Casson et al., 2009; Congdon et al., 1996; Foster et al., 2001; Kashiwagi et al., 2005; Kunimatsu et al., 2005). Angle closure disease, until recently, has been regarded as relatively rare in Caucasian populations (Azuara-Blanco et al., 2011; Day et al., 2012; Wang et al., 2013; Ng et al., 2008b) although according to Day et al. (2012). PAC disease is much more common in those >40years than previously estimated. With an ageing population cases are, therefore, expected to rise (Quigley, 1996) and ethnic differences between the two cohorts may well explain some of the excess of burden in China (Oh et al., 1994).

Many biometric traits are associated with PAC(G), the most common associations are with a short axial length, thick lens, shallow anterior chamber depth and hypermetropic refractive error (Lowe, 1970a; Lowe, 1970b; Lowe, 1969). A shallow central ACD has been historically noted for PACG being one of the earliest recognised risk factors (Congdon et al., 1997; Lowe, 1969; Tornquist, 1956) with high heritability (Alsbirk, 1975; He et al., 2008c; Yip et al., 2012). Surprisingly, given the relative prevalence’s of PAC(G), Congdon et al. (1997) found there was no greater proportion of small eyes or smaller mean AC depth among Chinese compared to European or African populations, see figure 10.1.

![Anterior Chamber Depth by Ethnicity](image_url)

Figure 10.1 The distributions of anterior chamber depth in 3 major ethnicities, from population based data (from Quigley, 2009) there is no greater proportion of Chinese patients with shallower chamber depth compared to two other ethnicities. (Congdon et al., 1997; Quigley, 2009a).

In a review by Lowe (1970a) on Caucasian eyes, unaffected individuals were reported to have ACDs between 3.03 and 3.15mm, compared with 2.31 and 2.38mm in AC(G). Congdon et al. (1997) found Caucasians, seen as part of the Baltimore Eye Study, had mean ACD of 3.07mm (men) and 2.99mm (women). Lowe (1969) found a threshold for risk of angle-closure started at 2.5mm with increased risk below this level. In the EPIC-Norfolk cohort, 7.3% of women and 6.5% of men fell into this “at risk” category (Foster et al., 2010).
Congdon et al. (1997) found hyperopia greater than 2DS in 31.8% of Caucasians, 22.1% Afro-Caribbean and 13.8% of Chinese eyes with PAC(G). Interestingly, the association of hyperopia is greater in Caucasian eyes than Chinese eyes. A review of literature reveals little mention of myopic PAC(G) (Chakravarti et al., 2007; Chhipa, 2009) despite this being a relatively common occurrence in Chinese populations. Lowe (1970a) reviewed 127 eyes of patients diagnosed with POAG, only 2 had myopia of greater than 2.0DS ranging between (-6.25 to -8.0). Marchini (2002) reported no cases of myopia (n=54) in patients with PACG (Marchini, 2002) while Barkana et al. (2006) described 20 patients with a spectrum of ophthalmic conditions leading to myopia and PAC. PAC(G) may not be restricted to short hypermetropic axial lengths however good population studies for myopic patients are lacking.

Anatomic differences (ACD, axial length, corneal radius of curvature and hyperopia >2.00 DS) do not explain the greater prevalence of angle closure in Chinese populations (Day et al., 2012; Lowe, 1969; Sihota et al., 2005). However, Congdon et al. (1997) did not include measures of lens thickness, lens position or vitreous chamber depth in their study.

There remain unanswered questions as to why PAC(G) is more common in some races rather than others (He et al., 2006b). Are there differences in other anatomical features, such as the lens thickness, that could account for the differences in prevalence? If so, is the mechanism of the disease different in different ethnic groups and should this impact on management.

10.1 Aim
The aim of this study is to compare the biometric data of Caucasian and Chinese patients with PAC(G). ACD, lens thickness, vitreous chamber depth and axial lengths along with other lens parameters are reported with reference to ethnicity, age and sex.

11 Methods
Retrospective, observational study comparing biometry in UK Caucasian and Singaporean Chinese patients with PAC(G).

11.1 Ethics
The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and had the approval the respective clinical research ethics committees in West Midlands UK and the Institutional Review Board of Singapore Eye Research Institute. Informed consent was obtained from all participants. Ethical approval
was gained under Birmingham Angle Closure Study: Anterior Segment Morphology in Angle Closure (IRAS Ref: 94244 - Portfolio Study ID: 12771).

11.2 Participants
We consecutively enrolled 302 subjects (151 UK Caucasian and 151 Singaporean Chinese patients) with a diagnosis of irido trabecular contact (ITC) or PAC(G) or with a history of an acute attack from two glaucoma clinics (BMEC and Singapore National Eye Centre (SNEC)). Subjects with history of use of any topical or systemic medication that could affect the ACA or pupillary reflex, or history of previous intraocular operative or laser surgery were excluded from the study. When both eyes of a subject were eligible, one eye was randomly selected.

11.3 Gonioscopy
The method for gonioscopy was standardised using SGGS. Gonioscopy was performed in the dark using a Goldmann 2-mirror lens. Indentation gonioscopy with a Sussman 4-mirror lens was used to establish the presence or absence of peripheral anterior synechiae (PAS). At SNEC 75% of the gonioscopy was performed by a glaucoma fellow (MN) the remainder by one of several glaucoma Consultants. Similar criteria were followed for classifying an eye as having PAC(G) before LPI. At BMEC gonioscopy was performed by one glaucoma consultant (WN).

PAC(G) was defined where the posterior pigmented trabecular meshwork was not visible for at least 180 degrees on non-indentation gonioscopy with the eye in the primary position.

11.4 Autorefraction
Refraction data was obtained with an autorefractor (Topcon Auto K KR7100D, Topcon Corp, Tokyo, Japan). Spherical equivalent was defined as sphere plus half cylinder.

11.5 Ocular biometry
Ultrasound biometry was used to obtain measurements of Anterior Chamber Depth (ACD), Lens Thickness (LT), Vitreous Chamber Depth (VCD), and axial length (AXL).

11.5.1 SNEC:
Ocular biometry was performed using contact A-scan ultrasonography (Model US-800; Nidek Co, Ltd., Tokyo, Japan) and an experienced Optometrist performed the scans.
11.5.2 BMEC:
Ocular biometry was performed using an immersion B-biometry technique (AVISO, Quantel Medical, Clermont-Ferrand, France). Immersion B–guided biometry is a two-dimensional axial section that can be transferred to immersion A-scan mode and represents the cross vector interfaces from anterior cornea to the macula. It allows correct identification of the ocular interfaces (Olsen, 1992). This was performed by myself or specialist ultrasonography technicians.

11.6 Biometric parameters
Axial length, lens thickness, anterior chamber depth, absolute lens position and lens axial length factor (LAF) were measured for all eyes. Where

\[ ALP = ACD + LT/2 \ (mm), \text{ and} \]
\[ RLP = (ACD + LT / 2) / AL \ (\text{no units}) \]
\[ LAF = LT / AXL \ (\text{no units}) \]

11.7 Statistics
Statistical analyses were performed using SPSS V.15.0 (SPSS, IBM Corporation, New York, USA) and Prism 6 (Graphpad Software, California, USA). Racial and gender differences in ACD, axial length, LT, auto-refraction, ALP, RLP were calculated.

The null hypothesis (H0) when analysing the paired difference between both ethnic groups was that the mean difference between the paired values is equal to zero (i.e. \( \mu_{\text{diff}} = 0 \)). Normality of distributions were assessed with the Kolmogorov-Smirnov test (sample size >50). Normally distributed data was analysed with a paired t test to elucidate whether there was statistically significant mean difference between the ethnic group means. For data that was not normally distributed several transforms were applied. If the transforms led to normal distributions then the transformed data was analysed with parametric tests. Sensitivity analysis was performed if the normality test failed. If the sensitivity analysis gave similar results to the t test – this will be used in discussions.

11.7.1 Exploring relationships between variables and ethnicity
Relationships between parameters, for each ethnic group, were assessed with the aid of scatter plots.

1. Axial length versus refractive error – do smaller axial lengths have hyperopic refractive error?
2. Lens thickness versus axial length – do smaller eyes have thicker lenses?
3. Lens thickness versus age – is lens thickness an age dependant variable?
4. ACD versus axial length – does a smaller eye have a shallower ACD?
Vitreous Chamber Depth is a biometric parameter important in myopia studies (verbal communication with Hema Radhankrishnan, University of Manchester). In view of this and myopia development studies, the relationships between VCD & ACD, LT and axial length were also explored.

12 Results

Gender and age are two potential confounding variables when looking at differences between the two samples. The ethnicity analysis, therefore, used matched pairs for age and gender. Of 151 patients in each group data was matched for 86 patients (26 males and 60 females in each cohort). All subsequent analysis is based upon this matched sub-group.

12.1 Age & Sex Matched Data

Demographic and ocular biometry data is shown in table 12.1. Age of diagnosis for each group is (63.73 ± 1.03) years.

Table 12.1 Demographics & Ocular Biometrics of Caucasian & Chinese Male (n=26) & Female Patients (n=60). Mean and standard deviation given for each parameter.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ethnicity</th>
<th>Male (n=26)</th>
<th>Female (n=60)</th>
<th>Male (n=26)</th>
<th>Female (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (AXL)</td>
<td>Chinese (SNEC)</td>
<td>22.84 ± 0.68</td>
<td>22.54 ± 0.80</td>
<td>22.56 ± 1.17</td>
<td>22.00 ± 1.41</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>22.56 ± 1.17</td>
<td>22.00 ± 1.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)</td>
<td>Chinese (SNEC)</td>
<td>2.60 ± 0.34</td>
<td>2.57 ± 0.30</td>
<td>2.39 ± 0.43</td>
<td>2.33 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>2.39 ± 0.43</td>
<td>2.33 ± 0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>Chinese (SNEC)</td>
<td>4.14 ± 1.05</td>
<td>4.10 ± 1.03</td>
<td>4.80 ± 0.64</td>
<td>5.04 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>4.80 ± 0.64</td>
<td>5.04 ± 0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>Chinese (SNEC)</td>
<td>4.68 ± 0.47</td>
<td>4.64 ± 0.56</td>
<td>4.89 ± 0.58</td>
<td>4.92 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>4.64 ± 0.56</td>
<td>4.92 ± 0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative Lens Position (RLP)</td>
<td>Chinese (SNEC)</td>
<td>0.21 ± 0.21</td>
<td>0.21 ± 0.26</td>
<td>0.22 ± 0.25</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>0.22 ± 0.03</td>
<td>0.22 ± 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>Chinese (SNEC)</td>
<td>0.18 ± 0.47</td>
<td>0.18 ± 0.05</td>
<td>0.21 ± 0.04</td>
<td>0.22 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>0.22 ± 0.04</td>
<td>0.22 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractive error (Rx)</td>
<td>Chinese (SNEC)</td>
<td>0.44 ± 2.06</td>
<td>0.10 ± 1.91</td>
<td>0.70 ± 1.21</td>
<td>1.50 ± 2.61</td>
</tr>
<tr>
<td></td>
<td>Caucasian (BMEC)</td>
<td>0.70 ± 1.21</td>
<td>1.50 ± 2.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Box plots of each parameter are shown in figure 12.1 any outliers were evaluated and included in the analysis.
12.2 Parametric Testing

12.2.1 Tests for Normality (Gaussian Distribution)

The normality test results (K-S test) are displayed in table 12.2. In Chinese patients PACD, LT, ALP are normally distributed (p>0.05). ACD, ALP, LT in Caucasian subjects are normally distributed. Distributions for refractive error (see figure 12.2) are slightly negatively skewed in Chinese patients and marked positively skewed in Caucasian patients.

Table 12.2 Shows Tests for Normality for each parameter. Normal Distributions are found for Significance (Sig) >0.05 (*). a. Lilliefors Significance Correction.
12.2.2 Difference between means

Difference between means, and transformed means (where necessary) are given in table 12.3. Tables 12.3 & 12.4 show that the ACD was deeper in Chinese subjects by 0.23mm (95% CI, 0.11 to 0.36mm), t(85)= 3.71, p<0.004, d=0.27. There are also highly significant differences for axial length, lens thickness, ALP, RLP, LAF and refractive error.

Table 12.3 Showing population mean difference for each parameter. Where: CI = confidence interval, d=effect size (mean/ standard deviation); d= effect size * Denotes large effect size, * denotes geometric. SQRT=square root, RSQRT=reciprocal of square root, RLog= Reciprocal of Logarithm, ACD= Anterior chamber depth, AXL= axial length, LT=lens thickness, ALP=absolute lens position, RLP=relative lens position, LAF=lens to axial length factor, VCD=Vitreous chamber depth, Rx=Refractive Error.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>t value</th>
<th>p value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQRT ACD</td>
<td>0.23*</td>
<td>0.11</td>
<td>0.36</td>
<td>3.71</td>
<td>&lt;0.004</td>
<td>0.27</td>
</tr>
<tr>
<td>RSQRT AXL</td>
<td>0.56*</td>
<td>0.32</td>
<td>0.79</td>
<td>47.57</td>
<td>&lt;0.0001</td>
<td>0.20</td>
</tr>
<tr>
<td>LT</td>
<td>-0.87</td>
<td>-1.13</td>
<td>0.62</td>
<td>-6.82</td>
<td>&lt;0.0001</td>
<td>-1.36*</td>
</tr>
<tr>
<td>ALP</td>
<td>-0.26</td>
<td>-0.42</td>
<td>-0.09</td>
<td>-3.20</td>
<td>0.0002</td>
<td>0.12</td>
</tr>
<tr>
<td>RLog RLP</td>
<td>-0.02*</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-20.24</td>
<td>&lt;0.0001</td>
<td>4.57*</td>
</tr>
<tr>
<td>Log LAF</td>
<td>-0.04*</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-5.64</td>
<td>&lt;0.0001</td>
<td>-1.65*</td>
</tr>
<tr>
<td>SQRT VCD</td>
<td>0.98*</td>
<td>0.55</td>
<td>1.36</td>
<td>71.53</td>
<td>&lt;0.0001</td>
<td>0.13</td>
</tr>
<tr>
<td>RSQRT Rx</td>
<td>-0.68*</td>
<td>-0.14</td>
<td>-1.28</td>
<td>37.71</td>
<td>&lt;0.0001</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Table 12.4 Comparative of biometric parameters for UK Caucasian & Singaporean Chinese patients with PAC(G). Table gives mean standard error of parameters, t-value and p value. * denotes parameter required transformation to assume normality.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ethnicity</th>
<th>Parameter</th>
<th></th>
<th>Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese (SNEC)</td>
<td>Caucasian (BMEC)</td>
<td></td>
<td>t value</td>
<td>p value</td>
</tr>
<tr>
<td>Axial Length (AXL)*</td>
<td>22.70 ± 0.08</td>
<td>22.17 ± 0.15</td>
<td></td>
<td>47.57</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)*</td>
<td>2.58 ± 0.03</td>
<td>2.35 ± 0.05</td>
<td></td>
<td>3.71</td>
<td>0.004</td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>4.11 ± 0.11</td>
<td>4.98 ± 0.06</td>
<td></td>
<td>-6.82</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Vitreous Chamber Depth*</td>
<td>15.93 ± 1.30</td>
<td>14.84 ± 1.32</td>
<td></td>
<td>71.53</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>4.90 ± 0.06</td>
<td>4.65 ± 0.06</td>
<td></td>
<td>3.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Relative Lens Position (RLP)*</td>
<td>0.21 ± 0.02</td>
<td>0.22 ± 0.03</td>
<td></td>
<td>20.25</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>0.18 ± 0.005</td>
<td>0.22 ± 0.004</td>
<td></td>
<td>-5.64</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Refractive error (Rx)*</td>
<td>0.20 ± 0.21</td>
<td>0.27 ± 0.06</td>
<td></td>
<td>37.71</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Inferential error plots in figure 12.3 indicate the spread of the data for each group.
12.3 Comparison of Males & Female with Ethnicity

Null hypothesis was that there is no difference between each parameter when analysing within the same gender. Differences between male and female biometry could mask findings within the pooled data. Therefore, comparisons between each gender were also undertaken. The small sample of males may cause some limitation in the findings.

12.3.1 Male Participants.

Table 12.5 shows test for normality for each parameter.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Kolmogorov-Smirnov Statistic</th>
<th>Kolmogorov-Smirnov df</th>
<th>Kolmogorov-Smirnov Sig.</th>
<th>Shapiro-Wilk Statistic</th>
<th>Shapiro-Wilk df</th>
<th>Shapiro-Wilk Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (AXL)</td>
<td>.076</td>
<td>26</td>
<td>.200</td>
<td>.976</td>
<td>26</td>
<td>.779</td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)</td>
<td>.072</td>
<td>26</td>
<td>.200</td>
<td>.981</td>
<td>26</td>
<td>.891</td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>.123</td>
<td>26</td>
<td>.200</td>
<td>.946</td>
<td>26</td>
<td>.182</td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>.117</td>
<td>26</td>
<td>.200</td>
<td>.976</td>
<td>26</td>
<td>.772</td>
</tr>
<tr>
<td>Relative Lens Position (RLP)</td>
<td>.124</td>
<td>26</td>
<td>.200</td>
<td>.974</td>
<td>26</td>
<td>.738</td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>.155</td>
<td>26</td>
<td>.111</td>
<td>.916</td>
<td>26</td>
<td>.035</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (VCD)</td>
<td>.061</td>
<td>26</td>
<td>.200</td>
<td>.991</td>
<td>26</td>
<td>.996</td>
</tr>
<tr>
<td>Refractive error (Rx) *</td>
<td>.238</td>
<td>26</td>
<td>.001</td>
<td>.729</td>
<td>26</td>
<td>.000</td>
</tr>
</tbody>
</table>

Table 12.6 shows t test results for male participants. There is no significant difference between the axial lengths t(25)=1.12 and p=0.27. Caucasian males had a slightly shallower ACD (2.39 ± 0.43) compared to their Singaporean counterparts (2.60±0.34) where t(25)= 2.17, p =0.04.
Table 12.6 shows results of t test for population of patients when comparing across Male patients (n=26) of both ethnicities. Shown below is the mean ± sd for each cohort, t score and p value. † Indicates no significant difference when p >0.05.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Chinese (SNEC)</th>
<th>Caucasian (BMEC)</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (AXL)</td>
<td>22.84 ± 0.68</td>
<td>22.56 ± 1.17</td>
<td>1.12</td>
<td>0.27</td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)</td>
<td>2.60 ± 0.34</td>
<td>2.39 ± 0.43</td>
<td>2.17</td>
<td>0.04</td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>4.14 ± 1.05</td>
<td>4.80 ± 0.64</td>
<td>-2.74</td>
<td>0.01</td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>4.68 ± 0.47</td>
<td>4.89 ± 0.58</td>
<td>-1.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Relative Lens Position (RLP)</td>
<td>0.21 ± 0.21</td>
<td>0.21 ± 0.26</td>
<td>-1.81</td>
<td>0.08</td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>0.18 ± 0.47</td>
<td>0.18 ± 0.05</td>
<td>85.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (VCD)</td>
<td>16.08 ± 1.23</td>
<td>15.34 ± 1.29</td>
<td>2.57</td>
<td>0.02</td>
</tr>
<tr>
<td>Refractive error (Rx) *</td>
<td>0.44 ± 2.06</td>
<td>0.70 ± 1.91</td>
<td>-23.91</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The lens was thicker in Caucasians (4.80±0.64) compared to the Chinese (4.14±1.03) where t(25)=−2.74 and p=0.01. We can therefore reject the null hypothesis for each of these parameters. There was no significant difference between both ethnicities with ALP (p=0.18) and RLP (p=0.08). There was a significant difference (p<0.0001) between refractive errors, Chinese (+0.44 ± 2.06) DS; Caucasian (+0.70 ± 1.91) DS.

12.3.2 Female Participants

Null hypothesis was that there is no difference between each parameter when analysing within the same gender. Table 12.7 shows test for normality for each parameter.

Table 12.7 Normality tests for each parameter. Normal Distributions are found for Significance (Sig) >0.05 (*). a. Lilliefors Significance Correction, df – degrees of freedom.

<table>
<thead>
<tr>
<th></th>
<th>Kolmogorov-Smirnov*</th>
<th>Shapiro-Wilk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (AXL)</td>
<td>.088 60 .200*</td>
<td>.890 60 .000</td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)</td>
<td>.074 60 .200*</td>
<td>.974 60 .225</td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>.090 60 .200*</td>
<td>.990 60 .907</td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>.062 60 .200*</td>
<td>.993 60 .976</td>
</tr>
<tr>
<td>Relative Lens Position (RLP)</td>
<td>.089 60 .200*</td>
<td>.967 60 .102</td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>.088 60 .200*</td>
<td>.981 60 .478</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (VCD)</td>
<td>.082 60 .200*</td>
<td>.980 60 .449</td>
</tr>
<tr>
<td>Refractive error (Rx) *</td>
<td>.142 60 .004</td>
<td>.914 60 .000</td>
</tr>
</tbody>
</table>

Table 12.8 shows the results of the paired t test of female participants. All ocular biometric parameters show highly significant differences.
Table 12.8 t test results for population of patients when comparing across female patients (n=60) of both ethnicities.* variable required transformation.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Chinese (SNEC)</th>
<th>Caucasian (BMEC)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (AXL) *</td>
<td>22.54 ± 0.80</td>
<td>22.00 ± 1.41</td>
<td>35.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anterior Chamber Depth (ACD)</td>
<td>2.57 ± 0.30</td>
<td>2.33 ± 0.52</td>
<td>3.025</td>
<td>0.04</td>
</tr>
<tr>
<td>Lens Thickness (LT)</td>
<td>4.10 ± 1.03</td>
<td>5.04 ± 0.83</td>
<td>-6.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Absolute Lens Position (ALP)</td>
<td>4.64 ± 0.56</td>
<td>4.92 ± 0.53</td>
<td>-2.94</td>
<td>0.005</td>
</tr>
<tr>
<td>Relative Lens Position (RLP) *</td>
<td>0.21 ±0.26</td>
<td>0.22 ± 0.03</td>
<td>16.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lens: Axial length Factor (LAF)</td>
<td>0.18 ± 0.05</td>
<td>0.22 ± 0.04</td>
<td>-5.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (VCD)</td>
<td>15.87 ± 1.33</td>
<td>14.63 ± 1.29</td>
<td>5.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Refractive error (Rx) *</td>
<td>0.10 ± 1.91</td>
<td>1.50 ± 2.61</td>
<td>20.14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

There were statistically significant differences for ACD (p=0.04) and for refractive error (p=0.001). Highly statistical differences can be seen for, AXL (p<0.0001), LT (p<0.0001), ALP (p=0.005), RLP (p<0.0001), LAF (p<0.0001), VCD (p<0.0001). Therefore the null hypothesis is rejected for each if these parameters.

Inferential error plots are shown in figure 12.4 indicating the spread of the data for each group.
Figure 12.4 Inferential Error bars showing the means & 95% confidence intervals (CI) for biometric parameters, between two groups of patients of different ethnicity and comparisons with gender (each of size n=86). Blue error bars denote Chinese subjects (n=26 for each ethnicity) and red error bars denote Caucasian subjects (n= 60 for each ethnicity).

12.4 Subtypes of PAC(G)

The data from this study can be further sub-divided on the basis of the type of PAC(G). Figure 12.5 shows the number of patients in each sub-type of PAC(G).

Figure 12.5 Bar chart of numbers of patients with each Sub-type of PAC(G). Where PAC=primary angle closure, PACG=primary angle closure glaucoma, patients with a history APPAC=acute primary angle closure or APACG= acute primary angle closure glaucoma.

The small sample sizes in many sub-types meant that biometric differences could not be statistically compared with any confidence. The PACG group is analysed where Chinese group (n= 53), Caucasian (n=21). Table 12.9 shows the mean (SD), Mann Whitney z value and p value for each parameter. There is no significant difference for the age of diagnosis, ALP and refractive error. Highly significant differences can be seen for LT, VCD and LAF. Less significant difference can be seen for AXL, ACD and RLP.
Table 12.9 Mean (SD), Mann Whitney z score and p value for patients with PACG. AXL=axial length, LT=lens thickness, VCD=vitreous chamber depth, LAF=lens to axial length factor, ALP=Absolute lens position, RLP=relative lens position, Rx=refractive error.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Chinese (n=53)</th>
<th>Caucasian (n=21)</th>
<th>z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td>64.40 ± 9.76</td>
<td>62.38 ± 10.94</td>
<td>-0.93</td>
<td>0.35</td>
</tr>
<tr>
<td>AXL</td>
<td>22.76 ± 0.81</td>
<td>21.73 ± 1.04</td>
<td>-3.51</td>
<td>0.004</td>
</tr>
<tr>
<td>ACD</td>
<td>2.58 ± 0.25</td>
<td>2.19 ± 0.45</td>
<td>-3.69</td>
<td>0.002</td>
</tr>
<tr>
<td>LT</td>
<td>4.00 ± 1.02</td>
<td>5.11 ± 0.60</td>
<td>-4.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VCD</td>
<td>16.18 ± 1.34</td>
<td>14.43 ± 1.09</td>
<td>-4.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LAF</td>
<td>0.18 ± 0.05</td>
<td>0.23 ± 0.03</td>
<td>-4.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALP</td>
<td>4.58 ± 0.50</td>
<td>4.75 ± 0.33</td>
<td>-1.22</td>
<td>0.22</td>
</tr>
<tr>
<td>RLP</td>
<td>0.20 ± 0.02</td>
<td>0.22 ± 0.02</td>
<td>-2.78</td>
<td>0.01</td>
</tr>
<tr>
<td>Rx</td>
<td>0.30 ± 1.98</td>
<td>1.83 ± 3.48</td>
<td>-0.80</td>
<td>0.42</td>
</tr>
</tbody>
</table>

12.5 Biometric Associations

12.5.1 Axial Length v Refractive Error

To demonstrate the association between refractive error and axial length a scatter plot is given in figure 12.6

Figure 12.6 Scatter plot to show axial length to refractive error relationship where O (blue circle) denotes Singaporean Chinese patients & △ (red triangle) denotes UK Caucasian patients.

There was no obvious correlation between refractive error and axial length for both cohorts, i.e. smaller axial lengths are not necessarily associated with a hypermetropic correction. The Chinese cohort show a spread of refractive error’s between hyperopia to myopia. Caucasian cohort shows a tendency towards hyperopia or emmetropia, there is a non-linear relationship between axial length and refractive error, i.e. the sharp truncation at 0DS and a trend for positive errors. Regardless of the varying axial lengths Caucasian patients show evidence of
emmetropisation and the Chinese cohort there show failure of emmetropisation or a failure to maintain emmetropia (Flitcroft, 2014; Flitcroft, 2013).

12.5.2 Vitreous Chamber depth

Figure 12.7a shows no simple relationship between VCD and refractive error. Figure 12.7b illustrates a negative correlation between VCD & LT, where longer VCD is associated with thinner lenses in the Chinese group and thicker lenses are associated with a shorter VCD in Caucasian eyes. Figure 12.9c shows a positive correlation between VCD and axial length, Caucasian eyes appear to be shorter with a smaller VCD and few outliers. Longer eyes with a longer VCD are seen in the Chinese cohort. Clearly shorter VCDs are seen in the shorter eyes of the Caucasian patients.

![Figure 12.7 Scatter plots to show relationship between: a) vitreous chamber depth & refractive error; b) vitreous chamber depth & lens thickness and c) vitreous chamber depth & axial length where ○ (blue circle) denotes Chinese patients & △ (red triangle) denotes Caucasian patients.]

12.5.3 Lens Parameter variations with age & axial length

The scatter plot in figure 12.8a shows no obvious correlation between lens thickness and axial length. There is no simple relationship between the two parameters for the Chinese cohort. Caucasian cohort appears to have thicker lenses with a range of axial lengths whereas the Chinese have much thinner lenses. There is no simple relationship between the two parameters for the Chinese cohort. Figure 12.8b shows no obvious linear relationship between lens thickness and age. Caucasian patients appear to have thicker lenses compared to Chinese counterparts regardless of the age who show varying lens thickness with age.
Figure 12.8 Scatter plots: to show relationship between a) lens thickness & axial length; b) lens thickness & age at diagnosis; where ○ (blue circle) denotes Chinese patients & △ (red triangle) denotes UK Caucasian patients.

Figure 12.9 shows no obvious correlation between LAF and age. Caucasian patients have a higher LAF regardless of age. Chinese patients show varying LAF at all ages.

Figure 12.9 Scatter plots: to show relationship lens to axial length ratio & age where ○ (blue circle) denotes Singaporean n Chinese patients. Where: ○ (blue circle) denotes Singaporean Chinese patients & △ (red triangle) denotes UK Caucasian patients.

**12.5.4 Anterior Chamber Depth v Lens Thickness**

Figure 12.10 shows there is negative correlation between ACD and lens thickness. There is little overlap of scatterplots for both ethnicities where the Caucasian group have thicker lenses associated with shallower ACD and Chinese patients have deeper AC’s associated with thinner lenses.
13 Conclusion

The purpose of this study was to investigate the ethnic variation in ocular biometrics between Caucasian and Chinese patients with PAC(G) (Congdon et al., 1997; Day et al., 2012; Oh et al., 1994; Yip et al., 2006). Previous ocular dimension studies, summarised in table 13.1, have shown that eyes with PAC(G) differ from normals. Vitreous chamber depths, ALP, RLP, LAF have been calculated when not given.

Table 13.1 Mean values (with standard deviations) for biometry measurements in patients with PAC(G) compared with normal, * Indicates values calculated by me. NG – not given.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>PAC(G)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD (mm)</td>
<td>2.80 (0.36)</td>
<td>1.80 (0.25)</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>2.80 (0.36)</td>
<td>2.96 (0.28)</td>
<td>(Lowe, 1970a)</td>
</tr>
<tr>
<td></td>
<td>3.08</td>
<td>2.31</td>
<td>(Tomlinson et al., 1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.35 (0.05)</td>
<td>Caucasian, BMEC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.58 (0.03)</td>
<td>Chinese, SNEC</td>
</tr>
<tr>
<td>Lens thickness (mm)</td>
<td>4.30 (0.31)</td>
<td>4.23 (0.69)</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>4.50 (0.34)</td>
<td>5.09 (0.34)</td>
<td>(Lowe, 1970a)</td>
</tr>
<tr>
<td></td>
<td>4.46 (0.42)</td>
<td>5.43 (0.46)</td>
<td>(Delmarcelle et al., 1976)</td>
</tr>
<tr>
<td></td>
<td>4.67</td>
<td>5.23</td>
<td>(Tomlinson et al., 1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.98 (0.06)</td>
<td>Caucasian, BMEC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.11 (0.11)</td>
<td>Chinese, SNEC</td>
</tr>
<tr>
<td>Axial Length (mm)</td>
<td>22.58 (0.78)</td>
<td>22.07 (0.69)</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>23.10 (0.82)</td>
<td>22.01 (1.06)</td>
<td>(Lowe, 1970a)</td>
</tr>
<tr>
<td></td>
<td>22.76 (0.78)</td>
<td>21.92 (0.70)</td>
<td>(Tomlinson et al., 1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.17 (0.15)</td>
<td>Caucasian, BMEC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.70 (0.08)</td>
<td>Chinese, SNEC</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (mm)*</td>
<td>15.24</td>
<td>15.14</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>15.80</td>
<td>15.12</td>
<td>(Lowe, 1970a)</td>
</tr>
<tr>
<td></td>
<td>15.01</td>
<td>14.38</td>
<td>(Tomlinson et al., 1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.84</td>
<td>Caucasian, BMEC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.01</td>
<td>Chinese, SNEC</td>
</tr>
<tr>
<td>RLP</td>
<td>0.23 (0.02)</td>
<td>0.21 (0.013)</td>
<td>(George et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>0.22 *</td>
<td>0.20 *</td>
<td>(Lowe, 1970a)</td>
</tr>
<tr>
<td></td>
<td>0.24 *</td>
<td>0.22 *</td>
<td>(Tomlinson et al., 1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.22 (0.03)</td>
<td>Caucasian, BMEC</td>
</tr>
</tbody>
</table>
There are ethnic variations between these studies. George et al studied Indian patients, Lowe Caucasians from Melbourne, Tomlinson (Tomlinson et al., 1973) Caucasians from Manchester. Caucasian patients with PAC(G) show thicker lenses than the Chinese and Indian counterparts. Indian and Caucasian patients show evidence of smaller axial lengths, thicker lenses, LAF >0.20.

The shallower ACD is in part due to a thicker and more anterior position of the crystalline lens. A thick lens plays an important role in the pathogenesis of PAC(G), decreasing ACD and increasing angle crowding. The relative size of the lens is represented by LAF. However, the association of PAC(G) between various lens parameters such as LP, RLP and LAF has not been established conclusively.

There are very few studies that have evaluated the biometrics of the eye between two ethnicities (Congdon et al., 1997). European eyes with PACG were thought to have deep ACD’s and the lowest rate of closure (Yip et al., 2006). This study shows that the distributions of ocular biometrics differ between Chinese and Caucasian cohorts. Chinese eyes have longer axial lengths, deeper anterior chambers, posterior ALP and longer VCD when compared to their Caucasian counterparts – who appear to have shorter axial lengths, thicker and more anterior lenses which takes up proportionally more room within the eye (i.e. higher LAF) with a smaller VCD. The Caucasian group show evidence of the typical ocular biometric traits associated with PACG.

### 13.1 Gender differences

Paired data from male patients suggests, despite the non-significant difference between axial length, that Caucasian have thicker lenses (4.80 ±0.64mm) with a shallower ACD when compared with Chinese (4.14 ±1.05mm) counterparts, where t(25)= -2.74, p=0.01. Caucasian females (22.00 ±0.52mm) had significantly shorter axial lengths where t(59)= -2.86, p=0.004)
compared to their Chinese counterpart (22.54 ±0.52mm). This is combined with a significantly shallower ACD, Chinese (2.57 ±0.30mm); Caucasians (2.33 ±0.52mm) where t(59)= -2.98 and p=0.003. Caucasian females had significantly different axial lengths (p=0.004), anterior chamber depths (p=0.003), lens thicknesses and all lens parameters.

These results are in agreement with the literature (Foster et al., 2010; Shufelt et al., 2005; Tornquist, 1953). In the EPIC-Norfolk study a group of female controls were found to have a shorter axial length than men by 2.1% (0.51mm), and shallower anterior chamber by 2.2% (0.07mm). This is similar to the Los Angeles Latino Study (0.47mm), where the difference in ACD was greater between men and women (0.12mm) (Shufelt et al., 2005). The ACD difference between English men and women (0.09mm) is almost identical to that identified by (Tornquist, 1953).

13.2 Anterior Chamber Depth

Anterior chamber depth (ACD) has been reported to be the most important anatomical risk factor for PAC(G) (Lowe, 1995b; Quigley, 2009a; Yip et al., 2006). ACD is shallow in females and decreases with increasing age (Alsbirk, 1988; Amerasinghe et al., 2008). This study shows that Caucasian patients have significantly shallower ACD compared to Chinese counterparts. This is confirmed by the negative correlation between ACD and lens thickness where an increase in lens thickness is seen to cause shallower ACD’s. As the position and/or thickness of the lens determine the ACD, these factors are also determinants of the risk of PAC(G).

13.3 Lens Factors

Lens thickness is found to be significantly greater in Caucasian (4.98 ±0.06mm) patients when compared to the Chinese cohort (4.11 ±0.11mm) where t(150)=4.83, p<0.0001. Caucasian patients in our study have thicker lenses across a wide range of axial lengths and there is no direct correlation between lens thickness and age of diagnosis. Chinese patients have varying lens thicknesses across all age ranges. The LAF was found to be significantly different between the two groups, Chinese (0.18 ±0.005) and Caucasian (0.22 ±0.004) where t(150)=4.83, p<0.0001. Previous research by Marchini et al. (1998) suggest that LAF>0.20 is a predictor of PAC(G). There was no obvious correlation between LAF versus age of diagnosis – but a tendency for LAF>0.20 regardless the age of diagnosis.

This study suggests that the LAF>0.20 in a Caucasian population is typically representative of lenticular mechanisms whereas the mechanism within the Chinese group (LAF<0.20) was more likely to be non-pupil block mechanism such as variations in the iris/ ciliary body, an anterior iris insertion or the position of the lens. A comparison of LAF is seen in table 13.1.
showing that Chinese cohorts have a lower LAF than Indian (George et al., 2003), Caucasian patients from Melbourne, Caucasians from Manchester and this study (Lowe, 1970b; Tomlinson et al., 1973). In this study a LAF>0.20 may be a typical finding in those with a 'lenticular' or 'phacomorphic' mechanism. Table 3.1 shows calculated LAF’s for previous studies where a higher LAF is seen in Caucasian groups.

The shallow ACD in the Caucasian group means that the equatorial lens plane is further forward than in the Chinese group. ALP or the central lens position is more posterior in Chinese patients. As the RLP is a ratio of ALP/AXL it is significantly lower in Chinese eyes.

13.4 Refractive Error
The mean refractive error in Caucasians (0.70 ±0.21DS) was significantly different from the Chinese (0.27 ±0.06DS) where t(85)=1.16, p=0.002. The scatter plots show that Caucasian patients were either hyperopic or emmetropic (rarely myopic) while Chinese patients show a central spread of ametropia with a mean refractive error of 0.27DS. Caucasian patients of varying axial lengths are emmetropic – small axial lengths are not necessarily associated with hypermetropia.

13.5 Vitreous Chamber Depth
The major structural correlate of myopia is the longitudinal elongation of the vitreous chamber (Gilmartin, 2004; McBrien et al., 2003). The Chinese cohort (15.93 ±1.30mm) show significantly longer VCD compared to Caucasian cohort (14.84 ±1.32mm) where t(85)= 5.65, p<0.0001.

Refractive errors develop from a mismatch of the eye’s refractive components (Gilmartin, 2004). This mismatch develops primarily because of disproportionate ocular growth mainly in the vitreous chamber. It is beyond the remit of this thesis to discuss all the theories of myopia, however, myopia is known to be a multifactorial disease that is related to both genetics and the amount of near work. The variation in emmetropisation in this Chinese cohort is evident when investigating the associations between several parameters, axial length, vitreous chamber depth and refractive error.

13.6 Comparison with other studies
This study shows significant differences between ocular biometrics between the two ethnicities. Congdon et al. (1997) compared American Caucasians, American African-Caribbean’s and Taiwanese Chinese with the hypothesis that Chinese had shallower ACD’s than do the Caucasian counterpart. They established that the distribution of ACD’s among
Chinese, Caucasian and African-Caribbean’s did not differ. Their study was based on a convenience sample of eyes from different ethnicities as opposed to an PAC(G) population. Their study did not yield any significant differences between ethnic groups a result that differs from the results of this study. Congdon et al. (1997) also describe a marginally significant difference between the prevalence of hyperopia among Chinese and Caucasian (0.03).

13.7 Study Limitations
This is a retrospective study, which does not contain corneal data. There were unequal distribution of PAC(G) sub-types, which limits the ethnicity comparisons and there were different ultrasound biometry techniques between the two centres. All of which are discussed below.

13.7.1 Sub-types of PAC(G).
Our sample was not balanced for sub-type of PAC(G) and this may partly explain differences in biometry. It is already known that extreme biometric findings i.e. smaller eyes with larger lenses, are seen in symptomatic (acute) PAC(G), table 13.2.

Table 13.2 Studies reporting ocular biometrics in PAC(G) where: PACS=Primary Angle Closure Suspect; ACD=anterior chamber disease; APACG=Acute angle closure glaucoma; CPACG=Chronic angle closure glaucoma; NP=not provided; CCT=central corneal thickness; LT=lens thickness; ACD=anterior chamber depth; AXL=axial length, LAF=Lens to axial length factor; ALP=Absolute lens position; RLP=relative lens position; *calculated by me. Adapted from (Razeghinejad et al., 2013)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Groups; Nos</th>
<th>Mean Age (sd)</th>
<th>CCT</th>
<th>LT</th>
<th>ACD</th>
<th>AXL</th>
<th>LAF</th>
<th>ALP*</th>
<th>RLP*</th>
<th>VCD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>He et al. (2007)</td>
<td>PACS: 72</td>
<td>NP</td>
<td>NP</td>
<td>4.07</td>
<td>2.05</td>
<td>22.5</td>
<td>1.81*</td>
<td>4.09</td>
<td>0.18</td>
<td>16.38</td>
</tr>
<tr>
<td>Sihota et al. (2005)</td>
<td>PACS: 19</td>
<td>37.19 (10.5)</td>
<td>560.98</td>
<td>4.00</td>
<td>3.06</td>
<td>23.21</td>
<td>1.72*</td>
<td>5.06</td>
<td>0.22</td>
<td>16.15</td>
</tr>
<tr>
<td>Ramani et al., (2007)</td>
<td>PACS: 57</td>
<td>52.4 (10.3)</td>
<td>480</td>
<td>4.27</td>
<td>2.24</td>
<td>22.23</td>
<td>2.10</td>
<td>4.23</td>
<td>0.19</td>
<td>15.72</td>
</tr>
<tr>
<td>Lan et al., (2007)</td>
<td>APACG: 33, CPACG: 41</td>
<td>65.9 (8.5) 63.9 (9.3)</td>
<td>NP</td>
<td>5.1</td>
<td>2.25</td>
<td>22.39</td>
<td>2.22</td>
<td>4.8</td>
<td>0.21</td>
<td>15.04</td>
</tr>
<tr>
<td>(Lim et al., 2006)</td>
<td>APACG: 73</td>
<td>61 (10.9)</td>
<td>NP</td>
<td>5.01</td>
<td>2.11</td>
<td>21.86</td>
<td>2.10</td>
<td>4.61</td>
<td>0.21</td>
<td>14.74</td>
</tr>
<tr>
<td>(George et al., 2003)</td>
<td>Occludable: 143</td>
<td>54.43 (9.23) 57.45 (8.5)</td>
<td>NP</td>
<td>4.4</td>
<td>2.53</td>
<td>22.07</td>
<td>1.99</td>
<td>4.73</td>
<td>0.21</td>
<td>15.14</td>
</tr>
<tr>
<td>Ramani et al. (2009)</td>
<td>PACS: 82</td>
<td>52.10 (10)</td>
<td>480</td>
<td>4.23</td>
<td>2.43</td>
<td>22.10</td>
<td>2.10</td>
<td>4.55</td>
<td>0.21</td>
<td>15.44</td>
</tr>
<tr>
<td>Salmon et al. (1994)</td>
<td>CPACG: 46</td>
<td>63.26</td>
<td>NP</td>
<td>4.73</td>
<td>2.24</td>
<td>22.43</td>
<td>2.11</td>
<td>4.61</td>
<td>0.21</td>
<td>15.46</td>
</tr>
</tbody>
</table>
Corneal data is not presented in reported cohorts. Other papers have evaluated corneal curvature, corneal thickness and have calculated corrected central ACD (Congdon et al., 1997).

13.7.2 Differences in ultrasound biometry.

The use of A scan in the Singaporean cohort and B Biometry on the Birmingham cohort may have introduced some differences. Axial lengths measured with the immersion method are, on average, 0.1-0.3mm longer than when measured by the contact method since no indentation of the globe occurs (Byrne, 1995; Shammas, 2004.) There are several potential limitations of A scan biometry, variable corneal compression and incorrect assumptions regarding sound velocity, which may lead to potentially incorrect distance measures.

Graph 13.1 shows () a comparison between IOL Master, B- Biometry and contact A scan biometry. This is own unpublished data of prospective double blind study examining 30 patients. There is no significant difference between the IOL Master and B-scan.

Immersion Vector B to A scan or “B-biometry” prevents corneal compression and a 2-dimensional B scan helps guide the superimposed vector A scan to the fovea. With a horizontal axial B scan approach the goal is to centre the cornea and lens while simultaneously displaying the optic nerve. The A scan is then adjusted to pass through the middle of the cornea as well as posterior and anterior lens echoes. This alignment ensures the vector will intersect the retina in the region of the fovea. This technique is important when the macula is on a sloping wall of a staphyloma, (paediatric biometry, examination under anaesthetic, mature cataracts and axial myopes). At BMEC the A scan is 0.24mm less than the B scan. Applying a correction factor is not appropriate for a different lab where patients of a different ethnicity have been assessed. However, applying this correction factor to the SNEC data will make the differences even more significantly different.
13.7.3 Patient Selection

The non-significant difference found amongst male subjects is likely to be due to the small sample size. However, ocular biometric differences in unaffected and PAC(G) eyes, between gender of varying ethnicities, have been described elsewhere (Congdon et al., 1997; George et al., 2003). There are socio-economic differences in the populations (rural/urban) which could have affected the results and there is growing evidence that Chinese populations in industrialized countries are undergoing a pronounced change in ocular biometric characteristics (higher rates of myopia in younger people; (He et al., 2009). Birmingham’s ReGAE (Research into Glaucoma and Ethnicity) highlighted that small hyperopic eyes with APAC are more likely to be present in socially deprived areas (Nessim et al., 2010), This emphasizes that caution is required when drawing inferences regarding longitudinal trends from cross-sectional data.

13.8 Summary of study

PAC(G) is emerging as a major cause of visual morbidity, especially in Asian people. This study looked at the anatomical differences between Caucasian and Chinese eyes. Thicker lenses were found in Caucasian eyes compared to the Chinese counterparts. The different emmetropisation process in the Chinese cohort highlights ethnic differences in ocular components and how they possibly modify themselves during development. Similar ethnic differences could lead to different morphological cause of PAC(G). Interestingly, the Chinese cohort, in whom a high prevalence of PAC(G) is established, does not demonstrate any biometric parameters known to be associated as an ocular risk for PAC(G). Regardless the differences between the two ethnicities this study demonstrates heterogeneous nature of PAC(G).

This study shows that in a matched age and gender population:

a) PAC(G) differences exists between the two ethnicities;

b) typical PAC(G) biometric findings (shallow ACD, small eyes) were found in the Caucasian cohort;

c) biometric variations differ between ethnic groups as do the mechanisms of PAC(G);

d) biometric variations exist with gender – where females have a smaller axial length, thicker lenses and anterior ALP. These differences are more pronounce in female Caucasians.

To my knowledge there is no other study, which has included the VCD in PAC(G) studies of ethnic variations. The longer VCD and ocular growth in Chinese patients may contribute to the reported varying prevalence’s of PAC(G) worldwide. The biometric ethnic differences lend support to the theory morphological differences of PAC(G).
14.1 Contributions

Table 14.1 detailing role of each author in this publication Y denotes significant contribution

<table>
<thead>
<tr>
<th></th>
<th>Concept/</th>
<th>Ethics</th>
<th>Recruitment</th>
<th>Acquisition of Data</th>
<th>Concordance Program</th>
<th>Analysis</th>
<th>Supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqi, R</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Henson, DBH</td>
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<tr>
<td>Nolan, W</td>
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<td></td>
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<td>Y</td>
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<tr>
<td>Good, P.A.</td>
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<tr>
<td>Stanton, R</td>
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<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Sung, V.S.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
</tbody>
</table>

All images were collected by Rizwana Siddiqi who has 14 years of experience collecting ultrasound images of the eye.

14.2 Project Summary

Primary Angle Closure (PAC(G)) is well known to occur in anatomically pre-disposed eyes where contact between the peripheral iris and trabecular meshwork causes mechanical impairment of aqueous outflow. The well-established relationship between the anatomy of ACA in PAC(G) has been described with gonioscopy. There is a view that treatment decisions and outcomes should be centred on disease morphology – and the efficacy of standard treatment (LPI) versus clear lens extraction needs re-evaluation. The complex nature of gonioscopy and its dependency upon skill set and experience make the identification of anterior segment morphology a difficult task. The ‘gold standard’ of gonioscopy is dependent on experience, where there is variation in both technique and skill and no simple method for documenting findings.

With the advent of imaging techniques (UBM with linear probes) it is possible to interpret anterior segment images using a set of CGS. The use of CGS has been successful in other areas within ophthalmology, including complications of contact lenses, Lens Opacification Classification Systems (LOCS), grading of gonioscopy findings, Van Herick's test, validated bulbar redness scales and prosthetic eye characteristics (Bailey et al., 1991; Bencic et al., 2005; Cantor et al. (2003); (Chong et al., 2000; Efron, 1998; Efron et al., 2001; Pine et al.,
CGS of UBM images can overcome problems, such as the poor identification of the scleral spur (Nolan, 2008) and the cumbersome nature of measuring anterior segment indices in a clinical setting. This chapter records the development of a CGS for PAC(G). It is hoped that the development and adoption of such scales will lead to a better understanding of the mechanisms of this type of glaucoma and how the eye responds to treatment.

### 14.3 Application to grading scales in Angle Closure

The selection of UBM scales for PAC(G) needs to be purposeful in order to identify the mechanism of an PAC(G). Psychophysical techniques can be employed to construct perceptual UBM scales. The utilisation of error scores (Donaldson, 1975; Farnsworth, 1957) and the inter-observer agreement can be used to develop a series of psychophysical scales. Inclusion and exclusion criteria are discussed within the methodologies of the project. Consensus will be used identify areas of confusion or inter-observer variability that can be pruned to produce a final CGS. This project uses the theories of pruning to eliminate areas of disagreement between observers and to produce a usable validated scale for PAC(G).

In CGS experiments, the clinical range of images for each characteristic needs to be considered. Extreme values can lead to distorted scales. To overcome potential scale distortion this project used perceptual scales whereby a group of observers order 8 images (between two end point images) with a technique similar to that described in section 7.4 and by (Schulze et al., 2007).

### 14.4 Aims

The study aims to:

- Develop a series of UBM grading scales for PAC(G);
- Provide reference consensus data from a group of observers;
- Apply psychophysical techniques to measure inter-observer error at each point of the scale;
- Apply theories of pruning to enhance the CGS functionality.

These aims seek to develop a series of UBM grading scales for PAC(G) in order to:

1. Classify the morphology of closure at the outset of managing a patient;
2. Standardise reporting of UBM findings at BMEC;
3. Assist management of the patient with PAC(G).
15 Methods

The method follows that of Schulze et al. (2007), Donaldson (1975); Farnsworth (1957) to rank a series of images, look for ranking errors within a group of observers and to select a final CGS set of no more than 7 images by pruning out images where ranking errors are high.

15.1 Ethical approval

Ethical approval has been given through the Integrated Research Application System (IRAS) for local ethical, NHS Permissions and NIHR Portfolio Adoption systems. The IRAS and UKCRN portfolio study numbers for each study can be seen in the table 15.1. UKCRN Study 12582 is the project described in this section.

Figure 15.1 IRAS & UKCRN Portfolio Study References for retrospective & prospective studies. * denotes project described in this report.

<table>
<thead>
<tr>
<th>UKCRN Portfolio Study ID</th>
<th>IRAS Ref</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>12582</td>
<td>77602</td>
<td>Grading Anterior Segment Morphology in Angle Closure *</td>
</tr>
</tbody>
</table>

15.2 Scale Development

This section uses some of Engeldrum (2001) processes to developing a scale. These are detailed in the following steps.

15.2.1 Patient Selection

Patients were enrolled retrospectively at the BMEC. Patients were identified from a dedicated PAC(G) database of over 960 patients. UBM images were obtained from patients with PAC(G) who attended the Department of Visual Sciences, BMEC between July 2008 and January 2011. A consultant ophthalmologist, Miss Winifred Nolan (WN), had performed gonioscopy. WN identified eyes with PACS or PAC(G). Any cases that had undergone treatment likely to alter the anterior segment (i.e. iridectomy, iridotomy, iridoplasty, and cataract surgery) were excluded. All patients were of European-derived ethnicity.

15.2.2 Acquisition of Reference Images.

Based upon a literature review a method of examining the anterior chamber was developed (Dorairaj et al., 2007; Hung et al., 1979; Liebmann, 2001; Mingying et al., 1997; Nolan et al., 2007b; Sakuma et al., 1997; Spaeth et al., 1995). The linear UBM probe (Quantel Medical, Clermont-Ferrand, France) allows examination of the entire AC as well as sectoral imaging.
of each quadrant. Images of the ACA’s were obtained in the temporal, nasal, inferior, and superior quadrants at each visit. Three standard axial image sections were obtained at 3, 6, 9 and 12 o’clock positions with normal room lighting and with the room lights off (~26cd/m$^2$ and ~0.4cd/m$^2$ respectively). Variations in accommodation were minimized by getting the patient to fixate a target on the ceiling. The probe was always perpendicular to the structure/quadrant of interest. To reveal the relationship between the iris and the ciliary body care was taken to ensure that radial perpendicular UBM scans were obtained. The gain was set to between 60 and 80dB, to have a clear display of the structures and minimize the signal to noise ratio (SNR).

15.2.3 Determine the task - Identifying UBM characteristics for PAC(G)

In order to generate purposeful grading scales a series of features needed to be identified. The following UBM features were selected following a review of the literature and review from two experts (RS & WN). Clinical experience, as recently reported by Jiang et al. (2010b), allows classification of size and rotation of the ciliary body, iris insertion, iris convexity, iris thickness and iris angulation. These are illustrated in figure 15.2 below. The seven different features selected to evaluate the morphology were:

1) Anterior chamber depth (ACD);
2) Iris thickness;
3) Iris profile;
4) Iris convexity;
5) Angulation of the iris root;
6) Ciliary body size;
7) Ciliary body position.

Although ACD can be measured by other imaging modalities, this parameter was included as a control for proof of concept.

Figure 15.2 Showing seven different features evaluated in patients with PAC(G): a) Anterior Chamber Depth (ACD), (b) Iris Thickness (IT), (c) Iris Profile, (d) Iris Convexity, (e) angulation of the iris root, (f) Ciliary Body Thickness, (g) Ciliary Body Position (CBP).
A 10-point grading scale for each characteristic was constructed using observer consensus. The consensus reached by the observers was utilised to ascertain discordant areas where pruning of the scale is most appropriate. These scales will range from minimal to severe – an example of this can be seen in figure 15.3.

![Figure 15.3](image)

Figure 15.3 Shows an example of a 4-point reference set for angulation of the iris root. The user will be asked to match a presented image with one of the images; user response may range between 1-4: with subdivisions to the nearest 0.5. 1 shows no angulation of the iris root increasing in size to 4.

### 15.2.4 Defining the UBM Characteristics

The grading features were defined a written description and a visual reference, see Figure 15.4.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Visual Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a True ACD</td>
<td><img src="image" alt="Image" /></td>
<td>Distance between the anterior surface of the lens &amp; corneal endothelium</td>
</tr>
<tr>
<td>b Iris Thickness</td>
<td><img src="image" alt="Image" /></td>
<td>Overall thickness and the thickness of the peripheral one third of the iris (termed basal iris thickness)</td>
</tr>
<tr>
<td>c Iris Profile</td>
<td><img src="image" alt="Image" /></td>
<td>Deviation of the shape of the iris profile from a flat horizontal line</td>
</tr>
<tr>
<td>d Convexity</td>
<td><img src="image" alt="Image" /></td>
<td>Curvature of the posterior surface of the iris</td>
</tr>
<tr>
<td>e Angulation</td>
<td><img src="image" alt="Image" /></td>
<td>The iris root makes an about change in the point of insertion from the ciliary body.</td>
</tr>
</tbody>
</table>
f  Ciliary Body Thickness

The greatest distance between a straight line. The apex of the ciliary body and the base.

g  Ciliary Body Position

Position of the CB ranging from posterior (more neutral) to a more anterior position. The absence of the ciliary sulcus indicates an anterior positioned CB. A present ciliary sulcus indicates a more posterior CB.

Figure 15.4 Showing Visual reference and verbal description of each grading characteristics.

15.2.5 Selection of UBM images

Figure 15.5 shows flow chart of the image selection process used to derive the reference set. Ten images for each characteristic were selected.

For each patient there were 28 UBM images (14 per eye). Images were graded for quality, according to (Engeldrum, 2001) “What level of the (unwanted) feature is acceptable?” The inclusion criteria for acceptable axial and sectoral images are:

**Axial image**: The entire AC was clear with visualization of the scleral spur, angle, ciliary body and anterior surface of lens.

**Sectoral image**: Visualization of the scleral spur, angle, ciliary body and anterior surface of the lens, a half chord of the iris. Images were matched for quality in terms of sharpness of focus, uniform illumination, and image centration.

15.2.6 Selecting observers

Eleven observers (Six males and five females) were enrolled into the study; all observers were clinicians: Consultant Ophthalmologists (CF, VS, WN); Professor (DH); Consultant Clinical Scientist (PG), NIHR Clinical Research Fellow (RS) & Medical Technical Officers: (RSt, JM, MA) and two researchers (YW and MB). Observers of mixed experience were selected in order to provide a realistic clinical set mix.
Figure 15.5 flow chart indicating selection of images
15.3 Collecting the responses of UBM perceptual scales

Image size is a well-known factor in quality judgments (Westerlink et al., 1989) therefore all UBM images were printed to the same size (180 x 130mm). For each grading feature, the eleven observers were asked to rank UBM images in increasing order.

Each observer independently performed this task in a controlled environment with identical illumination settings. The observers were masked to the results of the others. Eight images were randomly arranged on a table top between the anchored start- and endpoints. No intermediate severity levels were given. The observers were required to place each image within the designated anchored points. Their perception of each attribute is similar to the technique employed to perform the FM hue test, i.e. using a ‘spot the difference’ technique between adjacent images. Re-adjustment of images during the arrangement was allowed, and after completion of the task, the position of each image was recorded.

15.4 Analysis of scales

To analyse the strength of association between the psychophysical arrangements of every single observer, Spearman rho statistics were calculated (SPSS version 20) between each pair of observers. Spearman’s statistic can be used to measure pair wise correlation among observers using a scale that is ordered. The strength of correlation was analyzed for each single observer against each other, giving 110 correlations for each grading characteristic. Kendall’s W Coefficient of Concordance extends Spearman rho to more than two groups. This procedure is useful in studies in which three or more groups create rankings of items. This was used to evaluate the ordering of images between multiple observers (Pasisz et al., 2009).

15.4.1 Visualising Rank Data

The presentation of concordance in the form tables or matrices, while exact, is difficult to interpret/compare (Legendre, 2005; Vidmar et al., 2007) and so a method was sought to graphically display concordance that highlighted variations in rank order. Figure 15.6 gives examples of ranking by ‘arrangement by observer’ and ‘arrangement by object’ for Kendall’s Concordance Coefficients, W=1 (perfect) W=0.95 and W=0.41. Whilst an overview of concordance can be obtained, areas of discordance are difficult to detect with decreasing values of W.
Figure 15.6 shows example of visualizing concordance for 10 observers ranking 10 images (W). For W=1 or perfect concordance a) shows the inter-observer agreement of each image and b) shows ranking of order of each object. For W= 0.95 c) shows the inter-observer agreement of each image and d) shows ranking of order of each object. For W= 0.41 c) shows the inter-observer agreement of each image and d) shows ranking of order of each object.

Vidmar et al. (2007) described the use of pin-cushions and bubble plots to visualize concordance. Figure 15.7 shows a bubble plot of how images numbered 2-9 are placed by several observers (n=11) the x-axis is the order of ranking for each image. The size of the bubble denotes the number of observers agreeing to place an image at a particular rank, i.e. the radius denotes the frequency of ranking. The 'bigger the bubble' the better inter-observer agreement. Smaller bubbles show areas of discordance. The dashed line x=y resembles perfect concordance.
Figure 15.7 shows the rank order of placing 10 images in order Kendall’s concordance $W=0.96$; Large bubbles indicate observer agreement. Smaller bubbles indicate less agreement and the alternative rank can also be visualized. The red bracket indicates that images 4-6 are selected at rank order 4, 5 or 6 indicating areas of inter-observer confusion. The blue bracket denotes Images 7 and 8 are also transposed between rank 7 & 8. The dashed line indicates $x=y$ or $W=1$. The larger the bubbles respecting $x=y$ indicates rank order agreement.

The methodology of bubble plots will be used to visualise inter-observer concordance when constructing CGS. The bubble plot was produced using Microsoft Excel.

### 15.4.2 Standard error of measurement

The standard error of measurement is an estimate of the average standard error of measurement for all observers. This may also be defined, for the whole sample or population of examinees, as the standard deviation of the inconsistency errors or the standard deviation of the differences between raw scores and the corresponding true scores. The use of standard error of measurement can be seen when scoring the FM data (see section 7.3).

The test is scored by noting the UBM image numbers ($i_n$) that are placed at each of the 10 positions $n$. The size of the error score $\varepsilon$ is an indication of how well the UBM at $n$ is ordered with respect to its immediate neighbours, rather than a measure of how far away from its correct location it has been placed. The correct order was established by calculating the mode of all eleven observers.

Where

$$\varepsilon_n = |i_n - i_{n+1}| + |i_n - i_{n-1}|$$

The minimum value of $\varepsilon_n$, corresponding to correct order, is 2.

Subtotal error scores:

$$S_n = \sum \text{PAC(G) characteristic} \ (\varepsilon_n - 2)$$

Total error score:

$$T_n = \sum \text{all PAC(G) characteristic} S_n$$

Error score results were presented in tabular and scatter graph formats.
15.5 Reducing the 10 point scale

According to Schulze et al. (2007) that there should be up to 7 images in each grading scale. Using the group consensus could areas of disagreement/ confusion were identified scale. There is no established method to reduce the number of images in a CGS and it is beyond the scope of this thesis to develop a new method to do this effectively. However, data pruning can be seen in several other fields such as decision trees and artificial neural networks (ANN's).

To decide where to prune the 10-point scale I used the common areas of confusion and inter-observer error scores for each rank. Variances, high error scores are used to also remove images (define outliers/confusion areas with the highest variances/and error scores).

After pruning these areas, statistical inference tests were used to assess the strength of the reduced CGS. The strength of the CGS was analysed by re-calculating Spearman's statistic to re-measure pair wise correlation among subjects using a scale that is ordered. The strength of correlation for the normalized grades of the psychophysical scaling experiment were analysed for each single observer against each other, giving 110 correlations for each grading characteristic. Kendall’s W Coefficient of Concordance was recalculated for the ordering of images between multiple observers (Pasisz et al., 2009).

The pruning and re-pruning proved to be a complex task. Theoretically pruning makes the network less complex and improves the input output relationship so that it is simpler, smoother with fewer parameters. The assumption is made that when the scales are pruned the observer chooses appropriate bins according to a common sense approach.

16 Results

16.1 Selection of Images

Two hundred patients’ UBM records were reviewed, i.e. 5600 UBM images (200 x 28 images) to yield (after applying inclusion criteria) 82 axial and 122 sectoral images. Seventy images (10 per UBM feature) were selected by one observer (RS).

16.2 Validation of the Image Selection

Each observer completed the construction of 10-point grading scales within a mean time of 2.96 minutes (range 0.53 to 12:03 minutes).

The range of Spearman’s rho (ρ) for each characteristic can be seen in table 16.1. Kendall’s W and Crohnbach’s α can also be seen in the table. Reliability coefficients’ range from 0 (no agreement) to 1 (complete agreement). Spearman’s rank correlation coefficient showed high inter-observer correlation for ACD, iris thickness and convexity (ρ rho > 0.80). Kendall’s
Concordance for inter-observer agreement shows high concordance between ACD, iris thickness, iris profile, convexity and ciliary body size ($W>0.80$). Low concordance can be seen for angulation ($W=0.41$) and ciliary body position ($W=0.65$).

Table 16.1 showing Spearman $\rho$ Rho, Kendall’s Coefficient ($W$), time taken to complete the task for each UBM characteristics **Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spearman Rho Range</th>
<th>Kendall’s Concordance ($W$)</th>
<th>Mean Time ($\pm$ SD) (decimal minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>0.88**-1.00**</td>
<td>0.95</td>
<td>2.56 ± 1.56</td>
</tr>
<tr>
<td>Iris Thickness</td>
<td>0.52 - 1.00**</td>
<td>0.91</td>
<td>2.42 ± 1.74</td>
</tr>
<tr>
<td>Iris Profile</td>
<td>0.50 – 1.00**</td>
<td>0.84</td>
<td>2.56 ± 1.03</td>
</tr>
<tr>
<td>Convexity</td>
<td>0.37 – 1.00 **</td>
<td>0.79</td>
<td>3.61 ± 2.33</td>
</tr>
<tr>
<td>Angulation</td>
<td>-4.29 – 0.95**</td>
<td>0.41</td>
<td>3.79 ± 3.05</td>
</tr>
<tr>
<td>Ciliary Body Size</td>
<td>0.38 – 1.00 **</td>
<td>0.89</td>
<td>2.80 ± 1.54</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>0.17 – 0.98**</td>
<td>0.65</td>
<td>3.00 ± 2.57</td>
</tr>
</tbody>
</table>

16.3 Developing UBM perceptual scales.

In general, variability of inter-observer ranking was largest when ranking images in central ranking positions between 1-10. Inter-observer variability showed varied error scores as a result of transposition of images. Simple adjacent transpositions of two or three images were seen in some characteristics whilst other CGS were discordant. Image at position 1 & 10 are anchored end points and the construction of the in-between (ranks 2 to 9) scale is of interest for each UBM characteristic.

16.3.1 Anterior Chamber Depth

Figure 16.1a shows inter-observer agreement when ranking images in order of ACD. Perfect inter-observer agreement can be seen between RS, VS, CF & WN where i.e. $x=y$. Observers found ranking the ends of the scale easier (ranks 2 to 4 and 7 to 9).

Figure 16.1b shows inter-observer error scores for each ranked image. Corrected error scores ranged from 0-8.

Error scores of 4 indicate a two-image transposition and an error score of 8 indicate 2 x two-image transpositions. Figure 16.1c shows that the variance when constructing ten-point grading scale ranges from (0-0.69). Highest variance is seen at points 4,5 & 6, which correlates to the error scores found and in figure16.1b.

Mean time taken to complete the task was 2.56 ±1.46 minutes. The time taken for each observer can be seen in figure 16.1d.
Figure 16.1 a-f Graphs to illustrating results of 10–point-grading scale for true ACD. Where: 16.1(a) shows the rank order of 10 images of varying ACD where Kendall’s concordance W=0.96; 16.1(b) ACD Intra- observer error scores for each point of the grading scale, fixed end=points 1 & 10 are not shown here; 16.1(c) Bar chart to show observer variance when constructing a 10-point grading scale for ACD (fixed endpoints 1 &10 are not shown); 16.1(d) Bar chart to show time taken for each observer to construct scale; 16.1(e) Showing a concordance plot of ACD scale (W=0.95) and areas of confusion within the scale where: the larger the bubble the better the concordance; overlapping areas show confusion between observers. A 3-point transposition (error score = 8) of images 4,5 & 6 (red bracket) and a 2-point transposition (error score = 2) of images 7& 8 (blue bracket) can be seen; 16.1(f) Shows plot pruned concordance plot where dashed line denotes W=1. overall respecting near ‘perfect concordance’ which is represented by the dashed line where x=y; or (W=1).
Those with perfect inter-observer agreement took 1.81, 4.37, 3.22, 3.26, 3.33 minutes to conduct the task for RS, VS, CF, YFW and WN respectively.

Figure 16.1e shows a bubble plot of inter-observer concordance (W=0.95 where \( \chi^2 = 73.54, \) df=7, \( p<0.0001 \)). The overall concordance respects the \( x=y \) (near perfect concordance). Observers agree on their selection of images placed at rank 2, 3 and 9.

Transpositions for ACD are mainly two–image transpositions between 4-5, 5-6 7-8, i.e. where two images are swapped around. A three-image transposition can be seen in figure 16.1e and 16.2 between points 4 to 6 (4,6).

Figure 16.2 indicates the areas of confusion when constructing a 10-point grading scale. The blue shape denotes a two – point (image) transposition (error score = 2), the red denotes a three-point/image transposition (error score = 8).

Figure 16.2 is a simplified diagram of each of the points in the CGS’s. The transpositions are or areas of greatest confusion or variance lies are indicated. The blue shape denotes a two–point (image) transposition (error score=2), the red denotes a three-point/image transposition (error score=8). Overlapping areas show confusion between observers.

The scale was pruned in order to create a new ordinal data set. The pruned 7 point scale was 1=1; 2=2; 3=3; 4=4-6; and 5=7-8; 6=9; 7=10. Figure 16.1(e) shows the concordance of the original 10-point scale while figure 16.1(f) shows concordance after pruning and re-allocation of responses. By pruning the confusion areas into a new 7 point pruned scale, perfect concordance is achieved (\( x=y \)) where Spearman Rho 1.00, and W=1.00.

16.3.2 Iris Thickness

Figure 16.3a shows inter-observer agreement when ranking images in order of iris thickness. Perfect inter-observer agreement between PG, RS, CF, MB and WN where W=1 i.e. \( x=y \). Error scores were greatest when observers (DH and VS) constructed the mid ranges of the perceptual scale. Error scores of 4 indicate a two-image transposition as seen with observer RS and an error score of 8 indicate 2 x two image transpositions or 3 images that have been transposed (see figure 16.3b).

Figure 16.3(c) shows the variance when constructing ten-point grading scale ranges from (0.20-1.164).
Figure 16.3 Graphs illustrate results when constructing a 10-point CGS for iris thickness: 16.3(a) shows the rank order of 10 images of varying iris thickness; 16.3 (b) gives intra-observer error scores for each point of the grading scale, fixed endpoints 1 & 10 are not shown here; 16.3(c) gives a bar chart to show observer variance when constructing a 10-point CGS for Iris thickness (fixed endpoints 1 &10 not shown); 16.3d) bar chart to show inter-observer times to construct CGS; 17.3(e) Bubble Plot showing observer concordance (W=0.91). The larger bubbles display better agreement at each rank, 16.3(f) shows areas of confusion can be pruned into 1 of two concordance plots.
Highest variance is seen at points 4, 5 & 7, which correlate to the error scores found in figure 16.3b. This graph also indicates that ends of scale were more varied in construction in comparison to the ACD scale.

Time taken to complete the task was 2.42 ±1.7 minutes. Figure 16.3(d) shows time taken to complete the task for PG/RW/CF: 1.13; 1.66 and 6.50 minutes. Figure 16.3(e) shows a bubble plot showing inter-observer concordance of $W=0.91$ ($\chi^2=70.48$, df=7, p<0.0001), when constructing CGS for iris thickness.

There is little confusion where to place images in this CGS, although observers did find central ranking (images 4 & 5) difficult. Transpositions positions 2-4, 5-7, and 8-9.

Figure 16.4 indicates the areas of confusion when constructing a 10-point CGS for iris thickness. Areas of confusion are (2-4), (5-6), (8-9), (3,7) (3-4), (2-3). Transpositions involve 2, 3 or 5 images. In order to reduce confusion images with highest variances i.e. 3, 5 and 7 (with variances 0.49, 0.62, 1.16) are pruned.

Figure 16.4 is a simplified diagram of the each of the CGS positions. The transpositions are or areas of greatest confusion or variance are indicated. The blue shape denotes a two-point (image) transposition (error score=2); the red denotes a three-point/image transposition (error score = 8); the dark purple line denotes confusion when placing the images in these 5 positions. Overlapping areas show confusion overlaps between observers.

The scale was pruned in order to create a new ordinal data set. The pruned data was pooled with neighbouring points to create a new 5 point scale in which 1=1; 2=2-4; 3=5-7; 4=8-9 and 5=10. Two models are shown in figure 16.3(f & i). Perfect concordance is achieved (x=y) Spearman Rho 1.00, Concordance 1.00. Transposition of ranking images 3 and 4 can still be seen by one subject where Spearman Rho is 0.8 and Kendall's Coefficient is 0.91.
16.3.3 Iris Profile

Figure 16.5 Graphs to illustrating results of 10–point grading scale for iris profile. 16.5(a) shows the rank order of 10 images of varying iris profile where Kendall’s concordance $W = 0.84$; 16.5(b) Intra-observer error scores for each point of the grading scale, fixed end=points 1 & 10 are not shown here; 16.5(c) Bar chart to show observer variance when constructing a 10-point CGS for Iris profile (fixed endpoints 1 &10 are not shown); 16.5(d) shows a bar chart of inter-observer time to construct scale;
16.5(e) Bubble plot of concordance of ranking images – showing confusion when ranking images 2 & 3, 4& 5, 6& 7; 16.5(f) two alternative pruned concordance plot for iris profile.

Figure 16.5a shows inter-observer agreement for iris profile. Perfect inter-observer agreement, where x=y, was obtained for observers DH & CF. Observers found ranking the ends of the scale easier (ranks 2 to 3 and 5 to 7). Figure 16.5b shows: error scores for each ranked image with some confusion within middle images.

Overall error scores are higher in observer VS (21) and an overall transposition of adjacent images can be seen between ranks 2-3, 5-7, 8-9 and 2-4. Figure 16.5c shows that the variance when constructing ten-point grading scale ranges from (0.164-2.018). Maximum variance is seen at point 5, which correlates to the error scores, found in figure 16.5b. Figures 16.5 a-c and e indicate the variance throughout the scale.

Figure 16.5d shows mean time taken to complete the task was 2.56 ±1.03 minutes. Time taken to complete the task was longest for DH & CF (2.25 and 4.33 minutes respectively).

Figure 16e shows inter-observer concordance (W=0.84) where there are multiple areas of inter-observer disagreement ($\chi^2=64.67$, df=7, p<0.0001) near perfect concordance where W=1). Several areas of confusion can be seen (smaller bubbles) for images in the centre of the scale particularly for images 2 and 3. Images in the centre of the scale (i.e. images 4-7) were also variable.

Figure 16.5e & 16.6 indicate the areas of confusion when constructing a 10-point grading scale for iris profile. Areas of confusion for Iris thickness are either two image transpositions: (2-3), (6,7), (8-9) or 3 image transpositions (4-6) and (5-7). In order to reduce confusion areas and make steps more even images with highest variances namely 3,5 and 7 were identified for pruning to reduce the CGS to a 6-point scale.

The scale was pruned in order to create more ordinal data sets. The 10-point scale was pruned to a 5-point scale, 1=1; 2=2-3; 3=4-7; 4= 8-9 and 5=10. Figure 16.5e shows concordance of a 10-point scale. By pruning the CGS inter-observer agreement is improved.
In figure 16.5f two pruned models are shown perfect concordance is achieved \((x=y)\). Spearman Rho 1.00, Concordance 1.00. One observer can still see transposition of ranking images 3 and 4 where Kendall’s Coefficient is 0.82.

16.3.4 Convexity

Figure 16.7a shows inter-observer agreement when ranking images in order of convexity. Perfect inter-observer agreement, where \(x=y\), was obtained for observers PG, RS, VS and CF.

Mean time taken to complete the task was 3.60 ±2.33 minutes. Time taken for each observer to complete the task can be seen in figure 16.7d.

Comparatively, DH has two three-image transpositions at positions (3,4,5) and (6,7,8). RSt had similar transpositions between positions (3,4,5) and (7,8).

Error scores are higher between position 4 and 7 for RSt & DH. Figure 16.7b shows that high error scores can be seen for WN.

Figure 16.7c shows that the variance when constructing ten-point grading scale ranges from (0.27-2.26). Highest variance is seen at points 5,6 and 8,9, which correlates to the error scores found in figure 16.7b. This graph also indicates that ends of scale were more varied in construction than the ACD scale. Figure 16.7d shows inter-observer concordance \(W=0.79, (\chi^2=60.56, df=7, p<0.0001)\), where larger bubbles can be seen at the ends of the scale. Clusters of bubbles can be seen where images placed at ranks 3-5 are transposed and 6-8 are transposed. Overall larger variances can be seen when placing images around the centre of the scale.

Figure 16.7e & 16.8 indicate the areas of confusion when constructing a 10-point CGS for convexity. Areas of confusion for convexity are either two image transposition: (7-8) or 3 image transpositions (3-5) and (6-8). In order to reduce confusion images with highest variances images 3,5 and 7 will be pruned.
Figure 16.7 Graphs illustrate results of 10-point CGS for convexity. 16.7(a) shows the rank order of 10 images of varying convexity; 16.7(b) Intra-observer error scores for each point of the grading scale, fixed end-points 1 & 10 are not shown here; 16.7(c) Bar chart to show observer variance when constructing a 10-point grading scale for convexity (fixed endpoints 1 & 10 are not shown); 16.7(d) bar chart to show inter-observer times to construct CGS; 16.7(e) shows bubble plot of inter-observer concordance where Kendall’s concordance \( W = 0.79 \). The bigger the bubble shows the majority agreement. Confusion may be seen when placing images between ranks 3-5 and also 6-8; 16.7(f) shows bubble plot for a pruned 5-point scale.
Figure 16.8 shows a simplified diagram of the CGS positions were greatest confusion and variance lies. The blue shape denotes a two-point (image) transposition (error score = 2); the red denotes a three-point/image transposition (error score = 8). Overlapping areas show confusion between observers.

The scale was pruned into a new 5-point scale 1=1; 2=2-5; 3= 6-8; 4=9 and 5=10. Figure 16.7e shows concordance of a 10-point scale (areas of confusion may be seen) and 16.7f shows a new 5-point pruned scale, a concordance of W=0.85 is achieved (x=y).

16.3.5 Angulation

Figure 16.9 shows inter-observer agreement when ranking images in order of size of ‘Angulation.’ There was no whole scale inter-observer agreement. Transpositions varied between areas of confusion for the 8 intermediate images, areas of confusion where widespread, however, with most variation between positions 5-8. Observers found this scale is a difficult scale to arrange.

Error scores varied from 0 to 44, observer JM eliciting a high error score of 44 (figure 16.9b).

Figure 16.9c shows that the variance when constructing ten-point grading scale ranges from (0.82-8.07). Highest variance is seen at point 2, which correlates to the high error scores found in figure 16.9c. This graph also indicates that ends of scale were more varied in construction than other scales.

Mean time taken to complete the task was 3.79 ±3.05 minutes; time taken for each observer can be seen in fig 16.9d. PG had a shorter grading time than the other observers (1.22 minutes).

Figure 16.9e shows bubble plot of inter-observer concordance where Kendall’s concordance W=0.41, 3.9d shows observer times to construct CGS. There are no large bubbles in this plot. There is a discordant plot, which shows large variation in placing images throughout the scale.
Figure 16.9 Graphs to illustrating results of 10-point grading scale for angulation of the iris root; 16.9(a) shows the rank order of 10 images of varying angulation at the iris root where Kendall's concordance \( W = 0.4120 \); 16.9(b) Intra-observer error scores for each point of the grading scale, fixed end=points 1 & 10 are not shown here; 16.9(c) Bar chart to show observer variance when constructing a 10-point grading scale for angulation of the iris root (fixed endpoints 1 & 10 are not shown); 16.9(d) Bar chart to show inter-observer time to conduct task; 16.9(e) shows bubble plot of inter-observer concordance.
where Kendall’s concordance $W=0.41$. There are no larger bubbles in this plot. There is a discordant plot, which shows variation in placing images throughout the scale; 16.9(f) alternative pruned concordance plot for angulation.

Figures 16.9e & 16.10 show areas of confusion for angulation scales have larger confusion areas than any other UBM characteristic. There are no 2 or 3-point transpositions only 4-point transpositions ranging from (3,6), (4-7); 6-point confusion area stretching from points (2-7) and from (2,9). Images with highest inter-observer error scores: 2, 4, 6, 7, 9, were pruned.

Figure 16.10 shows a simplified diagram of the CGS positions where confused or greatest variance lies. The green line represents an area of confusion when placing images in 4 positions of the 10-point grading scale; the cyan represents an area of confusion of six points; the magenta shows confusion areas in all positions of the scale apart from the endpoints. Overlapping areas show confusion overlaps between observers.

The data was then pruned in order to create a more ordinal data set. The 10-point scale was pruned to a 4 point scale, 1=1; 2= 2-7; 3=8-9 and 4=10.

Figure 16.9f show concordance plots after pruning the CGS. Two models are shown near perfect concordance can be achieved ($x=y$) and large bubbles denoting more agreement amongst observers.

### 16.3.6 Ciliary Body Size

Figure 16.11a shows inter-observer agreement for ciliary body size. Perfect inter-observer agreement, where $x=y$, was obtained for observers PG and RS. Observers DH, VS and CF demonstrated greatest error scores.

Figure 16.11b shows greatest error score by observer VS, who volunteered that he found this task difficult and found difficulty placing images from position 3 to 9. Other observers found positions 6-9 most difficult to place. Figure 15.11c demonstrates variance when constructing ten-point grading scale ranges from (0.0-0.19). Variance was least at point 2; highest variance is seen at points 6-9, which correlates to the error scores, found in figure 16.11c.
Figure 16.11 Graphs illustrating results of 10-point CGS for ciliary body size: 16.11(a) shows the rank order of 10 images of varying ciliary body size; 16.11 (b) Intra-observer error scores for each point of the CGS, fixed end-points 1 & 10 are not shown; 16.11 (c) Bar chart to show observer variance when constructing a 10-point CGS for ciliary body size (fixed endpoints 1 & 10 not shown); 16.11 (d) shows a bar chart of inter-observer time to conduct task; 16.11 (e) shows a bubble plot of concordance where inter-observer agreement, where Kendall’s concordance \( W=0.90 \), can be seen at the ends of the scale;
however there appears to be a variation in ranking images 4-8; 16.11 (f) alternative pruned concordance plot for a 4-point CGS for ciliary body size.

Mean time taken to complete the task was 2.8 ±1.54 minutes. Time taken for each observer to complete the task can be seen in figure 16.11d.

PG and RS had shorter grading times than the other observers with zero error and perfect inter-observer agreement (Spearman rho). Figure 16.11e shows inter-observer concordance \( W=0.90 \) \( (\chi^2=69.06, \ df=7, \ p<0.0001) \). Larger images are seen at the ends of the scales and disagreement can be seen between ranks 4-9.

Overall, the CGS for ciliary body size shows inter-observer agreement at the beginning and the end of the scale and higher variability and error scores in the middle portion of the CGS. Figures 16.11e & 16.12 show areas of confusion for arranging scales for ciliary body size are: (4-5),(6-7), (8-9), (6-8), (3-9), (6-9) are a mixture of 2-6 images. Images 3, 5, 6, 7 and 9 were identified for pruning.

![Diagram of CGS confusion areas](image)

Figure 16.12 shows a simplified diagram of the points in the CGS where confused/greatest variance lies. The blue shape denotes a two – point (image) transposition (error score=2); the red denotes a three-point/ image transposition (error score=8); the green line represents an area of confusion when placing images in 4 positions of the 10-point grading scale; the royal blue represents an area of confusion of seven points. Overlapping areas show confusion between observers.

The 10-point scale was pruned to a 4-point scale, 1=1; 2=2-7; 3=8-9 and 5=10. Two models are shown with near perfect concordance 0.80–0.92.

**16.3.7 Ciliary Body Position**

Figure 16.13a shows inter-observer agreement for ciliary body position. Perfect inter-observer agreement could not be reached on this task, where x=y. Figure 16.13a shows little inter-observer agreement when ranking the perceptual UBM scales.

Figure 16.13a & b indicate multiple areas of confusion, where corrected error scores range from 0–36. Figure 16.13 a-c show little observer agreement, with varied error scores, high error scores can be seen for observer VS. Time taken for each observer to construct the task can be seen in figure 16.13d.
Figure 16.13 Graphs to results of 10–point CGS for ciliary body position: (a) shows the rank order of 10 images of varying ciliary body position; 16.13b) Intra-observer error scores for each point of the CGS, fixed end-points 1 & 10 are not shown; 16.13(c) Bar chart to show observer variance when constructing a 10-point CGS for ciliary body position; 16.13(d) shows bar chart of inter-observer time to conduct task; 16.13(e) shows a bubble plot of concordance where inter-observer agreement can be
see at the ends of the scale; however there appears to be a variation in ranking images 2-8; 16.13(f) 
two alternative pruned concordance plot for ciliary body position.

RSt, VS, MA & CF show greatest error scores with multiple confusion areas that ranged across all positions. Other observers showed common confusion between images (2,3) to (4,6).

Figure 16.13c indicate variance when constructing ten point grading scale ranges from (0.09-3.96). Highest variance is seen at points 5,6, which correlates to the error scores found in figure 16.13c. These indicate the level of variance when selecting an image for point 2. Inter-observer concordance W=0.65 ($\chi^2$=50.03, df=7, p<0.0001). Mean time taken to complete the task was 3.00 (±2.57) minutes.

Figure 16.13e shows a bubble plot of concordance. Kendall's concordance W=0.65. At the ends of the scale there appears to be a variation in ranking images 2-8. Figures 16.13e & 16.15 show areas of confusion for arranging scales for ciliary body positions are: (2-6), (2-7), (2-9). There are no simple 2, 3 or 4-point transpositions for this feature. Error scores, confusion scores and variances all show difficulty in selecting images even for point 2. Images with highest inter-observer error scores: 2,4,5,7 and 8 were pruned. Overall, the scale for ciliary body position shows high variability, error scores, and low concordance from the beginning of the scale to rank 9.

1 2 3 4 5 6 7 8 9 10

Figure 16.14 demonstrates the points in the grading scale that were confused/where greatest variance lies. The burgundy shape denotes a 5 – point (image) transposition (error score = 2); the cyan denotes a six-point/ image transposition; the magenta line represents an area of confusion when placing images in 8 positions of the 10-point grading scale; Overlapping areas show confusion between observers.

To create a more ordinal data set the 10-point scale was pruned to a 4-point scale, 1=1; 2=2-6; 3=7-9 and 4=10, to improve inter-observer agreement. Two models are shown below. Near perfect concordance can be achieved (x=y) and large bubbles denoting more agreement amongst observers. Pruned concordance is nearly =1.
16.3.8 Error Scores for UBM perceptual scales

Psychophysical methods of measuring error were used to determine which UBM characteristics for PAC(G) demonstrate least inter-observer error. Figure 16.15 shows overall inter-observer error range (27-140).

![Figure 16.15 Graph to show inter-observer error scores for each observer and CGS scale. Where the CGS for angulation, followed by ciliary body position have the higher error scores compared to any other CGS for all observers.](image1)

Figure 16.16 gives the error scores for each of the scales, which varied from 28 to 140. Error scores were lowest when observers were observing ACD. Error scores increased for convexity, iris thickness, iris profile, and ciliary body size and increased even further for angulation and ciliary body position.

![Figure 16.16 showing CSS corrected error scores. Corrected error score of “0” highlights zero error score. Error scores are broken down for each observer.](image2)
16.4 Time Taken

Mean time to construct a perceptual scale was 2.96 minutes. Mean times taken to construct scales for each characteristic can be seen in figure 16.17. Mean times were much longer for observer CF. For each observer iris profile, convexity, angulation & ciliary body perceptual scales took longer to construct. Observers RS & PG showed little variation between time taken to construct all scales.

![Time Transposed](image)

Figure 16.17 Graphs indicating time taken (minutes) to construct grading scales for PAC(G).

16.5 Levels of Confusion

Figure 16.18 shows the number and magnitude of confusions for each CGS. Two image transpositions occur more frequently in grading scales for ACD, iris thickness, convexity and ciliary body size. Larger areas of confusion (5, 6 or 8 image) may be seen in angulation, ciliary body size & ciliary body position. The high frequency of larger areas of confusion can be seen predominantly for angulation, which has been shown elsewhere to have the highest inter-observer error scores.

![Confusion Levels](image)

Figure 16.18 shows that smaller areas of confusion i.e. 2 image transpositions occur more frequently in grading scales for ACD, Iris Thickness, Convexity & ciliary body size. Larger areas of confusion (5,6 or 8 image areas of confusion) may be seen in angulation, ciliary body size & ciliary body position. The
high frequency of larger areas of confusion can be seen predominantly for Angulation, which has been shown elsewhere to have the highest inter-observer error scores.

### 16.6 Pruning the Scales – Eliminating Confusion

Pruning a CGS makes the network less complex and improves the input-output relationship (i.e. another step closer to generating a scale appropriate for clinical use). Removing outliers by pruning gives simpler, smoother functions, with fewer parameters, that have better interpolation and extrapolation properties. To analyse the strength of association between the psychophysical arrangements of every single observer, a Spearman rho statistics was calculated between each pair of observer. Spearman's statistic can be used to measure pair wise correlation among observers using a scale that is ordered. The strength of correlations for the normalized grades of the psychophysical scaling experiment were analyzed for each observer against each other, giving 110 correlations for each grading characteristic. Kendall’s W Coefficient of Concordance was used to evaluate the ordering of images between multiple observers (Pasisz et al., 2009).

Table 16.2 shows a comparison of Kendall’s concordance for the 10-point scale compared to the pruned concordance. ACD was reduced to a 7-point scale; Iris thickness, profile, convexity, ciliary body size were all reduced to a 5-point scale: whereas angulation and ciliary body position were reduced to a 4-point scale. Overall improvement can be seen in all scales apart from angulation.

Table 16.2 number of scale points in pruned scale, & Kendall's Coefficient each UBM characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of points in scale</th>
<th>Pruned Kendall’s Concordance</th>
<th>10 Kendall’s Concordance (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>7</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>Iris Thickness</td>
<td>5</td>
<td>0.92</td>
<td>0.91</td>
</tr>
<tr>
<td>Iris Profile</td>
<td>5</td>
<td>1- 0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>Convexity</td>
<td>5</td>
<td>0.85</td>
<td>0.79</td>
</tr>
<tr>
<td>Angulation</td>
<td>4</td>
<td>0.41 – 0.21</td>
<td>0.41</td>
</tr>
<tr>
<td>Ciliary Body Size</td>
<td>5</td>
<td>0.92 – 0.80</td>
<td>0.90</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>4</td>
<td>-1 - 1</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).**

### 17 Discussion

The advancement of medical imaging is a major feature of ophthalmic care. CGS are well-utilized tools for the recording and monitoring of ocular conditions (Bailey et al., 1991; Chong et al., 2000; Efron, 1998; Efron et al., 2001; Jiang et al., 2010b; Pine et al., 2012; Schulze et al., 2007). Eleven clinicians were asked to construct a 10–point scale for each of 7 different...
features of PAC(G). The 7 features describe the various morphological features of PAC(G) as seen via UBM. The findings of this study indicate that a ‘consensus’ based approach may be used to construct a common CGS. The results are discussed in more detail below.

17.1 Validation of Image Selection and Inter–observer Correlation

Reliability coefficients were used to assess inter-observer reliability of ranking. Kendall’s Concordance for inter-observer agreement shows high (near perfect) concordance between ACD, iris thickness, ciliary body size (W>0.90), followed by iris profile (W=0.84) and convexity (W= 0.79). Lowest concordance can be seen for angulation (W=0.41) and ciliary body position (W=0.65).

The Spearman’s rank (ρ) correlation coefficients between each pair of observers were best for ACD & iris thickness followed by convexity and ciliary body size (table 16.2). This demonstrates that each observer was able to adopt this new psychophysical method of scaling. Poor inter-observer correlations were seen for iris profile, ciliary body position and angulation. This range of reliability statistics suggests that some features were easier to analyse and construct into a scale than others. It may be the ‘visual task’ of linear assessment of depth or size (ACD, iris thickness, ciliary body thickness) has greater inter-observer correlation than assessing shapes (convexity) combined with an assessment of relationship with adjacent structures such as angulation and ciliary body position.

A previous study by Efron et al. (2001) has shown “that observers in their study found it more difficult to grade corneal staining than the other two clinical conditions tested, i.e. (conjunctival redness and papillary conjunctivitis), as evidenced by the significantly higher reliability scores indicated for corneal staining.” This too may be due to differences in the type of visual task required by the observer. As inferred by Efron 2001 “The ability to detect differences between, or changes in, the severity of clinical grading images may be inferred from reliability scores where lower reliability scores imply that an observer can more confidently assume that a difference in a grading estimate is due to a true change in clinical circumstances, and not to a change in the application of a grading system”. The results from this study demonstrate a significant inter-observer difference when constructing scales of different morphological features.

The practical relevance of reliability indices in the clinical setting still remains unclear. There are various suggestions that reliability or agreement coefficients should be labelled as ‘perfect,’ ‘poor’ etcetera. Guideline coefficients of 0.6, 0.7 and 0.8 have been used as a minimum standard for reliability coefficients. However, when ‘pruning’ the data an improvement in coefficients needs to be evident.
17.2 Comparison with other UBM studies

Jiang et al. (2010b) introduced a qualitative method of grading anterior chamber structures, such as the iris and ciliary body, in a sample of PACS and controls. They found poorer inter-observer kappa statistics in particular for angulation, ciliary body size and position (k= 0.65). Their findings may be, in part, due to the nature of the visual task and the construct of the scales. Their scales were based upon ‘best clinician’ opinion rather than on ‘consensus’. In our study, other features such as lens vault and iris insertion could have been described. However, the focus of this study was to find a method to construct CGS.

In contrast to a studies by Jiang et al. (2010b) and Ku et al. (2013), advances in probe technology for the assessment of the ACA by linear UBM enables an entire sweep of the anterior chamber and a measurement of pupil size. Not only does linear UBM allowed more objective and detailed imaging of relevant structures associated with PAC(G) such as the iris and ciliary body, it is now more clinician and patient friendly.

17.3 Error Scores

Inter-observer error scores for each observer ranged from 27-140. The lowest error scores were for PG & RS. Observer VS had the largest error scores and shortest construction times for each grading scale. The sum of all error scores were least when observers were observing ACD, convexity, iris thickness, iris profile, CB Size, drastically increasing for angulation and CB position.

17.4 Areas of Confusion

Two image transpositions occurred more frequently in grading scales for ACD, iris thickness, and convexity and ciliary body size. Larger areas of confusion (5, 6 or 8 image areas of confusion) may be seen in angulation, ciliary body size & ciliary body position. The high frequency of larger areas of confusion can be seen predominantly for angulation, which has been shown elsewhere to have the highest inter-observer error scores and lowest reliability indices.

17.5 Reducing the scale size

In keeping with the established recommendations for CGSs, scale sizes of five to seven images were viewed as optimum (Chong et al., 2000; McMonnies et al., 1987; Miller, 1994; Schulze et al., 2007; Woods, 1989). Combining areas of inter-observer confusion reduced each of the PAC(G) scales. Pooling responses from points where there is confusion improves the reliability indices such as Kendall’s concordance and Spearman Rho. This ‘fusing’ or combining of ranks is analogous to ‘merging’ the images that fall in the confusion.
zone. Pruning the scales lead to increased reliability statistics for ACD, iris thickness, iris profile, convexity, ciliary body size and ciliary body position. Despite the extensive pruning Kendall’s Concordance remains low for angulation (W= 0.41).

The presence of confusion at specific regions of the scale implies unequal steps within a grading scale. The affect of pruning these zones would, in theory, create a CGS with more equal steps. Logically the merging of 2 positions, e.g. 3 & 4, would be replaced by an image representing the midpoint e.g. 3.5. Thus to translate this work into a feasible clinical scale additional observers may be required on the already pruned scales.

17.6 Observer differences

There is no ‘gold standard’ set standard of UBM images that describe the morphology of PAC(G). For each difference detected the clinician has to question whether this is due to observer variability. Does it represent a hard feature to analyse? Is the visual reference easy to understand? If an observer views familiar images often enough and has experience of seeing a large range of clinical image pathologies they can often quickly detect an abnormality.

Although this project focuses on a consensus, one of the familiar observers appeared to match against a mental or implicit picture of a normal image. An inexperienced observer has no mental picture of a normal image and therefore must scan the images for a longer period in order to detect an abnormality. Studies have also shown that personality type may influence task when evaluating pathology (Helle et al., 2010).

Experiments show that observers perform reasonably well for linear structures and less well for non-linear structures. The identification of size and thickness seems to be easier than other characteristics.

The development of the CGS is based on a consensus from clinician’s and others with an ophthalmology background. The ‘best observer’ model, while widely used to derive CGS instruments, is less appropriate than one based upon a ‘consensus. The consensus approach allows pruning based on error scores and is better suited for rolling out into a clinical environment.

18 Summary

The results of this study indicate that the construction of CGS was possible for the assessment of ophthalmic ultrasound images and that analysis of shapes may be more difficult and subject to a greater variability. All scales under investigation exhibited high
levels of repeatability. The discrepancies in error scores suggest there are inter-observer differences in medical image perception (MIP) and each CGS may be employing different visual task when analysing the feature in question.

Using an observer consensus technique is a promising method for the development of a CGS. The use of UBM CGS in other studies lack appropriate scale construction and reliability indices.

Qualitative assessment to classify size and rotation of the ciliary body, iris insertion, iris convexity, iris thickness, and iris angulation (Jiang et al., 2010b) is much needed. The interpretation of these features may benefit from the development of CGS. A simple, qualitative grading tool potentially provides clinicians and researchers a fast, useful pictorial reference. This series of CGS overcome the limitations of quantitative assessment and identification of the SS. They offer a potential to monitor changes in morphology: pre and post treatment; under various lighting conditions and in various quadrants. The methodologies described in this chapter allow clinicians to: potentially develop their own scales and provide a reliable means to describe the morphology of closure. In order to roll out a CGS tool it needs to be validated. The following chapter gives the results from a validation trial of the pruned scales.
Chapter 4 Project 3

19 Repeatability of the UBM Grading Scales

19.1 Contributions

Table 19.1 Indicating role of each researcher in this project “Y” confirms significant contribution

<table>
<thead>
<tr>
<th></th>
<th>Concept/Design</th>
<th>Software Mockup</th>
<th>Programming Software &amp; Help files</th>
<th>Acquisition of Data</th>
<th>Analysis</th>
<th>Supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqi, R</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Henson, DBH</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Nolan, W</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

19.2 Abstract

Aim

The aim of this study was to analyze the performance of several CGS, which may help to characterize of the morphology of PAC(G).

Methods

Images of the anterior segment using a linear UBM were sourced from a large image bank at BMEC to generate seven 5-point CGS for PAC(G) using a prior consensus based experiment. The performance of each CGS was measured by evaluating repeatability data from 11 observers, from four centres. Each observer graded 105 randomly presented images. Inter-observer, within test and test-retest repeatability for CGS are evaluated in this project. This project included the development of a software package to present the images (CGS and test) and record observers responses.

Results

Mean inter-observer repeatability (ICC) was 0.81. High inter-observer repeatability (>80) was established for ACD, iris profile, convexity, ciliary body thickness. Poorer ICC was found for ciliary body position (0.42). Mean within test repeatability was 0.60 across all CGS. Within test repeatability was highest for ACD (0.98) and lowest for iris thickness (0.36) and angulation (0.45). Mean test-retest repeatability across all CGS was 0.73. Highest test-retest repeatability (>0.80) was established for ACD, iris profile and ciliary body size. Lowest test-retest repeatability was found for Angulation (0.41).

Conclusions

Overall the UBM CGS have excellent inter-observer and test-retest repeatability. The CGS provides clinicians and researchers with a simple and convenient pictorial reference for assessing, comparing, and monitoring UBM features for PAC(G).
20 Introduction

Clinical grading scales remain the most widely used tool in clinical practise to characterize the morphology of disease (Bailey et al., 1991). Having used a consensus-based approach to produce each CGS in Chapter 3, this study will analyse the performance of a modified pruned set.

The process of using a CGS depends on how patterns (images) are analysed and interpreted. This project is a task based upon pattern recognition, spatial localisation of the area of interest and the comparison against a reference set of images (Sabih et al., 2011).

The performance of measurements obtained through any tool is judged upon reliability, precision, repeatability, and accuracy. Across many disciplines these terms are used interchangeably or synonymously (ISO, 1994). In psychophysics the terms validity and accuracy appear to be used interchangeably and precision is used synonymously for the term reliability (Schulze et al., 2007). According to the International Organization for Standardization (ISO) standard for “Accuracy (trueness and precision) of measurement methods and results” (ISO 5725-2), the terms “trueness” and “precision” are used to describe the “accuracy” of a measurement (ISO, 1994). Trueness refers to the closeness of the mean of the measurement results to the actual value and precision refers to the closeness of agreement within individual results. The precision of a measurement tool is defined as the “closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.”

ISO definitions are more appropriate for quantitative research. The validity of a psychometric test is established through correlation with observer opinion or behaviour. In the context of this project, “grading precision” refers to inter-observer differences. The precision of a CGS tool is the degree to which repeated measurements under unchanged conditions show the same results and is related to reproducibility and repeatability.

According to Davidshofer et al. (2005) there are four types of grading precision: parallel-form, within test, inter-observer and test-rest, see table 20.1. In this study, inter-observer within test and test-retest repeatability are evaluated.

As the same test is conducted twice differences between scores are due solely to measurement error (Davidshofer et al., 2005). These repeatability conditions require that the same observers perform the same measurement procedure with the same system, under the same operating conditions and in the same location, on the same images over a short period of time (NIST (1994)).
Table 20.1 to show various types of precision according to Davidshofer et al. (2005)

<table>
<thead>
<tr>
<th>Type of precision</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel-Forms</td>
<td>Two different tests using the same content with different equipment</td>
</tr>
<tr>
<td>Within-test</td>
<td>Items within a test, to assess the internal reliability between items.</td>
</tr>
<tr>
<td>Test-Retest</td>
<td>The same test at two different times and gaining the same results each time.</td>
</tr>
<tr>
<td>Inter-Observer</td>
<td>Two or more individuals to rate the scores of a psychometric test,</td>
</tr>
</tbody>
</table>

Test-retest repeatability was assessed using a number of statistical tests, which are discussed below.

Coefficient of repeatability (COR) describes the degree of scatter for repeated measurements on the same objects. The COR is the standard deviation (SD) of the differences between test ($d_1$) and retest ($d_2$) session for all measurands multiplied by 1.96 (or 2) i.e.

$$\text{COR} = 1.96 \times \sqrt{\frac{(d_2 - d_1)^2}{n - 1}}$$

The smaller the COR, the better the repeatability of the measurements. The Bland and Altman plot may also be used to graphically display the repeatability of a method.

Limits of agreement (LOA) measure the differences between test and retest measurements that are quantified as the COR. The LOA’s are the limits of the 95% confidence interval (i.e. COR) that are plotted with respect to the mean of the differences between test and retest for all objects. The upper and lower LOA are calculated respectively by:

$$d \pm 1.96 \times sd$$

Upper and Lower LOA’s may be interpreted as the range between which a repeated measurement can be expected to lie without representing a statistically significant change.

Intraclass correlation coefficient (ICC) estimates the variability of measurements between sessions to the overall variability between measurands. The ICC will be high (i.e. approach 1.00) if most of the variance is between measurands and will approach zero if most of the variance is between sessions. It is hoped that the use of these tests will enable the validation of these scales.
21 Aim

The overall aim of this study is to validate the performance of the UBM CGS formulated for PAC(G). More specifically the objectives of this project are:

- To provide a design solution to validate the CGS
- To produce a software package to validate the CGS
- To establish the inter- and intra-observer repeatability of the CGS.

22 Methods

This method employed to conduct this project encompass: ethical approval, patient selection, acquisition of the images, production of the grading scales, writing of a software package as well an evaluation of the repeatability of the CGS.

22.1 Ethical approval

Ethical approval has been given through the Integrated Research Application System (IRAS) for local ethical, NHS Permissions and NIHR Portfolio Adoption systems. The IRAS and UKCRN portfolio study numbers for each study can be seen in the table 22.1. UKCRN Study 12582 is the project described in this section.

Table 22.1 IRAS & UKCRN Portfolio Study References for retrospective & prospective studies. * denotes project described in this report.

<table>
<thead>
<tr>
<th>UKCRN Portfolio Study ID</th>
<th>IRAS Ref</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>12582</td>
<td>77602</td>
<td>Grading Anterior Segment Morphology in Angle Closure *</td>
</tr>
</tbody>
</table>

22.2 Patient Selection

Patients were enrolled during a study conducted at the BMEC. A consultant ophthalmologist, Miss Winifred Nolan (WN), performed gonioscopy. WN identified eyes with PACS or PAC(G). All patients were of European-derived ethnicity. Images of the anterior segment using a linear UBM were sourced from a large image bank at BMEC.

22.3 Production of the grading scales

Images were obtained as described in chapter 3. The data from the scaling experiment (see table 22.2) recommended that the majority of the CGS be pruned to 5-points i.e. iris thickness, iris profile, convexity and ciliary body size. In a pictorial Likert-type scale (CGS) it is recommended that a series tests should have the same number of points in each scale
(Burns et al., 2008). For this reason each image series was made up of 5 images. Each series of CGS can be found in Appendix B. To assist in the standardisation of conditions software package was designed - details of which are provided in 22.5.

Table 22.2 In Chapter 3 it was recommended the CGS(s) were pruned to the number given in the corresponding right hand column.

<table>
<thead>
<tr>
<th>CGS</th>
<th>Number of points in CGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>7</td>
</tr>
<tr>
<td>Iris Thickness</td>
<td>5</td>
</tr>
<tr>
<td>Iris Profile</td>
<td>5</td>
</tr>
<tr>
<td>Convexity</td>
<td>5</td>
</tr>
<tr>
<td>Angulation</td>
<td>4</td>
</tr>
<tr>
<td>Ciliary Body Size</td>
<td>5</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>4</td>
</tr>
</tbody>
</table>

22.4 Observers
The question of how many observers are required to validate a CGS tool is undefined in the literature. Eleven ophthalmologists were recruited to grade the test images. These observers were glaucoma specialists from four centres, 2 from Manchester Royal Eye Hospital (MREH), 3 from Moorfields Eye Hospital, 2 from Queen Elizabeth Birmingham and 4 from BMEC. A brief, 5-minute, training session was conducted whereby observers were instructed how to grade (see the paragraph below). Each observer then graded 2 randomly selected images under my supervision to verify that the correct grading approach was being adopted.

22.5 Design Solution for Validation of the CGS

22.5.1 Aim of Software
The aim of the software is to present the observer with a set of images to be graded against the reference scale. The images to be graded represented a spectrum of cases seen at BMEC.

22.5.2 Software Objectives
Twelve test UBM gray scale images were selected for each CGS (anterior chamber depth, iris thickness, ciliary body thickness, ciliary body position, convexity, angulation). The software randomized the presentation sequence of the 12 images for each CGS. Each observer graded each image using the reference CGS.

22.5.3 Overall Software Structure
The programming language Visual Basic 2010 Pro (Microsoft Visual Basic 2010, Washington, USA) was used to develop the software package. This is an object orientated programming (OOP) language, packaged as a Microsoft Windows application providing easy
and familiar setting for the program users/observers. Dr Explain (Indigo Byte Systems, LLC, USA) was used to develop help files.

The overall software structure consists of many components (or layers), which communicate with each other, see figure 22.1. The process of software design required an understanding of how each layer interacts within the software architecture. Image files were stored within the data layer along with the results.

![Software Architecture Diagram]

Figure 22.1 Shows the logical architecture of the design software. This is typically a three basic layers consisting of: presentation, business and data layers.

The presentation layer contains components that implement and display the user interface and manage user interaction. This layer includes controls for user input and display, in addition to components that organize user interaction.

### 22.5.4 Mode of Software environment

After development and testing the software (.exe) file was loaded on to a laptop (HP Pavilion Touch Smart 14 Notebook PC 14" Touch Screen, Intel® Core™ i3 processor, 8GB Memory, 1TB Hard Drive). All data was collected with this laptop in order to standardise the display conditions.

### 22.5.5 Plan of Software Solution

A program layout plan is detailed in Appendix C The software starts with a login interface, a screenshot of which can be seen in figure 22.2.

The software includes a help facility; a screenshot can be seen in figure 22.3. The help facility is fully functional, with searchable keywords, indexed, context sensitive help as well as tool tips. Context sensitive help is obtained from a specific point in the software, providing
help for a particular situation. Tool tips appear when the user hovers the pointer over an item.

![Help drop down menu](image)

Figure 22.2 Showing a print screen of the login window. The orange labels highlight the various areas of the help menu. 1= the help drop down menu, in order to see details of 2, the help manual, 3, retrieve contact details for technical support and 4, information about the software.

![Screen shot of an introductory page of help manual](image)

Figure 22.3 Screen shot of an introductory page of help manual. The left hand side shows the help subdirectory. The manual has an index, search facility and can be accessed through the help menu toolbar, context sensitive help (by dragging a question mark over a particular area) and tool tips (by hovering the pointer over an area and tips appear).

## 22.6 Sample Pictures and Assessment Criteria.

For each CGS a sample of 12 UBM images of various levels of severity were selected from the archives of the UBM. The order of the pictures was randomized for each experimental session.
Following login, observers were presented with a UBM image (centre of screen) and were required to match this to an image in the CGS (as seen in figure 22.4). Each of the observers graded the 12 test UBM images. Thirty three percent of UBM images were repeated to evaluate within-test repeatability. The experiment started with the ACD CGS and worked through each scale. Responses were saved in a Microsoft Excel file. A flow chart of the sequence of events can be seen in figure 22.5. Where possible observers repeated this experiment after a minimum interval of 4 weeks, with the same test images presented in a different random order (test-retest repeatability).

Figure 22.4 Screenshot of main image presenting a randomized image in the centre of the screen. The users were asked to observe each image in the CGS and then click one of the images that closely matches the random images.

22.7 Data Analysis.

Statistical analyses were performed using SPSS V.15.0 (SPSS, IBM Corporation, New York, USA) and Prism 6 (Graph pad Software, California, USA).

The KS test was used to check if differences between test and retest scores were normally distributed. Inter-rater reliability was calculated using: averaged test-retest differences, ICC and LOA.
Start

Welcome & Login Page

Message box: prompt to login

Input Name,

Yes

Saved Data Excel

Instruction Page

Written, Image files & audio file

Buttons: Next, Cancel

Main quiz page

Menu Tool Bar – Welcome, Introduction, Help, About

6 buttons – one for each characteristic

6 image files

Next initiated by clicking on characteristic buttons

Reference set of 5 images shown, labelled 0 to 4

Picture Box, Show Image Box, Images stored in database

Picturebox presents an image in random manner

User views image & match image against reference set

User selects closest match

Display Results

Is this first time the user

Yes

Message Box: instruct user to repeat test in 4 weeks’ time

No

Message Box: Thank you

Feedback questionnaire

6 questions: 5 Radio buttons options & 1 comment box

Save All

End

Figure 22.5 Flow chart of software flow for user.
23 Results

This study included 1680 ratings for 7 CGS for 11 observers'. Immediate term repeatability is tested in all observers. Short-term repeatability (four weeks) was assessed in 5 out of 11 observers.

23.1 Inter-observer Repeatability

Table 23.1 shows a high ICC (>0.80) was found for ACD, iris profile, convexity, angulation, ciliary body thickness. For iris thickness ICC is 0.69 indicating a good level of internal consistency. For CBP: ICC is 0.42 indicating a poor level of internal consistency. Overall, averaged across subjects, test-retest ICC is 0.77 (0.51 –1.00 95%CI).

Table 23.1 Intra-class Correlation (ICC) with 95% Confidence Interval (CI).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>0.98</td>
<td>0.97, 0.99</td>
</tr>
<tr>
<td>Iris Thickness</td>
<td>0.69</td>
<td>0.39, 0.87</td>
</tr>
<tr>
<td>Iris Profile</td>
<td>0.98</td>
<td>0.94, 0.99</td>
</tr>
<tr>
<td>Convexity</td>
<td>0.89</td>
<td>0.77, 0.95</td>
</tr>
<tr>
<td>Angulation</td>
<td>0.77</td>
<td>0.55, 0.91</td>
</tr>
<tr>
<td>Ciliary Body Thickness</td>
<td>0.96</td>
<td>0.93, 0.99</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>0.42</td>
<td>-1.13, 0.77</td>
</tr>
</tbody>
</table>

23.2 Within-Test Repeatability

Table 23.2 shows within-test repeatability for all observers A-I.

Table 23.2 Within-test repeatability for observers A-I. Highest repeatability is denoted by a dark green box (1.00) and “0” repeatability is denoted by a white box. A-C are from Moorfield’s Eye Hospital, D-G are from BMEC, H and I are from Queen Elizabeth Hospital (Birmingham) and J and K are from Manchester Royal Eye Hospital.
A ratio of ≥0.60 was achieved in 4 of the CGS. Figure 23.2 shows mean within-test was greater than 0.60 (mean) for observers A, B, G, I, J and K. Figure 23.1 shows mean intra-observer agreement for each observer when compare to the overall mean (indicated by the dashed line).

Figure 23.1 Graph to show within-test agreement proportion for each observer. Bar indicate observer mean ± 95 % confidence interval. Dashed line indicates overall observer mean. Where: M= Moorfields’ Eye Hospital, BMEC= Birmingham & Midland Eye Centre, QE= Queen Elizabeth Hospitals (Birmingham) and MREH= Manchester Royal Eye Hospital).

Figure 23.2 shows mean within-test ratio for each CGS compared to the overall mean (indicated by the dashed line). Inter-observer agreement is higher than the average mean (0.60) for Anterior Chamber Depth, Iris profile, Ciliary body thickness and ciliary body position.

Figure 23.2 Graph to show mean within test agreement ratio for each CGS. Bars indicate CGS means ±95% confidence interval. Dashed line indicates overall mean for each CGS.
23.3 Test-Retest Repeatability

Five out of 11 observers performed the test on two separate occasions. The Kolmogorov-Smirnov test indicated that the differences in test-retest data were normally distributed. Overall averaged across subjects, test-retest ICC is 0.77 (0.51 –1.00 95% Confidence Interval).

23.3.1 Anterior Chamber Depth CGS

Table 23.3 gives the ICC for anterior chamber depth for each of the 5 observers who repeated the grading after 4 weeks.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.93</td>
<td>0.65, 0.95</td>
</tr>
<tr>
<td>E</td>
<td>0.83</td>
<td>0.57, 0.94</td>
</tr>
<tr>
<td>I</td>
<td>0.87</td>
<td>0.65, 0.95</td>
</tr>
<tr>
<td>J</td>
<td>0.92</td>
<td>0.76-0.97</td>
</tr>
<tr>
<td>K</td>
<td>0.96</td>
<td>0.89-0.99</td>
</tr>
</tbody>
</table>

Figure 23.3 shows Test-Retest plots for ACD and Bland Altman plots.
Figure 23.3 shows test-retest repeatability graphs for Anterior Chamber Depth CGS where left hand column (a, c, e, g, i) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b, d, f, h, j) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.

Test-Retest plots show good agreement with a strong positive linear correlation between test and retest for all observers. Bland-Altman Plots (see Figure 23.3) show excellent agreement (small LOA) can for all observers.

### 23.3.2 Iris Thickness CGS

Table 23.4 gives the ICC for Iris Thickness for each of the 5 observers. Figure 23.4 shows test-retest plots for iris thickness and the Bland Altman plots for observers D and E.
Table 23.4 Internal Correlation Coefficient (ICC) and 95 % Confidence Intervals (CI) for Iris Thickness CGS.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.59</td>
<td>0.22, 0.86</td>
</tr>
<tr>
<td>E</td>
<td>0.75</td>
<td>0.43, 0.89</td>
</tr>
<tr>
<td>I</td>
<td>0.72</td>
<td>0.17, 0.91</td>
</tr>
<tr>
<td>J</td>
<td>0.69</td>
<td>0.07, 0.90</td>
</tr>
<tr>
<td>K</td>
<td>0.80</td>
<td>0.41, 0.93</td>
</tr>
</tbody>
</table>

Test-Retest plots are examples of a good repeatability (Observer E) and fair repeatability (Observer D). The graphs for the other 3 observers can be seen in Appendix D (section 27.4.2).

![Illustration](image)

Figure 23.4 shows test-retest repeatability graphs for Iris thickness CGS where *left hand column (a,c)* show Test-Retest plots where the thin solid line indicates the linear correlation line between both tests and the dashed line indicates 95 % confidence interval. *Right hand column (b, d)* the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s \( (\bar{d} \pm 1.96 \times sd) \) are shown as dashed solid lines.

### 23.3.3 Iris Profile

Table 23.5 gives the ICC for Iris Profile for each of the 5 observers.
Table 23.5 Internal Correlation Coefficient (ICC) and 95% Confidence Intervals (CI) for Iris Profile CGS.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.95</td>
<td>(0.72, 0.96)</td>
</tr>
<tr>
<td>E</td>
<td>0.95</td>
<td>(0.84, 0.98)</td>
</tr>
<tr>
<td>I</td>
<td>0.93</td>
<td>(0.79, 0.97)</td>
</tr>
<tr>
<td>J</td>
<td>0.98</td>
<td>(0.93, 0.99)</td>
</tr>
<tr>
<td>K</td>
<td>0.95</td>
<td>0.87, 0.99</td>
</tr>
</tbody>
</table>

Figure 23.5 shows test-retest plots and Bland Altman plots for iris profile for Observer D. Test-Retest plots (see appendix D, section 27.4.3 for plots from other observers) demonstrate a strong positive linear correlation for all observers and small LOA in the Bland-Altman Plots.

![Test-Re-test Plot for Observer D](image1)

![Bland-Altman Plot for Observer D](image2)

Figure 23.5 shows test-retest repeatability graphs for Iris profile CGS where left hand column (a) show Test-Re-test plots where the thin solid line indicates the linear correlation line with both tests and the dashed line indicates 95 % confidence interval. Right hand column (b) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.

23.3.4 Convexity

Table 23.6 gives the ICC for convexity for each observer. Figure 23.6 gives the test-retest plot and Bland Altman plot for convexity CGS for Observer I. Appendix D shows graphs for all observers (section 27.4.4).

Table 23.6. Showing Internal Correlation Coefficient (ICC) and 95 % Confidence Intervals (CI) for Iris Convexity CGS

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.71</td>
<td>0.23, 0.91</td>
</tr>
<tr>
<td>E</td>
<td>0.75</td>
<td>0.27, 0.92</td>
</tr>
<tr>
<td>I</td>
<td>0.75</td>
<td>0.26, 0.92</td>
</tr>
<tr>
<td>J</td>
<td>0.35</td>
<td>-0.97, 0.78</td>
</tr>
<tr>
<td>K</td>
<td>0.83</td>
<td>0.48, 0.94</td>
</tr>
</tbody>
</table>
Test-Retest plots generally show good positive agreement and small LOAs with the exception of Observer J who has a poor ICC.

![Graph of Test-Retest Plot for Observer I and Bland-Altman Plot for Observer I]

Figure 23.6 shows test-retest graphs for convexity CGS where left hand column (a) show Test-Retest plots where the thin solid line indicates the linear correlation line with both tests and the dashed line indicates 95% confidence interval. Right hand column (b) the LOAs for each scale plotted vs. the mean difference as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times s.d$) are shown as dashed solid lines.

23.3.5 Angulation

Table 23.7 gives the ICC for angulation for each observer. Observers I and K have a good ICC (>0.70).

Table 23.7 Internal Correlation Coefficient (ICC) and 95% Confidence Intervals (CI) for Angulation CGS.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.37</td>
<td>0.09, 0.79</td>
</tr>
<tr>
<td>E</td>
<td>-0.11</td>
<td>-2.23, 0.63</td>
</tr>
<tr>
<td>I</td>
<td>0.79</td>
<td>0.37, 0.93</td>
</tr>
<tr>
<td>J</td>
<td>0.13</td>
<td>-1.6, 0.71</td>
</tr>
<tr>
<td>K</td>
<td>0.78</td>
<td>0.35, 0.93</td>
</tr>
</tbody>
</table>

Figure 23.7 shows test-retest plots and Bland Altman plots for Observers E and I. Appendix D gives the Bland and Altman plots for all observers (section 27.4.5). Test-Retest plots show a negative and poor agreement for observer E whereas I shows a good positive agreement between Test-Retest. This result is confirmed in the Bland-Altman Plots where the LOA are large.
Figure 23.7 shows test-retest graphs for Angulation CGS where left hand column (a, c,) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95 % confidence interval. Right hand column (b, d) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.

**23.3.6 Ciliary Body Thickness**

Table 23.8 gives the ICC for ciliary body thickness for all 5 observers.

Table 23.8 Internal Correlation Coefficient (ICC) and 95% Confidence Intervals (CI) for Ciliary body Thickness (CBT) CGS.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.90</td>
<td>0.70, 0.97</td>
</tr>
<tr>
<td>E</td>
<td>0.87</td>
<td>0.64, 0.96</td>
</tr>
<tr>
<td>I</td>
<td>0.85</td>
<td>0.55, 0.95</td>
</tr>
<tr>
<td>J</td>
<td>0.75</td>
<td>0.25, 0.92</td>
</tr>
<tr>
<td>K</td>
<td>0.67</td>
<td>0.08, 0.89</td>
</tr>
</tbody>
</table>

Figure 23.8 shows test-retest for ciliary body thickness CGS and the Bland Altman plot for observer E. Appendix D gives the graphs for the other observers (section 27.4.6). Test-Retest plot show good agreement for Observer E. The Bland-Altman Plot has small LOA.
Figure 23.8 shows test-retest repeatability graphs for Ciliary Body thickness CGS where left hand column (a) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s (d ± 1.96 × sd) are shown as dashed solid lines.

23.3.7 Ciliary Body Position

Table 23.9 gives the ICC for ciliary body position for each observer D. Observers D and I demonstrate poor ICC (<0.70).

Table 23.9 Showing Internal Correlation Coefficient (ICC) and 95% Confidence Intervals (CI) for Ciliary Body Position CGS.

<table>
<thead>
<tr>
<th>Observer</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.41</td>
<td>-0.74, 0.80</td>
</tr>
<tr>
<td>E</td>
<td>0.71</td>
<td>0.10, 0.82</td>
</tr>
<tr>
<td>I</td>
<td>0.69</td>
<td>0.10, 0.90</td>
</tr>
<tr>
<td>J</td>
<td>0.89</td>
<td>0.67, 0.89</td>
</tr>
<tr>
<td>K</td>
<td>0.70</td>
<td>0.10, 0.90</td>
</tr>
</tbody>
</table>

Figure 23.9 shows test-retest, Bland-Altman plots for Observers D, and E. Appendix shows graphs for other observers. Test-Retest plots show poor positive agreement for Observer D but relatively good agreement for Observer E. In 23.9a there is an aggregation of matching against the second “2” and third images (“3”). The Bland-Altman Plots show large differences in the LOA. Appendix D gives the graphs for the other observers (section 27.4.7).
Figure 23.9 shows test-retest repeatability graphs for Ciliary Body position CGS where *left hand column* (a,c) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. *Right hand column* (b, d) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.

Table 23.10 summarises the inter observer repeatability for all CGS.

Table 23.10 To show a comparison of Inter-Observer and Intra-observer repeatability

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inter-Observer</th>
<th>Within-test</th>
<th>Test-retest</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>0.98</td>
<td>0.98</td>
<td>0.92</td>
</tr>
<tr>
<td>Iris Thickness</td>
<td>0.69</td>
<td>0.36</td>
<td>0.71</td>
</tr>
<tr>
<td>Iris Profile</td>
<td>0.98</td>
<td>0.67</td>
<td>0.95</td>
</tr>
<tr>
<td>Convexity</td>
<td>0.89</td>
<td>0.52</td>
<td>0.67</td>
</tr>
<tr>
<td>Angulation</td>
<td>0.77</td>
<td>0.45</td>
<td>0.39</td>
</tr>
<tr>
<td>Ciliary Body Thickness</td>
<td>0.96</td>
<td>0.61</td>
<td>0.81</td>
</tr>
<tr>
<td>Ciliary Body Position</td>
<td>0.42</td>
<td>0.73</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean</td>
<td>0.81</td>
<td>0.62</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Inter observer repeatability is good for all CGS with the exception of ciliary body position. Within test repeatability was >0.60 for ACD, iris profile, ciliary body thickness and ciliary body position. Iris thickness, convexity and angulation showed the lowest values. Test-retest repeatability was >0.80 for ACD, iris thickness, iris profile and ciliary body thickness, >0.60 for convexity and ciliary body position. Poorest repeatability was seen for angulation.

24 Discussion

The CGS were designed to provide a qualitative, repeatable, rapid assessment of images. Psychophysical scaling, “consensus approach” and pruning techniques in Chapter 3, were used to generate equal perceptual step-sizes for each CGS. Using a range of ophthalmologists from 4 ophthalmic centres, the results of our study indicate that our new CGS performed very well.

Test-Retest repeatability was good for ACD, iris thickness, iris profile, convexity and ciliary body thickness for all observers. Poorer repeatability can be seen for Angulation and Ciliary Body Position for Observers D and E, who are both based at BMEC. Observer I had excellent repeatability ranging from 0.69–0.93 (ciliary body position to ACD). Interestingly, poorer test-retest repeatability (0.55) was seen for observers from BMEC.

There are a number of possible factors, which may influence the reliability of grading estimates when using a CGS tools:

1. the **type of tool** (computer/ printed); Displaying images on a high resolution monitor gives a high degree of realism (Efron et al., 2002) when compared to printed scales.

2. the **complexity of the visual task**; In chapter 3 I suggested that inter-observer discordance might result from the nature of the “visual task” i.e. “areas” rather than linear visual tasks. Wells et al. (2004) confirmed in clinical practice, linear visual tasks are easier than judgements of area. This is seen when comparing linear cup-to-disc ratios versus subjective area estimations of cup area to disc area (Varma et al., 1992). The within-test repeatability in the current study was lower for iris thickness, angulation and convexity. The repeatability results for angulation again highlighted the problems observers have in making judgements of angulation. This again suggests that the scale should be pruned to less than 5 grades (as suggested in Chapter 4).

3. The processes with which patterns are analysed and interpreted depend, upon the **physical parameters** of the image such as the detection of changes in brightness, edge detection or shape detection.

4. The complex interplay of several **personal attributes** of the observer: neurophysiological, psychological and psycho-emotional factors (Helle et al., 2010). In medical image perception, test-retest repeatability may be affected by mood,
personality traits, making a “safe choice”, motivation, emotional strain or the itinery for the day (Helle et al., 2010) spatial localisation of the area of interest and the comparison with known patterns (Sabih et al., 2011).

5. Observers are limited to picking one of five of the reference images. Although not formally assessed some observers had a desire to express a choice to interpolate or extrapolate image to the nearest 0.5 grading interval. This may have reduced some test-retest differences. Generally, it can be seen there is an aggregation of scoring around central grades of the CGS. This could be interpreted as a need for training or selecting a “safe choice”.

6. According to Efron et al. (2003b) grading performance is also dependent upon the “clinical set” i.e. the knowledge base, training of CGS and experience of the grader.

The central assumption when using CGS is that the observer is forced to isolate a particular feature from the whole UBM image. “Feature selection” assumes the medical image contains many redundant features. When interpreting medical images in a clinical setting we are able to make rapid judgments of multiple morphologies, it is unknown how many structures can be examined simultaneously and how many types of deformations are identifiable in one instance.

The ISO standard does not stipulate conditions of the test-retest or “experience” interval. Therefore, this study presented two measures of repeatability, within-test and test-retest. In the within-test measure results are more likely to include a “carryover effect” i.e. when observers remember their original grade. This could account for some of the differences between within-test and test-retest measures.

The findings of this study exceeded the reliability indices reported with other grading systems such as the Moorfields’ Bleb Grading Scale (Wells et al., 2006), lesion types in the Macular Photocoagulation Study (1996) and the size of lesions on fluorescein angiograms (Friedman et al., 2000). The study findings of Jiang et al. (2010b), also on PACG, found “acceptable reliability” (0.61-0.87 for intra-observer and 0.68-0.94 for inter-observer). With the exception of ciliary body position the current study had higher repeatability measures than Jiang for all shared measures.

Jiang et al. (2010b) constructed three-point scales using the “two best clinician” to devise the scales. Validation of their CGS included the author as well as one of the “best clinicians” a validation bias. The scales were not validated by independent observers and or validated by a different set of observers.

Many publications have reporting “grading accuracy” as “the closeness between test result and an accepted reference value (Efron et al., 2001; Schulze et al., 2007). However, when
some parameters lack standardisation of measurement or cannot be measured e.g. ciliary body position or angulation, “grading accuracy” is not an appropriate terminology.

Despite possible limitations, CGS are well-utilized tools for the recording and monitoring of ocular conditions. Clearly, the spectrum of UBM morphologies indicates that both pupil block and non-pupil mechanisms can co-exist and contribute to the mechanism of closure. Further refinement of this work makes this an exciting potential method for grading UBM images.

This project confirms that various clinicians from multiple centres are able to successfully grade UBM images. These scales are intended for use in a clinical setting in order to characterise the morphology of closure as well as implement a standardise UBM reporting system. High levels of agreement were found for most CGS, with good inter- and intra-observer agreement. Further progress and refinement of these CGS should give ophthalmologists a more powerful tool for grading anterior segment morphology in PAC(G) that could be used to evaluate the effectiveness of treatment.
Chapter 5 Summary & Future Work

25 Discussion

25.1 Summary of Thesis

PAC(G) is emerging as a major cause of visual morbidity, especially in Asian people. There is also an increased awareness of PAC(G) in Caucasian patients.

In chapter 2, I evaluated the biometric differences between Caucasian & Chinese patients with PAC(G). This study found a thicker lens in shorter Caucasian eyes compared to an age and sex matched Chinese cohort. Whereas the Chinese cohort display axially longer eyes, with significantly longer vitreous chamber depth and disproportionate anterior and posterior chambers. Collectively, these attributes suggest that PAC(G) in Chinese eyes differs from that in Caucasians where pupil block mechanism predominate (Oh et al., 1994; Wang et al., 2013).

Chapter 3 detailed a novel way to construct CGS. Although there are many Likert-type CGS, there are no standardised techniques to aid the construction of these tools. This chapter reported the construction of CGS using the technology of linear UBM to generate images. The study adopted an inter-observer consensus approach using psychometric error scoring to evaluate inter-observer error, concordance measures to evaluate ranking and pruning methods to reduce the CGS’s to an appropriate size. The consensus approach allows pruning based on error scores and, as subjects are of varying experience, it is better suited for rolling out into a clinical environment. Although recent studies attempt qualitative analysis of UBM or AS-OCT (Jiang et al., 2010b; Ku et al., 2013; Lin et al., 1994), there are no set standards to qualitatively evaluate the morphology of PAC(G) using the UBM.

Chapter 4 evaluates the performance of seven pruned grading scales. These were evaluated within a new software package written specifically for this task. The results of this chapter indicate that the scales are overall highly repeatable and reliable. This simple grading tool provides clinicians and researchers with a fast, useful pictorial reference. These scales may be used to monitor changes in morphology under various lighting conditions. The methodologies adapted in Chapters 3 and 4 allow clinicians to potentially develop their own scales. This offers a standardised methodology that can be used by practitioners as a consistent and reliable means to describe the morphology of closure. These CGS allow a means to standardise clinical reporting without depending upon the limitations of identifying the SS.

There are many stones still left unturned leading on from the work in this thesis some of which are discussed in the following section.
26 Further Work

26.1 Iris Insertion CGS

The CGS included in this study did not include one for iris insertion, which may have a role to play in the development of (G). Dorairaj et al. (2007) pointed out S-type (or non-basal) iris insertions can potentially leave a space between the peripheral iris and the trabecular meshwork, which may preserve function of the trabecular meshwork (Wang et al., 2013). Work developing a CGS for iris insertion has commenced and validation of using this scale is in working progress.

26.2 Assessing the morphology of closure

The potential benefits of basing first line treatment on the results of anterior segment imaging, with or without a CGS, need to be established in a prospective trial that takes into factors such as ethnicity and refractive history. Current first line treatment is LPI, which may not be ideal in all patients. An alternative approach is lens extraction (Nolan, 2006). Some insight into the most appropriate first line treatment is likely to come from EAGLE study.

According to Ku et al. (2013) eyes with thicker overall and basal iris thicknesses are more likely to have PAC(G) than controls. Ku et al also reported an increased likelihood of PAC(G) in the presence of basal iris insertion, mild iris angulation, and a large ciliary body. However, relevance of these findings and benefits of continued anterior segment imaging throughout the patient’s clinical pathway requires more formal assessment. Longitudinal studies to assess the relative importance of biometric and demographic risk factors, and the use of anterior segment imaging to evaluate the risk/benefit profile of interventions are needed. Prospective data is currently been collected as part of the Birmingham Angle Closure Study (UKCRN ID Study 12771). The CGS developed in this thesis will be used to evaluate the UBM images.

26.3 Linking PAC(G) with myopia

This study highlighted a difference in the distribution of refractive errors within the Caucasian and Chinese PAC(G) cohorts. Further work is needed to establish whether or not this is a unique finding related to PAC(G) or is a common finding in research that looks at the morphological differences between ethnicities.

The variation of emmetropisation in Chinese eyes is evident when investigating the associations between several parameters: axial length and refractive error; vitreous chamber depth and refractive error and axial length and vitreous chamber depth. Which leads us to the question: does the process of emmetropisation or failure to maintain emmetropia in
Chinese eyes lead to a greater propensity towards myopia? (Park et al., 2004) Does this contribute to the excess burden of PAC(G) in Asian eyes (Park et al., 2004)?

Initially, PAC(G) and myopia may appear to be diseases with somewhat opposite biometric features. Where shallow anterior chamber, short axial length, small corneal diameter and steep curvature and a thick, relatively anteriorly positioned lens are considered to be risk factors for PAC(G). In contrast, myopia is characterized as a longer axial length, flat corneal curvature, and thinner lens (Zadnik et al., 2004). Among these biometric parameters, shallow anterior chamber and narrow drainage angle width were considered to be the most relevant traits for PAC(G). Increases in axial length and vitreous length have been shown to be the best anatomic features for the onset and progression of myopia (Saw et al., 2005; Zadnik et al., 2004).

Refractive error develops due to excessive axial eye size and as a result of accelerated post-natal eye growth (as opposed to changes in the cornea or lens power (Zadnik et al., 2004). In myopes there is known disruption to the emmetropisation process (verbal communication with Hema Radhakrishnan) where the drivers of growth in the sclera (McBrien et al., 1999; McBrien et al., 2000) – cause post-natal lengthening of the eye. The anterior chamber becomes deeper and wider therefore stretching the lens equatorially and causing thinning of the anterior-posterior lens. As a result the eye elongates, myopia develops and the sclera thins. The excess of myopia in Asian eyes might well be correlated to the burden of PAC(G) (Park et al., 2004). The Guangzhou Twin Eye Study, (He et al., 2008b) attempted to determine the cause of associations of PAC(G) and myopia-related traits by exploring underlying relationships among AL, ACD, and AOD. Wojciechowski et al. (2003) reported that the increase in the prevalence of myopia among younger Chinese was an alternative explanation for the apparently more rapid decrease in PAC angle depth with age among the Chinese. The younger cohort with higher rates of myopia might have deeper AC’s than those of the older cohort who were not exposed to the same myopic factors.

26.4 Socio-economic links with PAC(G)

Future work is required in the area socioeconomic status of patients with PAC(G). The influence of ethnicity, environmental factors on biometric differences and the type of PAC(G) may well play a part in the morphology of closure. In Research into Glaucoma and Ethnicity (ReGAE), by Nessim et al. (2010), post-code analysis of patients with APAC revealed a significant association with the level of deprivation. However, the impact of socio-economic status and refractive error may well help to phenotype other sub-types of PAC(G).
27 Appendices

27.1 Appendix A: Comparison of Axial length measurement between A, B scan & IOL Master

The unpublished data (own data) below was a prospective double blind study examining 30 patients with three methods of biometric measurement: A scan, B scan and IOL Master. The results below show mean and confidence intervals when comparing the three biometric modalities. B scan biometry is not significantly different from measurements obtained (bottom).

![Graph showing mean and 95% CI for each biometric modality]

**Figure 27.1 Mean & 95 % CI for each biometric modality**

![Graph showing 95% Confidence Intervals between each mode of Biometry using Tukey's multiple comparison test]

**Figure 27.2 95% Confidence Intervals between each mode of Biometry using Tukey's multiple comparison test**
27.2 Appendix B: Pruned Grading Scales (Project 3)

27.2.1 Anterior Chamber Depth

27.2.2 Iris Thickness
27.2.3 Iris Profile

27.2.4 Convexity
27.2.5 Angulation

27.2.6 Ciliary Body Position
27.2.7 Ciliary Body Thickness
27.3 Appendix C: Chapter 4 Program Layout

The below is a list of each page of the software with sub-lists of functions/ requirements to construct the classes and sub-classes.

- **Login Page**
  - Welcome Prompt
  - Input boxes for Name, Post, Affiliation
  - Enter button
  - Cancel button
  - Message box prompt if user clicks “Enter” without filling details
  - Enter button – to navigate to the next page.

- **Help Function**
  - Explain use of the CGS
  - Show instructions how to analyse the UBM features
  - Full functional Help manual written with Dr Explain
    - Context help
    - Tool Tops
  - Click Enter button for next section (or characteristic)
  - Exit Button – with message box prompt to cancel.

- **Main grading page**
  - Menu Strip toolbar
    - Welcome, Instructions,
    - Help (Help pages, technical support and contacts, About software)

- **Characteristic Matching (repeat this page for each grading feature)**
  - Menu Strip toolbar
    - Welcome, Instructions,
    - Help (Help pages, technical support and contacts, About software)
  - 5 reference images – each is an active button.
  - Images displayed in randomised order for sixty seconds.
  - User clicks on one of the CGS for the nearest match to the random image presented.
  - Exit Button
  - Save button – to save responses to excel worksheet
  - Repeat 75 more images.
  - Exit greeting

- **Results button**
  - Menu Strip toolbar
    - Welcome, Instructions,
    - Help (Help pages, technical support and contacts, About software)
  - Statistics to be calculated in excel
27.4 Appendix D: Chapter 4 Intra-Observer Results

27.4.1 Anterior Chamber Depth

- Test-Retest Plot for Observer D
- LOA Plot for Observer D
- Test-Retest Plot for Observer E
- Bland-Altman Plot for Observer E
- Test-Retest Plot for Observer I
- Bland-Altman Plot for Observer I
- Test-Retest Plot for Observer J
- Bland-Altman Plot for Observer J
Figure 27.3 shows short-term repeatability graphs for anterior chamber depth CGS where left hand column (a,c,e,g, i) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b, d, f, h, j) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s (\( \overline{d} \pm 1.96 \times sd \)) are shown as dashed solid lines.

27.4.2 Iris Thickness
Figure 27.4 shows short-term repeatability graphs for iris thickness CGS where left hand column (a, c, e) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b, d, f) the LOAs for each.
scale plotted vs. the mean difference as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.

27.4.3 Iris Profile

Test-Retest Plot for Observer D

Bland-Altman Plot for Observer D

Test-Retest Plot for Observer E

Bland-Altman Plot for Observer E

Test-Retest Plot for Observer I

Bland-Altman Plot for Observer I
Figure 27.5 shows short-term repeatability graphs for iris profile CGS where left hand column (a, c, e) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b, d, f) the LOAs for each scale plotted vs. the mean difference as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s (\(d \pm 1.96 \times sd\)) are shown as dashed solid lines.
27.4.4 Convexity

Test-Retest Plot for Observer D

LOA Plot for Observer D

Test-Retest Plot for Observer E

Bland-Altman Plot for Observer E

Test-Retest Plot for Observer I

Bland-Altman Plot for Observer I

Test-Retest Plot for Observer J

Bland-Altman Plot for Observer J
Figure 27.6 shows short-term repeatability graphs for convexity CGS where *left hand column* (a, c, e) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. *Right hand column* (b, d, f) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.
27.4.5 Angulation

Test-Retest Plot for Observer D

Bland-Altman Plot for Observer D

Test-Retest Plot for Observer E

Bland-Altman Plot for Observer E

Test-Retest Plot for Observer I

Bland-Altman Plot for Observer I
Figure 27.7 shows short-term repeatability graphs for angulation CGS where left hand column (a, c, e) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95 % confidence interval. Right hand column (b, d, f) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.
27.4.6 Ciliary Body Thickness

Test-Retest Plot for Observer D

Bland-Altman Plot for Observer D

Test-Retest Plot for Observer E

Bland-Altman Plot for Observer E

Test-Retest Plot for Observer I

Bland-Altman Plot for Observer I
Figure 27.8 shows short-term repeatability graphs for ciliary body thickness CGS where left hand column (acme) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95% confidence interval. Right hand column (b, def.) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA’s ($d \pm 1.96 \times s.d$) are shown as dashed solid lines.
27.4.7 Ciliary Body Position

(a) Test-Re-test Plot for Observer D

(b) Bland-Altman Plot for Observer D

(c) Test-Re-test Plot for Observer E

(d) Bland-Altman Plot for Observer E

(e) Test-Re-test Plot for Observer I

(f) Bland-Altman Plot for Observer I

Test-Re-test Plot for Observer J

Bland-Altman Plot for Observer J
Figure 27.9 short-term repeatability graphs for ciliary body position CGS where left hand column (a, c, f) show Test-Retest plots where the thin solid line indicates the linear correlation line between tests and the dashed line indicates 95 % confidence interval. Right hand column (b, d, e) the LOAs for each scale plotted vs. the mean difference (d) as determined in the test/retest session. The thin solid line indicates the mean of test/retest differences. The upper and lower LOA's ($\bar{d} \pm 1.96 \times sd$) are shown as dashed solid lines.
27.5 Appendix E Funding & Contributions

27.5.1 Funding
This PhD formulates part of a NIHR Clinical Doctorate Research Fellowship

27.5.2 List of Conference Contributions (Posters)


27.5.3 List of Publications

- S Low, R Siddiqi (2011). Anterior Segment Optical Coherence Tomography and Ultrasound Biomicroscopy in Glaucoma. CML Ophthalmology (Volume 21(1))
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