Diplomate Case 4: Angle closure spectrum disease

ABSTRACT

Although open-angle glaucoma is generally more common than the angle-closure form, patients with angle-closure glaucoma tend to have worse visual prognosis and higher rates of blindness. Patients with acute angle closure tend to have better visual outcomes in comparison to patients with intermittent or chronic closure, due to an increased likelihood to present to the eye care practitioner early enough with the onset of symptoms. Case detection of patients with angle closure is critical for preventing vision loss, as early intervention strategies tend to have reasonably good outcomes. The current gold standard of anterior chamber angle assessment is gonioscopy, even in the face of non-invasive technologies that allow rapid imaging of the angle. As a result, grading systems of angle closure focus almost exclusively on the gonioscopic findings, which makes this a critical skill in the glaucoma patient. This report describes a case of a patient with primary angle closure, and highlights the importance of gonioscopy in clinical assessment of the glaucoma suspect.

INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness, and its prevalence is expected to increase over time due to the ageing and longevous population in most parts of the world.[1, 2] Although open-angle glaucoma is generally more common in most parts of the world, patients with angle-closure glaucoma tend to have worse visual prognosis and higher rates of blindness.[3-5] In angle-closure, obstructed aqueous outflow can cause significant increases in intraocular pressure that then leads to glaucomatous nerve damage and field loss. Acute angle closure, which is the form of the disease that is classically described in medicine with its "hot" eye and significant visual and systemic symptoms (e.g. Lowe et al.[6]), involves a hard and fast increase in intraocular pressure with accompanying anterior ocular signs (corneal oedema, bulbar injection) and leads to glaucomatous nerve damage through a necrotic process, contrasting with the usual slow, apoptotic process occurring in open angle glaucoma.[7] Patients with acute angle closure, interestingly, tend not to have vision loss commensurate with the severity of presentation precisely because these patients commonly present promptly to the eye care practitioner to receive ophthalmic care.[8] Indeed, in some studies in high-risk groups, most patients may not be symptomatic at all (approximately 65-86%),[9-11] nor does the symptom necessarily predict final visual outcome.[12]

Case detection of non-acute or symptomatic forms of angle closure disease appears to be opportunistic, and in fact relies significantly on practitioner skill with the goniolens to accurately assess the anterior chamber angle. The sinister nature of intermittent or chronic angle closure, creeping up from narrow angles, bears some similarity with open-angle glaucoma in the quiet nature of the disease process. In such cases, early detection and intervention is paramount to patient case detection, though sadly overall patients with glaucoma still present with significant vision loss at the point of diagnosis.[13] Furthermore, it is not uncommon to find cases of undetected angle closure disease in a significant proportion of patients in the ophthalmic population, including those who have previously received a diagnosis of open angle glaucoma.[14]

The present case illustrates a patient presenting with angle closure spectrum disease. The appropriateness of the management was contingent upon accurate diagnosis, which was supplemented using advanced imaging modalities. Various techniques used in the assessment of the anterior chamber angle are extensively discussed.

CASE REPORT

A 65 year-old European female was referred for an opinion regarding the anterior chamber angle. She had no presenting ocular symptoms of note, such as blurry vision, redness, soreness, floaters, flashes or haloes around lights. She did not report symptoms of nausea or vomiting. She had no history of prior ocular injuries, surgeries, laser or disease of note. She did not have a family history of glaucoma or blindness. Her medical history was unremarkable, with no diabetes, hypertension, hypotension, thyroid disease, sleep apnoea or migraine.

Best corrected acuities were 20/20 OD and OS with manifest refraction of +2.75/-0.75x90 OD and +2.50/-0.75x90 OS. Pupil testing was unremarkable with no relative afferent pupillary defect. Extraocular motilities were full.

Intraocular pressures (Goldmann applanation tonometry) at 10:01 am were 11 mmHg OD and 13 mmHg, in the context of central corneal thicknesses of 555 microns OD and 550 microns OS found using Scheimpflug imaging (Pentacam HR; Oculus). Both were within the normative range. Her axial length was 22.70 mm OD and 22.78 mm OS found using the IOL Master (Carl Zeiss Meditect, Dublin, CA).

Slit lamp biomicroscopy of the anterior segment showed very narrow van Herick angle estimation (<0.1:1 temporally OU). There was a dense corneal arcus in both eyes. The conjunctiva was clear and quiet in both eyes. There were early age-related cataracts (grade 1) in both eyes. The iris

appeared flat with no evidence of transillumination defects. The anterior chamber was otherwise quiet.

Stereoscopic fundus examination showed a small-sized disc with shallow cup in both eyes (Figure 1). The neuroretinal rim and adjacent retinal nerve fibre layer reflectivity appeared intact in both eyes, with no evidence of a disc haemorrhage. The macula was also clear. There were some drusen temporal and supero-temporal to the fovea OD and OS, respectively. Optical coherence tomography results of the optic nerve head, retinal nerve fibre layer and ganglion cell-inner plexiform layer thickness were all within the normative range and showed no evidence of glaucomatous damage (Figures 2 and 3).

Gonioscopy was performed using a G4 lens (Volk Optical Inc., Mentor, OH) following instillation of topical anaesthetic (oxybupracaine) and the application of a viscous coupling fluid. The gonioscopic results were: pigmented trabecular meshwork inferiorly, anterior trabecular meshwork nasally and Schwalbe's line or no structures superiorly and temporally OD and OS. The iris contour was steep in most areas. Where the pigmented trabecular meshwork could be seen, the level of pigmentation was moderate. Indentation gonioscopy was subsequently performed and revealed deeper angle structures (scleral spur and ciliary body band) in the quadrants of narrowing. Goniophotographs were taken for this patient in primary case under dim illumination (Figures 4-7).

Further imaging of the anterior segment was conducted. Scheimpflug imaging showed anterior chamber depth of 2.10 mm OD and 2.13 mm OS, and chamber volume of 81 mm^3 OD and 87 mm^3 OS (Figures 8-9). Optical coherence tomography measurements of lens vault along the horizontal meridian were 650 microns OD and 550 microns OS (Figures 10-11). Anterior chamber angle instrument-derived parameters are shown in Figures 12 and 13. High resolution scans of the anterior chamber angle found using the Spectralis supplemented these images by providing more confident

visualisation of pertinent angle features, including: Schlemm's canal, the scleral spur and the ciliary body band (Figure 14).

Finally, standard automated perimetry was conducted (Figures 15-16). In the right eye, there was a cluster of reduced sensitivity superiorly that was statistically significant (five contiguous points of reduction, of which two points were $p < 1\%$). The Glaucoma Hemifield Test was borderline and the pattern standard deviation result was identified as statistically significant (2.54 dB at $p < 2\%$). Although the fixation losses were flagged as outside the acceptable range (3/14 > 20%), the gaze tracker showed a steady gaze during the test. The left eye's result showed only two isolated points of reduction of low significance, with no other statistical anomaly.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSIS

Clinical guidelines utilise subtly different grading systems for the different stages of angle closure disease. The implication of such scales is that it constitutes a continuum or ordinal scale of progressive disease, with a break point where treatment is indicated. Therefore, the differentials for this presentation included:

- Open angle glaucoma suspect
- Open angles/open angle glaucoma
- Narrow and non-occludable angles
- Narrow and occludable angles
- Primary angle closure suspect
- Primary angle closure
- Primary angle closure glaucoma
- Secondary angle closure

Given that the angles were narrow or closed in most quadrants, open angle glaucoma disease was firstly ruled out, leaving the spectrum of angle closure disease. There was no pertinent medical history that would suggest a drug-induced angle closure (such as topiramate), and no other features in the anterior segment suggestive of masses that would be obstructing outflow (such as an iris cyst). As indentation gonioscopy revealed deeper structures within the angle, and common causes of synechiael or secondary mechanical closure such as neovascularisation at the angle or uveitis were also ruled out. Thus, the remaining differentials were: narrow but non-occludable angles, narrow and occludable angles, primary angle closure suspect, primary angle closure and primary angle closure glaucoma. The features of each of these conditions, as adapted from the Centre for Eye Health protocols and several publications are summarised in Table 1.

Table 1: Angle and other clinical features of angle closure spectrum disease[15-17]

Angle status	Other clinical features	Diagnosis
No iridotrabecular contact (pigmented trabecular meshwork seen) and fully open	No elevated intraocular pressure, no other anomalies of the angle, disc or fields	Open, normal angles
Iridotrabecular contact (pigmented trabecular meshwork not seen) in one or fewer quadrants	No elevated intraocular pressure, no other anomalies of the angle, disc or fields	Narrow but non-occludable angles
Iridotrabecular contact (pigmented trabecular meshwork not seen) in two quadrants	No elevated intraocular pressure, no other anomalies of the angle, disc or fields	Narrow and potentially occludable angles
Iridotrabecular contact (pigmented trabecular meshwork not seen) in three or more quadrants	No elevated intraocular pressure, no other anomalies of the angle, disc or fields	Primary angle closure suspect
Iridotrabecular contact (pigmented trabecular	One or both of: elevated intraocular pressure or	Primary angle closure

meshwork not seen) in three or more quadrants	peripheral anterior synechiae; normal optic disc and fields	
Iridotrabecular contact (pigmented trabecular meshwork not seen) in three or more quadrants	One or both of: elevated intraocular pressure or peripheral anterior synechiae; plus glaucomatous disc and/or fields	Primary angle closure glaucoma

Using this diagnostic matrix, the patient at present fits into the category of primary angle closure suspect (no elevated intraocular pressure or synechiae seen; no glaucomatous disc and inconclusive visual field results), with both eyes appearing similarly. Given this stage of diagnosis, the patient was presented with two options, as per the current Australian guidelines for glaucoma management. Firstly, she could elect to be referred to a local ophthalmologist for evaluation. Secondly, she could elect to be referred internally to the Centre for Eye Health Glaucoma Management Clinic, which is a satellite clinic of the local health district ophthalmology department for onward referral for surgical treatment. The patient elected for the second option and was seen in the Glaucoma Management Clinic six days later with an attending ophthalmologist.

At the subsequent visit with the consulting ophthalmologist, the patient underwent repeat gonioscopy. The ophthalmologist agreed with the previous gonioscopic findings, and laser peripheral iridotomy versus lens extraction was discussed. Due to a combination of good vision, intraocular pressures within the normative range and minimal cataracts, laser peripheral iridotomy was preferred. She was referred for laser within the Prince of Wales Hospital Eye Clinic (a public hospital clinic) to be performed two weeks later, right eye first, left eye second.

DISCUSSION

Definition and spectrum of angle closure disease

Although the open-angle form of glaucoma is typically more common amongst all cases of glaucoma in many populations across the world, angle closure glaucoma is responsible for half of the cases of blindness due to glaucoma.[1] As with primary open angle glaucoma, primary angle closure is more common compared to secondary causes.[18] Also similar to open angle glaucoma, aspects of primary angle closure disease that have been debated include causation, natural history, classification and staging, the role of technologies and clinical techniques in the assessment, and treatment protocols, particularly in early disease.[17, 19] Specifically, understanding the spectrum of angle closure disease is important as it guides intervention and prognostication, similar to the manner in which open angle glaucoma is treated. Although many large scale, randomised clinical trials and meta-analyses are available for open angle glaucoma or ocular hypertension,[20-23] much less evidence is available for angle closure disease, in part due to the constraints by its clinical presentation.

One classification system that endeavours to provide a clinical guide for assessing potential progression and intervention by the stage of severity has been provided by Thomas and Walland,[17] modified from the International Society Geographical and Epidemiological Ophthalmology (ISGEO) classification. This system suggested five categories: normal, open angles; primary angle closure suspect; primary angle closure; primary angle closure glaucoma; and acute primary angle closure. The authors further provide a series of definitions for each of these categories of primary angle closure disease. A normal, open angle is defined as visibility of the posterior trabecular meshwork in two or more quadrants. A primary angle closure suspect status is defined by the authors as greater than or equal to 180 degrees of posterior trabecular meshwork not visible on gonioscopy. For both of these categories, a normal disc and normal intraocular pressure are

required. As the angle closure disease becomes more advanced, with a greater degree to which the pigmented trabecular meshwork cannot be visualised and increased intraocular pressure, there is a corresponding increased risk of developing primary angle closure glaucoma. Of note, the authors have emphasised the importance of proper gonioscopic technique.[19, 24]

This particular scheme contrasts significantly with other clinical guidelines, and reflect the definitions used by primarily Australian and New Zealand ophthalmologist and optometrists. Other clinical guidelines may vary in terms of the cut-off visible structure. For example, the Asia Pacific Glaucoma Guidelines suggest visibility of the scleral spur in at least 180 degrees as the cut-off for open angles.[25] This may in part be due to the difficulty in distinguishing between the anterior and posterior trabecular meshwork in some patients. This may also be related to the American Academy of Ophthalmology guidelines, which merely state visibility of the "trabecular meshwork" as the cut-off, without separating the two layers.[16] The International Council of Ophthalmology guidelines are notably vague, with no clear separation of staging beyond stable or unstable glaucoma.[26, 27] Another staging system has been suggested by Sihota[28] in an attempt to amalgamate several different subtypes of angle closure disease into a simplified form, but yet this also suffers from the weakness of not necessarily being a continuum (see below for further discussion). All of the above systems state that the presence of synechiae is important, as it is suggestive of chronic appositional closure.[29] However, further commentary[30] has suggested differences between types of synechiae – high and low – which may indicate different stages of chronicity or phenotypes of angle closure disease. This requires further ongoing investigation.

Another important distinction is the intermediate stage of angle narrowing that lies between a completely open and normal angle and the primary angle closure suspect stage. For example, the American Academy of Ophthalmology guidelines suggest that non-visibility of the trabecular meshwork in three or more quadrants represents the discrete stage of primary angle closure suspect, and that non-visibility of two quadrants only represents a narrow but only potentially-occludable

angle.[16] The question is: is the distinction between anterior and posterior trabecular meshwork important? This will be discussed more below.

Overall, these systems each have their own strengths and limitations, and these broadly reflect the current shortcomings of our understanding of angle closure disease. Firstly, there are inconsistencies regarding the stage denoting normal and open angles. The categorical system of Thomas and Walland[17] seems to imply that a normal angle can range anywhere from being wide open with ciliary body band seen to up to two quadrants with only posterior trabecular meshwork seen. However, could the range between ciliary body band and trabecular meshwork still indicate a spectrum with a progressively narrowing anterior chamber angle? This second description grading the anterior chamber angle appears to be more compatible with a disease with a spectrum of severity and facilitates titration of patient care with a changing clinical course. For example, with age-related ocular changes such as cataract progression, it is not uncommon to find decreased visibility of angle structures and narrowing of the chamber parameters,[31] and so being able to distinguish between a wide open angle (such as ciliary body band seen) with a borderline narrow angle (such as posterior trabecular meshwork barely seen) is important.

A second point of contrast is the inconsistency by which the trabecular meshwork is used as a cut-off for occludable angles. Guidelines seem to refer to this cut-off as either the posterior (pigmented) trabecular meshwork,[25] or simply as the trabecular meshwork.[26] Anatomically, the posterior trabecular meshwork seems to be a more logical structure attempt to visualise, as it represents the approximate location of Schlemm's canal.[32] One possible reason for limiting the description is the difficulty by which the layers are clinically distinguished, particularly in patients with no or minimal pigmentation of the trabecular meshwork.[33] A strategy for visualising Schlemm's canal is putting pressure against the angle to cause blood reflux through Schlemm's canal. This occurs physiologically because temporary occlusion of blood flow through the episcleral venous plexus means that outflow is also blocked in Schlemm's canal.[34] This sign may also be identified in some

cases of ocular pathology. Nonetheless, even this technique may make it difficult to distinguish the trabecular layers. The result of using trabecular meshwork alone without specifying anterior or posterior is potentially a less conservative cut-off for determining angle closure. Though intuitive, no study to date has examined this.

Thirdly, a limitation of these systems is that they only state the gonioscopic findings with respect to the visible angle structures. One of the challenges in gonioscopy is discerning whether the non-visibility is due to apposition or due to an irregular iris contour. Indeed, although the iris is an important structure in recording gonioscopy results, it is not mentioned as a significant landmark in any of these grading systems. Specifically, the aetiology of progressively narrowing angles may be due to a variety of causes, one of which is a steepening of the iris contour, such as due to enlargement of cataracts. This represents another limitation of gonioscopy as a technique, as descriptions of the iris contour is limited to qualitative grades (flat, regular, steep, plateau), unlike the staging system used for the angle structures.

Further to the above, the gonioscopic grading appears inconsistent across test conditions. As mentioned, the lighting conditions for testing are critical for accurate determination of the angle. Alongside this, the pupil size is important: mydriatic conditions may also cause iridotrabecular contact even in cases where the angles appeared wide open at baseline or in relatively low-risk or normal patients.[35-38] However, few current clinical guidelines specifically state all of the conditions under which gonioscopy should be performed.[16]

Another major limitation of the grading schemes is that, unlike open-angle glaucoma, progression rates and treatment titration is unclear on the basis of the categorical scale, and that there is little robust evidence to guide best clinical practice. Instead, the recommended treatment paradigms and review schedules appear to mainly be driven by the risk of progression resulting from only a handful of small-scale studies,[39-41] none of which are particularly related to each other, thus making

extrapolation difficult. For example, the studies by Thomas et al[39, 40] utilised a different definition of primary angle closure suspect compared to the study of Yip et al.[41] This will be further developed in the section below.

The natural history of angle closure spectrum disease

As a corollary to the major limitations described above, the natural history of angle closure disease is poorly understood, again unlike primary open-angle glaucoma. One of the features of angle closure disease that makes it less conducive for measurement of progression is the discreteness of the scales used in measuring the anterior chamber depth to determine the degree of closure. In contrast, several of the parameters measured in primary open-angle glaucoma can be quantified and hence determination of progression or change is made easier; these include clinical features such as: cup-to-disc ratio, retinal nerve fibre layer thickness, ganglion cell-inner plexiform layer thickness, and visual field indices (mean deviation, pattern deviation and event analysis using visual field sensitivity).[42, 43] There are a number of limitations to methods that suggest an ordinal value assignment for the discrete structures visible on gonioscopy (for example: 0 for Schwalbe's line and 4 for ciliary body band). One of the potential barriers to standardisation of such an ordinal scale is the implication that the numerical values may be mistaken for a scalar unit: structures that are equidistant apart in terms of the stage of disease severity. Instead of resembling the scalar parameters used in open-angle glaucoma, the ordinal scale may instead bear more similarities to diseases like macular degeneration or cataract in which there are also ordinal, but not necessarily equidistant, scales.

Another problem with this scale is its clinical utility: at present, there is no clear advantage of using an ordinal scale, as final diagnostic determination is based on a complete view of the angle. In diseases such as macular degeneration, it is informative to use a scoring system for determining

disease diagnosis, staging and prognostication (progression to late macular degeneration).[44] Again, because of the lack of understanding of the natural history of angle closure disease, such a scoring system would optimally require an associated level of risk for progression, for example, from grade 3 to grade 2 in a quadrant representing a certain percentage increased risk of developing angle closure. An interesting analogy is in fact mean deviation in standard automated perimetry in open-angle glaucoma: although statistical software packages tend to analyse the results using a linear regression function, the actual natural history of visual field progression tends to be nonlinear instead.[45] Could the progression of stages of angle closure disease be nonlinear too? This also hearkens to the significant limitations of existing and widely used gonioscopy grading schemes (see below).

It is important to elicit the normal age-related change in the anterior chamber angle, and how the angle closure disease process overcomes this magnitude of change. Part of this involves understanding other age-related changes occurring in the eye that are related to the risk of angle closure. One of the most significant age-related changes in anterior segment morphology is in the crystalline lens, which thickens with age.[46-48] This then causes shallowing of the anterior chamber, with increased axial occupation by the lens, which is subsequently a risk factor for angle closure. Interestingly, age-related changes in axial length have been debated; instead, it appears that the crowding of the anterior segment plays a bigger role in angle closure disease.[49-51] Instead, one could question whether such changes are significant in the context of anterior segment changes. This hypothesis has been supported by the presence of angle closure disease in patients with high myopia[52-54] and long axial lengths.[55] Though the risk of angle closure decreases significantly with longer axial lengths, crowded anterior segment features still elevate the overall risk. Since corneal thickness and curvature do not change significantly with age, the shallowing of the anterior chamber depth appears mostly related to the crowding due to the crystalline lens.

Whilst the use of continuous variables are an attractive avenue to pursue in lieu of fixed gonioscopic grading schemes, the significant overlap between normal and disease groups precludes the routine clinical use of automated indices. Further study is required in this area.

Gonioscopy: a historical perspective and evolution of the technique

Gonioscopy was first suggested in the late 1800s by Trantas.[56] Early reports of angle assessment using gonioscopy tended to focus on methods to maximise the view of the angle, such as through compression, lens tilt or gaze rotation. This was likely a product of the culture of having only pilocarpine available for glaucoma treatment, and hence a high threshold for a narrow angle, relative to the definitions of today.[57, 58] Thus, if at any time there were angles that were open on the gonioscopic view, then the angle was considered to be open.

More recently, there has been a shift towards structures visible only on primary gaze for staging angle narrowing, rather than manipulative gonioscopy.[24] Further to this, it became abundantly apparent that illumination conditions dramatically affect the angle appearance.[59-62] Such has the importance of correct conditions for gonioscopic evaluation been discussed that some have even raised suggestions of exploiting such conditions, such as light-dark changes or prolonged dark adaptation, as indices for angle closure or provocative testing.[60, 63] One example is the modified dark adaptation provocative test,[63] in which a patient is dark adapted for three minutes and has anterior segment imaging repeated; this test reportedly yields reasonable agreement and sensitivity compared to gonioscopy (notably, this study used anterior segment optical coherence tomography).

At present, gonioscopy remains the gold standard of viewing the anterior chamber angle and for determining its width and relevant signs for the purposes of grading angle closure spectrum disease.[64] However, the technique is not without its problems, and these are discussed below, with additional context of other imaging or testing modalities provided.

Limitations of gonioscopy in clinical practice

Although gonioscopy is the current gold standard for assessment of the anterior chamber angles, its clinical use is limited by the subjectivity of the technique. A number of named gonioscopy grading schemes currently exist and are used in practice to varying degrees, further confounding the subjectivity. The Shaffer system[65] describes angles from grade 0 to 4, depending on the width in degrees (0 to 35-45^{o}). The interpretation of these extremes is that a grade of 0 means that the angle is closed in part or along the entirety of the circumference while a grade of 4 (or indeed 3) indicates an angle that is impossible to close. The Scheie system[66] describes angles from "wide" to "IV" (no structures visible). The Spaeth grading scheme[58] is one of the most complex grading systems. Its grade describes the insertion angle (structure; capital Roman letter: A, anterior to Schwalbe's line; to E, extremely deep with >1 mm ciliary body band seen), the magnitude of the angle (in degrees), the configuration of the iris (small Roman letter: b, bowing anteriorly; p, plateau configuration; f, flat; c, concave) and the grade of the trabecular pigmentation. Depending on which scheme is used, there can be significant inconsistencies between clinicians and may be a source of variability in angle assessment in practice.

Instead of fixed grading schemes that are variably adopted in practice, a more practical recommendation may be to simplify the grading by listing out the pertinent features seen during the exam: the deepest visible structure, the amount of pigmentation and the contour of the iris. Thus, instead of relying upon numerical or arbitrarily nominal grades, the use of familiar nomenclature may be more conducive for clinical communication.

Aside from its mode of recording and correlation with stages of angle closure disease, a number of practical concerns regarding gonioscopy remain. With the advent of electronic patient records (ePR), there is another identifiable gap in clinical practice: how should one go from recording

goniograms to a written record card? Further to this, common ePRs used in optometry or ophthalmology may not have a specific section for anterior chamber angle assessment, nor one specifically for gonioscopy results. We have recently implemented a new ePR in our clinic specifically for patients undergoing glaucoma assessment, which provides directed forms for gonioscopic findings. Further improvements to this system could be the use of drop-down menus for consistency in record keeping.

However, before considering the implementation of consistent ePRs into clinical practice, there is the major issue of gonioscopy performed in routine clinical optometric practice. A number of studies have highlighted the relative infrequency at which gonioscopy is performed in private practice by optometrists and ophthalmologists, even across multiple health care contexts.[67-74] Many optometric registration boards demand a level of clinical competency that includes being able to perform gonioscopy as a requirement for registration, especially for more recent graduates for whom this is represents a logical expansion of clinical practice. However, several barriers to gonioscopy have been cited, including: the lack of confidence, the lack of demand for such services, the lack of training and limited accessibility to equipment.[72, 75] Although gonioscopy is acknowledged to be an integral part of the glaucoma assessment, it is the skill that is least exercised by practicing optometrists. Additional training or certification processes to assist in this skill have been suggested, but the uptake appears to be limited to niche groups of optometrists. This is a significant problem that needs to be tackled from a number of practical directions.

Should gonioscopy remain as the gold standard? Comparison with other techniques

Despite the above limitations, gonioscopy remains the current gold standard for anterior chamber evaluation. To overcome aspects of gonioscopy that limit its clinical use, several non-invasive techniques of measuring the angle have been suggested.

Limbal anterior chamber depth estimation by the van Herick technique

One of the simplest screening methods is the limbal anterior chamber depth estimation, using the van Herick technique. Originally described by van Herick and colleagues in 1969,[76] the technique is: offsetting the slit lamp illumination arm by 60^{o} temporally, using a bright, narrow beam directed perpendicularly to the ocular surface at the limbus and then comparing the depth of the peripheral anterior chamber depth to the thickness of the cornea. The result is a ratio or percentage, depending on nomenclature. The original grading scheme suggested by van Herick et al[76] consisted of four grades: less than 25%, 25%, greater than 25% and up to 50% and greater than 100%. Interestingly, this grading scheme did not include a grade for category 50-100%. This is because that particular study did not commonly find a gonioscopically occludable angle in patients with van Herick angle of >50%, and thus, for the purpose of screening for the risk of angle closure, such a grade was unimportant. Based on the original study, a screening cut-off of less than 25% was used for flagging patients at risk of angle closure.

Several cut-off values have been suggested for limbal anterior chamber depth. Foster et al.[77] examined three different cut-offs for van Herick ratios for their sensitivity and specificity. The traditional less than 20-25% cut-off has been found to have a sensitivity of 56-89% and a specificity of 89-99%, depending on the study.[11, 78, 79] A cut-off of less than or equal to 15% had a sensitivity of 84% and a specificity of 86%. A cut-off of less than or equal to 25% had a sensitivity of 99.2% and specificity of 65.5%.

Aside from the ease of use and widespread availability (one only needs a slit lamp), one of the originally documented strengths of van Herick is its high inter-observer reproducibility.[11, 77] (Foster et al 2000, Thomas et al 1996). As the temporal limbus is used as the screening angle of interest (it tends to be shallower compared to the nasal angle), this technique therefore relies on the limbal area

being clear. Lesions like pterygium or corneal scarring can impeded the appearance of the limbal anterior chamber depth, representing a significant limitation of the technique. More interestingly, Javed et al.[80] provided commentary that borderline narrow angles presented a potential clinical conundrum. They found that van Herick grades 1 (less than 25%) and 4 (greater than 100%) were highly repeatable, grades 2 and 3 were not. While grade 3 is less problematic as it is unlikely going to be associated with an increased risk of angle closure, grade 2 can be considered to be borderline narrow. Perhaps a more liberal criterion such as less than or equal to 25% should be considered.

The high repeatability of the van Herick technique has been shown to be an advantage over gonioscopy (kappa = 0.29 compared to kappa = 0.54). As an initial screening method for narrow angles, van Herick appears to be superior to gonioscopy. This has been further examined by Jindal et al.[81] who examined the repeatability of limbal anterior chamber depth amongst optometrists and agreement with ophthalmologists. Two grading schemes were used: the traditional 4-point scale and the modified 7-point scale suggested by Foster et al.[77] Importantly, using both systems, very few cases of narrow angles were discordantly estimated amongst all observers, again reinforcing the application of van Herick as a screening technique. However, whilst the modified 7-point scheme appears to produce greater repeatability compared to the 4-point scheme, the practical implications of this is not known: does it actually impact upon the final patient management if both systems perform equally well in screening patients with narrow angles?

Smith's test for anterior chamber depth

Another non-invasive test that is readily performed on the slit lamp is Smith's test[82] for the anterior chamber depth. Proposed in 1979, the method is: horizontal slit beam, illumination arm positioned at 60^{o} temporally, slit lamp system set at the optical axis of the eye in primary gaze, focus beam on the cornea (assisted with fluorescein as required), and then finally adjust the slit beam height until

the blurred and focussed slit images are joined. The resultant slit beam height is multiplied by 1.31 to obtain an estimate of anterior chamber depth in mm. Another application of Smith's test is in estimating sag depth for contact lens fitting. A recent study has suggested a Smith's test cut-off of less than 2.50 mm, which has a sensitivity of 76.5% and specificity of 70.5%.[83] Although this this is similarly non-invasive and accessible, the relatively poorer sensitivity and specificity compared to van Herick begs the question regarding its actual utility and additive nature.

Scheimpflug imaging

This technique describes the change in the focal plane that occurs when a camera lens is tilted. Instead of having a flat focal plane (i.e. where the lens plane and film plane are aligned such that they are exactly parallel such as in normal cameras), the film plane is tilted, shifting the plane of sharp focus to the intersection point of the film and lens planes. This allows examiners to obtain slit images of the anterior segment of the eye that retain depth.[84]

This technique has shown promise as a non-invasive measurement technique for the anterior chamber. Rossi et al.[85] showed good diagnostic ability of the commercially available Pentacam using automated anterior chamber angle, depth and volume measurements to find occludable angles vs. normal open angles. However, their study had only a small number of subjects, and did not group occludable angles by severity level. The cut-offs suggested by Rossi et al.[85] are (AUROC in brackets): anterior chamber angle, 22.4^{o} (0.94); anterior chamber depth (edge), 1.12 mm (0.91); anterior chamber depth (central), 1.93 mm (0.89); and anterior chamber volume, 84 mm^3 (0.89).

Grewal et al.[86] also examined Pentacam and anterior-segment optical coherence tomography parameters in open angle and narrow angle eyes. There were significant differences in both anterior chamber depth (2.70 ± 0.38 vs. 2.06 ± 0.38, in mm) and anterior chamber volume (146.5 ± 35.5 vs. 95.6 ± 20.6, in mm^3). However, there was significant overlap when considering the overall range of

values that these could take. For anterior chamber depth, the ranges were 1.8-4.16 mm for open and 1.59-2.86 mm for narrow angles. For ACV, the ranges were 76-248 mm^3 for open and 58-137 mm^3 for narrow angles. They used a final cut-off value of 2.45 mm for anterior chamber depth (sensitivity 89.3%, specificity 72.6%) and 113 mm^3 for anterior chamber volume (sensitivity 90%, specificity 88.2%).

Other studies have also shown similar overlap in the anterior segment parameters between normal, narrow angle and angle closure patients.[87-89] Arising from these overlaps, there have been a number of criticisms of Scheimpflug imaging for the angle. The technique does not allow detailed imaging of the angle structures of ciliary body as can be achieved by ultrasound micromicroscopy. It also does not permit detailed visualisation of neovascularization, peripheral anterior synechiae or other abnormalities of the angle. The reflectivity and photographic nature of the scan means that anatomical details within the angle may be lost, unlike in anterior-segment optical coherence tomography. Essentially, Scheimpflug imaging can only view the angle approach.

Anterior segment optical coherence tomography

Optical coherence tomography is a technique that uses low-coherence interferometry to obtain high-resolution images of the eye. The instrument generates 2- or 3-dimensional tomographic images by measuring the echo time delay of light back-scattered from ocular tissues. Light from a low coherence light source is split into two paths with a beam splitter directing it to two arms of an interferometer. Light reflectance is compared between that which is reflected by a mirror and that which is back-scattered by the ocular tissues. Complete travel of the light beam is called an A-scan, analogous to ultrasound using sound waves. These are then combined to produce a B-scan to give a more complete axial cross-section of the ocular tissues.

Diplomate case 4: Primary angle closure

Though optical coherence tomography for imaging the eye was first introduced in 1991,[90] it was not until 1994 when it was first introduced for the anterior segment.[91] Much later, instruments using a longer operating wavelengths (such as 1310 nm) have overcome issues with resolution and scan depth, as absorption of this wavelength by water is less than that typically used for retinal imaging (such as 860 nm).[92] At this wavelength, there is less scattering loss and greater penetration into the anterior segment tissue. Notably, several posterior eye imaging instruments such as the Cirrus or Spectralis use a shorter wavelength (840 nm), but have anterior lens modules that allow for imaging of the anterior segment. In the case of the Cirrus, an additional 60D lens means that anterior segment imaging can be obtained by overlapping the source and mirror images, allowing for a scan depth of 5.8 mm. The Spectralis permits anterior segment scans by sacrificing part of the corneal image.

One recent instrument that has a specifically longer wavelength are the Casia swept-source frequency domain optical coherence tomograph, allowing for a scan area of 16 x 16 mm and depth of 6 mm. The A-scan rate of 30,000 Hz allows for a three-dimensional reconstruction of the anterior segment. A summary of currently available commercially available instruments is provided below.[93] Axial resolution essentially refers to depth, while transverse resolution essentially refers to lateral resolution.

OCT Type	Manufacturer	Optical Source	Axial resolution (optical)	Transverse resolution	Scan Speed (A-Scans per second)	Scan Depth	Maximum Scan Width
Visante OCT	Carl Zeiss Meditec, Dublin, CA	SLD 1310 nm	18 μm	60 μm	2000	6 mm	16 mm
Slit Lamp OCT	Heidelberg Engineering, Heidelberg, Germany	SLD 1310 nm	<25 μm	20-100 μm	200	7 mm	15 mm
Cirrus OCT	Carl Zeiss Meditec,	SLD 840 nm	5 μm	15 μm	27,000	2 mm	6 mm

	Dublin, CA						
Spectralis OCT	Heidelberg Engineering, Heidelberg, Germany	SLD 820 nm	7 μm (optical)	20 μm	40,000	2 mm	6 mm
Optovue iVue	Optovue, Inc, Fremont, CA	SLD 840 nm	5 μm	15 μm	26,000	2–2.3 mm	13 mm
Nidek RS 3000	Nidek, Gamagori, Japan	SLD 880 nm	7 μm	15 μm	53,000	2 mm	8 mm
Revo NX	Optopol, Zawiercie, Poland	SLD 830 nm	5 μm	18 μm	110,000	2.4 mm	16 mm
CASIA SS-1000 OCT	Tomey Corporation, Nagoya, Japan	SS laser 1310 nm	10 μm	30 μm	30,000	6 mm	16 mm
Triton OCT	Topcon Corporation, Tokyo, Japan	SS laser 1310 nm	8 μm	30 μm	100,000	6 mm	12 mm

Some of the angle structures can be visualised on anterior-segment optical coherence tomography, and many of its quantitative indices require accurate localisation of these points, including Schwalbe's line, the scleral spur and the ciliary body. Visibility of Schlemm's canal is also advantageous where possible. The nasal and temporal angles are easier to visualise compared to the superior and inferior angles due to less interference from the eyelids.[94, 95] However, there are many cases where structures cannot be visualised.[96] Other potential errors and artefacts may result due to anatomical or pathological features of the eye, such as arcus or pterygium. Quantitative assessment of the angle using several parameters have been suggested (Table 2).[97-99]

Parameter	Definition
Anterior chamber width (ACQ)	Horizontal scleral spur-to-spur distance (mm)
Lens vault (LV)	Perpendicular distance between the anterior pole

	of the crystalline lens and the horizontal line joining the two scleral spurs (microns)
Iris thickness (IT)	Measured at 750 microns or 2000 microns from the scleral spur; the radial distance from the scleral spur (microns)
Iris curvature (IC)	Draw a line from the most peripheral points to the most central point of the iris epithelium; then, draw a perpendicular line extended from this line to the point of greatest convexity: this is the iris curvature (in mm)
Anterior chamber area (ACA)	Cross sectional area of the anterior segment bounded by the corneal endothelium
Anterior chamber volume (ACV)	Vertical line drawn through the midpoint of the anterior chamber area which is then rotated 360^{o} about this vertical axis to obtain volume in mm^3
Angle opening distance (AOD) at 500 microns	Distance between the cornea and iris at 500 microns measured perpendicularly from the scleral spur (microns)
Trabecular iris space area (TISA)	The area of the trapezium from the AOD backwards into the scleral spur ($microns^2$)
Angle recess area (ARA)	The triangular area between the trapezium of the trabecular iris space area in towards the angle

	(microns^2)
Trabecular-iris contact length (TICL)	The distance over which the iris is contacting the trabecular meshwork (in microns)

In light of the challenges facing determination of anterior segment parameters due to difficulties in visualising structures like the scleral spur, one interesting alternative has been proposed: the Schwalbe's line to iris distance (S-I distance), which is the shortest distance in microns between Schwalbe's line to the anterior border of the iris.[100] This has been shown to correlate reasonably well with Schaffer angle grades, but requires ongoing investigation and validation.

Although these parameters are important in angle closure, no firm cut-off values have been established at this stage. Wang et al.,[99] for example, showed only very small differences between iris thickness at 750 microns (0.476 versus 0.453 mm) and at 2000 microns (0.491 versus 0.482 mm), for non-angle closure and angle closure patients, respectively. Even though there are statistically significant differences between the groups, overlap and the small clinical differences that could make these be difficult to reliably separate.

Ultrasound biomicroscopy

Ultrasound biomicroscopy has had a long history of use for anterior chamber angle assessment. The use of a higher frequency transducer allows reduced penetration depth to around 5 mm, but increases the resolution of the imaged structures, with lateral and axial resolutions estimated to be 40 and 20 microns. In comparison to optical coherence tomography which uses light waves, ultrasound biomicroscopy uses sound waves for imaging the eye. This means that it is able to image the ciliary body, unlike optical coherence tomography.

However, similar to optical coherence tomography, there are a number of limitations to ultrasound biomicroscopy, one of which is confusion as to where to put the apex of the angle when measuring it in degrees (at the level of the scleral spur, or at the level of the greatest angle depth).[101] Other factors that affect the ultrasound biomicroscopy measurement and interpretation include: variation in image acquisition (alignment on the eye, failure to control accommodation, failure to control room illumination and controlling the directions of gaze), image analysis (manual placement of measurement calipers, which may confound metric reproducibility), and the lack of widely accepted quantitative normative values of imaged structures such as the iris and ciliary body dimensions. This is even in the context of studies that suggest that diagnoses of plateau iris should be made with ultrasound biomicroscopy in the presence of an anterior positioned ciliary body.[102]

Understanding angle closure disease pathophysiology using advanced imaging

Angle closure disease is defined by the narrowing of the anterior chamber angle and eventual iridotrabecular contact, which then leads to increased intraocular pressure and optic nerve damage. Several anatomical locations have been highlighted as regions of interest in angle closure disease, and these have been subsequently used to differentiate subtypes of the disease.[103] Unlike open-angle glaucoma, in which the treatment tends to almost solely address intraocular pressure modification, angle closure disease has different avenues for therapy depending on the causative factor. As a result, adjunctive imaging technologies may assist in determining the most appropriate treatment for the individual patient.

Pupil block angle closure

Firstly, in the pupillary block aetiology, aqueous humour cannot pass from the posterior chamber to the anterior chamber due to iridolenticular touch.[104] The build up of pressure posterior to the iris causes anterior bowing of the iris at the angle, thus causing iridotrabecular contact. Importantly,

pupillary block can coexist with other aetiologies of angle closure disease. Although it has been described to be the most common cause of angle closure disease, its therapeutic treatment, typically through the application of a laser peripheral iridotomy, frequently results in residual, chronic closure. In such cases, it becomes apparent that it is not the sole aetiology underpinning angle closure disease, and other differentials such as plateau iris, a phacomorphic component or other secondary retroiridal causes should be explored (see more below).

There is a constellation of anterior segment parameters used to describe the risk for pupil block. Parameters such as the anterior chamber depth and the angle width are common amongst a slew of techniques including gonioscopy. The advent of advanced imaging techniques such as optical coherence tomography have led to the development of alternative measurements such as the trabecular iris angle, angle opening distance and trabecular iris surface area. However, whilst these parameters may be useful in identifying patients at risk of angle closure disease, no single parameter is used for the diagnosis of pupil block as a solitary aetiology. This reflects one of the issues with considering pupil block in isolation, as it commonly coexists with other aetiologies of angle closure disease and only through the application of therapeutic intervention, such as peripheral iridotomy, can they be revealed.

Plateau iris configuration or syndrome

Secondly, plateau iris is an anatomical variant of the iris where an anteriorly rotated ciliary body has occluded the ciliary sulcus, causing the peripheral iris to appear flat and in some cases appose the trabecular meshwork.[105] There are several signs that are commonly seen in plateau iris configuration in clinical practice. One sign is the characteristic hook-like insertion of the iris into the angle, and the otherwise flat iris plane towards the pupil. Interestingly, the angle width may range from wide open to the ciliary body to almost closed (apposition), depending on the patient.

Notably, the anterior chamber depth is typically normal or deep, unlike some other types of angle closure. As mentioned above, it is common to find patients that have residual angle closure even after laser peripheral iridotomy, and the most common cause of this residual closure is plateau iris syndrome. Note that it is only referred to as "syndrome" if it follows unsuccessful initial treatment using iridotomy[106] (occurring in up to a third of patients[107]); the term "plateau iris configuration" is used if sufficient pupillary block is relieved with treatment.

One of the prime techniques used to visualise plateau iris configuration is ultrasound biomicroscopy. As light waves from optical coherence tomographs cannot penetrate the scleral or uveal tissue, the configuration of the ciliary body can be difficult to determine using such non-invasive techniques alone. Ultrasonography, on the other hand, produces sound waves that are able to penetrate into deeper tissue, at the cost of technique resolution. Despite its utility, ultrasound biomicroscopy has a number of limitations. Even though it is a relatively older technique in comparison to optical coherence tomography, it is likely less readily available. Part of this stems from the significant skill required to perform this technique. It is subject to substantial intra- and inter-individual variability, depending on factors such as application pressure, practitioner positioning and patient positioning. Specifically, the application of pressure and the direction of application – whether on- or off-axis – may affect the configuration of the ocular structures. For this reason, other options for imaging and diagnosing plateau iris are needed for more widespread clinical use.

Although optical coherence tomography has limitations in penetrating the ocular tissues to visualise the ciliary body, it is able to very readily image the iris-cornea-angle relationship. As one of the characteristic features of plateau iris is its distinctive hook-like shape of the iris as it enters the angle, optical coherence tomography is able to capture this information readily and with arguably greater repeatability in comparison to ultrasound biomicroscopy. From this, clinicians may be able to infer or strongly suspect a plateau iris configuration. Another potential iris sign is the flatness of

the iris contour, with or without the presence of the double hump sign. Again, optical coherence tomography may be informative.

Lens-induced or phacomorphic angle closure

Thirdly, lens-induced or phacomorphic angle closure occurs as a result of a large and thickened cataractous lens which pushes the peripheral and central iris forward.[108] Typically, the lens vault is increased due to the thickness of the iris, leading to pupil block and appositional closure.[109, 110] Due to potential differences in the location of lens thickening, this can overlap with pupil block and plateau iris causes. However, unlike uncomplicated plateau iris configuration, the anterior chamber depth tends to be shallow, corresponding to the increase in lens thickness.

The lens thickness may be difficult to visualise en face, and even with gonioscopy. The shadow test, the oblique orientation of a light source to the cornea, may be able to provide an impression of the iris contour and perhaps the degree of lens protrusion, but it is highly subjective and has poor repeatability. The use of anterior segment imaging can provide more precise measurements of the lens thickness, and, more importantly, the lens vault. The lens vault is defined as the perpendicular distance between the scleral chord and the anterior surface of the lens, and provides an impression of how much of an anterior shift there is of the lens, which may consequently increase crowding of the anterior chamber.[111] Given this, it would not be unusual to have a shallow anterior chamber depth, small anterior chamber volume and correspondingly narrow angle parameters.[98, 112]

Anterior segment imaging that reveals a contribution of the lens to angle closure disease may provide further support for cataract surgery as a treatment modality, rather than peripheral iridotomy. Following cataract surgery, the prediction is a reduction in lens vault and its other associated parameters.[111]

Atypical angle closure: ciliary body, aqueous misdirection or other space-occupying lesions

Fourthly, atypical causes of angle closure occur posterior to the lens-iris diaphragm. Ciliary block, aqueous misdirection or other space-occupying lesions are rare causes of angle closure. In aqueous misdirection, also known as malignant glaucoma, the iris does not necessarily bow forward (unlike pupil block), and it is typically discovered following intervention which does not appear to relieve the iridotrabecular apposition.[113-115] In ciliary block or aqueous misdirection, aqueous fails to move from the posterior chamber to anterior chamber due to an obstruction such as the vitreous face (vitreous block) or ciliochoroidal swelling (effusion), leading to an increase in pressure posterior to the iris.[115] Ultrasound biomicroscopy is useful in these cases to examine the retroiridal space for uveal effusions or plateau iris. As mentioned above, there is value in ultrasound biomicroscopy in such cases in comparison to light-based instruments such as optical coherence tomography due to its increased tissue penetrance.

However, these anatomical classifications of angle closure do not account for mechanical pulling or attachment of the iris to the cornea: that which occurs in synechiael angle closure. Any process that leads to chronic iridotrabeular touch can propagate synchiae formation, eventually potentially resulting in 360 degrees of complete closure. Specific, common causes of synechiae formation include anterior uveitis and neovascular glaucoma. In these causes, inflammation and neovascular membrane cause contraction of the iris towards the cornea, respectively, thus leading to synechiae formation.

It is evident from the above descriptions of the multifaceted pathophysiology of angle closure disease that imaging modalities play a significant role in determining the underlying aetiology and therefore guiding treatment. Due to the known limitations of each imaging technique, a multimodal imaging and diagnostic approach is typically recommended.

Patient-tailored medicine using a Bayesian approach to disease diagnosis

The process of diagnosis for the patient presented in the present case report illustrates the consideration given to the role of imaging in combination with other standard clinical techniques. With the initial van Herick and gonioscopy results showing angle closure disease, the application of anterior segment optical coherence tomography highlighted areas of iridotrabecular contact in regions where the scans were performed. The amount of lens vault and the iris curvature appeared concordant with the lack of significant cataract in the slit lamp examination. In combination with her normal visual acuities, this guided treatment towards laser peripheral iridotomy, rather than cataract surgery (see further discussion below).

In the present case, both eyes had angle closure disease, so often the question is: which eye to treat first? It is uncommon to treat both eyes simultaneously in non-glaucomatous or non-acute presentations of angle closure, much like chronic open angle glaucoma. In cases of pre-glaucomatous or borderline disease, often the eye that exhibits a greater amount of closure is treated first. In the present case, there was no eye preference due to relative symmetry.

To treat, or not to treat: considerations of asymptomatic disease

One of the features common between open angle and angle closure disease is that they can be asymptomatic. Treatment in most cases is to prevent further structural or functional loss. There appears to be a paradigm shift towards earlier detection and intervention, whereby patients with structural anomalies without necessitating function may also undergo treatment.

In angle closure disease, this translates to potentially earlier treatment prior to the onset of primary angle closure, in which there is elevated intraocular pressure and/or synechiae formation, or primary

angle closure glaucoma, in which there is obvious glaucomatous damage. Though aggressive treatment of the stages of angle closure leading up to chronic and irreversible structural changes may be warranted and recommended in many jurisdictions, the evidence for this should be carefully considered.

There are few natural history studies of angle closure disease, and it is unlikely that ethical approval would be provided for a large enough clinical trial to monitor patients with angle closure suspect status on no or sham treatment. If considering one of the few pieces of evidence available for examining the progression from primary angle closure suspect to primary angle closure, it appears the only 22% of patients will progress from the former to the latter stage in a five year period.[39] None of the patients developed blindness, primary angle closure glaucoma or acute primary angle closure. In another report on the same cohort, it was found that 28.5% of patients with primary angle closure progressed to primary angle closure glaucoma over five years.[40] Notably, this definition of primary angle closure suspect status was non-visibility of the pigmented trabecular meshwork in over 180^{o} (two quadrants). This definition is significant: it is more sensitive than the three quadrant criteria used by some reports, but is less specific, meaning that potentially patients who may never have progressed to primary angle closure could have been included in the study, thereby lowering the overall progression rate figure. If we therefore consider the progression from primary angle closure suspect to glaucoma, this means that only 6.3% of patients had progressed from the former to the latter.

These progression rates may also be dependent upon ethnicity (discussed further below). A study in predominantly white Caucasian patients by Wilensky et al.[116] showed an overall risk of progression from primary angle closure suspect to primary angle closure of 19% over three years.

In another study by Yip et al.,[117] they reported a proportion of progression from normal open angles to primary angle closure suspect status of 20.4% over a six year period. This figure appears quite

high overall, but there are several points of interest with respect to the study population. One notable point of interest is in the study name itself: this population was high risk – a Mongolian population. It would therefore be expected that the rate of progression is higher. Another point of interest is that they defined normal as pigmented trabecular meshwork in two or more quadrants, as per the International Society Geographic and Epidemiology Ophthalmology definition. Again, this relates back to a problem inherent in this definition: patients with ciliary body band visible in those same quadrants are regarded as the same as those with pigmented trabecular meshwork visible only.

Currently, the American Academy of Ophthalmology has summarised the overall risk of conversion to approximately 25% over five years.[16] This figure can then be suitably titrated depending on their individual risk factors.

Although the majority of patients do not exhibit eventual progression from primary angle closure suspect to primary angle closure glaucoma or acute primary angle closure, those that do tend to have more visually devastating consequences. Thus, there appears to be a compelling reason to treat such patients. The question remains though: leading up to the point of primary angle closure suspect status, when should intervention be suggested, given this paradigm of early detection and treatment?

Risk factor analysis for guiding management

As alluded to above, there are populations that are notably more high risk compared to others for developing angle closure disease, and these may provide additional guidance for the point of intervention. Several risk factors have been identified. Generally well-accepted demographic risk factors for angle closure disease include: older age, family history, female sex, and Asian/Inuit ethnicity.[118-121] These risk factors have a biological basis, as these groups represent those with smaller general ocular biometry, and hence greater risk of anterior segment crowding.

Previous suggestions have also included hyperopia as a risk factor for angle closure disease.[122, 123] A hyperopic refractive error is an attractive target, as it is relatively simple to screen in comparison to other modalities such as anterior chamber angle assessment. The initial rationale for hyperopia as a risk factor for angle closure disease was that it may be associated with a shorter axial length and hence smaller overall ocular biometry. There are a number of flaws with this assumption. Hyperopia, like any refractive error, may be driven by both axial and refractive causes; the latter is probably unlikely to affect ocular biometry. Hyperopia also tends to be more common in those with smaller ocular biometry anyway, and hence it may be an epiphenomenon, rather than a direct risk factor for angle closure disease.[52, 124, 125]

One of the most compelling arguments against hyperopia as a risk factor is the steady prevalence and incidence of angle closure disease in high risk populations such as Asian ethnic groups despite the concurrent myopia epidemic.[54] If hyperopia were the cause, myopia should be relatively protective against angle closure disease and hence there should be a decline in the prevalence and incidence. Instead, it appears that although the prevalence of myopia is increasing in the at risk populations, the steady angle closure disease prevalence has been driven by ocular biometric parameters of the anterior segment remaining small and crowded. Thus, the current thinking is that hyperopia may be an epiphenomenon, rather than a direct risk factor for angle closure disease.

As mentioned above, the development of cataracts appears to be a risk factor for glaucoma. Although it may be related to ageing, its role in the phacomorphic aetiology of angle closure suggests a larger contribution of cataracts, in comparison to hyperopia.

Another widely-cited risk factor for angle closure disease is Asian ethnicity when considered relative to Caucasian or African American races. Numerous epidemiological studies have shown that Asian eyes typically have narrower angles – considered at risk of closure – and rates of blindness due to angle closure glaucoma tend to be higher in these groups. An important

consideration is an ethnically-diverse population with a large subset of Asian patients. More relevant to certain parts of the world, and far more rare in Australia, is the Eskimo or Inuit ethnic group, which has been suggested to be the highest risk group.[126, 127] The main mechanistic factors behind these ethnic groups having greater risk is likely related to ocular biometry. However, this distinction has also led to a very interesting discussion on the evolutionary aspects of angle closure disease.[128]

Management of angle closure spectrum disease

As mentioned above, though the majority of patients without glaucomatous change or those with few risk factors for conversion to late stage disease may not eventually progress, the consequences of angle closure tend to be more dire and acute in comparison to chronic open angle glaucoma. As such, patients with earlier stages of the disease may still undergo prophylactic treatment. Typically, modern treatment of angle closure can be divided into two main interventions: laser peripheral iridotomy or lens extraction. Additionally, some patients may be candidates for laser peripheral iridoplasty.

A management algorithm that has been suggested broadly divides patients into two main categories: pre-presbyopic without cataracts, who would be more suitable for laser peripheral iridotomy; and presbyopic with cataracts, who may benefit more from lens extraction. However, these are guidelines only, and should also be tailored to the individual patient.

Laser peripheral iridotomy

In laser peripheral iridotomy, a laser is used to create an opening in the peripheral iris, creating a passageway between the anterior and posterior chambers.[129] The laser is typically placed in the

superior aspect of the iris, a short distance away from the limbus. A recent study has suggested placing the hole at the temporal positions instead,[130] but this has been highly debated,[131] with no conclusive evidence of greater reduction in dysphotopsia using this method.[132, 133] More recently, an inferior placement of the iridotomy has been suggested.[134]

Typically, iris crypts are targeted to reduce the difficulty in producing a patent iridotomy. In light irises, it is typically conducted using a neodymium:yttrium-aluminium-garnet (Nd:YAG) laser using the following settings: power, 4-8 mJ; pulses per burst, 1-3; fixed spot size. However, in darker irises, more energy is typically required, and it is not unusual to firstly pre-treat using an argon laser to create a crypt. In this procedure, sequential argon laser is performed. Firstly, the anterior border of the iris is removed (power, 300-400 mW; duration, 0.05 s; spot size 50-100 mm). Then, the iris stroma is removed (power, 900 mW; duration, 0.03-0.04 s; spot size 50 mm). The Nd:YAG laser is then used to remove the iris pigment epithelium (power, 1.7-3 mJ; pulses per burst, 2; spot size, fixed).[135-138] The goal is for iris pigment to be released and the aqueous and anterior capsule to be visible. There are different recommendations for iridotomy size, ranging from at least 200 microns to 500 microns in size.[139, 140] More evidence is required in this area.

Laser peripheral iridotomy is generally considered to be safe. Some potential complications of the procedure include: postoperative intraocular pressure spike, intraocular inflammation (anterior uveitis), iris bleeding and hyphema, focal cataract, posterior synechiae, visual symptoms (such as haloes around lights and glare) and local corneal decompensation. To prevent postoperative intraocular pressure spike due to acute inflammation and pigment liberation, topical intraocular pressure lowering medication is usually prescribed for short-term therapy (brimonidine or apraclonidine).[141, 142] Short-term topical steroids (such as prednisolone acetate) may be used to reduce anterior uveitis or peripheral synechiae due to the release of prostaglandins in the anterior chamber.[143, 144] Iris bleeding or a small hyphema are common following Nd:YAG, as it is a photodisruptive device.[145] It can be controlled by applying pressure in the globe. Again, this is

transient. Focal cataracts or lens dislocation can develop if the iridotomy site is too close to the pupil, and can be due to excessive heat from argon laser or from direct tissue disruption from the Nd:YAG laser.[146, 147] There may be a similar mechanism behind local corneal decompensation and oedema.[148]

One of the more common complications of iridotomy is the occurrence of visual symptoms, reported in approximately 5-10% of patients.[149] These can be visually disturbing and take a number of different forms, including: shadows, ghosting, linear dysphotopsia, haloes, glare or diplopia. The risk factors such as iridotomy placement, coverage and size, for resultant dysphotopsia have been debated. For example, Spaeth et al.[150] showed that patients with partially covered or fully exposed iridotomies have a greater incidence of visual disturbances. As mentioned above, Vera et al.[130] suggested that temporal placement of the iridotomy may result in fewer disturbances, due to fewer aberrations with no tear meniscus present. On the other hand, Congdon et al.[151] showed no significant effect of any of these risk factors. This remains a subject of considerable debate and is dependent upon the individual surgeon.

Laser peripheral iridotomy has largely replaced surgical iridectomy.[152] As it is less invasive, such as reducing the effects on the corneal endothelium, iridotomy tends to be preferred, at least in the initial phase. However, iridectomy may still play a role in later stage disease, if manipulations of the ciliary body are also required to further reduce intraocular pressure.

Another type of laser surgery is laser peripheral iridoplasty.[153] This has been shown to be a niche procedure suggested for a subset of patients with persistent angle closure or iridotrabecular contact following laser peripheral iridotomy.[154] In this procedure, the iris stroma is debulked using an argon laser to reduce the thickness of the peripheral iris and to cause contraction of iris tissue away from the cornea, thereby reducing synechiae formation.[155, 156] This procedure has had good success in

some studies,[157-163] but minimal effect in others.[155] However, it may be an option in patients who are pre-presbyopia and without cataracts to have a surgical-sparing treatment.

Lens extraction

Lens extraction is suggested in cases of patients where the phacomorphic component is significant or if the patient is presbyopic or has significant cataracts. Unlike laser peripheral iridotomy, lens extraction significant alters the anterior segment biometry, which, as mentioned above, has implications for future progressive risk of angle closure.[164, 165] By removing the contribution of the lens bulk within the anterior segment, the iris naturally moves posteriorly, thus resulting in deeper anterior chamber depth, increased anterior chamber volume and widening of the anterior chamber angle. Notably, this will not alter the iris parameters.

Aside from typical potential complications in intraocular surgical procedures, one adverse effect of lens extraction is the loss of accommodation in the pre-presbyopic eye. Correction of refractive error can be a benefit to some patients with high refractive errors.[166, 167]

Evidence-based treatment

Unlike chronic open angle glaucoma, there are few large clinical trials that have examined the efficacy of these treatments in preventing further glaucomatous damage or progression of angle closure spectrum disease. Two landmark clinical trials are the EAGLE study[168] and the Zhongshan Angle-closure Prevention (ZAP) Trial.[169] The initial reports of these trials have now been reports.

In the ZAP trial,[169] 775 Chinese patients aged 50-70 years diagnosed as primary angle closure suspect (less than 180 degrees of pigmented trabecular meshwork visible) underwent laser

peripheral iridotomy in one eye and were followed for 18 months. A number of interesting results have been reported.[170] Firstly, around a quarter of eyes had persistent angle closure after iridotomy. Secondly, at two weeks after laser, the angle width of treated eyes increased significantly. However, after around 6 months, the angle width began narrowing in the treated eye, though at a slower rate in comparison to the control group. Thus, a longer trial is required to better understand the long-term prognosis following treatment.

Other trials in high risk populations (Mongolia and India) have suggested benefits of laser in terms of reducing the risk of acute angle closure attacks. Though synechiae may still develop following treatment, no patients in either study experienced an acute angle closure attack or glaucomatous changes.

The EAGLE study[168] on the other hand examined the role of early lens extraction for treatment of primary angle closure glaucoma. The patient cohort was slightly different[171]: phakic patients 50+ years old with no evidence of cataract, with primary angle closure with intraocular pressure greater than 30 mHg or primary angle closure glaucoma with intraocular pressure greater than 21 mmHg in at least one measurement, and without advanced glaucoma (mean deviation less than -15 dB and cup-disc ratios of less than 0.9). In this study, patients were randomised to clear lens extraction (note that patients were phakic and had no significant cataract) or laser peripheral iridotomy in order to compare the two treatment modalities. Other interventions were permitted to be performed as required in order to reach a target pressure of 15-20 mmHg, or for rescue.

There were numerous outcomes measures for this study. The clear lens extraction group had higher quality of life scores. They also had lower intraocular pressures (by approximately 1.3 mmHg) at 36 months when compared to the laser peripheral iridotomy. Fewer additional treatments (drops, incisional glaucoma surgery) were required for the patients who had undergone cataract surgery compared to the laser group. Lens extraction was more expensive, on average, compared to

peripheral iridotomy ($3154 versus $1900). This represented potential increased cost-effectiveness with lens extraction over iridotomy.[172] There was a slight difference in level of visual acuity favouring lens extraction, but visual fields were similar.

Overall, the results of the EAGLE trial reinforce the role of lens extraction. The results reveal interesting conditions under which lens extraction may be useful. Firstly, patients with angle closure disease with elevated intraocular pressure appear to benefit from lens extraction. Secondly, where lens extraction may be useful in other situations, such as in high refractive errors or significant cataract where patients may benefit from improved vision. Finally, where there is a significant phacomorphic component or an imminent phacomorphic component, then the patient may benefit from lens extraction instead of beginning first with a laser peripheral iridotomy.

When this evidence is applied to the present case, arguments could be made for either iridotomy or cataract surgery. Arguments for cataract surgery included early onset cataracts, moderate hyperopic refractive and her age (already minimal to no accommodation left). However, arguments against lens extraction include her relatively minimal cataracts, her good vision, the lack of a clear phacomorphic component and the intraocular pressure was within normal limits. One important consideration is the acceptance by the patient: are they amenable to undergoing surgery at this stage or not? In this particular case, the patient elected for laser peripheral iridotomy at present, as she felt that her vision was still acceptable. Another consideration is cost: in this particular case, as she was a public hospital system patient, iridotomy represented the more cost-effective option in the short-term.

CONCLUSIONS

Angle closure spectrum disease can potentially be more devastating than open angle glaucoma. The careful assessment of patients using a slew of anterior chamber angle examination techniques is

858 required to diagnose, stage and prognosticate the disease. Current treatments are guided primarily
859 by gonioscopic findings and historical risk factors. In time, there may be a paradigm shift towards
860 utilisation of advanced imaging modalities to complement this examination process. Two main
861 treatment options are available, and the results of long-term clinical trials are eagerly awaited to
862 provide more guidance for optimal patient management.

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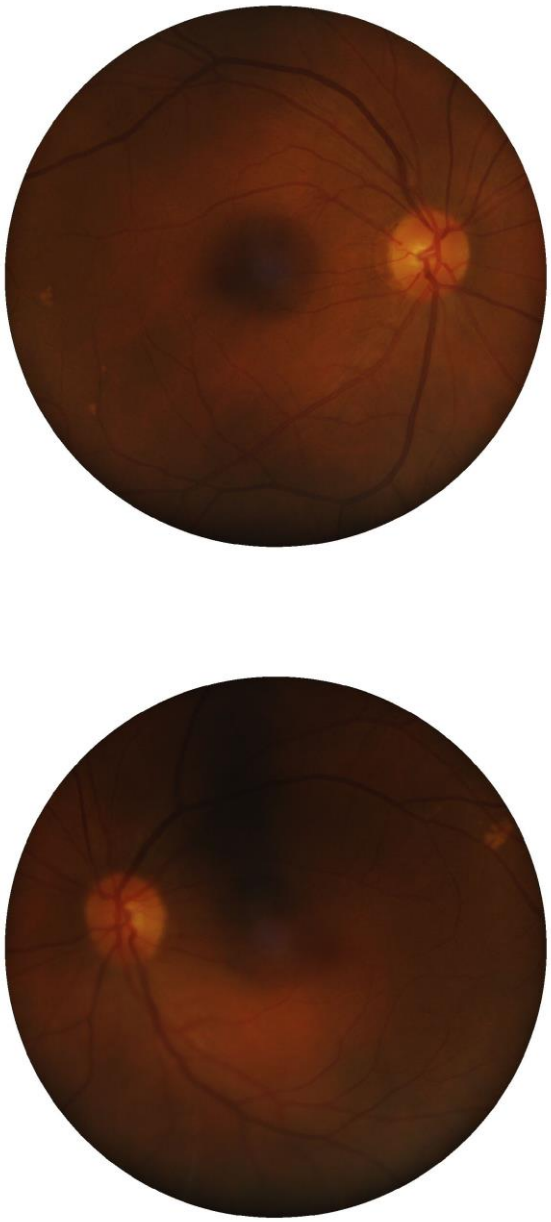


Figure 1: Colour fundus photographs of the posterior pole of the right and left eyes (Kowa nonmyd 7, Kowa Medical, Sendai, Japan)

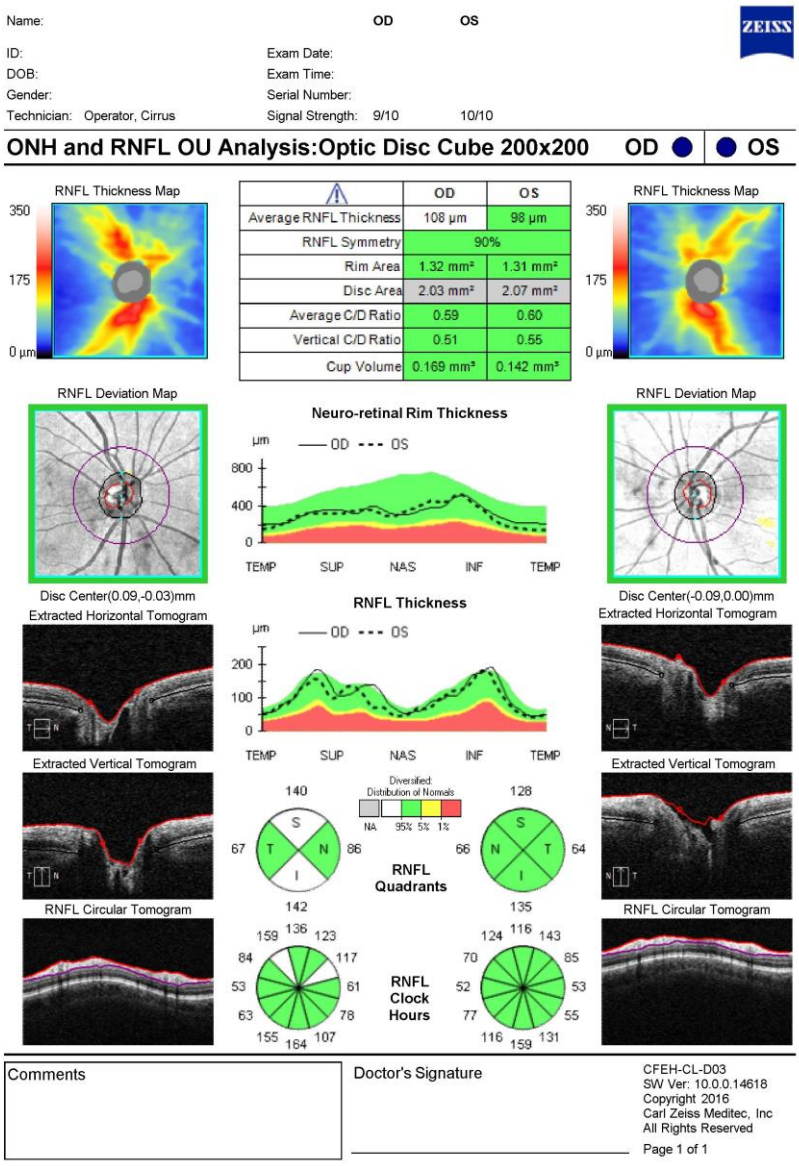
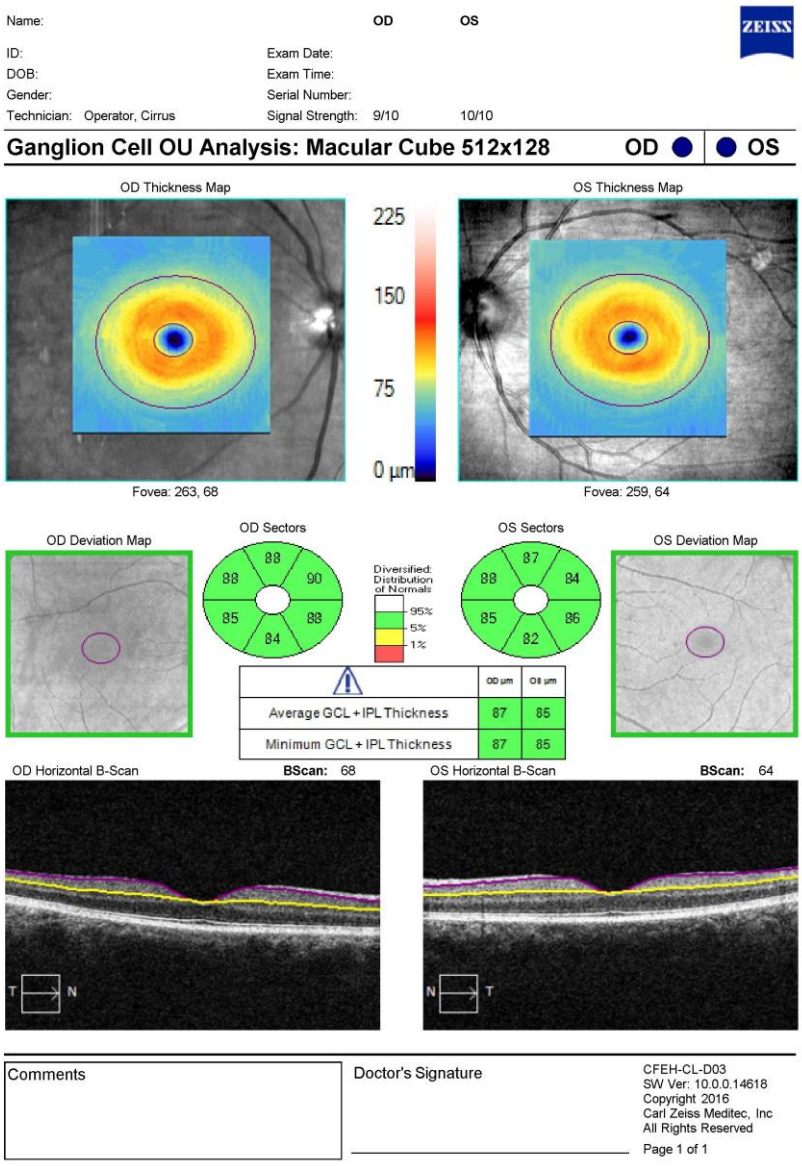


Figure 2: Optical coherence tomography of the optic nerve head and retinal nerve fibre layer for right and left eyes (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA).



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874 **Figure 3:** Ganglion Cell Analysis printout (ganglion cell-inner plexiform layer thickness) for right

875 and left eyes (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA).

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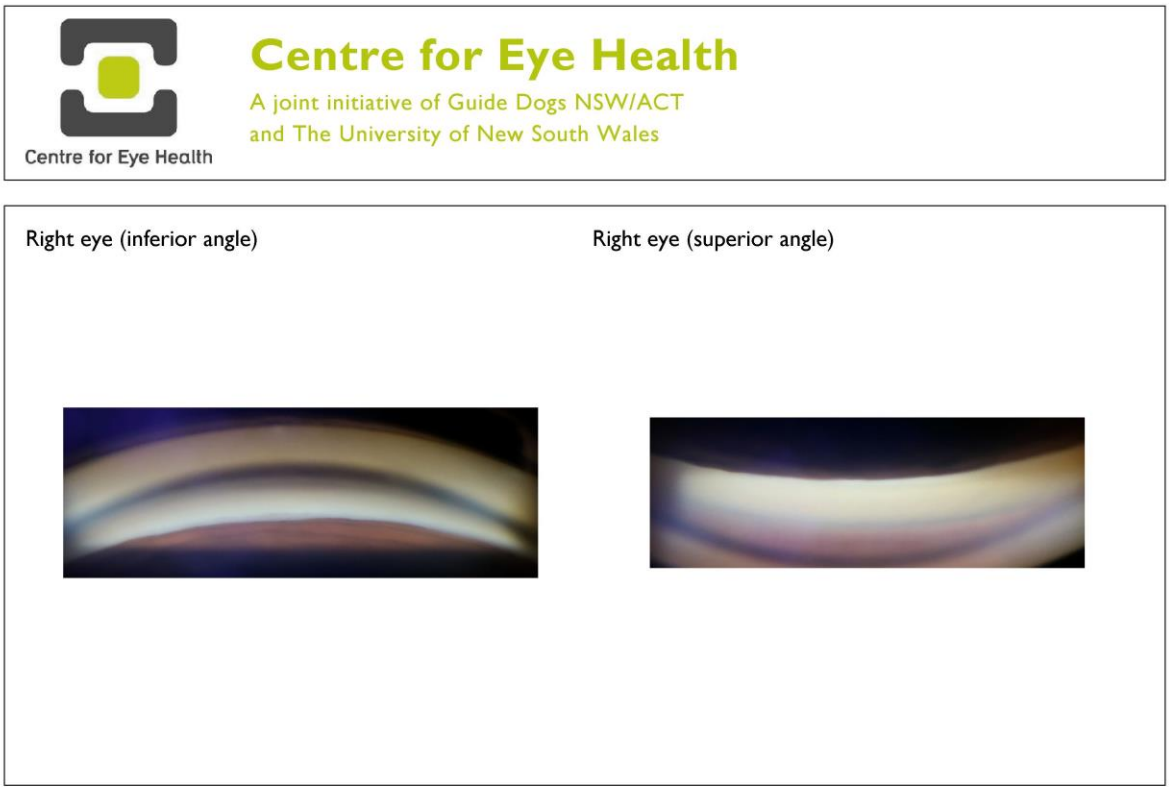

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879 **Figure 4:** Superior and inferior goniophotographs of the right eye (G4, Volk Optical, Inc., Mentor,
880 OH) taken under dim illumination settings (10% neutral density filter, no peripheral flash, 10%
881 illumination, 16x magnification, ISO 200, aperture 2; BX 900 and Canon 50D, Haag Streit AG,
882 Koeniz, Switzerland and Canon, Inc., Tokyo, Japan).

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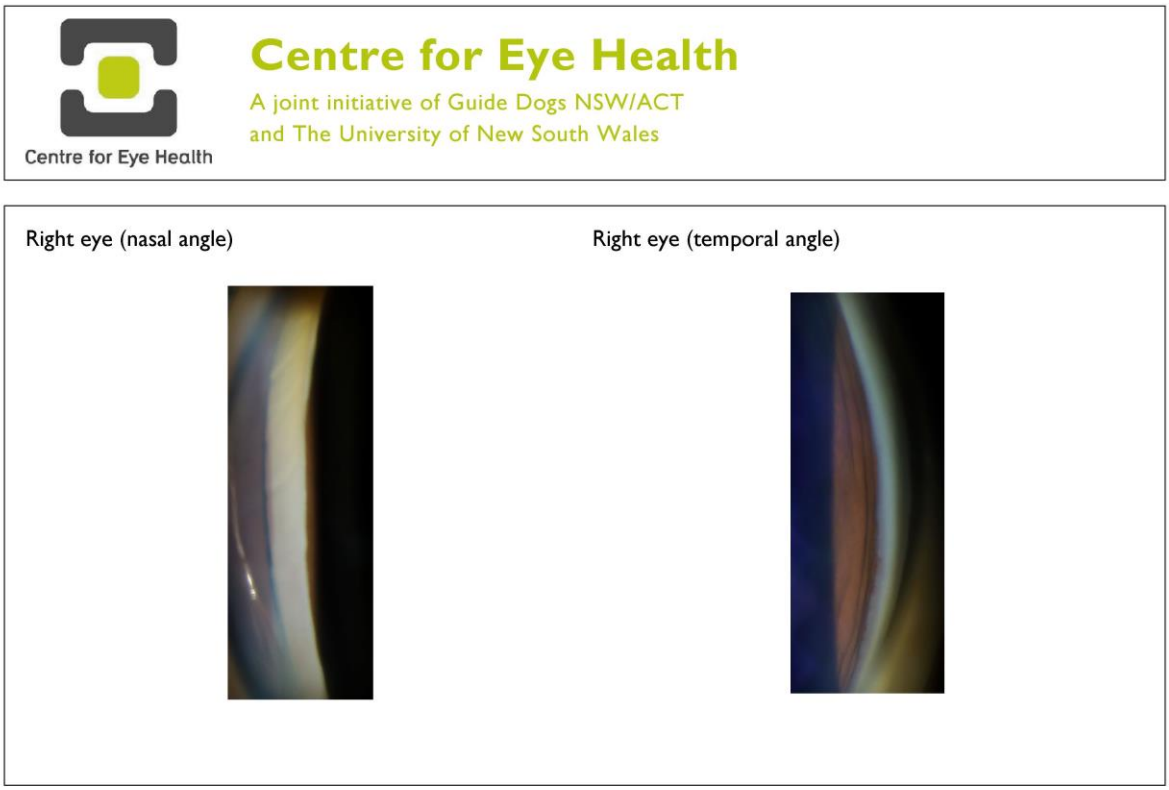

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886 **Figure 5:** Nasal and temporal goniophotographs of the right eye, as per Figure 4.

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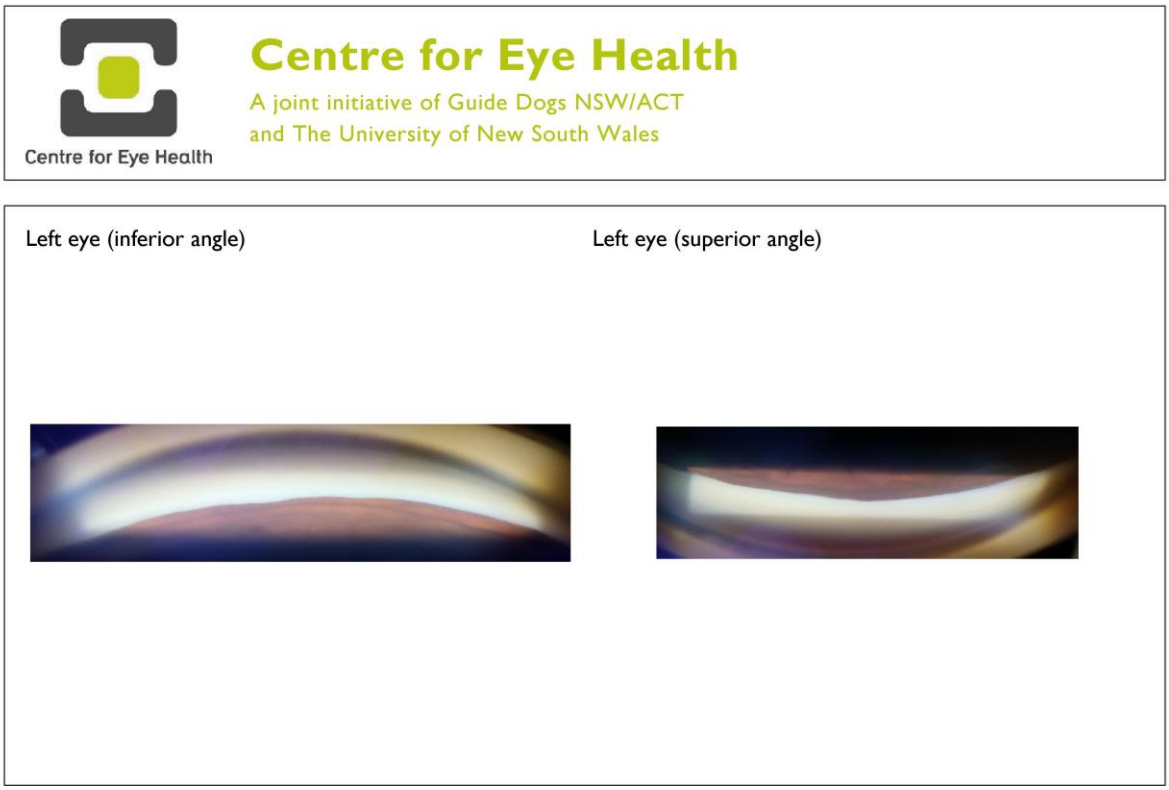

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891 **Figure 6:** Superior and inferior goniophotographs of the left eye, as per Figure 4.

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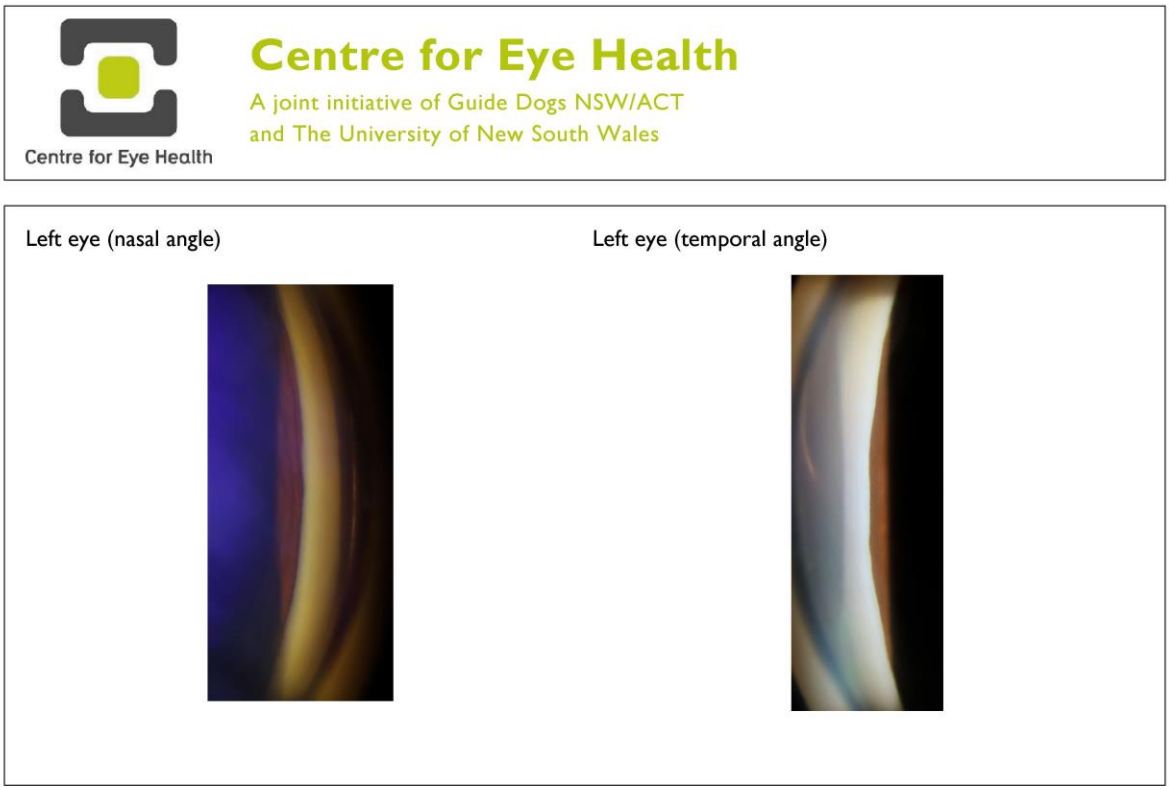

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896 **Figure 7:** Nasal and temporal goniophotographs of the left eye, as per Figure 4.

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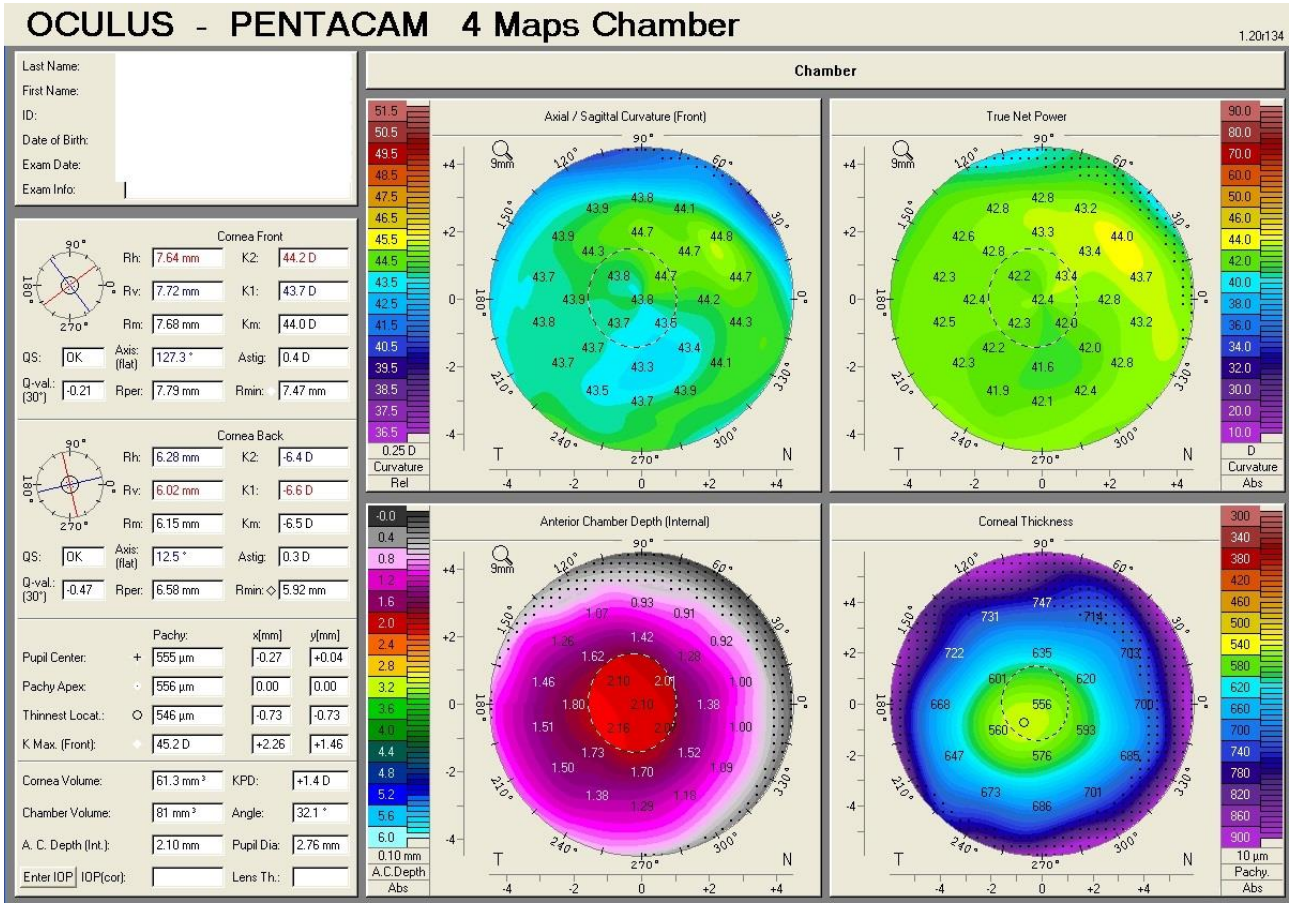


Figure 8: Scheimpflug imaging of the anterior segment of the right eye (Pentacam HR, Oculus Inc., Wetzlar, Germany). The 4 Maps Chamber printout was examined as it shows the distribution of anterior chamber depth across the anterior segment (approximately 8 x 8 mm radius).

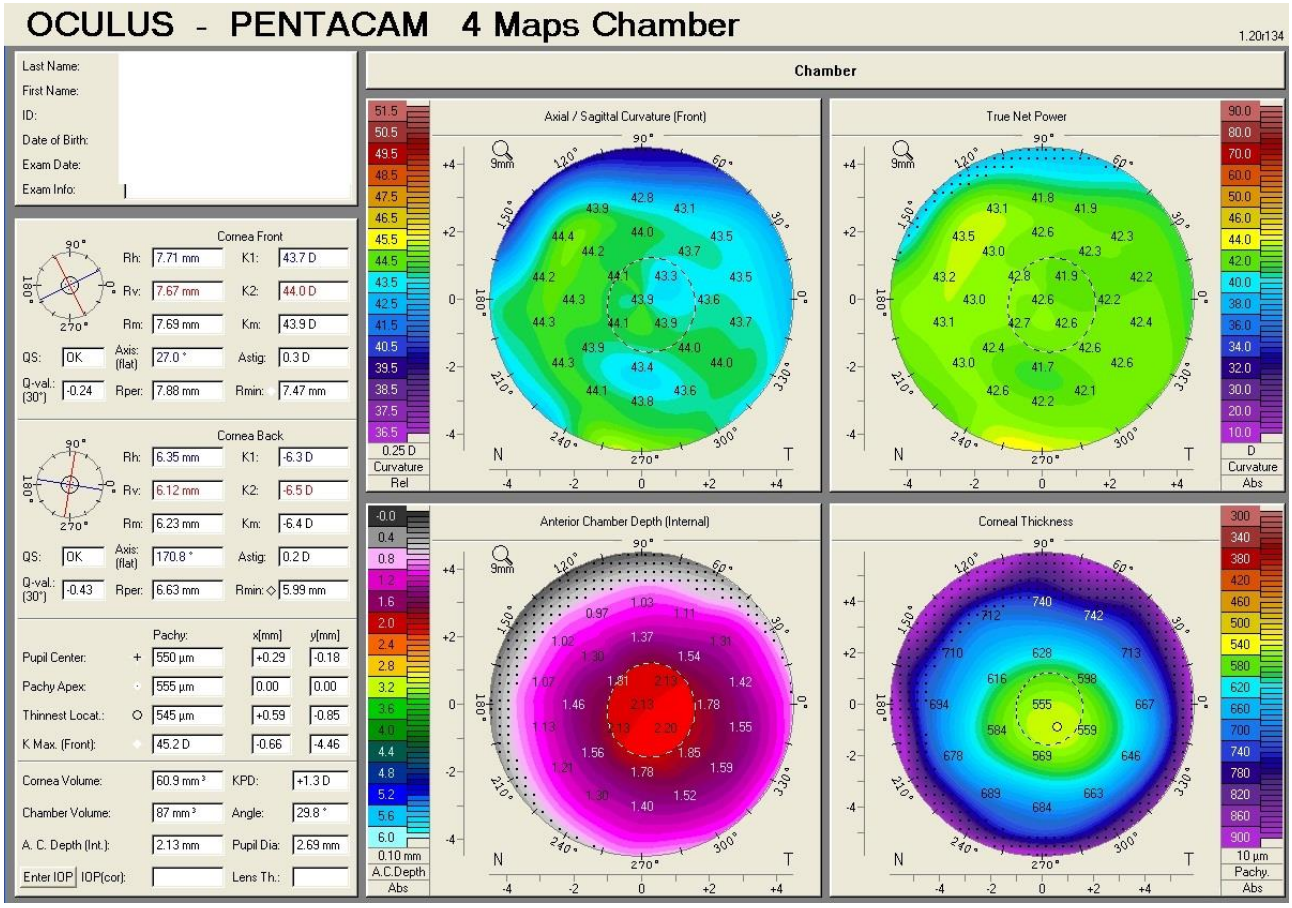


Figure 9: Scheimpflug imaging of the anterior segment of the left eye, as per Figure 8.

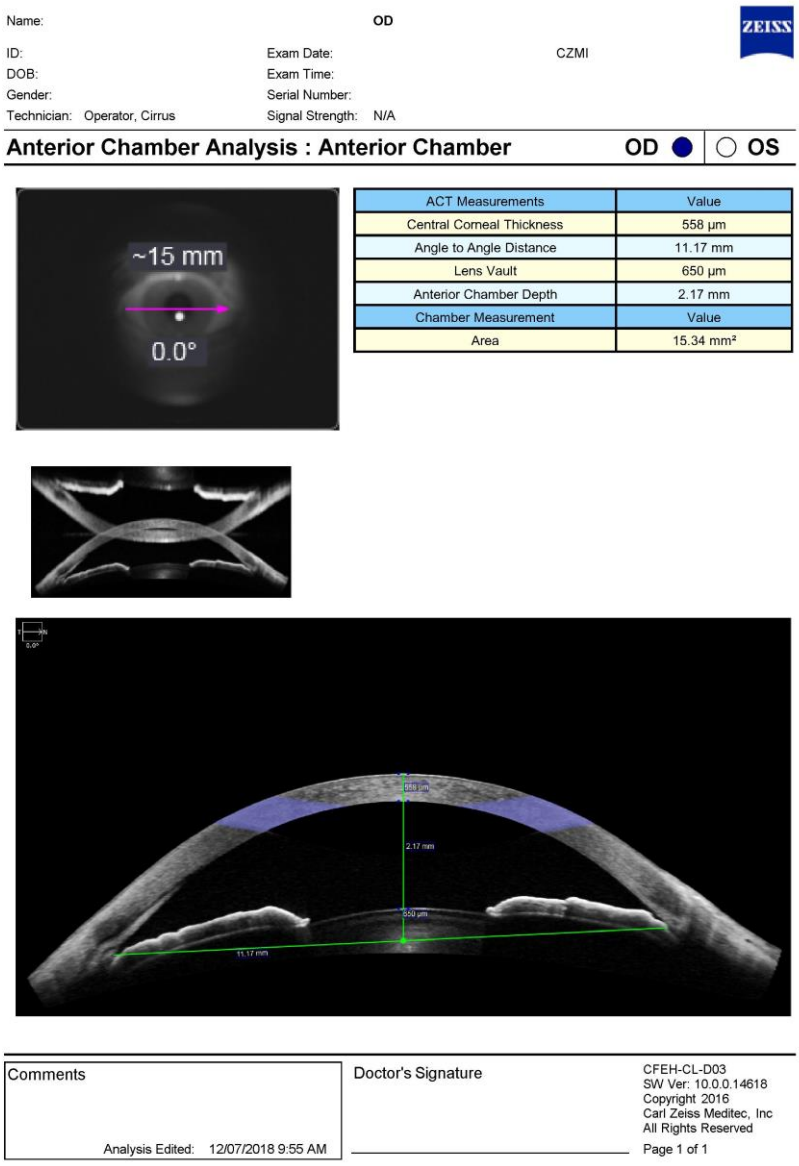


Figure 10: Anterior segment optical coherence tomography Anterior Chamber Analysis results for the right eye (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA). Note that the horizontal spur-to-spur chord was generated manually, with the anterior chamber depth and lens vault inferred from this value.

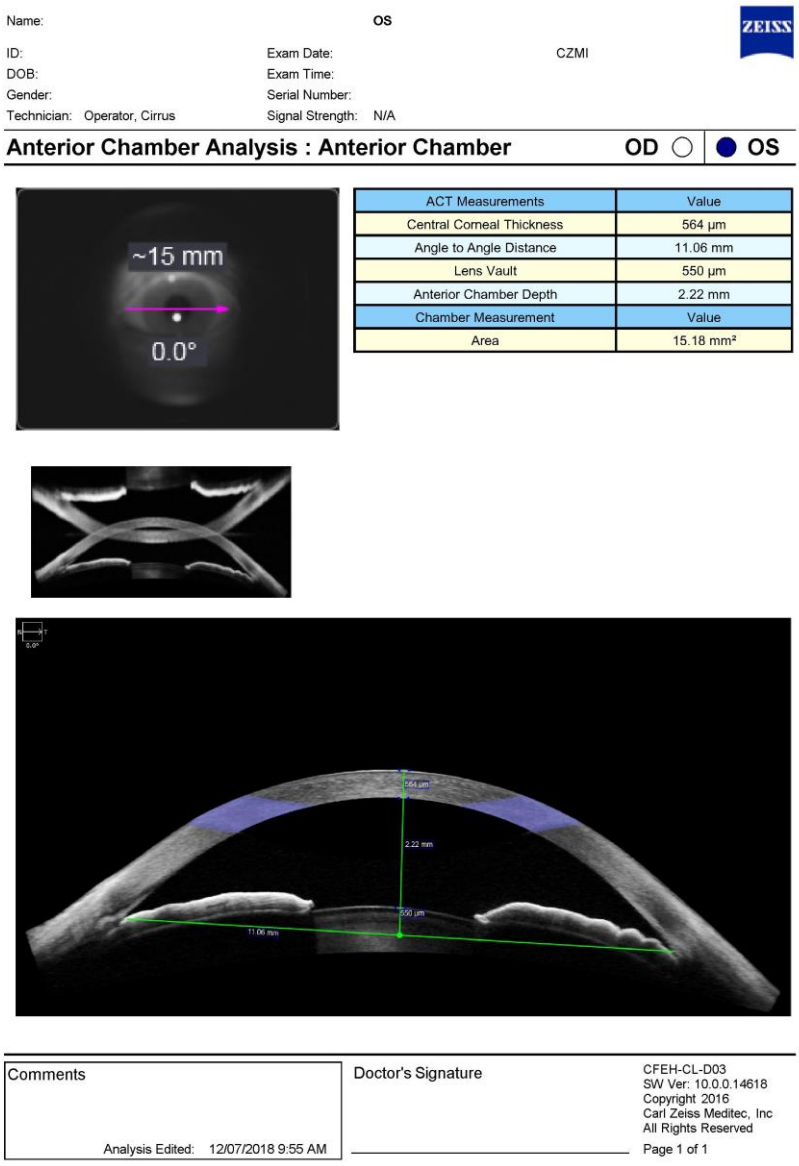


Figure 11: Anterior segment optical coherence tomography Anterior Chamber Analysis results for the left eye, as per Figure 10.

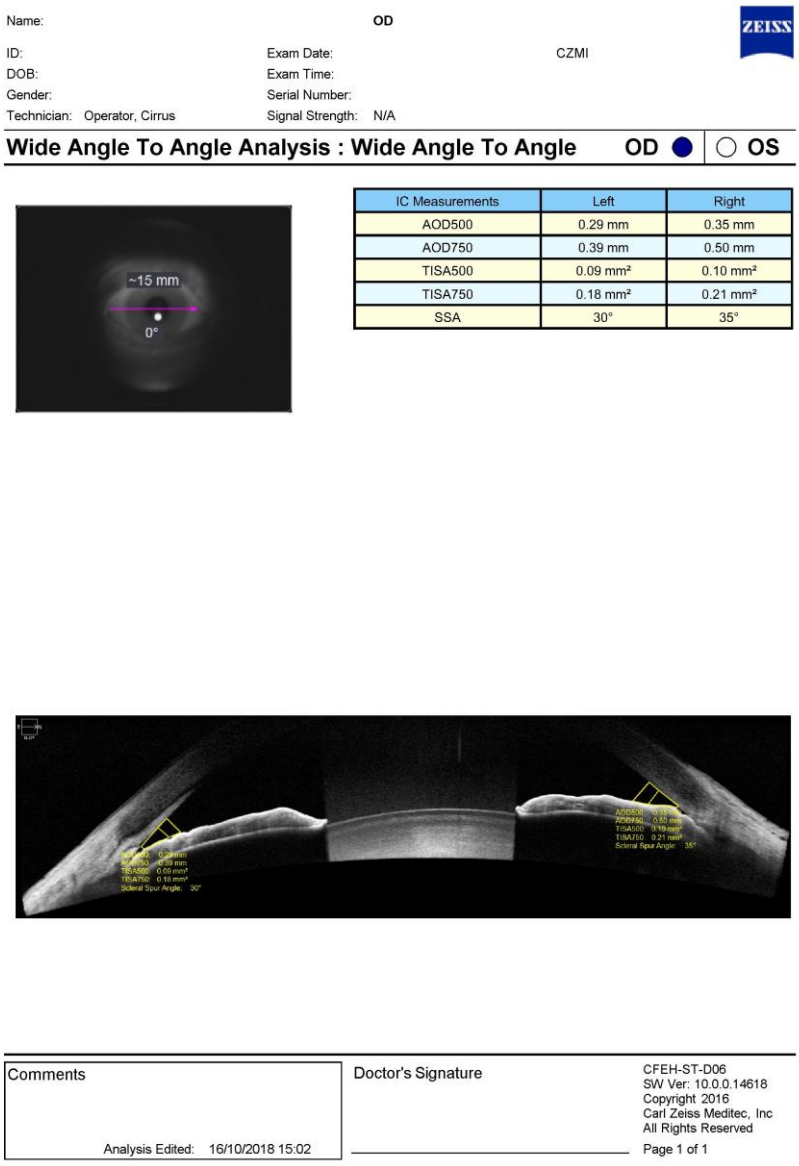
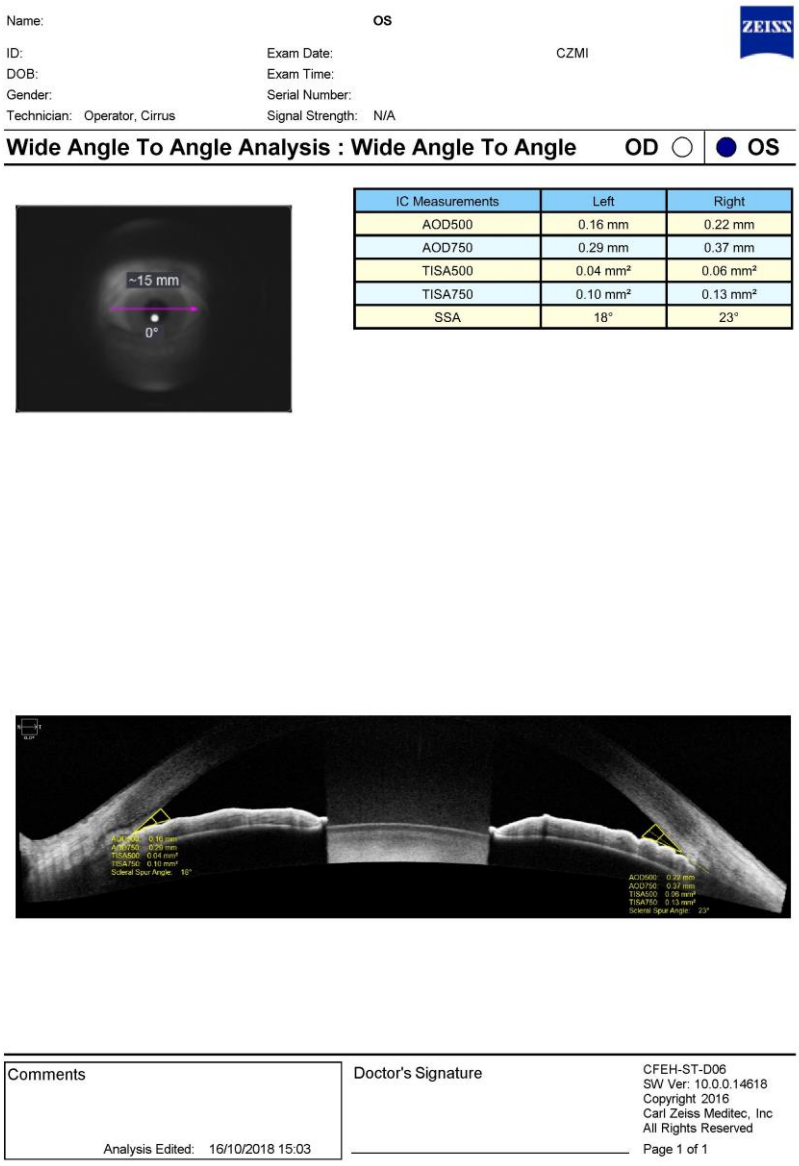


Figure 12: Anterior segment optical coherence tomography Wide Angle to Angle results for the right eye (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA). The areas of interest were manually segmented to generate the numerical outputs.



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927 **Figure 13:** Anterior segment optical coherence tomography Wide Angle to Angle results for the

928 left eye, as per Figure 12.

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Figure 14: High resolution anterior segment optical coherence tomography of the angles (1 ACA scan, Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) for the nasal and temporal angles of right and left eyes. Note that the higher resolution allows more confident visualisation of Schlemme's canal, the scleral spur and ciliary body, in comparison to Figures 10-13.

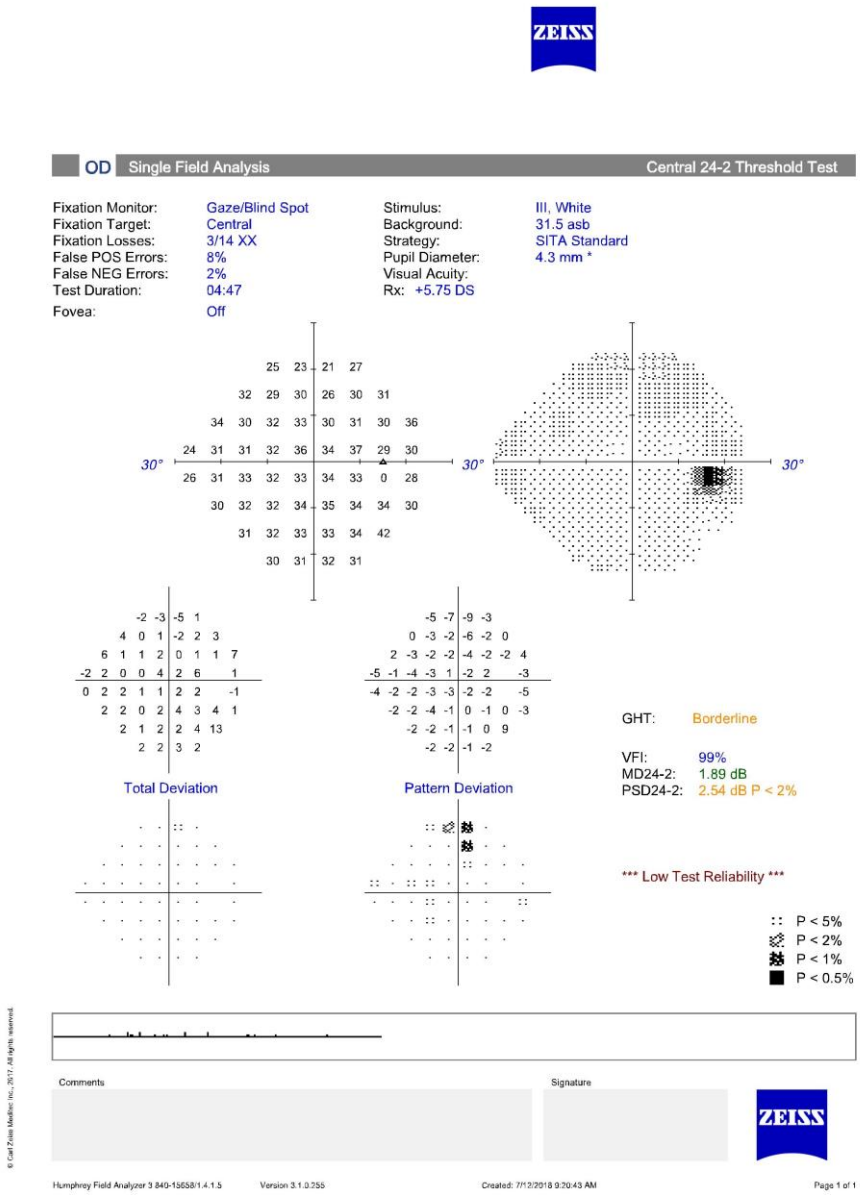

Figure 15: Standard automated perimetry results of the right eye (Humphrey Field Analyzer, 24-2 test grid, SITA-Standard; Carl Zeiss Meditec, Dublin, CA).

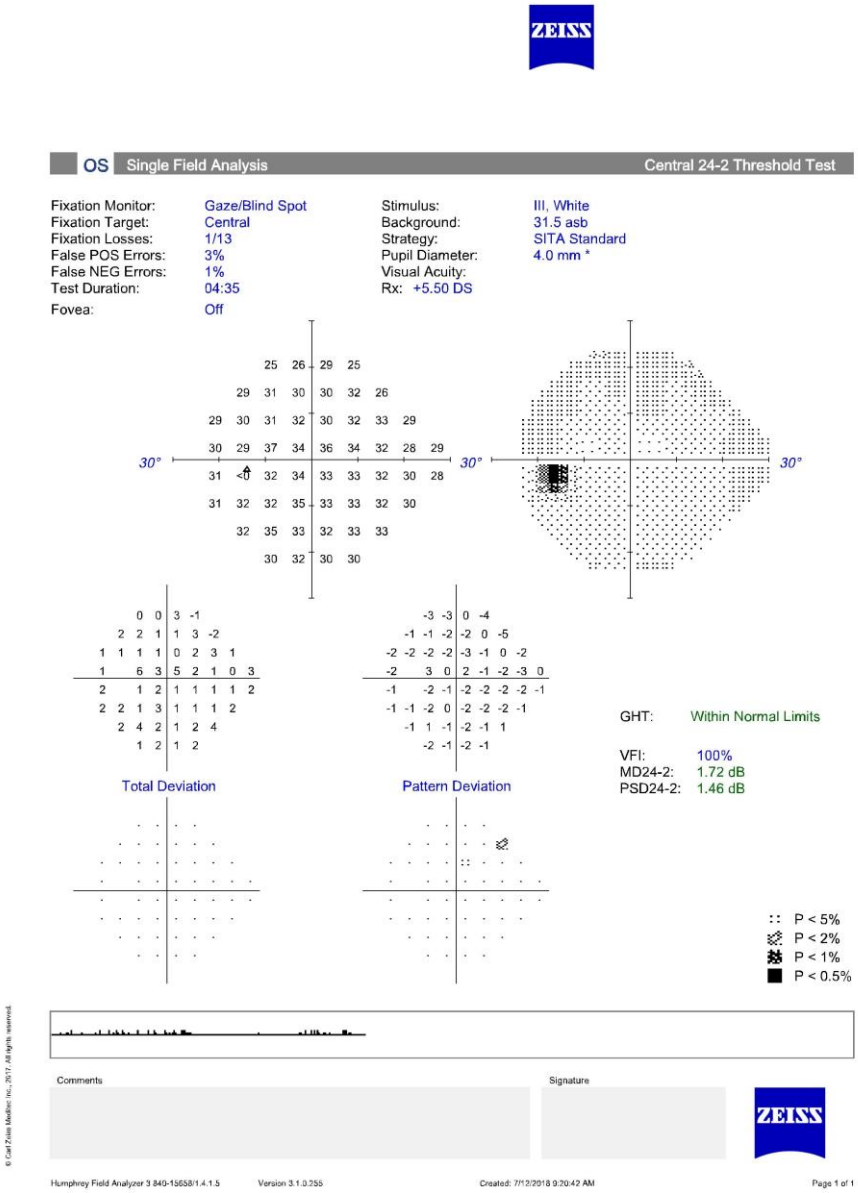

Figure 16: Standard automated perimetry results of the left eye, as per Figure 15.

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