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Title: Detection of glaucoma progression by perimetry and optic disc photography at different stages of the disease: results from the Early Manifest Glaucoma Trial.

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Abstract: **Purpose:** To compare the earliest detection of progression in visual fields and monoscopic optic disc photographs at different stages of manifest glaucoma.
Methods: This study evaluated 306 eyes in 249 patients with manifest open-angle glaucoma included in the Early Manifest Glaucoma Trial (EMGT). All patients in the trial were followed up regularly by standard automated perimetry and monoscopic optic disc photography, and the median follow-up time was 8 years. Progression was assessed in series of optic disc photographs and in series of visual fields using glaucoma change probability maps and the predefined EMGT progression criterion. The proportion of progressions detected first in visual fields and the proportion detected first in optic disc photographs were compared at different stages of glaucoma severity defined by the perimetric mean deviation (MD) of the baseline visual field.

Results: Assessment of 210 eyes with early visual field loss, 83 eyes with moderate field loss, and 13 eyes with advanced field loss showed that, among the eyes exhibiting progression, the progression was detected first in the visual field in 80%, 79% and 100%, respectively. The predominance of visual field progressions at all stages was still apparent when using narrower (3-dB) MD intervals for staging.
Conclusion: In the EMGT material on eyes with manifest open-angle glaucoma, the initial progression was detected much more often in the visual field series than in the optic disc photographs at all stages of disease.

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Detection of glaucoma progression by perimetry and optic disc photography at different stages of the disease: results from the Early Manifest Glaucoma Trial.

Purpose: To compare the earliest detection of progression in visual fields and monoscopic optic disc photographs at different stages of manifest glaucoma. Methods: This study evaluated 306 eyes in 249 patients with manifest open - angle glaucoma included in the Early Manifest Glaucoma Trial (EMGT). All patients in the trial were followed up regularly by standard automated perimetry and monoscopic optic disc photography, and the median follow - up time was 8 years. Progression was assessed in series of optic disc photographs and in series of visual fields using glaucoma change probability maps and the predefined EMGT progression criterion. The proportion of progressions detected first in visual fields and the proportion detected first in optic disc photographs were compared at different stages of glaucoma severity defined by the perimetric mean deviation (MD) of the baseline visual field. Results: Assessment of 210 eyes with early visual field loss, 83 eyes with moderate field loss, and 13 eyes with advanced field loss showed that, among the eyes exhibiting progression, the progression was detected first in the visual field in 80%, 79% and 100%, respectively. The predominance of visual field progressions at all stages was still apparent when using narrower (3 - dB) MD intervals for staging. Conclusion: In the EMGT material on eyes with manifest open - angle glaucoma, the initial progression was detected much more often in the visual field series than in the optic disc photographs at all stages of disease.

EMGT; glaucoma stage; open - angle glaucoma; optic disc; progression; visual field

It is currently widely assumed that structural progression precedes functional progression in glaucomatous eyes. However, available evidence is conflicting, indicating that structural progression occurs first in one subset of patients, and functional progression first in other subsets, and there is often surprisingly weak agreement between the two modalities in longitudinal studies (Miglior et al. [37] ; Kerrigan - Baumrind et al. [27] ; Artes & Chauhan [3] ; Anderson [2] ; Hood & Kardon [26] ; Gonzalez - Hernandez et al. [16] ; Harwerth et al. [20] ;

Leung et al. [30] ; Leite et al. [28] ; Malik et al. [32] ; De Moraes et al. [11] ; Banegas et al. [5] ; Raza & Hood [42]). The guidelines of the World Glaucoma Association and the European Glaucoma Society advocate regular monitoring of both structural and functional changes, particularly in patients with early glaucoma damage (Medeiros et al. [34] ; The European Glaucoma Society [46]). Nonetheless, when resources are limited, the question arises as to whether follow - up using both structural and functional methods are necessary at all stages of the disease. To the best of our knowledge, no longitudinal clinical studies have compared the value of following structural and functional progression at different stages of manifest glaucoma.

The Early Manifest Glaucoma Trial (EMGT) evaluated the effectiveness of reducing intraocular pressure (IOP) in previously untreated open - angle glaucoma (Leske et al. [29]). The EMGT results represent an unusual longitudinal material comprising regular and long - term prospective follow - up of both the visual field and the optic disc. Accordingly, the EMGT data are well suited for studying structural and functional progression at different stages of the disease spectrum. The aim of this study was to compare the earliest detection of glaucoma progression in series of visual fields and optic disc photographs at different stages of the disease.

Patients and Methods

Patients were recruited to the EMGT (National institutes of Health ClinicalTrials.gov identifier NTC00000132. Date of registration: September 23, 1999) primarily through a large population - based screening based on optic disc appearance and IOP performed between 1992 and 1997 (Leske et al. [29]). In all, 255 patients aged 50–79 years were included and randomized 1:1 to treatment with argon laser trabeculoplasty plus betaxolol 5 mg/ml B.I.D. (Betoptic®, Alcon, Fort Worth, TX, USA), or to no treatment. Having at least one eye with a reproducible glaucomatous visual field defect as determined by the glaucoma hemifield test (GHT) of the Humphrey perimeter (Carl Zeiss Meditec, Dublin, CA, USA) was required for eligibility, thus subjects could have one or both eyes included in the study. Patients with one or more of the following were not eligible: advanced visual field loss with mean deviation (MD) worse than −16 dB or threat to fixation; mean of all prestudy measurements of IOP >30 mmHg; any IOP measurement >35 mmHg in at least one eye. The patients that were included underwent follow - up every 3 months for the first 4 years. Visual fields were examined at each visit, whereas optic disc photography was performed every 6 months; with one additional photograph 3 months after baseline. After 4 years, a minority of patients were shifted to follow - up visits every 6 months, if deemed suitable by the treating ophthalmologist.

The present investigation was conducted according to the tenets of the Declaration of Helsinki and the patients provided informed consent. The study was approved by the Ethics Committee of the University of Lund (Sweden) and the Committee on Research Involving Human Subjects of the State University of New York at Stony Brook (USA).

Visual field progression was determined according to predetermined criteria. Tentative field progression was defined as three or more of the same test locations in glaucoma change probability maps showing statistically significant progression compared to baseline in two consecutive visual fields (Bengtsson et al. [6] ; Leske et al. [29]). If tentative progression occurred, the patient was scheduled for an additional visit 1 month later to confirm visual field progression in the same test locations. The date of the third of these visual fields was defined as the date of the visual field progression. The glaucoma change probability maps were based on the pattern deviation to eliminate effects caused by media opacities or cataracts. In our analyses, visual field progressions meeting these criteria were not considered to represent true glaucoma progression, if either of the following applied: the findings could be explained by other conditions or the same three or more test locations did not indicate sustained change in subsequent visual fields.

In the EMGT, fundus photography was performed through a dilated pupil using a modified 30° Zeiss fundus camera and Kodachrome 64 film until the technique was changed in 2005, and thus, up to 11 years of follow - up photographs were obtained with the same instrument. The photographs were digitized for this study. Baseline images were defined as photographs from the 3 - month visit, rather than those acquired at the prerandomization baseline visit, to avoid any possible changes in optic disc configuration caused by introducing pressure - lowering treatment (Tan & Hitchings [45] ; Prata et al. [41]). Fundus photographs obtained after 2005 were not used in our analysis, as this would have prevented masking of the temporal order of images.

The three disc readers (BB, AH, HMÖ) independently evaluated each optic disc to identify progression. The disc reading procedure is described in detail elsewhere (Öhnell et al. [39]). Briefly, the readers were masked to the temporal order of the photographs and all other patient data. Pairs of photographs from the 3 - month visit and the last available photographs were presented in random chronological order and were mixed with control pairs comprising two different photographs obtained at the same visit. Any progression that was detected in the pair analysis had to be sustained throughout the rest of the series when the three disc readers subsequently judged the whole series of the same eye unmasked for temporal order. The date when progression was first observed defined the date of optic disc progression. Complete sequences of fundus photographs for all eyes were also analysed by one of the readers (HMÖ) to rule out that any additional progressions could be detected in this manner. Disagreement between the readers was settled through consensus.

The disc reading was performed in a dimly lit room using high - quality computer screens that could magnify photographs to the desired size. Progression was determined as changes in the course of vessels on the optic disc surface or visible changes in the disc rim configuration (e.g. evident increased notching). Changes in pallor or peripapillary atrophy were not considered as evidence of progression nor were the occurrence of optic disc haemorrhages. Our group (Öhnell et al. [39]) has published a random sample of a dozen optic discs deemed to have progressed to illustrate the magnitude of changes required to classify a disc as progressing.

The glaucoma stage at baseline was determined by visual field status. Primarily, we used the perimetric MD intervals presented in the Hodapp–Parrish–Anderson Glaucoma Grading Scale (GGS) (Hodapp et al. [25]). The studied eyes were categorized as having early field loss (MD ≥ −6 dB), moderate field loss (−12 dB ≤ MD < −6 dB) or advanced field loss (−20 dB ≤MD < −12 dB). In reality, the group with advanced field loss only included eyes with MD values down to −16 dB, which was the lower limit for eligibility in the EMGT. In as much as this acknowledged GGS is rather crude, with wide intervals for MD, and also considering that the EMGT mainly included eyes with early - to - moderate field loss, we performed a subanalysis using finer grading of MD in 3 - dB intervals.

Statistical analysis

Inter - rater agreement among the disc readers was calculated using the arithmetic mean of Cohen's kappa values and prevalence - and bias - adjusted kappa (PABAK) values. (Light [31] ; Byrt et al. [7] ; Hallgren [17]). The percentage distribution between structural and functional progression was determined in each of the subgroups according to the Hodapp–Parrish–Anderson GGS and the narrower MD - groups in 3 - dB intervals. Cumulative incidence functions (Marubini & Valsecchi [33]) were computed for the different GGS stages. Competing events were optic disc progression first, visual field progression first and death occurring within 6 months from the last follow - up visit. In the early and moderate glaucoma groups, confidence intervals for the various cumulative incidences at 96 months (median follow - up time) were determined using a bootstrap technique with 1000 repetitions and patient as cluster, as some patients provided both eyes as study eyes

(Efron & Tibshirani [12]). For eyes in which progression had occurred, we also calculated the conditional probability that optic disc progression or visual field progression occurred first. In the early and moderate glaucoma groups, robust 95% confidence intervals were determined using patient as cluster variable (Williams [49]). In the advanced glaucoma group, all patients contributed one eye each, and hence, standard confidence intervals were used for both cumulative incidences and conditional probabilities. Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp. released 2013. ibm statistics for Macintosh, version 22.0. Armonk, NY: IBM Corp.) and stata (StataCorp. 2015. stata: Release 14. Statistical software. College Station, TX: StataCorp LP.)

Results

The 255 patients included in the EMGT had a median age of 68 years at baseline, and 66% were female. In our study, nine eligible eyes in six patients had to be excluded because the follow - up was too short to allow detection of any progression (i.e. fewer than two fundus photographs or three visual fields were available after baseline). Thus, 306 eyes in 249 patients remained for our analyses, and both eyes were investigated in 57 of the patients. The median follow - up time was 96 months (8 years), with a minimum of 9 months and a maximum of 132 months.

At baseline, glaucoma was early in 210 eyes, moderate in 83 eyes and advanced in 13 eyes according to the GGS. The median MD values for the three groups were −2.96 dB, −7.96 dB and −13.44 dB, respectively. Corresponding mean IOP values at 3 months were 17, 17 and 18 mmHg.

In our assessments, three of the studied eyes that fulfilled the EMGT visual field progression criterion were classified as having no glaucomatous field progression: one of those eyes developed haemianopia during follow - up, and the progression initially identified in the other two eyes was not sustained during the rest of the visual field series. The inter - rater reliability for the three disc readers gave an arithmetic mean of Cohen's kappa of 0.500, and the arithmetic mean of the PABAK was 0.634, representing substantial agreement. None of the control pairs were erroneously rated as 'progression' by the disc readers. In 222 eyes, all three disc readers agreed on the existence of progression or not after individual classifications. Consensus was reached for the remaining 84 eyes.

Visual field progression was detected first about four times more often than optic disc progression in both the group with early and the group with moderate defects (Table [NaN] and Fig. [NaN]). All progressions were detected first in the visual field in the group with advanced defects, but this group included considerably fewer eyes than the other two groups. The conditional probability that the first type of progression would be detected in the visual field, given that any type of progression occurred, was 80% [robust 95% confidence interval (CI) 72%–86%] in the early damage group, 79% (robust 95% CI: 67%–88%) in the moderate group and 100% (one - sided 97.5% CI: 63%–100%) in the advanced group. After 96 months of follow - up, the cumulative incidence of visual field progression occurring first was found to be 53% (95% CI: 46%–60%), 55% (95% CI: 43%–67%) and 67% (95% CI: 34%–86%) for the three groups, respectively (Fig. [NaN] A–C). During the same month, the corresponding values for optic disc progression occurring first were 12% (95% CI: 8%–17%), 14% (95% CI: 7%–22%) and 0%.

Type of progression detected first depending on glaucoma stage

	Visual field progression first n (%)	Optic disc progression first n (%)	Simultaneous progression n (%)	No progression n (%)	Total
MD ≥ −6 dB	109 (52)	27 (13)	1 (0)	73 (35)	210

−12 dB ≤MD < −6 dB	46 (55)	12 (14)	0 (0)	25 (30)	83
−16 dB ≤ MD < −12 dB	8 (62)	0 (0)	0 (0)	5 (38)	13
Total	163 (53)	39 (13)	1 (0)	103 (34)	306

Repeating the same calculations using the narrower 3 - dB MD intervals yielded a similar proportion of progressions detected by structural and functional methods in the four groups where MD values ranged from normal to −12 dB, with markedly more extensive detection of visual field progression before optic disc progression. Likewise, none of the eyes in the group with MD worse than −12 dB showed optic disc progression first (Fig. [NaN]).

Discussion

Visual field progression prior to optic disc progression appeared to have occurred considerably more often than optic disc progression prior to visual field progression, and this was noted at all stages of glaucoma, and possibly even more frequently in advanced glaucoma. Though, the number of eyes with advanced glaucoma in the EMGT was few. Nevertheless, we could not confirm the assumption that structural progression precedes functional progression in glaucomatous eyes.

The present results on optic disc progressions differ from those published in the first EMGT report 227(Heijl et al. [23]), which were obtained at an optic disc reading centre by flicker chronoscopy of disc photographs. During the EMGT, it became clear that visual fields had a greater impact on the outcome of evaluations, and hence, the Data Safety and Monitoring Committee closed the EMGT's optic disc reading centre in 2002. In the current investigation, we reanalysed all series of digitized monoscopic fundus photographs in a masked fashion and strived to achieve high sensitivity. We also used a longer follow - up time and detected considerably more optic disc progressions than in our earlier report (Heijl et al. [23]).

A strength of the present study is that it used material from the EMGT, which was a randomized, prospective, screening - based trial that had long follow - up time and hence provided unique regular documentation of both the visual fields and the optic discs. Fundus photographs were collected every 6 months and visual fields every 3 months. As we had such long follow - up, it was possible to maintain also high specificity, by requesting that progression detected in any of the modalities could be confirmed to persist during the follow - up, except if progression was noted at the very end of follow - up. Non - sustained progression was not considered true glaucoma progression. The visual field criterion in EMGT has earlier been demonstrated to show a high specificity (Heijl et al. [24] ; Artes et al. [4]), and also in the present study, only three patients were found to be false positives during follow - up and not considered true progression. That none of the control discs were erroneously marked as 'progression' is also a measure of specificity.

We used the EMGT criteria for visual field progression, where the date of progression is set at the third of the visual fields determining progression, mostly 4 months after the first of the three visual fields. In contrast, the first optic disc photograph where we could detect optic disc progression was used as the date of progression. This would even out the disparity in time intervals for the different modalities, and for simultaneous progressions; it would represent a slight advantage for detection of progression in the optic disc. Treatment was generally initiated or changed after the first progression was detected, and therefore, any possible subsequent progression in the other modality could theoretically be delayed. Consequently, only the first type of progression detected was taken into consideration in our analyses.

A weakness of our study is that we used monoscopic fundus photographs, while stereoscopic fundus photographs are often regarded as the preferred method for assessing the status of the optic disc. However, monoscopic fundus photographs were used in EMGT, and they are also commonly employed in clinical practice, although in that context they are seldom subjected to such rigorous analysis as in the present study.

Earlier reports have not found any substantial difference in the ability of monoscopic versus stereoscopic photographs to determine the diagnosis of glaucoma (Varma et al. [47] ; Chan et al. [8]), but longitudinal comparisons in detecting progression is lacking. It would have been interesting to compare visual field progression with that identified by modern imaging techniques using built - in interpretation tools. However, such methods were not available when the EMGT was initiated, and results thus far have been conflicting regarding the ability of those techniques to predict visual field loss (Chauhan et al. [9] , [10] ; Mohammadi et al. [38] ; Artes & Chauhan [3] ; Strouthidis et al. [44] ; Heeg & Jansonius [21] ; Weinreb et al. [48] ; Leung et al. [30] ; Medeiros et al. [36] ; Schrems - Hoesl et al. [43]).

To the best of our knowledge, this is the first longitudinal clinical report to describe the structure–function relationship in different stages of manifest glaucoma. Only a few studies have assessed the structure–function relationship longitudinally in patients with manifest glaucoma and the results have been inconsistent. For example, (Chauhan et al. [9] , [10]) showed that structural progression occurred first more often, whereas Miglior et al. ([37]) found substantially more functional progression in eyes with glaucoma. De Moraes et al. ([11]) reported slightly more visual field progressions among their glaucoma cases retrospectively.

The findings of different investigations regarding the detection of structural and functional progressions depend on the methods used to detect structural and functional changes, as well as the stage of glaucomatous disease in the study population and the follow - up time. The effect of choice of method used to detect progression is demonstrated by the fact that even for different structural methods, the correlation is rather poor (O'Leary et al. [40] ; Banegas et al. [5]). The studies conducted by Kerrigan - Baumrind et al. ([27]) and Harwerth et al. [18] ; Harwerth et al. ([19]) are frequently cited as supporting the assertion that structural progression precedes functional progression. Notwithstanding, as has previously been pointed out by other authors, (Hood & Kardon [26] ; Malik et al. [32]) the mentioned investigations do not fully support this claim, because there is very large variability in the visual field loss noted at different levels of measured loss of retinal ganglion cells. In contrast, Raza & Hood ([42]) concluded that statistically significant retinal ganglion cell loss did not occur more often than statistically significant visual field loss among preperimetric and early glaucoma cases. The curvilinear relationship that has been suggested (Harwerth et al. [18] ; Leite et al. [28] ; Medeiros et al. [35] ; Alasil et al. [1]) is likely a result of the logarithmic scaling of the visual field, as described by Garway - Heath et al. ([14] , [15]); Garway - Heath ([13]) and Leite et al. ([28]) The studies advocating a curvilinear relationship have compared logarithmic visual field loss of the entire field or sectors of the field with different measures of structural deterioration. Instead, we used glaucoma change probability maps in which certain points show significant deterioration, often in the vicinity of earlier field loss. This ability to detect progression in previously less affected points in the visual field is not as dependent on the degree of earlier damage in other areas of the visual field (Heijl et al. [22]), which might explain why functional progression was detected essentially equal often throughout different stages of manifest glaucoma in our study. Still, comparing with our earlier published results showing an equal ability to detect progression with monoscopic optic disc photographs and automated perimetry in eyes with preperimetric glaucoma (Öhnell et al. [39]), it is somewhat surprising that we could not detect a higher proportion of optic disc progressions during earlier stages of manifest glaucoma, with a gradual increase of perimetric progression through more advanced stages of the disease.

In conclusion, our evaluation of series of visual fields and optic disc photographs of eyes in the EMGT with early - to - moderate field loss showed that progression occurred first in the visual field more often than in the optic disc, regardless of the stage of the disease.

Footnotes

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Graph: Percentage distribution of visual field progression and optic disc progression occurring first in the different Glaucoma Grading Scale groups. Visual field progression occurred first much more frequently than optic disc progression in all groups.

Graph: Cumulative incidence functions for eyes with early (A), moderate (B) and advanced (C) field loss at inclusion in the Early Manifest Glaucoma Trial. The graphs show cumulative incidences for the competing events; visual field progression first, optic disc progression first and death first occurring within 6 months from the last follow - up visit.

Graph: Percentage distribution of visual field progression and optic disc progression occurring first in eyes categorized according to MD at baseline in 3 - dB intervals. The relationship between structural and functional progressions was similar in all groups. In the first group (MD values better than −3 dB), 17% of eyes showed optic disc progression first and 44% showed visual field progression first. Corresponding rates for the other four groups were as follows: 9% versus 60%, 16% versus 53%, 12% versus 60% and 0% versus 62%.

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By HannaMaria Öhnell; Anders Heijl; Harald Anderson and Boel Bengtsson

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Title: A collaborative care pathway for patients with suspected angle closure glaucoma spectrum disease.

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Abstract: Background: Currently, no specific collaborative care pathway exists that distinguishes open angle glaucoma from narrow angle or angle closure disease. This study evaluates a newly developed referral and collaborative care pathway specifically for patients with angle closure spectrum disease.Methods: The medical records of consecutive patients referred to the Centre for Eye Health for glaucoma assessment were examined, six months before (Pre Suite) and after (Post Suite) the introduction of a novel referral pathway for anterior chamber angle assessment (Angle Suite). Patient demographic and clinical data, the referral letter and practitioner characteristics were extracted.Results: Angle Suite (n = 77) patients had an appointment much sooner compared to Pre (n = 383) and Post Suite (n = 425) patients (p < 0.0001). Following the introduction of Angle Suites, there was a reduction of incidental angle closure disease found in routine, non-angle closure glaucoma assessment. Onward referral was required by 36.4 per cent of patients referred for suspected angle closure disease, while the rest could be discharged back into the community (13.0 per cent) or reviewed at the Centre for Eye Health (50.6 per cent). Multinomial logistic regression found that the presence of an angle description in the referral letter improved the true positive rate for angle closure disease (p < 0.0001).Conclusions: The clinical pathway may reduce the number of incidental angle closure patients and improved the timeliness of appropriate clinical care delivered to a subset of patients who may benefit from prompt medical attention. This pathway provides an opportunity for appropriately staffed and equipped collaborative care clinics to reduce the burden on tertiary level ophthalmic facilities.

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A collaborative care pathway for patients with suspected angle closure glaucoma spectrum disease

Background: Currently, no specific collaborative care pathway exists that distinguishes open angle glaucoma from narrow angle or angle closure disease. This study evaluates a newly developed referral and collaborative care pathway specifically for patients with angle closure spectrum disease. Methods: The medical records of consecutive patients referred to the Centre for Eye Health for glaucoma assessment were examined, six months before (Pre Suite) and after (Post Suite) the introduction of a novel referral pathway for anterior chamber angle assessment (Angle Suite). Patient demographic and clinical data, the referral letter and practitioner characteristics were extracted. Results: Angle Suite (n = 77) patients had an appointment much sooner compared to Pre (n = 383) and Post Suite (n = 425) patients (p < 0.0001). Following the introduction of Angle Suites, there was a reduction of incidental angle closure disease found in routine, non-angle closure glaucoma assessment. Onward referral was required by 36.4 per cent of patients referred for suspected angle closure disease, while the rest could be discharged back into the community (13.0 per cent) or reviewed at the Centre for Eye Health (50.6 per cent). Multinomial logistic regression found that the presence of an angle description in the referral letter improved the true positive rate for angle closure disease (p < 0.0001). Conclusions: The clinical pathway may reduce the number of incidental angle closure patients and improved the timeliness of appropriate clinical care delivered to a subset of patients who may benefit from prompt medical attention. This pathway provides an opportunity for appropriately staffed and equipped collaborative care clinics to reduce the burden on tertiary level ophthalmic facilities.

Keywords: collaborative care; eye care; glaucoma; gonioscopy; narrow angles; referral refinement

Glaucoma is the second leading cause of irreversible blindness worldwide.[1] A key parameter of the glaucoma workup is assessment of anterior chamber angle geometry, used to divide glaucoma into the open-angle and closed-angle forms.[2] Although open-angle glaucoma is the most common form in many parts of the world, angle closure glaucoma has a higher prevalence in certain populations (Asia accounts for over 50 per cent of total angle closure glaucoma cases, with its prevalence generally twice as high as other regions) and its manifestations can be more visually devastating in some patients.[3] Case detection of either form of glaucoma is typically opportunistic within primary eye care, with early detection and effective treatment critical to preserve visual function and quality of life.

The increase in prevalence of glaucoma, as a consequence of an increasing ageing population, will continue to place a burden on health-care systems, particularly where patients with poorly defined risk factors are referred to an ophthalmologist for diagnosis and management.[4] Collaborative care models in which primary care optometrists deliver diagnostic and treatment services may assist in alleviating the stress upon the relative shortage of ophthalmology services, by specifically reducing the incidence of false positive referrals to ophthalmologists and improving the maintenance of appropriate clinical follow-up for glaucoma suspect patients.[[5], [7], [9]] In doing so, ophthalmology services can be directed to the treatment of specific patients with glaucoma, address other demands for specialised eye care, and may ultimately represent cost savings to the health-care system.[[10]]

One specific question regarding collaborative care pathways for patients suspected of having glaucoma is the difference between referrals for open angle and angle closure spectrum disease. Excluding patients with symptomatic acute angle closure, patients with narrowing of the angle or intermittent/chronic forms of angle closure may present a challenge for clinical triage staff, particularly given the importance of preventing an acute attack of glaucoma and identification of visually devastating chronic forms of angle closure.[12]

Current clinical guidelines are not clear on the time frame for patients to be seen for narrow angles, especially with respect to early stages of the spectrum.[[13], [15]] Patients with narrowing of the angles may or may not require intervention based on the degree of angle narrowing and other associated findings such as historical risk factors and fellow eye findings.[[16]] Addressing this question can potentially optimise patient eye-care pathways with appropriate triaging of these patients, improving the final clinical outcome.

The purpose of the present study was to investigate the efficacy of a newly developed and activated pathway – the Angle Suite – in triaging and managing patients with suspected angle closure spectrum disease. Referral letter content, clinical findings and final outcomes for patients referred to the Centre for Eye Health (CFEH) before and after the implementation of the Angle Suite were assessed, and were compared to an existing glaucoma referral pathway (Glaucoma Suite). The hypothesis was that the implementation of the Angle Suite would shorten times to appointment, assessment and reporting for patients with angle anomalies, resulting in a more appropriate time period between the initial suspected diagnosis and ophthalmological care.

Methods

The medical records of patients attending CFEH between August 2017 and August 2018 were reviewed. The inclusion criteria for this study included the patient being 18 years or older, referred for glaucoma assessment, having completed a full glaucoma assessment at CFEH, and provided written informed consent for their de-identified records to be used for research purposes. Exclusion criteria included: patients who had not provided consent, patients who had an incomplete examination or patients in whom the record could not be read (for example an incomplete or illegible referral letter).

The study adhered to the Declaration of Helsinki and ethics approval was provided by the Human Research Ethics Committee of the University of New South Wales.

CFEH clinical protocols

CFEH is an intermediate-tier, referral-only eye clinic to which patients from the general community are referred for diagnosis and treatment.[6] The typical workflow for patients referred to CFEH begins with a referral from an external practitioner, typically a community optometrist. This letter is triaged by a CFEH optometrist and the patient is then seen in the CFEH clinic by a staff optometrist.

Clinical examination findings are compiled into an overall report with a diagnosis and recommended management (Figure S1). Another senior optometrist within CFEH or an ophthalmologist from the local health district countersigns this report. CFEH is staffed by multiple optometrists, but all follow the same diagnostic criteria and clinical examination protocols. Similarly, reviewing ophthalmologists follow the same diagnostic and management protocol agreed upon by CFEH and the Prince of Wales Hospital Ophthalmology Department. Although subtle inter-examiner differences could be possible, they were minimised through strictly defined protocols. The management recommendations are based on current clinical guidelines for eye care in Australia followed by optometrists and ophthalmologists.[[2], [4], [14]]

Services offered by CFEH have been explained elsewhere.[[5], [18]] Within a Glaucoma Suite, a battery of glaucoma-related tests (Table) are performed for the patient, and a final diagnosis and recommended management are provided. For the purpose of this study, the files of patients who had received an initial referral for a Glaucoma Suite were extracted.

Comparison of clinical tests performed as per standard protocol for Glaucoma Suites and Angle Suites

Glaucoma Suites	Angle Suites
Visual acuities	Visual acuities
Standard automated perimetry (Humphrey Field Analyzer 24-2 SITA-Standard [Carl Zeiss Meditec, Dublin, CA, USA])	Standard automated perimetry (Humphrey Field Analyzer 24-2 SITA-Standard [Carl Zeiss Meditec, Dublin, CA, USA])
Pupil reflexes	Pupil reflexes
Slitlamp biomicroscopy	Slitlamp biomicroscopy
Applanation tonometry	Applanation tonometry
Gonioscopy (Goldmann 3-mirror, G4 or Sussman [Volk Optical, Mentor, OH, USA])	Gonioscopy (Goldmann 3-mirror, G4 or Sussman [Volk Optical, Mentor, OH, USA]); gonioscopy photography
	Indentation gonioscopy
Pachymetry (Pachmate DGH55 [DGH Technology, Inc, Exton, PA, USA]; or Pentacam HR [Oculus, Wetzlar, Germany])	Pachymetry (Pentacam HR [Oculus, Wetzlar, Germany])
	Anterior chamber depth and volume (Pentacam HR [Oculus, Wetzlar, Germany])
	Axial length (IOL Master [Carl Zeiss Meditec, Dublin, CA, USA])
	Ultrasound biomicroscopy (Reflex Ultrasound Biomicroscope [Reichert Technologies, Depew, NY, USA])
Dilated fundus examination (tropicamide 0.5%)	Undilated fundus examination
Fundus photograph (central 45°, stereoscopic optic nerve head [Kowa nonmyd 7; Kowa Medical, Sendai, Japan])	Fundus photograph (central 45°, stereoscopic optic nerve head [Kowa nonmyd 7; Kowa Medical, Sendai, Japan])
Optical coherence tomography (Cirrus Optic Nerve Head/Retinal Nerve Fibre Layer, Ganglion Cell Analysis [Carl Zeiss Meditec, Dublin, CA, USA])	Optical coherence tomography (Cirrus: Optic Nerve Head/Retinal Nerve Fibre Layer, Ganglion Cell Analysis, Anterior Chamber Volume, Wide Angle-to-Angle [Carl Zeiss Meditec, Dublin, CA, USA]; Spectralis: Anterior Chamber Angle [Heidelberg Engineering, Heidelberg, Germany])

1 † Performed as required.

The Angle Suite protocol (Table) was developed to specifically provide a comprehensive examination of the anterior chamber angle. In addition to routine gonioscopy, the Angle Suite included more detailed angle-related assessments and a standardised protocol for goniophotography. While gonioscopy is the current gold standard for anterior chamber angle assessment, several anterior segment imaging modalities that do not rely on device contact with the eye are clinically useful, each with their own strengths and limitations.[[20]]

In both Glaucoma Suites and Angle Suites, referring clinicians are required to fully complete a template referral form and indicate that glaucoma testing is requested. The Angle Suite additionally requires a description of a suspected narrowed or closed angle. Referrals are reviewed and triaged by an experienced optometrist working at CFEH. For all Glaucoma Suite referrals, patients are given the next available non-urgent appointment, while for all Angle Suite referrals, appointments are made within two weeks (sooner if intraocular pressures are reported to be 21 mmHg or greater).

Diagnosis of angle closure spectrum disease

Angle closure spectrum disease refers to a range of potential presentations of progressively narrowing anterior chamber angles with endpoints including occlusion of the angle and consequent damage to the optic nerve and visual field. CFEH protocols have adapted the grading methods suggested by Thomas and Walland[2] and the International Society for Geographical and Epidemiological Ophthalmology.[22] The grades for angle closure spectrum disease used in the present study are as

follows: open angles, narrow but non-occludable angles (non-visibility of the posterior trabecular meshwork in < 180°), narrow and potentially occludable angles (180–270° of posterior trabecular meshwork not visible), primary angle closure suspect (PACS; ≥ 270° of posterior trabecular meshwork not visible without elevated intraocular pressure, peripheral anterior synechiae or glaucomatous damage), primary angle closure (PAC; PACS plus elevated intraocular pressure and/or peripheral anterior synechiae present), primary angle closure glaucoma (PACG; PAC plus glaucomatous damage at the optic disc and/or visual field). Cases where secondary causes of angle closure were observed were termed secondary angle closure.

The diagnosis of angle closure spectrum disease as per the above grading system was fully made using gonioscopy performed by the examining clinician, with agreement by an ophthalmologist. This is because anterior segment imaging devices, although supplementary, do not provide information for grading the degree of closure. Management recommendations were commensurate with the diagnosis: open angles were discharged back to the community practitioner; narrow and non-occludable angles were reviewed at CFEH; and narrow and potentially occludable or worse angles had a recommendation of onward referral to an ophthalmologist for management.

Data extraction

Demographic, logistical and clinical data from the patients meeting the inclusion criteria were extracted. Demographic data included gender, age, ethnicity and residential postcode. Logistical data included: information from the referral letter (date of referral and referral letter content), referring clinician information (date of first optometric registration and therapeutic qualification[23]), time to referral review, time to appointment, time to report writing and time to report transmission. Clinical data of interest included the final diagnosis and recommended management (discharge to the practice of the referring clinician, review at CFEH or referral to an ophthalmologist).

The Angle Suite referral pathway was introduced on 12 February 2018, with the first appointment on 2 March 2018. Prior to this, all glaucoma-related referrals were treated similarly for triaging purposes. Thus, patients attending CFEH for the first time for a Glaucoma Suite prior to March 2018 (August 2017 to February 2018: six months) were extracted and referred to as the Pre Suites group, before the introduction of the Angle Suite. Patients seen between March and August 2018 constituted a group following the introduction of the Angle Suite, who were referred for an Angle Suite or a traditional Glaucoma Suite (referred to as the Angle Suite and Post Suite groups, respectively).

Statistical analysis

Statistical analysis was carried out using GraphPad Prism version 7 (GraphPad, La Jolla, CA, USA). Descriptive statistics were used to analyse the scalar data and the chi-squared test was used to compare the proportion data. $P < 0.05$ was considered statistically significant for pairwise comparisons between Pre Suite and Post Suite groups, and a $p < 0.002$ was considered to be statistically significant when accounting for multiple comparisons between three groups.

For determining the effect of referral letter characteristics on a final diagnosis of angle closure spectrum disease, a multinomial logistic regression analysis using SPSS Statistics v25 (IBM Corporation, Armonk, NY, USA) was conducted. Angle status was binarised as the dependent variable, with therapeutic endorsement status of the referrer, referral letter content (whether or not angles were described) and concordance between angle description and diagnosis, tested as predictors of the model.

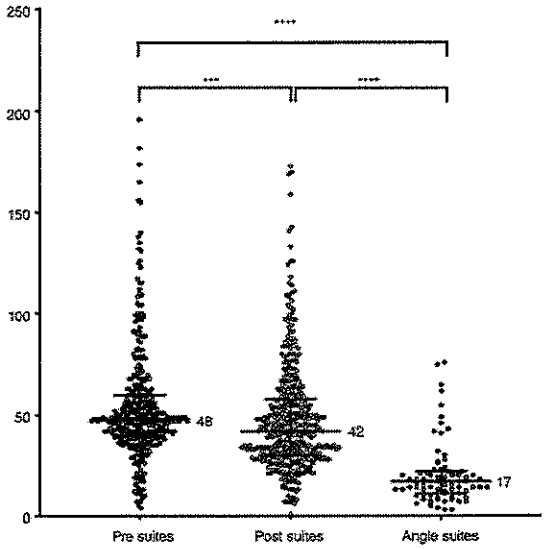
Results

During the study period, there were 383 eligible patients in the Pre Suite group, 425 in the Post Suite group and 77 in the Angle Suite group (Table). Angle Suite patients had a significantly shorter amount of time to appointment compared to both Pre Suite and Post Suite groups ($p < 0.0001$) (Figure and Figure S1). Post Suites also had a slightly shorter time to appointment compared to Pre Suites ($p = 0.0002$). A similar tendency to report time was found. A number of outlier data points contributed to the upwards skew of the times to appointment and report, as some patients deferred their appointments due to personal reasons.

Patient demographic characteristics

	Pre Suites (n = 383)	Post Suites (n = 425)	Angle Suites (n = 77)
Age, years, mean (SD)	54.6 (13.2)	54.8 (13.6)	59.2 (12.0)
Gender, male:female, n	176:207	210:215	37:40
Ethnicity, n (%)			
Caucasian	180 (47.0%)	235 (55.3%)	44 (57.1%)
East Asian	150 (39.2%)	120 (28.2%)	22 (28.6%)
Indian or Pakistani	26 (6.8%)	34 (8.0%)	10 (13.0%)
Aboriginal or Pacific Islander	10 (2.6%)	7 (1.6%)	1 (1.3%)
Hispanic	12 (3.1%)	10 (2.4%)	0 (0%)
African	1 (0.3%)	5 (1.2%)	0 (0%)
Other/mixed	4 (1.0%)	14 (3.3%)	0 (0%)
Residential distance, km, median (interquartile range)	17.7 (8.1–31.2)	19.9 (8.1–29.7)	17.8 (8.1–32.7)

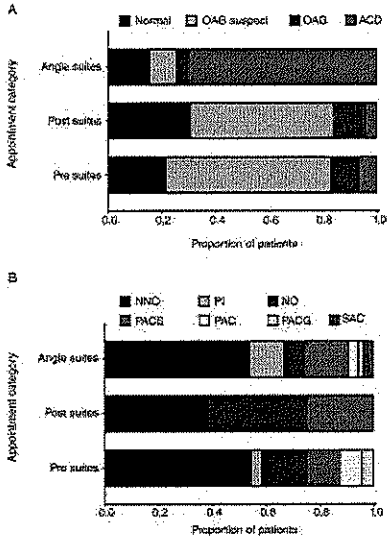
- 2 † Kruskal-Wallis test showed that the Angle Suite patients were significantly older than both Pre Suite and Post Suite patients ($H(3) = 9.701$, $p = 0.0078$).
- 3 ‡ No difference between groups, $\chi^2 = 0.9681$, $p = 0.6163$.
- 4 § There was a significance difference in ethnic distributions between groups $\chi^2 = 27.57$, $p = 0.0064$.
- 5 ¶ Kruskal-Wallis test showed no significant difference between groups ($H(3) = 0.1454$, $p = 0.9299$).



*Time (days) for each appointment to the appointment-made step from the time of referral receipt. Horizontal lines indicate median and interquartile range, and the median value has also been included on the right-hand side of the line for the corresponding group. The asterisks indicate the level of statistical significance (***p < 0.001; ****p < 0.0001).*

Number of patients with angle closure spectrum disease

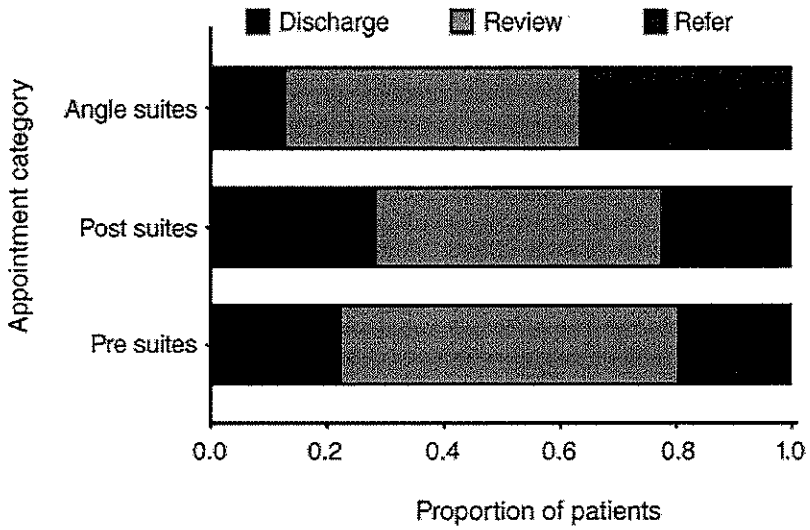
The final diagnoses for the patients in each group were divided into: normal (no evidence of glaucomatous disease), open angle glaucoma suspect (suspicious signs but insufficient for a diagnosis of glaucoma), open angle glaucoma and angle closure spectrum disease (Figure A). Due to the nature of the clinic, there were significantly more patients in the Angle Suite group diagnosed with angle closure disease. The Post Suite cohort had an approximately one-third reduction in angle closure disease diagnosis in comparison to the Pre Suite cohort (6.6 per cent versus 4.0 per cent, but this was not statistically significant, $\chi^2 = 2.432$, $p = 0.1189$).



A: Proportion of patients sorted into final diagnostic group for patients of each appointment category (n: Angle Suite, 77; Post Suite, 425; Pre Suite, 383). ACD: angle closure disease. OAG: open angle glaucoma. B: Distribution of subtypes of angle closure disease within the relevant patients for each appointment category (n: Angle Suite, 54; Post Suite, 16; Pre Suite, 24). NNO: narrow and non-occludable, NO: narrow and occludable, PAC: primary angle closure, PACG: primary angle closure glaucoma, PACS: primary angle closure suspect, PI: plateau iris, SAC: secondary angle closure.

Most patients with diagnosed angle closure spectrum disease did not require ophthalmological intervention in the Pre Suite (58.3 per cent) and Angle Suite groups (66.7 per cent), as did many of the Post Suite patients (37.5 per cent) (Figure B). Only a small percentage of patients had a stage of angle closure disease that required prompt intervention in the Pre Suite (13.6 per cent) and Angle Suite groups (9.3 per cent). No patient in the Post Suite group required urgent referral.

More patients required referral in the Angle Suite group compared to the Pre Suite and Post Suite groups ($\chi^2 = 9.744$, $p = 0.0077$) (Figure). Approximately two-thirds of patients did not require onward referral and could be either discharged back to community optometry care or monitored in a co-management setting. When considering all patients with a diagnosis of angle closure disease who required onward referral, Angle Suite patients (n = 22) had a much shorter time to appointment based on the information provided in the referral (median: 16.5 days, interquartile range [IQR]: 11.5–20.5 days) compared to both Pre Suite (n = 12; median: 44.5 days; IQR: 25.8–58.8 days; p = 0.0010) and Post Suite groups (n = 16; median: 34.5 days; IQR: 26.3–56.0 days; p = 0.0003).



Distribution of final recommended management plan for all patients for each appointment category (n: Angle Suite, 77; Post Suite, 425; Pre Suite, 383)

Referral letter content and referrer characteristics Pre and Post Suites

The proportion of times that the anterior chamber angle was described in all glaucoma referral letters was significantly greater following the introduction of the Angle Suites (Post Suite plus Angle Suite, 26.5 per cent) than prior to its introduction (Pre Suite, 14.6 per cent). Of the patients referred following the introduction of the Angle Suite, the proportion of patients triaged into the general clinic (Glaucoma Suite) with descriptors of open angles was no different from that of the Pre Suite cohort, suggesting that Angle Suite availability potentially addressed a previously unmet need among referring clinicians and community patients presenting for examination.

True and false positive and negative rates of all referral letters mentioning a description of the angle (Pre Suite, n = 54; Post Suite plus Angle Suite, n = 133) were next examined. The true negative rate (open angles mentioned in the letter and open angles found in the patient) was 100 per cent (28/28) for the Pre Suite and was 92.9 per cent (52/56) for the Post Suite plus Angle Suite. The true positive rate (narrow angles mentioned in the letter and angle closure glaucoma spectrum disease found in the patient) was 73.1 per cent (19/26) for the Pre Suite and 70.1 per cent for the Post Suite plus Angle Suite (54/77). These were similar between the two periods. The proportion of cases diagnosed with angle closure spectrum disease in the Pre and Post period where the angle was not described in the referral letter were 37.5 per cent (9/24) and 75.0 per cent (12/16), respectively.

Referrer characteristics

The proportion of times that a patient was referred by a unique optometrist with therapeutic endorsement was 56.4 per cent (66/117), 55.3 per cent (84/152) and 59.6 per cent (29/47) for Pre Suite, Post Suite and Angle Suite patients, respectively, with no significant difference between the groups ($\chi^2 = 0.6103$, $p = 0.7370$). The median (IQR) times (years) from initial date of optometric registration were 10.8 (4.5–19.5), 12.1 (4.4–20.3) and 11.4 (6.3–20.2), respectively, again with no significant difference between the groups ($H(3) = 2.355$, $p = 0.3081$).

Multinomial logistic regression showed that addition of the referral characteristics improved the fit between the model and data ($\chi^2 = 210.0$, Nagelkerke $R^2 = 0.427$, $p < 0.0001$). Of the predictors, whether or not the angle was described in the referral letter ($p < 0.0001$) and whether the angle description was concordant with the final diagnosis ($p < 0.0001$) were significant; whether or not the referrer was therapeutically endorsed ($p = 0.182$) and time since registration ($p = 0.816$) did not contribute significant effects to the model.

Discussion

The present study evaluated the effect of a new, recently activated referral pathway on improving triaging effectiveness and patient outcomes for angle closure spectrum disease. This pathway was put in place after noting that other existing glaucoma-specific patient pathways[[4], [6], [9]] do not necessarily regard angle closure spectrum disease as a distinct entity requiring a separate triage process. In doing so, this study sought to evaluate potential reasons for pathway utilisation in order to guide further improvements to the system.

Majority of patients referred for secondary care do not require onward referral

The present study identified a potential clinical pathway for patients with suspected angle closure spectrum disease, where the majority of patients do not require onward ophthalmological assessment. The overall proportion of all patients who could be discharged back into the community for ongoing optometric care (20.1 per cent) was similar to some previous reports[[6], [11], [24]] and was lower than others.[[7], [25], [27]] Specifically with regard to patients referred for angle assessment, gonioscopic findings were not once noted in the referral letter, indicating a gap in current community optometry that is addressed in the present model.

Notably, although gonioscopy is a current graduate level clinical competency in optometry in Australia[28] and is one of the clinical tests expected to be performed in the comprehensive assessment of glaucoma, its use is not widespread in community practice.[29] Its use in glaucoma assessment is also less frequent in non-glaucoma specialist ophthalmologists compared to glaucoma specialist ophthalmologists in Australia and New Zealand.[[30]] Cited barriers include confidence, accessibility to equipment and subjectivity.

The characteristics of patients referred for a routine glaucoma assessment remained unchanged when comparing Pre and Post Suites, with the demand for angle-specific services disproportionate to the number of cases previously identified in the general clinic. In combination with the finding that the number of patients referred for glaucoma assessment as a whole increased in the Post Suite period suggests a previously unfulfilled demand for services.

A large portion of patients can be managed in the community or in shared care rather than needing shorter-term ophthalmology referral, but our results were centred around the CFEH model of care. There is potential for this model to be implemented in a more diverse community setting, rather than centralised, so long as appropriate diagnostic tools, criteria and quality control measures are implemented. This is a consideration for development of future similar, community-based models across a range of clinical settings to alleviate the public health burden of unnecessary referrals.

Importance of angle assessment in the triaging process by letter content

Multinomial logistic regression analysis highlighted the importance of having the angle appearance noted in the referral letter as part of the triaging process. A significant proportion of angle closure disease cases were misdiagnosed as open angle glaucoma disease in the Pre and Post Suite groups, similar to the study of Khan et al.[32] The rates of occludable angles requiring referral in lieu of routine open angle glaucoma disease management was notably higher than that found by Bourne et al.[33] and by Varma et al.,[34] but were lower than that in the study of Seider et al.[35] in a Chinese-American population. This was likely due to a combination of the difference in patient cohort, threshold for referrals and the clinician group that was studied. In comparison, the triaging system of Angle Suites, increased the hit rate for angle closure disease diagnosis to 70.1 per cent, with the additional benefit of decreasing waiting times to appointment. Previous studies have shown that more comprehensive referral letter content assists in the triaging process.[[32]]

The pattern of referrals for Angle Suites suggests that there is a subset of community practitioners who may benefit from additional training in anterior segment evaluation in glaucoma, with consequent further benefits to this triaging process.[36] Proformas for referrals stipulating a checklist may also be useful.[37] Depending on the expected proportion of angle closure glaucoma within all cases of glaucoma seen within the community, the failure to distinguish the two by simply noting angle status may present a significant problem in community optometry, as noted by previous studies.[32] A glaucoma-specific electronic patient record form has been recently suggested.[38] Manual checklists of pertinent items to include in glaucoma-related referrals have also been suggested.[37] This is a practical consideration for the individual clinician and should be tailored to the demands of the health-care system.

This study found that therapeutic endorsement and time since registration were not significant factors. The finding of time since registration, which may be a surrogate to years in practice and clinical experience, not being a contributing factor appeared contrary to the findings of Davey et al.[24] This may be due to the confounding effect of recent graduate experience, where there may be greater exposure to more recent clinical techniques and updated knowledge, which may then counterbalance the clinical experience of older optometrists. This is therefore similar to the work of Ly et al.,[39] who investigated diagnostic accuracy of macular degeneration. Practitioners utilising the pathway at this stage may represent a subset of clinicians that may not have access to anterior segment assessment techniques in their practice or have the confidence for assessing borderline cases.

Limitations

This study was cross-sectional in nature and although two different time points were used, it was not a parallel cohort study. Thus, there may still be a degree of longitudinal bias in patient extraction. Furthermore, there were few cases where the final treatment or prognostic outcome could be confirmed, due to the nature of CFEH as a referral-only intermediate-tier clinic.[6] Notably though, of the 12 patients in the Angle Suites group who required intervention (laser or surgical), four met the criteria for collaborative care within the local health district and were managed by the CFEH collaborative care glaucoma clinic.[5]

Few glaucoma guidelines state a review period for the different stages of angle closure spectrum disease, stemming from a relatively poor understanding of the natural history of angle closure disease.[40] Disease staging, management and the capacity to provide an accurate prognosis will continue to evolve and the development of further evidence-based clinical pathways should carefully consider these.

This study did not measure whether this pathway resulted in over-referral or over-monitoring of patients. A conservative referral or review period is likely more appropriate than discharging at-risk patients due to potentially visually devastating consequences of angle closure. A long-term study would be useful for following up the outcomes of these patients to measure this aspect of the pathway.

Conclusions

This study describes the development and implementation of a unique clinical pathway for the subset of patients with suspected angle closure spectrum disease, which has potential for wider dissemination so long as appropriate clinical expertise and equipment are in place. The new pathway reduces appointment wait times and identifies that most patients benefit from intermediate-tier review, reducing onward ophthalmological referral. The results also highlight the importance of careful referral letter writing, as the ability of the referring clinician to interpret and report on the anterior chamber angle examination results significantly impacts the triaging process.

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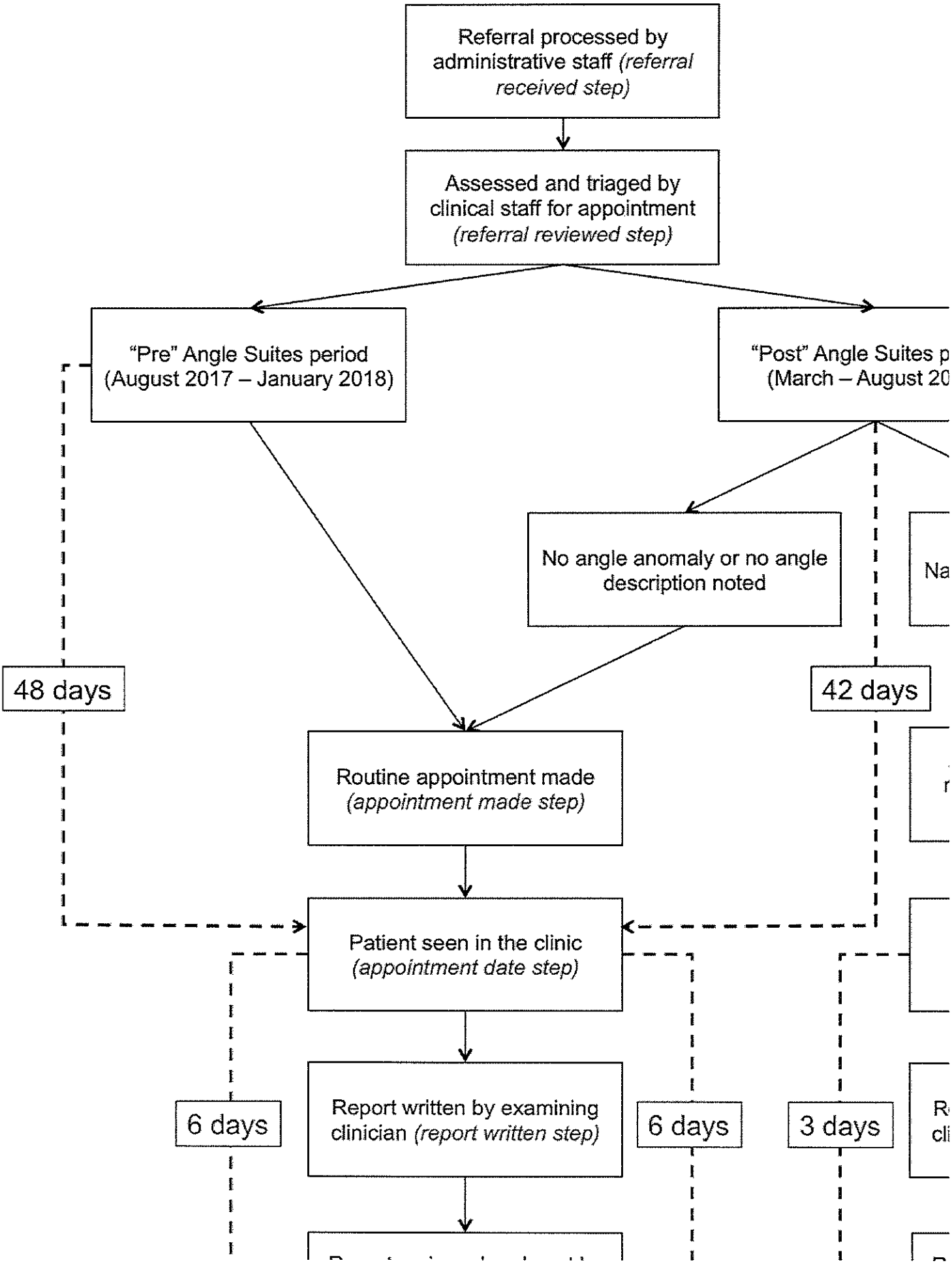
Referral processed by administrative staff (referral received step)
Assessed and triaged by clinical staff for appointment (referral reviewed step)
"Pre" Angle Suites period (August 2017 – January 2018)
"Post" Angle Suites p
(March – August 20
No angle anomaly or no angle description noted
Na
48 days
42 days
Routine appointment made (appointment made step)
Patient seen in the clinic (appointment date step)
6 days
Report written by examining clinician (report written step)
6 days
3 days

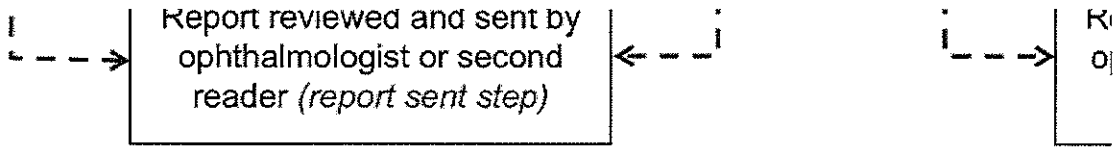

Figure S1. Clinical workflow at Centre for Eye Health for glaucoma-specific referrals relevant to the present study. The dashed arrows indicate the times determined in the study between key points in workflow. The blue dashed lines indicate time from referral receipt to appointment, and the green lines indicate time from appointment to reporting.

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