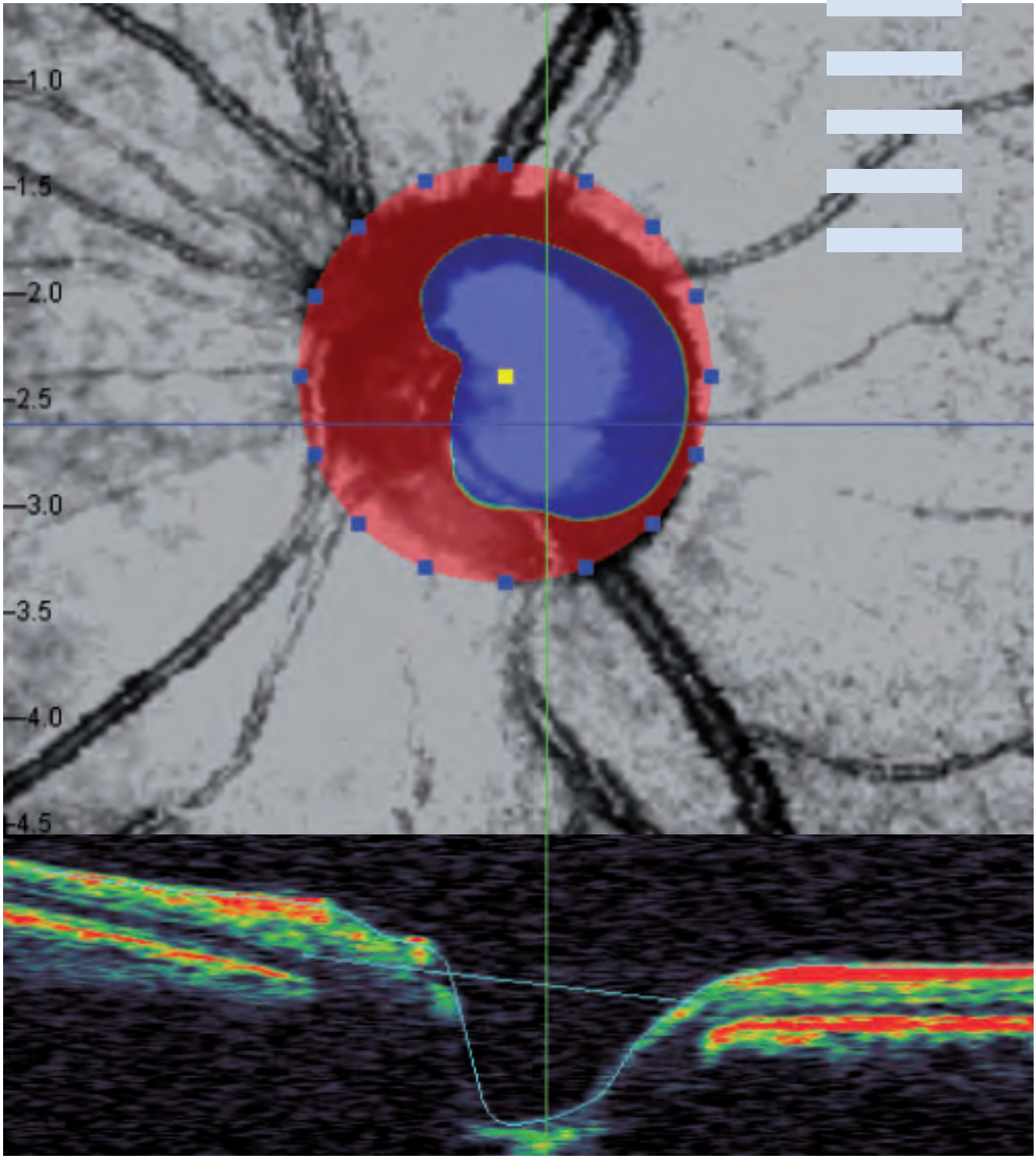
Supplement to
AUSTRALIAN OPTOMETRY

Special issue GLAUCOMA

pharma

March 2010



- Clinical decision-making
- Fixed combination therapies
- Case reports
- Shift from IOP to optic disc
- Genetic testing
- Sturge-Weber syndrome
- Disc cupping assessment
- The 21 mmHg myth
- Asymmetric POAG

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PBS Information: This product is listed on the PBS for the treatment of open-angle glaucoma and ocular hypertension.

*Low IOP is associated with reduced progression of visual field defect in patients with glaucoma.[3,4]

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Full PI approved by the TGA on 4 February 2003, last amended 20 November 2006. Pfizer Medical Information 1800 675 229. **References: 1.** Goldberg I et al. Eur J Ophthalmol 2008; 18(3): 408–416. **2.** Hedman K et al. Surv Ophthalmol 2002; 47(Suppl 1): S65-S76 **3.** The AGIS investigators. Am J Ophthalmol 2000; 130: 429-440. **4.** Goldberg I. Surv Ophthalmol 2003; 48(Suppl 1): S3-S7. 01/10 McCann Healthcare XALAT0065/OP/FIRE_MA

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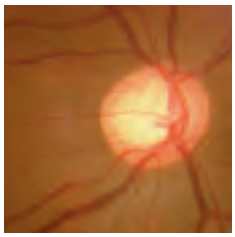
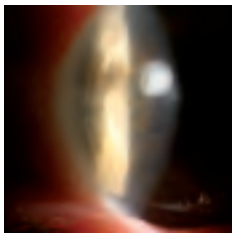
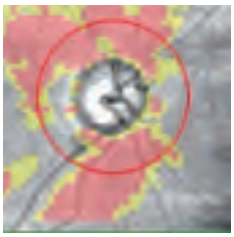
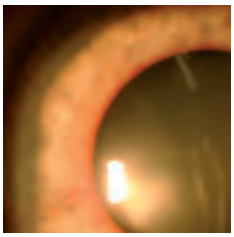
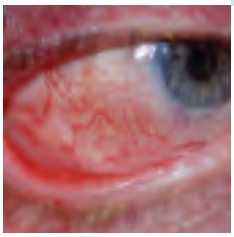

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COVER
OCT image of a glaucomatous disc

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Clinical decision-m

Dr Murray Fingeret
OD

Diagnosing glaucoma is often not easy. The practitioner may need to recognise subtle signs such as a thinning of the neuroretinal rim, mild retinal nerve fibre layer (RNFL) loss or a shallow visual field defect. The following is a guide to the steps involved in diagnosing open angle glaucoma (OAG) and the subtle signs associated with its development, of which you should be aware.

Initial examination

The first step in the examination process is history-taking and acquisition of personal data. Certain ethnic groups such as those of African descent are at greater risk of developing OAG. Patients of Asian descent are at greater risk of developing chronic angle closure glaucoma, which can resemble OAG. Family history is significant so when a concern develops a practitioner can ask the patient to check whether any of their family members have glaucoma, although a negative response does not necessarily mean that glaucoma does not exist. Often on return to the practice patients say that they did not realise their sister or mother has the disease.

Past occurrences of trauma or ocular inflammatory disease need to be documented, with the anterior and posterior segment evaluated for signs of disease or trauma. It is important to enquire about the patient's systemic health as well as any medications they may be using. Certain medications such as oral beta blockers may reduce intraocular pressure (IOP) and mask an elevated measurement, while steroid use may be associated with IOP elevation. Finally, enquire about cardiovascular disease as well as a history of low blood pressure.

After obtaining the history, other parts of the initial comprehensive examination include the assessment of the anterior segment comprising pupil examination and assessment with a biomicroscope, a screening assessment of the anterior chamber angle, intraocular pressure measurement, blood pressure measurement, screening assessment of the visual field, dilated view of the optic nerve, RNFL and retinal periphery.

If any of the signs come back positive indicating the possibility that glaucoma may be present or could develop in the future, tests need to be performed to complete the assessment. These tests include repeating the measurement of the IOP, assessing the anterior chamber angle with gonioscopy, documentation of the optic nerve/RNFL with retinal photography and imaging, and performing a threshold perimetric test. Additionally, optic nerve imaging (GDx, HRT and OCT) as well as selective perimetry (SWAP, FDT and HEP) may be useful in determining if glaucoma is truly present.

Total package

The pupillary examination and anterior segment assessment are often done early in the examination sequence. The swinging flashlight test, assessing for a Marcus-Gunn pupil reaction, occurs when the pupil dilates once the light hits the eye. Usually the pupil constricts when light enters the eye in question. A Marcus-Gunn pupil can be a manifestation of OAG. Other pupillary abnormalities need to be explained with further examination. The slitlamp assessment is geared to look for signs of secondary forms of glaucoma such as pigment dispersion, pseudoexfoliation, neovascularisation of the angle or iris, or signs of anterior segment trauma.

The intraocular pressure is measured with the time and instrument recorded in the patient chart. IOP measurements can vary throughout the day and be more labile in patients with glaucoma so several readings taken at different times are often needed to complete the assessment package. Goldmann tonometry is still the preferred test when glaucoma is suspected although other forms of tonometry are being introduced and validated. If the IOP is determined to be elevated or glaucoma discovered, gonioscopy needs to be performed to assess the anterior chamber angle. The width of the

FDT	frequency doubling technology
GHT	Glaucoma Hemifield Test
HEP	Heidelberg Edge Perimetric
HFA	Humphrey Field Analyzer
HRT	Heidelberg Retinal Tomograph
IOP	intraocular pressure
ISNT	inferior superior nasal temporal
OAG	open angle glaucoma
OCT	optical coherence tomography
PPA	peripapillary atrophy
PXE	pseudoexfoliative
RNFL	retinal nerve fibre layer
SWAP	short wavelength automated perimetry
TSNIT	temporal superior nasal inferior temporal

aking can be tricky

To correctly diagnose glaucoma, assess and compare all your tests' results to determine whether the patterns fit

angle and structures visible need to documented, as well as other findings such as synechiae, pigmentation, abnormal blood vessels, recession or pseudoexfoliative (PXE) material, all of which may be associated with elevated IOP.

Assessing optic nerve

A crucial part of the exam is the assessment of the optic nerve. One method to document the optic nerve and retinal nerve fibre layer is with the five Rs technique.

The first step is to assess the optic disc size, recognising that optic discs come in different sizes with the cup size proportional to the optic disc size. Large optic discs will have large cup/disc ratios and small optic discs will have small cupping. The second step is to assess the neuroretinal rim, which is evaluated using the ISNT rule in which the inferior rim in a healthy person is thickest, followed by the superior rim, nasal rim and the temporal rim being the thinnest. This often gives a horizontal or round cup shape; a vertical cup shape is often a red flag.

The third step is to evaluate the retinal nerve fibre layer, watching for loss that is typically localised. RNFL loss is easier to visualise when the fundus is darker and is more difficult in lightly pigmented eyes.

The fourth step is assessment for optic disc haemorrhages, which have a splintery appearance. The area to evaluate is at the optic disc border, with haemorrhages often bisecting the edge of the optic disc.

The last step is to assess the area outside the optic disc for peripapillary atrophy (PPA). There are two forms of PPA, zone alpha and zone beta, with zone alpha occurring in many healthy patients and zone beta more common in glaucomatous eyes. PPA can change over time, similar to enlargement of the cup/disc ratio. Finally, the horizontal and vertical cup/disc ratio needs to be recorded.

Imaging can be useful to assess the RNFL and optic disc, especially in hard to assess eyes. In regards to the diagnosis, it can provide valuable information about the RNFL integrity as well as size of the optic disc and thickness of the neuroretinal rim. It also establishes a baseline to be used for the measurement of change over time. The Heidelberg Retinal Tomograph (HRT) and GDx RNFL analyser were the first optic nerve/retinal nerve fibre imaging instruments, followed by time domain optical coherence tomography (Stratus OCT). Spectral Domain OCTs have been available for about two years and offer improved resolution along with the ability to register images that are taken over time. Depending on the instrument, you may be able to evaluate the RNFL, optic nerve or macular region for glaucomatous loss.

Functional evaluation

After the structural assessment, a functional evaluation needs to be done using threshold perimetry. For the HFA perimeter, the 24-2 SITA Standard visual field test is the most common, keeping in mind that the learning curve is real.

The first test may show diffuse or widespread loss that disappears on the second or third examination. The first area assessed on the print-out is whether the correct test was used, the correct eye tested and the appropriate corrective Rx put in place. Most perimeters are based on a distance correction (optical infinity), although the HFA uses a near correction.

The second step is to assess reliability by appraising false positives, false negatives and fixation losses. The most important reliability indicator is false positives, with as few as five to 10 per cent possibly being significant. Only elevated false negatives may occur with other reliability indices being adequate when a scotoma is present. The total and pattern probability symbols are assessed, with a greater number of points flagged on the total side being associated with learning or media opacities. A greater number of points flagged on the pattern side may be associated with elevated false positive responses. The media is relatively clear and the patient is a good test taker when the number of points is similar on both.

The pattern of points flagged is assessed and whether they are clustered together, and if so, their number and location, and level of significance found. The Glaucoma Hemifield Test (GHT) is evaluated with the message Outside Normal Limits needing to be explained as this is often associated with field loss and glaucoma damage being present. The severity of the field may be graded based on the number of points flagged, whether fixation is involved and if one or both hemifields are involved.

The structure-function relationship describes a situation in which optic nerve/RNFL loss is the most common sign of early glaucoma damage with visual field damage occurring at a later time. It is therefore not unusual to see a patient with OAG who has only optic nerve damage. A careful assessment and corroboration would be useful in finding loss on imaging tests.

An interim step between optic nerve and standard visual field loss is the use of selective perimetry. SWAP and FDT were introduced 15 years ago and may detect field loss when the standard perimetric test is full. They have a value in glaucoma suspects when the question of glaucoma has not been determined.

Diagnosing glaucoma can be difficult and complex, requiring the practitioner to take into account a series of tests. It is important that the different tests are evaluated against each other to determine if the patterns fit. For example, nerve damage greater in one eye will have a greater amount of field loss, and the more damaged eye usually has a higher IOP even when the IOP is in the so-called normal range. Damage found inferiorly to the RNFL or optic disc will manifest with superior field loss.

Diagnosing glaucoma requires all the tests to be evaluated together. When the diagnosis is questionable, watching the patient over time for change is another method to diagnose glaucoma, which requires the periodic documentation of the optic nerve and visual field.

You can't screen all Australians so

Help your patients with opp

With the focus of glaucoma shifting from IOP to the optic disc, practitioners must ensure that their skills meet the mark

Dr Lance Liu
MBBS FRANZCO

CCT	central corneal thickness
CDR	cup-to-disc ratio
GAT	Goldmann applanation tonometer
IOP	intraocular pressure
ISNT	inferior superior nasal temporal
ITC	iridotrabecular contact
PACG	primary angle closure glaucoma
PAS	peripheral anterior synechiae
POAG	primary open angle glaucoma
RNFL	retinal nerve fibre layer
SAP	standard automated perimetry
SWAP	short-wavelength automated perimetry

This article outlines the recent evidence on the clinical signs of glaucoma and optic disc documentation, and an approach to assessing a patient for this disease.

Glaucoma is the second leading cause of irreversible blindness in the world. It is defined as a progressive loss of ganglion cells that leads to structural changes in the retinal nerve fibre layer (RNFL) and optic disc and functional changes in the visual field.

The two most common types of glaucoma are primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG), which exist in all of the glaucoma epidemiological studies.

One of the main problems we face with glaucoma is that it is essentially an asymptomatic and asymmetrical disease. In the early stages, it is usually detected incidentally on routine testing but many patients present with advanced disease with visual field loss or symptoms of extremely high intraocular pressure (IOP). Although it is not feasible to screen the whole population for glaucoma, one can perform opportunistic screening on patients who present for an eye examination, regardless of their presenting problem.

Optic disc

As glaucoma is a progressive optic neuropathy, the key to making a diagnosis is to examine the optic disc. Instead of assessing the amount of cupping, we now focus on examining the neuroretinal rim to look for signs of damage (Figures 1 and 2).

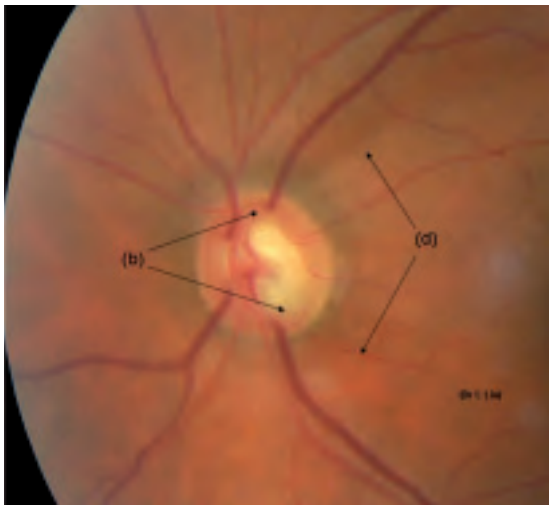

Figure 1. Digital colour image of the optic disc showing focal thinning of the neuroretinal rim (B) and RNFL defects (D)

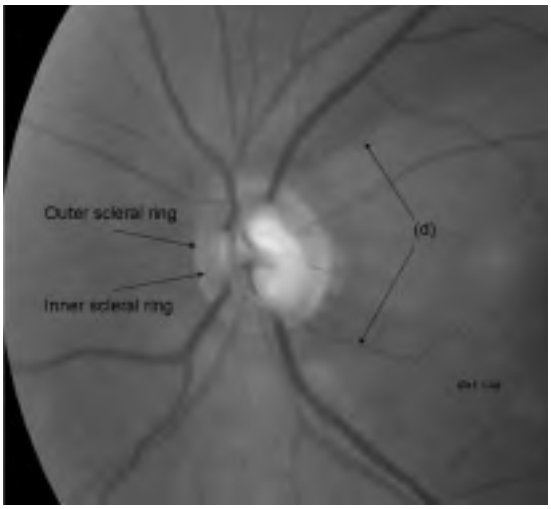

Figure 2. Digital red-free image of the optic disc showing focal thinning of the neuroretinal rim (B) and RNFL defects (D); the scleral ring is outlined

ortunistic examination

This includes seeing if:

- it obeys the ISNT (inferior superior nasal temporal) rule, which applies to about 83 per cent of the population
  - normally the ISNT neuroretinal rim
- focal thinning or notch(es) are present
- a drance haemorrhage is present (associated with optic disc progression)
- RNFL defects are present
  - 60 per cent of RNFL defects develop a corresponding visual field change
  - 90 per cent of those with a visual field defect already have a corresponding RNFL defect
- in the presence of focal loss of the neuroretinal rim, there are changes in the peripapillary atrophy over time
  - temporal peripapillary atrophy is normal in 80 per cent of the population
- there are differences in the optic disc appearance between the two eyes.

The presence or the development of any of the signs outlined above is important in the diagnosis of glaucoma. A glaucomatous visual field defect may also be associated with these signs but it does not need to present in the diagnosis of glaucoma (also known as pre-perimetric glaucoma).

Intraocular pressure

Intraocular pressure is now regarded as a risk factor for developing glaucoma, instead of being part of the diagnostic criteria. The mean IOP in the population is 11.8-18.7 ± 3.3-4.7 mmHg depending on the ethnic race and the instrument that was used to measure the IOP. An IOP measurement with a Goldmann applanation tonometer (GAT) is the gold standard but there are variable levels of agreement with other IOP measuring instruments such as Perkins and Tonopen. One must remember that eye pressure can vary throughout the day and one normal reading does not exclude the fact that the patient does not have glaucoma.

Recently, it has been shown that the central corneal thickness (CCT) can influence the IOP results measured with a GAT. The mean CCT in the population is 540 microns but, in general, a thinner cornea is associated with a low IOP and a thicker cornea is associated with a high IOP. This is becoming increasingly important given that laser refractive surgery can affect the IOP measurements. Although there are nomograms that try to correct the IOP measurements, the current consensus is that the CCT should be considered as a risk factor for development or progression of glaucoma.

Angle

Gonioscopy determines which type of glaucoma the patient has. Gonioscopy should not only be performed on patients whom you suspect to have glaucoma, for which it is mandatory, but also be performed on all patients to assess whether they are at risk of developing the disease. Conventionally, gonioscopy requires light to examine whether the angle is open by looking for the pigmented trabecular meshwork.

Recent evidence shows that angles that look 'open' in the light can be closed in the dark, leading to iridotrabecular contact (ITC). This can cause the IOP to rise due to appositional closure, synechial closure or damage to the trabecular meshwork itself. One can assess whether the angle is at risk of closure by using the Van Herick and central anterior chamber depth. Although highly specific, these tests have a 62 to 84 per cent sensitivity of detecting angle closure.

Gonioscopy should now be performed to assess whether the angle is closed by looking for ITC or signs of ITC. You need only greater than 90 degrees of closure before the patient is at risk of a rise in IOP. The angle is open if ITC is not present.

Risk factors

A patient's risk factors for glaucoma may help in the diagnosis and treatment of, or identify whether the patient is at risk of developing, this disease. Apart from IOP, the risk factors for POAG include age, race, a family history of glaucoma, myopia, central corneal thickness, diabetes, hypertension, steroid use (topical, ointment, oral) and blunt ocular trauma.

The risk factor for developing PACG is ITC. This can be ascertained only by performing gonioscopy to see whether the angle is closed. Gonioscopy should be part of the normal ocular examination in all patients to determine the type of glaucoma or whether they are at risk of developing glaucoma.

During the slitlamp examination of the anterior segment, risk factors for secondary glaucoma may be found and include pigment dispersion, pseudoexfoliation, uveitis, ocular trauma or rubeosis.

Clinical examination

The eye examination should be divided into two parts:

1. the primary exam to determine the cause of the presenting problem
2. the secondary exam to exclude whether the patient has any other ocular problems not related to the presenting problem; for example, does the patient have or is at risk of developing glaucoma?

History

Apart from the primary presenting problem, the patient's history should enquire about:

- glaucoma risk factors
- a medical history that may influence treatment options such as asthma, emphysema, cardiac history or sulphur allergies.

Optic disc examination

First, the optic disc should be examined using a high magnification lens such as a 60 D or 78 D lens, with the pupil dilated. You must first ensure that the patient is not at risk of developing angle closure when the pupil is physiologically dilated by performing gonioscopy to assess whether the angle is closed.

Second, you need an overall view of the optic disc and the surrounding anatomy. This includes measuring the vertical diameter of the optic disc with the height of the slitlamp beam. The appropriate correction factor needs to be applied, depending on the lens you use, to determine if you are dealing with a large, medium or small optic disc. You then need to examine the neuroretinal rim carefully and distinguish it from the scleral ring. Using red-free light to examine the optic disc can sometimes help with this distinction (Figure 2). The neuroretinal rim ends at the inner edge of the scleral ring—using the outer edge of the scleral ring can lead to overestimation of the neuroretinal rim thickness.

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Opportunistic examination

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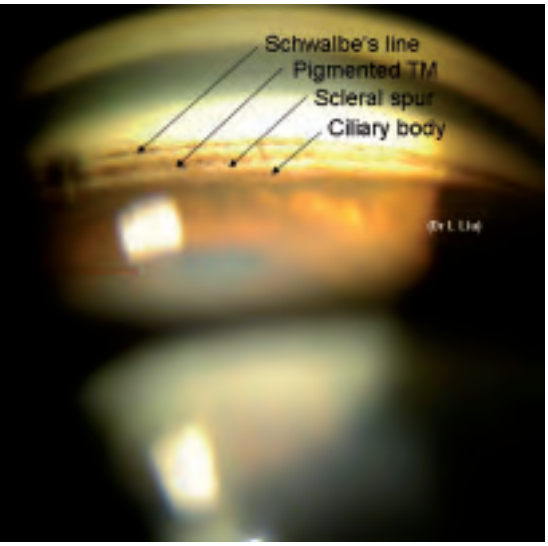

Figure 3. Anatomical features of the drainage angle

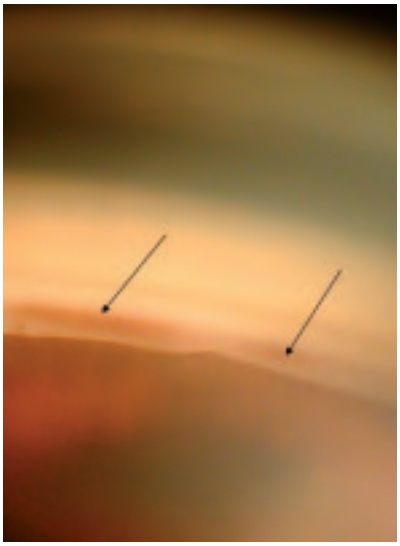

Figure 4. An example of patchy pigmentation of the trabecular meshwork

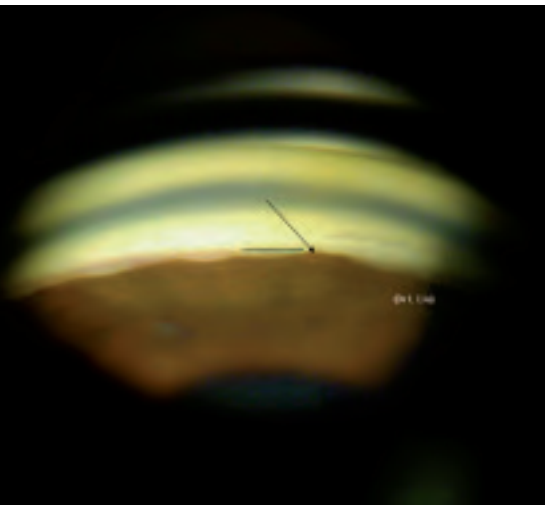

Figure 5. An example of peripheral anterior synechiae

Third, you need to assess whether there is any damage to the optic disc. This includes examining the surrounding RNFL with red-free light, then finishing with a complete examination of the peripheral retina. Tilted optic discs are harder to assess and may require other investigations to determine whether glaucomatous damage is present.

IOP measurement

Ideally, this should be performed using a GAT. After instilling a drop of local anaesthetic with fluorescein, the tonometer head should measure the central cornea with the prism aligned along the steepest axis. A thick fluorescent tear meniscus may give an erroneous low IOP reading and vice versa. Care should be taken not to apply pressure to the eyeball or orbit when measuring the IOP.

Gonioscopy

There are two types of gonio lenses used to examine the angle. The gold standard is the Goldmann type of lens which, because of its large diameter, allows one to view the angle with little corneal indentation that can artificially open up the angle. It requires the use of coupling fluid, which can blur the examiner's and patient's view for up to 30 minutes. The other type is a Zeiss/Posner/Sussman type of lens which has a smaller diameter and uses the patient's tears as the coupling fluid. It is easier to indent the cornea and open the angle with this type of lens but it does not blur the patient's vision afterwards.

To examine the angle, instil a drop of local anaesthetic into the eye before applying the gonio lens to the cornea. Using a wide slitlamp beam of light, you need to

1. Identify the anatomical structures, in particular the trabecular meshwork (Figure 3), by:
- using the corneal wedge sign to identify Schwalbe's line or
- indent the cornea to see the scleral spur.
2. Look for signs of ITC or angle closure (appositional or synechial):
- patchy pigmentation of the trabecular meshwork (Figure 4)
- peripheral anterior synechiae (PAS) (Figure 5)
- Signs of previously raised IOP.
3. Look for ITC with dark room gonioscopy (Figure 6 & 7):
- In a completely dark room, use a 1 mm X 1 mm slitlamp beam to examine the angle, taking care not to shine light into the pupil.

The angle can be documented with the Spaeth, modified Scheie's or the Shaffer classification.

You may image the angle in the dark to confirm and document angle closure or ITC. Anterior segment OCT has been shown to be better in detecting ITC than gonioscopy.

An educational video entitled 'Is the Angle Open or Closed? A video guide to modern gonioscopy' can be found in the glaucoma section of the video gallery under education online at www.apaophth.org.

Documenting optic disc

In the past, the cup-to-disc ratio (CDR) was used to document the appearance of the optic disc. It has been shown that the CDR can vary according to the size of the optic disc; larger discs have larger cupping and smaller discs have smaller cupping. There is poor interobserver and intraobserver agreement when documenting with CDR over time. The current consensus is to document the optic disc with imaging.

If you suspect the patient has or is at risk of developing glaucoma, you need to document the optic disc anatomically (struc-

turally) and physiologically (functionally). Structurally, the gold standard for documenting the optic disc is with photographs (preferably stereo) (Figure 1). HRT is also widely used but GDx, OCT, FDT or retinal thickness analyser are still being evaluated. The recent consensus states that there is no one better imaging modality over any of the others.

Functionally, you can document the optic nerve using visual field testing. White-on-white or standard automated perimetry (SAP) is the gold standard (Figure 8) but the results are dependent on the patient's ability to perform the test. This can be improved by explaining the test to the subject, and ensuring that the correct patient data is inserted into the visual field machine, a proper refractive correction is in place and the patient's pupil is continually monitored. The print-out shows the raw data and the final results are compared to a normative database. One then needs to interpret whether the visual field results are consistent with a glaucomatous visual field defect

It is important to correlate the visual field test results with the appearance of the optic disc, otherwise there may be non-glaucomatous pathology present. Other testing strategies, such as short-wavelength automated perimetry (SWAP), blue-yellow, FDT, HRP and flicker perimetry, try to test for glaucomatous field loss earlier than what SAP detects, but the literature does not consistently support this.

Because the patient needs to lose between 30 and 50 per cent of the ganglion cells before you can see changes in SAP, it is better to image the optic nerve in the pre-perimetric stages of glaucoma. When visual loss is present, SAP is better at monitoring progression. Practically, one usually alternates between the structural and functional tests.

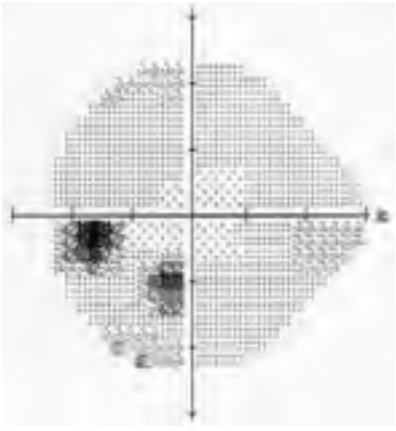

Figure 8. Standard visual field test of the patient in Figure 1

Risk calculator

A risk calculator assesses the probability of the patient developing open angle glaucoma based on the clinical findings, which may help in the treatment decision-making process. Version two is available but is still being refined.

Summary

The definition of glaucoma has changed over the years with the focus having shifted from the IOP to the optic disc. A diagnosis of glaucoma is made when there is damage to the optic disc in the presence of other risk factors. Because it is essentially an asymptomatic disease, all patients should be assessed for glaucoma or for risk factors as early intervention can reduce the chance of visual loss, especially angle closure.

The diagnosis of glaucoma is based on a detailed examination of the optic disc, looking for damage, in the presence of any glaucoma risk factors and requires further treatment. If the optic disc looks normal but there are numerous risk factors for developing glaucoma such as family history, narrow angles and raised IOP, the patient needs a baseline image of the optic discs and/or a visual field. The patient should then be monitored on a regular basis, looking for any changes of the optic nerve head, IOP and the angle. Gonioscopy should be repeated at the same time as it can lead to a rise in IOP and increase the risk of optic nerve damage.

Disclaimer

The article aims to be a guide for assessing glaucoma. Further information can be found in the various glaucoma guidelines: Asia Pacific, European Glaucoma Society and American Academy. The author has no opinion or financial interest in any of the products mentioned.

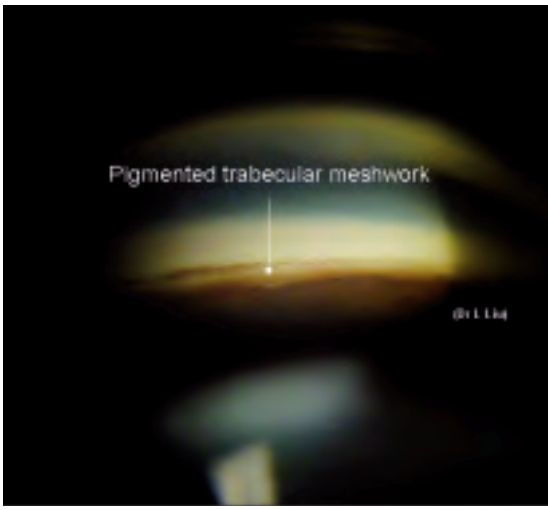

Figure 6. An open angle seen in the light

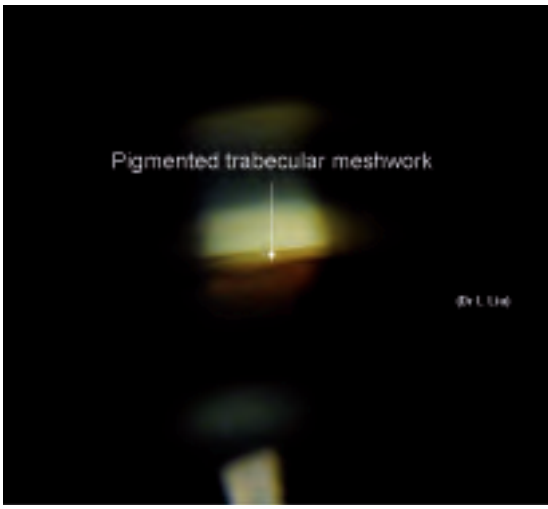

Figure 7. A closed angle seen in the 'relative dark' in the same patient as in Figure 6

Normal tension and the 21mmHg myth

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The current nomenclature in open angle glaucoma has been in place for several decades. Primary open angle glaucoma (POAG) is associated with an IOP prior to treatment of more than 21 mmHg; normal tension glaucoma (NTG) is glaucoma occurring where the IOP is less than 21 mmHg. Is NTG a different disease from POAG? How did we derive our attachment to 21 mm Hg as the demarcation between 'normal' and 'abnormal'?

In 1966, Hollows and Graham[1] reported the findings of a population-based survey undertaken in Wales. They looked at 4,231 subjects over the age of 40 years and found 20 cases of glaucoma. They also defined the population mean IOP, which was about 15 mmHg, with a roughly normal distribution, showing a slight skew to the right. By approximating a normal distribution, the range of normal within two standard deviations became 10 to 21 mmHg. This has become known as 'normal' IOP.

Because glaucoma has been known to be associated with elevated IOP, and because disease is clearly 'abnormal', IOP > 21 mmHg eventually became a shorthand way of recognising glaucoma. This occurred, incidentally, despite Hollows's study being the first to demonstrate that glaucoma could occur with a 'normal' IOP: 7/20 glaucoma cases detected had an IOP < 21 mmHg.

Many surveys undertaken since then—Baltimore, Beaver Dam, Blue Mountains—have shown that a sizeable proportion of the new glaucoma cases have IOP < 21 mmHg. Because these 'normal tension' glaucoma cases were unexpected, it was postulated that this may be a different disease or even a 'pressure-independent' disease.

There developed a vogue for recommending that all NTG cases undergo neuroimaging and a range of other diagnostic testing to ascertain the cause of the patient's presentation with an apparently glaucomatous picture yet with a 'normal' IOP.

Population 'normal' does not equate to individual 'normal' (safe). The relevant IOP is the IOP that is greater than that which the patient's optic nerve can tolerate. There is no conceivable reason that the risk should be present at > 21 mmHg, but disappear at < 21 mmHg.

While elevated IOP remains the single greatest risk factor for development of glaucoma, it may not be unreasonable to assume that, for the individual patient, glaucoma may occur along a continuum of IOP, depending on the sensitivity of that individual's optic nerves to IOP. There is a strong case to be made for discarding the figure of 21 mmHg in any consideration of the individual with glaucoma. Reference to it will neither confirm nor exclude the presence of glaucoma, and 21 mmHg is irrelevant as a general therapeutic target pressure.

Is normal tension glaucoma a different disease?

Phenotypical features that are seen in NTG patients include optic disc haemorrhages, peripapillary atrophy, focal notching of disc rim, stable or stuttering progression, VFL in paracentral areas, hemifield loss and a history of migraine or vasospasm.

What happens if these 'distinctive features' of NTG are explained not by a distinct disease but by factors such as myopia, CCT/hysteresis, diurnal variation, scleral collagen/rigidity or disc haemorrhage tamponade failure (physiological variations)?

There is also a potential selection bias, described by Caprioli and colleagues[2], in looking at visual fields. NTG is said to be associated with a greater prevalence of paracentral visual field loss. These losses

There is no reason for the risk of glaucoma to be present at > 21 mmHg but disappear at < 21 mmHg

In a nutshell

- **To detect cases, one must examine the optic nerve head even in the setting where IOP fails to provide an alert by being > 21 mmHg.**
- **NTG is not a diagnosis of exclusion. One may comfortably diagnose glaucoma if the features are otherwise entirely typical.**
- **If NTG is suspected but the field and disc features are not typical, then an alternative diagnosis and investigation must be considered, and neuro-imaging will almost certainly be required.**
- **Therapy is sometimes withheld until progression is demonstrated, depending on the stage of the disease. Once treatment is required, prostaglandins are often the first-line treatment.**

correspond to disc notches and nerve fibre layer drop-out.

Which patient with normal IOP is more likely to have a visual field performed, the one with disc notches or the one with concentric cupping lacking any specific notches? Compare this to the situation with elevated IOP, where the concentric cupping might more commonly be thought to warrant a field test.

The usual caution that is urged in diagnosing glaucoma with a low IOP is to ensure that an alternative diagnosis such as a pituitary fossa lesion or intrinsic optic nerve disease is not missed. These cautions are appropriate but apply equally to high tension as to low tension disease. In the presence of atypical features, such as if a visual field test suggests any vertical midline respect or temporal-greater-than-nasal loss, or if an optic nerve demonstrates atrophy or oedema rather than cupping, then neuro-imaging is certainly indicated.

Consider also the possibility that the diagnosis of glaucoma is correct, but not of NTG; the patient may have POAG with wide diurnal variation of IOP, glaucomatocyclitic crises, or undetected primary angle closure glaucoma (PACG).

Treating normal tension glaucoma

In some senses the distinction from a therapeutic standpoint between POAG and NTG is of little consequence; the treatment options available are essentially the same, that is, lowering of IOP.

The Collaborative Normal Tension Glaucoma Study[3] remains the key study guiding the approach to treatment, where IOP was lowered by at least 30 per cent in the treatment arm. Progression rates were three times higher in the untreated versus the treated group, although 20 per cent of the treated group continued to progress despite IOP lowering > 30 per cent, and 50 per cent of the untreated group showed no progression.

Some of the therapies that are dependent on the level of IOP relative to episcleral venous pressure may not work as well as usually expected and for this reason the prostaglandin class of medication—which lowers IOP by uveoscleral outflow and is therefore independent of episcleral venous pressure—may be the most appropriate first-line treatment. Much of the promise shown for alternative therapies working through neuroprotection or blood flow has yet to be realised in properly conducted studies. High hopes were held for memantine in this regard but results of a recent phase 3 study were disappointing.

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Fixed-combination are twice as

The most recent addition to the armamentarium of antiglaucoma drugs in Australia is timolol 0.5%/bimatoprost 0.03% (BTFC, Ganfort 0.3/5). Fixed-combination products (FCs) such as timolol have the combined efficacy of two ocular hypotensive drugs and the convenience of a two-drug treatment regimen in a single container. This article discusses and compares available FCs comprising timolol as an invariant with a PG analogue latanoprost (LTFC) or travoprost (TTFC), or prostamide bimatoprost (BTFC).

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Composition timolol/prostaglandin FC glaucoma therapies

The composition of timolol/prostaglandin FCs is shown in the Table (below). In addition to timolol 0.5%, a non-selective beta adrenergic receptor blocker, all FCs contain the component prostaglandin analogue or prostamide (PG) in the same concentration as the PG monotherapy. They all contain benzalkonium chloride (BAK) preservative in the same concentration as the PG monotherapy, with BTFC having the lowest concentration (0.005%).

Prescribing patterns for FC drugs

PG FC glaucoma drugs have been available in Australia for several years. LTFC was Pharmaceutical Benefits Scheme (PBS) listed for ophthalmologists in April 2006, TTFC in December 2006 and most recently BTFC in August 2009. All three drugs are now PBS listed for optometric use.

Prescription numbers for timolol, PG and FC PG glaucoma treatments in Australia are shown in Figure 1. The most frequently prescribed glaucoma therapy by ophthalmologists and optometrists combined is

Trade name(s)	Drug(s)	Preservative (benzalkonium chloride %)	Peak IOP reduction from baseline (%)[9]	Dispensed price for maximum quantity ($)[8]
Tenopt Timoptol	timolol 0.5%	0.01	-27	12.62 – 15.57
Lumigan	bimatoprost 0.03%	0.005	-33	42.14
Xalatan	latanoprost 0.005%	0.02	-31	42.14
Travatan	travoprost 0.004%	0.015	-31	42.14
Ganfort	timolol 0.5%/ bimatoprost 0.03%	0.005	NA*	46.82
Xalacom	timolol 0.5%/ latanoprost 0.005%	0.02	NA*	46.82
DuoTrav	timolol 0.5%/ travoprost 0.004%	0.015	NA*	46.82

* no meta-analysis data available

Comparison of individual components and PG fixed-combination glaucoma therapies

BAK benzalkonium chloride
BTFC bimatoprost timolol fixed-combination
FC fixed-combination
IOP intraocular pressure
LTFC latanoprost timolol fixed-combination
PBS Pharmaceutical Benefits Scheme
TTFC travoprost timolol fixed-combination

therapies convenient

Optometrists need to understand the components of fixed-combination agents to avert double prescribing of timolol and the associated increased risk of side-effects

latanoprost monotherapy, with about 1.45 million prescriptions written each year. Timolol is the next most frequently prescribed glaucoma therapy but the number of prescriptions for this treatment has been decreasing in recent years. Prescriptions for LTFC and TTFC are less frequent but their numbers are increasing rapidly. There is no meaningful data on BTFC prescriptions at the time of writing this article.

Effectiveness of PG FC drugs versus unfixed components

Efficacy of glaucoma therapies can be considered in peak intraocular pressure (IOP) reduction, trough IOP reduction and control over the 24-hour cycle. Meta-analysis results for peak IOP reduction from baseline for timolol 0.5% and PG monotherapy are listed in the Table. Recent meta-analysis confirmed PG FC therapies are equally effective in lowering IOP as their non-fixed components[1] for LTFC and TTFC. BTFC was not studied.

Advantages of FC

Up to 50 per cent of ocular hypertension or open-angle glaucoma patients require more than one drug to control IOP.[2] Analysis of pharmacy data suggests patient persistence is improved using FC therapy (35.3 per cent) compared to patients on two separate bottles (27.2 per cent), although remaining suboptimal.[3] South East Asia Glaucoma Interest Group guidelines recommend maximising the likelihood of patient adherence by using the least complex regime possible, which in many cases will require the use of FC agents.[4]

The three PG FC products are preserved with BAK in the same concentration as the PG monotherapy (Table). Use of the FC agents avoids the separate dose of BAK in the timolol component of the comparable non-fixed regime, thus reducing the preservative load to the eye. BAK is thought to be responsible for ocular surface inflammatory changes[5] and is recognised as an allergen for allergic blepharitis. Reducing the ocular surface dose of BAK may help reduce ocular surface disease associated with long-term glaucoma therapy.

FC may also reduce the 'washout effect' when two or more glaucoma treatments are given with inadequate spacing between treatments.[6] FC agents may also be a more cost-effective treatment than the comparable unfixed regime. The Table demonstrates the dispensed price for maximum quantity for timolol, PG and PG FC drugs.[7] The price for FC drugs is lower than the total for the unfixed components.

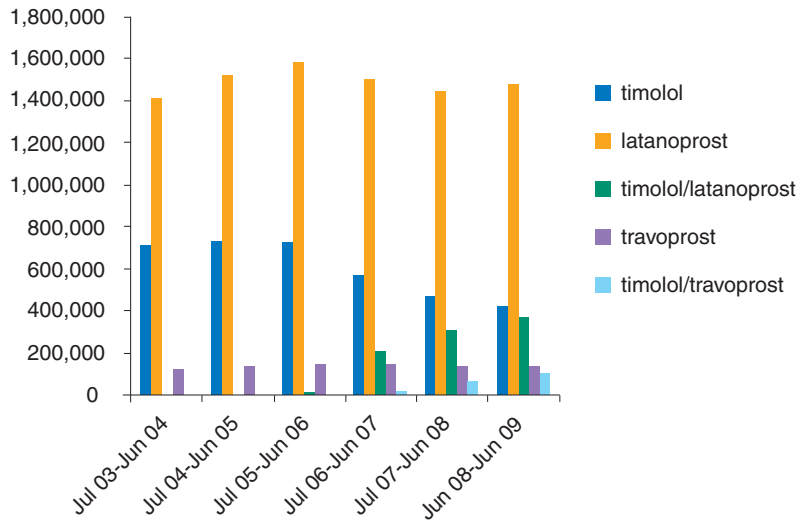

Figure 1. Comparison of PBS prescriptions by ophthalmologists and optometrists of timolol/prostaglandin FC glaucoma therapies and their components July 2003 to June 2009. Data downloaded from www.pbs.gov.au. Timolol includes 0.25%, 0.5%, 0.25% XE, 0.5% XE and 0.1% formulations. BTFC is not included due to insufficient data.

Disadvantages of FC

FC side-effects include those of the individual components. Minor local side-effects of timolol include burning, stinging and foreign body sensation. Potential systemic side-effects are significant and include bronchospasm, bradycardia, heart block and affecting lipid profile. Local side-effects of PG are the most common and include hyperaemia, foreign body sensation, lash growth, pigmentation of iris and periorbital skin, reactivation of herpetic keratitis and cystoid macula oedema; systemic side-effects are unlikely. BAK side-effects include stinging and burning. Allergic reactions can develop to any of the components and be difficult to clarify.

FCs limit the ability of ophthalmologists to individually tailor glaucoma treatment. Timolol is an invariant ingredient in FCs so when it is contraindicated, FCs are not able to be used. Optometrists need to understand the components of FC agents, and avoid double prescribing of timolol and associated increased risk of side-effects.

Continued page 12

Fixed-combination therapies twice as convenient

From page 11

- **Eye care professionals in Australia now have three PG FC therapies to use for treating patients with open-angle glaucoma or ocular hypertension.**
- **FCs have the advantage of two treatments in one bottle and may improve patient compliance, reduce exposure to BAK preservative, reduce wash-out effect and be more cost-effective for the community.**
- **Weak evidence suggests BTFC may be the most effective in lowering IOP.**
- **There is insufficient evidence comparing the side-effects of the PG FC.**

Comparison of timolol/prostaglandin FC

There are no published meta-analyses comparing the effectiveness of the three PG FC treatments. A recent meta-analysis concluded that timolol and PG are the most effective intraocular lowering agents in glaucoma patients,[8] with bimatoprost resulting in maximum peak IOP reduction from baseline (Table 1). A recent meta-analysis comparing the three PG analogues suggested a greater efficacy of bimatoprost compared with latanoprost at all time points and travoprost during the daytime.[9] Bimatoprost has also been shown to be associated with greater efficacy than latanoprost in a meta-analysis of direct comparison studies.[10] Timolol and PG are thought to have an additive effect, with FC not inferior to the unfixed components. This would suggest that the bimatoprost/timolol combination may be the most effective but there are no meta-analyses comparing the three agents. A recent clinical trial comparing BTFC with LTFC found a higher percentage of patients in the BTFC group to have a higher mean IOP reduction than with LTFC.[11] The trial found TTFC borderline more effective than LTFC in reducing IOP over the 24 hours after dosing.[12] Clinical studies are lower quality evidence than meta-analyses but suggest LTFC might be the least effective PG FC in lowering IOP.

All PG FC therapies have local side-effects of the PG component as noted above. Some investigators consider hyperaemia as one of the most significant side-effects and a reason for patient discontinuation of therapy. A recent meta-analysis of tolerability of PG found incidence of hyperaemia was less with latanoprost and travoprost compared with bimatoprost.[12] Another meta-analysis found use of latanoprost associated with a lower incidence of hyperaemia compared with travoprost and bimatoprost.[13] Again, there are no meta-analyses comparing tolerability or hyperaemia of PG FC. BTFC phase 3 studies submitted to the European Medicines Agency demonstrated reduced incidence of hyperaemia compared with bimatoprost monotherapy, hypothesised to be due to a beta-blocker inhibition of nitric oxide production.[14] This is consistent with anecdotal reports. At this stage no conclusions can be drawn regarding side-effects for the PG FC therapies.

Place of FC therapy

Given that over 40 per cent of patients require more than one glaucoma treatment to control IOP, FC therapy should be considered to rationalise treatment when the patient is being treated with the unfixed combination and when monotherapy is insufficient. In rare circumstances, FCs are used as initial treatment for patients who present with very high pressures, although this indication is not listed in the Australian PBS.

FCs, as with all glaucoma treatment, should be individualised, taking into account glaucoma type, patient ocular risk factors such as eye colour and ocular co-morbidities, and patient systemic risk factors.

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Sturge-Weber syndrome induced glaucoma

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Glaucoma occurs in from 30 to 70 per cent of patients with SWS and can be difficult to manage

Sturge-Weber syndrome (SWS) is a congenital neurocutaneous disease characterised by the triad of facial capillary malformation, leptomeningeal angioma and ocular vascular abnormalities.[1] Also known as encephalotrigeminal angiomatosis, SWS is a rare, sporadic disorder estimated to occur in about one in 50,000 births.

Although patients with the classic form of SWS demonstrate all three of the anomalies mentioned above, incomplete forms exist in which only two of the conditions manifest.[2]

The facial capillary malformations of SWS are commonly referred to as port-wine stains or nevus flammeus. Caused by dilated vessels in the superficial vascular plexus, port-wine stains appear at birth as red areas with distinct borders. Over time, the stain typically becomes darker, thickened and raised. Port-wine stains alone occur in about three in 1,000 births and can occur anywhere on the body.[3] Port-wine stains in patients with SWS always involve the area innervated by the ophthalmic division of the trigeminal nerve (the eyelid and forehead) and often extend to involve other areas of the face.[1]

Leptomeningeal angiomas are found in nearly 98 per cent of patients with SWS and can lead to severe, progressive neurological damage.[4] Seizures are the most common manifestation, occurring in from 23 to 83 per cent of patients. The seizures often manifest before two years of age.[1] Mental retardation and developmental delay are found in about half of patients with SWS.[1,4] A direct correlation between extent of cognitive deficits and age of seizure onset has been found.[5]

Ocular vascular malformations found in patients with SWS consist of dilated, tortuous vessels of the conjunctiva, episclera, retina and/or choroid ipsilateral to the port-wine stains. Choroidal hemangiomas, evident as flat or slightly elevated, dark red, diffuse, 'tomato catsup' lesions are found in from 40 to 71 per cent of SWS patients.[1,4] Glaucoma occurs in from 30 to 70 per cent of patients with SWS and typically develops during one of two peak periods.[4,5]

The first period occurs during infancy and is thought to arise mainly due to anterior chamber anomalies similar to those found in children with primary congenital glaucoma.[3,4] The second period occurs during adolescence and early adulthood, where increases in intraocular pressure (IOP) are thought to be primarily due to increased episcleral venous pressure.[3,4] Other nonvascular ocular abnormalities associated with SWS include iris heterochromia, optic disc coloboma and cataracts.[1]

Glaucoma in patients with SWS can be difficult to manage. The following report recounts a case of a patient with SWS and resulting glaucoma that continues to progress despite maximum tolerated medical therapy and multiple glaucoma laser procedures.

Case report

A 51-year-old Caucasian male with SWS presented for continued care of his unilateral glaucoma. The patient first began topical treatment for elevated intraocular pressure in his right eye at age 18 years. He had tried numerous topical and oral medications and had a 360-degree argon laser trabeculoplasty (ALT) in 1996 as well as a 360-degree selective laser trabeculoplasty (SLT) in 2006, which was repeated in 2009.

At the time of examination he was taking one drop Alphagan P 0.15% tid OD, one drop levobunolol 0.5 % bid OD and qam OS, and 50 mg methazolamide po bid. The patient's medical history was positive for chronic sinusitis and mixed hyperlipidemia. Although neuroimaging studies have found moderate cerebral and cerebellar atrophy, a right cerebellar arteriovenous malformation and calcification of the anterior falx, the patient's medical history was negative for seizures and developmental deficits.

Continued page 14

Sturge-Weber syndrome

From page 13

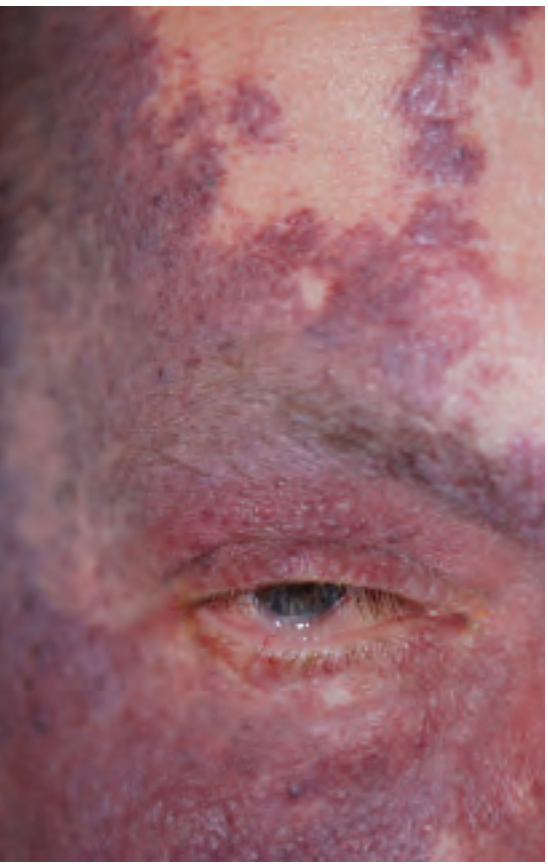

Figure 1. Distribution of port-wine stain

An extensive port-wine stain covering most of the right side of his face and much of the left side (eyelid and forehead spared on left side) was noted on examination (Figure 1). Best corrected visual acuities were 20/40 OD, 20/20 OS. Pupil reactivity showed a marked right afferent pupillary defect. Biomicroscopic examination revealed dilated, tortuous episcleral and conjunctival vessels of the right eye (Figure 2). Intraocular pressures were 24 mmHg OD, and 17 mmHg OS. The patient's anterior chambers were open and of normal architecture on gonioscopy. Ophthalmoscopic examination showed cup-to-disc ratios of 0.99 OD (Figure 3), and 0.85 OS with an otherwise normal fundus appearance.

A Humphrey visual field central 24-2 threshold test showed extensive arcuate defects in the right eye and no defects in the left eye (Figure 4). Imaging with optical coherence tomography (OCT) demonstrated significant thinning of the retinal nerve fibre layer (RNFL) in the right eye, consistent with end-stage glaucoma (Figure 5). The left eye was shown to have full, robust RNFL 360 degrees around the nerve head despite a cup-to-disc ratio of 0.85. The patient continues to be actively managed for his glaucoma.

Discussion

Due to the nature of the disorder, most if not all SWS patients will be aware of their diagnosis of the disease before they enter the practice. Eye-care providers must understand which findings put patients with SWS at risk for developing complications such as glaucoma, as well as the most efficacious treatment modalities for SWS patients with glaucoma.

The distribution and extent of facial port-wine stains can help predict the risk of SWS patients developing glaucoma. When port-wine stains encompass the forehead and/or upper eyelid (the area innervated by the ophthalmic division of the trigeminal nerve) the risk for eye and brain involvement ranges from 10 to 60 per cent.[5,6] Larger port-wine stains involving the area of the face innervated by the maxillary division of the trigeminal nerve can put the patient at even higher risk for neurologic and/or ocular involvement.[4] Due to the strong association with leptomeningeal angiomas, it has been recommended that SWS patients whose ophthalmoscopic examination reveal choroidal hemangiomas be referred for neuroimaging.[1]

Management of glaucoma in patients with SWS can be difficult. The most appropriate type of treatment depends on when

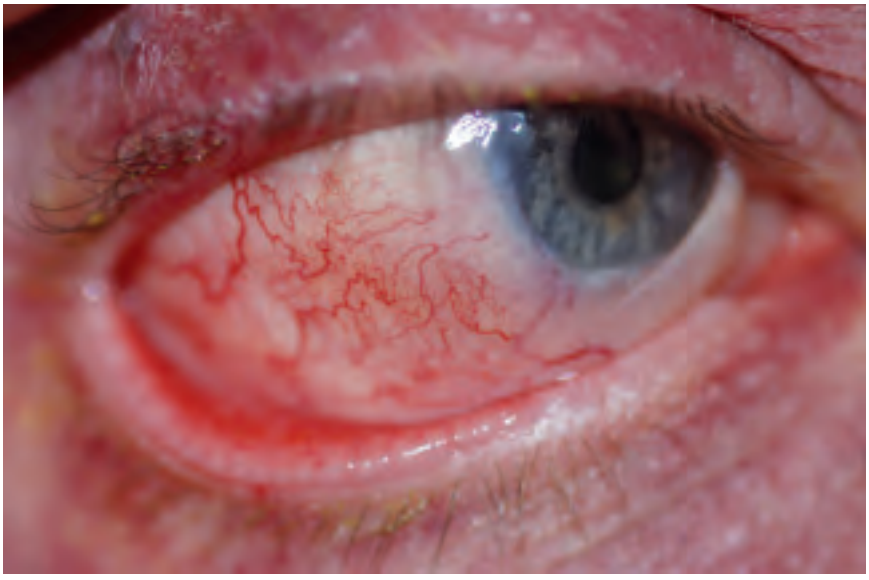

Figure 2. Dilated, tortuous vessels of the conjunctiva and episclera

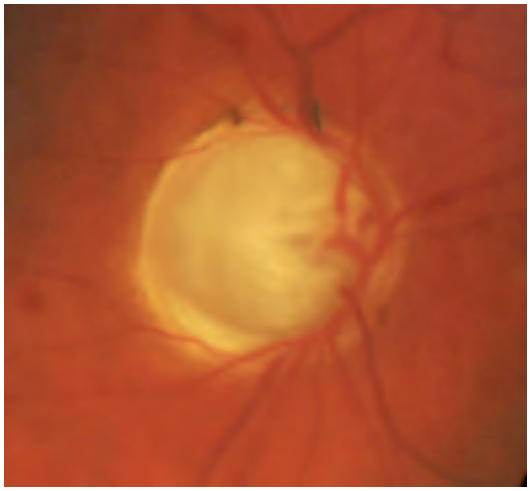

Figure 3. Extensive cupping of the right optic nerve head

Figure 4. Central 24-2 Humphrey visual field threshold test of the right eye demonstrating dense arcuate defects

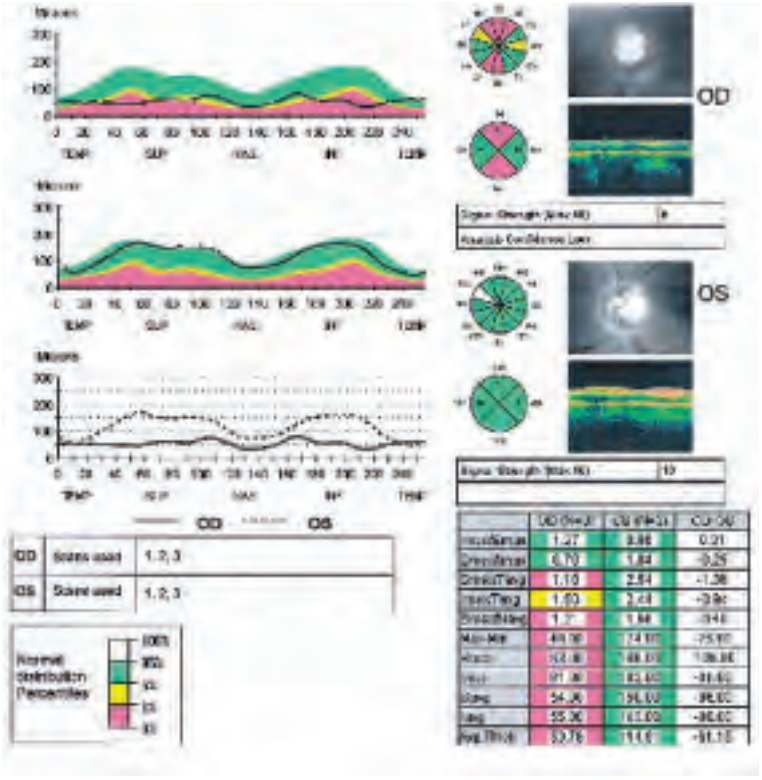

Figure 5. Stratus OCT Fast RNFL thickness scan showing significant thinning of the RNFL OD

the patient develops glaucoma. Those SWS patients that develop glaucoma at birth or during infancy are affected by anterior chamber angle anomalies and seem to benefit most from goniotomy or trabeculotomy procedures as first-line treatment.[4] Patients who maintain normal IOPs throughout childhood only to see pressures increase during adolescence/early adulthood are affected by increased episcleral venous pressure. These patients can be treated like any glaucoma patient with outflow problems.

Topical and oral ocular hypotensive medications are often useful but typically show decreased efficacy compared to patients with primary open angle glaucoma.[4] In the majority of cases, medical therapy alone will be inadequate. Laser trabeculoplasty is sometimes helpful in the management of glaucoma in SWS patients but is often less effective than in other glaucoma patients. Cyclodestructive procedures can be effective but are typically reserved for eyes with low visual potential.[4]

Filtering procedures such as trabeculectomies and tube shunts are often useful in reaching target IOPs. Success of the filtering procedures is impeded by high rates of intraoperative and postoperative complications. The most common surgical complications in SWS patients include choroidal and episcleral haemorrhage and choroidal effusion.[1, 4]

Though SWS is rare, its implications can be profound. Understanding how distribution of port-wine stains relates to ocular involvement can help identify those at greatest risk for developing glaucoma. When managing SWS patients with glaucoma it is important to understand which treatment modalities are appropriate and what their expected outcomes may be.

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Neovascular glaucoma

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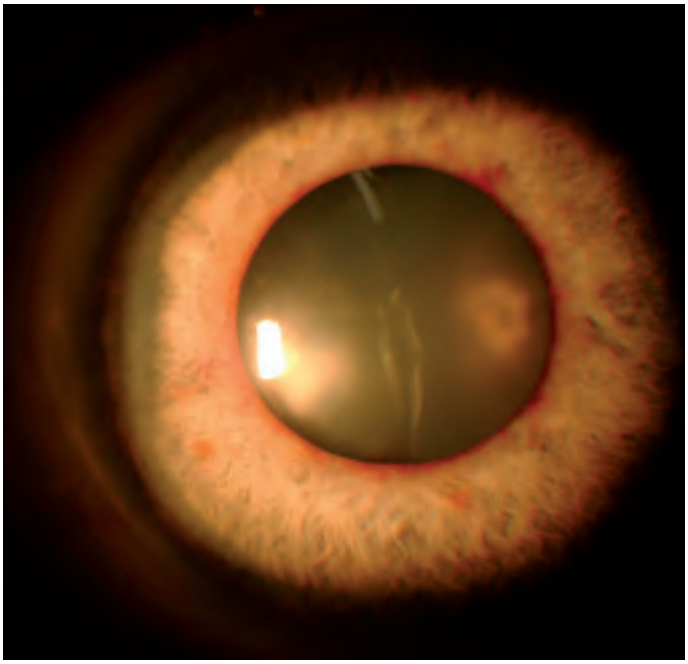
The risk of neovascular glaucoma in ischaemic eye disease is a reason for vigilance in primary eye care

Neovascular glaucoma (NVG) is a secondary glaucoma caused by new vessels growing into the anterior angle and iris, usually following an episode of ocular or retinal ischaemia. There are many possible causes of NVG, the most frequent being diabetic retinopathy, ischaemic central retinal venous occlusion (CRVO) and ocular ischaemic syndrome.[1,2] Epidemiological research[3] has shown that central retinal artery occlusion is not as strong a risk factor for the development of NVG as previously thought.



Rubeosis iridis, active neovascularisation over the surface of the iris. Photo: Dr Lance Liu

CRVO	central retinal venous occlusion
IOP	intraocular pressure
NGV	neovascular glaucoma
PRP	pan-retinal photocoagulation
VEGF	vascular endothelial growth factor

Detailed descriptions of NVG are available from peer-reviewed sites on the internet.[4,5] In its advanced state, NVG is an intractable, blinding and often painful condition. The presentation is characterised by:

- very high intraocular pressure, often associated with ocular pain
- rubeotic iris visible by slitlamp biomicroscopy (bright red new vessels growing within the normally-pigmented iris stroma)
- neovascular invasion of the trabecular meshwork and anterior angle, visible with gonioscopy
- very reduced visual acuity or absence of light perception
- ophthalmoscopic evidence of a causative retinal ischaemic event.

The risk of NVG developing is greatly reduced if the primary ischaemic retinal event is discovered and treated early. Fundus fluorescein angiography may be required to assess the relative degree of ischaemia and consequent risk of neovascularisation. Thus early referral of patients with any newly-discovered retinal ischaemic disease is essential.

Classical treatment of retinal ischaemic disease involves the use of pan-retinal photocoagulation (PRP) to obliterate ischaemic retina. In theory, this will reduce the production of the chemical mediators in damaged retina that trigger neovascularisation. The risk of neovascularisation is not reduced if the period between the ischaemic event and PRP therapy is greater than 90 days.[6]

The development of the therapeutic antibodies to vascular endothelial growth factor (anti-VEGF) such as Avastin (bevacizumab) and Lucentis (ranibizumab) has significantly improved the outlook for patients in the early stages of developing NVG, at least in terms

of reducing the risk of neovascular angle closure.[7,8,9] Retrospective studies have shown that intravitreal injections of anti-VEGF can at least temporarily reverse the course of iris and anterior angle neovascularisation, providing improved anatomical outcomes and reduced IOP. Because the action of anti-VEGF injections is temporary, patients normally also require PRP to permanently remove ischaemic areas of retina. They also may require ongoing ocular hypotensive medication or surgery to reduce IOP to acceptable levels.

About 45 per cent of patients with ischaemic CRVO are likely to develop NVG. The risk increases rapidly in the first 100 to 200 days after the ischaemic event.[7]

The optometrist has a critical role to play in the detection and referral of patients at risk of developing NVG.

First, any patient showing signs and symptoms of ocular ischaemic syndrome, CRVO or proliferative diabetic retinopathy, should be referred urgently for medical assessment. These patients need to be examined frequently in the following weeks to detect any neovascular changes. Early obliteration of new vessels with PRP, together with intravitreal injections of an anti-VEGF agent, can halt the proliferation of new vessels, including the development of neovascular glaucoma.

Second, as a part of their annual or bi-annual retinal screening, diabetic patients should also have their irises examined to rule out the presence of early iris rubeosis. Older diabetic patients are at an increased risk of developing NVG after cataract surgery[10] and close examination of peripheral retina and iris might be considered as a part of their later follow-up examination.

Third, it should be remembered that early rubeotic changes in the iris may be invisible to the naked eye. Routine examination of the anterior eye, including the iris, should include careful examination of the iris stroma with slitlamp biomicroscopy to detect new vessel formation potentially linked to a hidden ischaemic condition. This should include gonioscopy in cases of patients at risk of developing NVG.

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Avert errors in prescribing combination medication

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Respiratory function, cystoid macular oedema, sensitivity to the preservative BAK and double-dosing are among many factors to be considered when prescribing combination drops

Combination glaucoma medications are being used more frequently as new and better drops become available. Errors in prescribing these medications are more common than you may realise. They can be easily avoided by familiarising yourself with the drugs contained in the fixed combination medications and their concentrations.

Several possible errors or oversights can occur when prescribing fixed-combination glaucoma medications. One example is prescribing redundant medications. This happened in a case in which a patient had elevated intraocular pressure (IOP) from the topical steroids he was using to treat his iritis. The patient was taking Combigan (timolol 0.5% and brimonidine 0.2%) twice a day for his glaucoma. To further reduce pressure, the practitioner prescribed Timoptic (timolol 0.5%) twice a day. Thankfully, the pharmacist detected the error. This doubled or greater dose of timolol would not decrease the IOP but would certainly increase the risk of side-effects.

In an editorial in *Clinical and Surgical Ophthalmology* in 2008, Dr Leonid Skorin Jr tells of a patient who was referred to him for selective laser trabeculoplasty.[1] This patient had been using Cosopt (timolol 0.5% and dorzolamide 2%) twice a day and Trusopt (dorzolamide 2%) twice a day. His practitioner felt that maximal medical therapy had been tried and he was now ready for laser treatment. Clearly there is a problem here. This redundancy of medications may seem obvious but it is a mistake that could easily happen if you are not careful. You must be familiar with the ingredients of the brand names as the drug names may not always be self-revealing.

Other possible errors could include the following scenarios.

- Be careful not to prescribe a combination medication (all of which contain timolol 0.5%) for an asthmatic patient or someone with other respiratory difficulties without first asking about their respiratory function.[2,3] Alternatively, the patient may have a cardiac condition and a combination medication containing a beta-blocker might be incorrectly prescribed. Beta-blockers can exacerbate many cardiac conditions. Caution must be taken if a patient is using systemic beta-blockers as serious additive adverse effects may manifest when a topical beta-blocker is added.[4]
- You may have a pseudophakic patient with glaucoma and want to switch them to a combination drop. It is conceivable that a combination containing a prostaglandin analogue could be prescribed without fully considering the possibility of causing (or exacerbating) cystoid macular oedema (CME).[5,6] A history of CME has been shown to be a relative contraindication to topical prostaglandin analogue use although more compelling evidence may enlighten this situation.[7,8] Stronger contraindications to prostaglandin analogue use include a history of herpes simplex keratitis, anterior uveitis or complicated intraocular surgery.[9]
- A crucial aspect of managing glaucoma involves establishing a treatment regimen that achieves the maximum therapeutic effect with the simplest administration and the greatest patient tolerability.[4] All of the combination glaucoma medications contain benzalkonium chloride (BAK) as a preservative. BAK is the most common preservative used in topical ophthalmic preparations. The possibility of an adverse reaction in a patient with a history of sensitivity or toxicity to BAK should be considered.
- All of the combination drops containing prostaglandin analogues are once a day dosing, usually in the evening. Timolol 0.5% is the other component of these combination drugs. Timolol can be dosed as once or twice a day when given on its own. The prescribing practitioner may think that because the patient is using timolol 0.5% twice a day, the patient should take the combination drop twice a day as well. If the combination medication contains a prostaglandin, this would be a mistake because some studies

Trade name	Component 1	Component 2	Frequency
Cosopt (Merck)	Timolol 0.5%	Dorzolamide 2%	bid
Xalacom (Pfizer)	Timolol 0.5%	Latanoprost 0.005%	qd
DuoTrav, Extravan (Alcon Laboratories)	Timolol 0.5%	Travoprost 0.004%	qd
Combigan (Allergan)	Timolol 0.5%	Brimonidine 0.2%	bid

Fixed-combination glaucoma medications

have shown that doubling the dose of a prostaglandin analogue can reduce the efficacy of the medication.[10]

Any of these errors are possible if you are not familiar with the combination medications that are available. Combination drops for glaucoma have been around since the 1960s when pilocarpine and epinephrine were combined because of their additive effects. These two drugs represented the only two classes of IOP-lowering agents that were available at the time.[11] With the introduction of timolol in 1978, fixed combinations of timolol and pilocarpine, and timolol and epinephrine increased convenience for patients in the 1980s and 1990s. These combinations had some issues such as differences in optimal administration frequencies for component drugs and instability of the mixture.[11] Newer classes of IOP lowering medications allow combinations that deliver greater efficacy and fewer side-effects.

Currently, the most commonly used classes of glaucoma medications are the prostaglandin analogues, beta-adrenergic antagonists, alpha-adrenergic agonists and topical carbonic anhydrase inhibitors. There are six fixed-combination drops available, one of which has just been released.[12,13] All of them have timolol 0.5% as a component (Table).

There are some definite advantages to using fixed-dose combination eye-drops. Since each drop delivers two medications, the patient will instil fewer drops each day. This is a benefit in itself simply because of the added convenience and comfort to the patient, as well as the reduced complexity of the dosing regimen. There is also decreased exposure of the ocular surface to preservatives and less wash-out effect.[11] All of these add up to a greater probability of compliance with the therapy, leading to better control of intraocular pressure.

There are some disadvantages in combination medications. The medications are combined into one solution and so the concentrations are not adjustable, and the dosing frequency may not be ideal for a particular patient. For example, Cosopt contains dorzolamide and timolol and is given twice a day. This is acceptable for timolol but dorzolamide is often administered three times a day on its own. Timolol should not be given three times a day. This raises another disadvantage. The combined components may not always provide the same efficacy as the individual components administered concurrently.

Glaucoma is already a complicated condition to diagnose and treat. It does not need to be further complicated by introducing confounding variables into the treatment. If practitioners take a few minutes to familiarise themselves with the ingredients and concentrations of the combination glaucoma medications, some potentially frustrating or harmful mishaps can be avoided.

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Genetic testing in a new decade

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Recent scientific advances have substantially improved opportunities for diagnosis, management and assessment of genetic risk.

Ophthalmology has a long history in medical genetics. Nearly 25 centuries ago Hippocrates recognised that the trait of blue eyes was inherited and in 350 BC, Aristotle commented on the transmission of vision impairment across generations.[1] Colour blindness was one of the first human genetic traits to be identified and linked to the X-chromosome, observed by Swiss ophthalmologist Johann Horner in the 1870s.[2] Today, more than 400 genes that cause or contribute to ophthalmic conditions have been cloned or mapped.

Genetics in glaucoma

A family history of glaucoma has long been recognised as a major risk factor for developing the disease. The Rotterdam Eye Study found first-degree relatives (parents, children and siblings) of those with glaucoma had 10 times the risk of developing the disease compared to the general population.[3] The Glaucoma Inheritance Study in Tasmania (GIST) reported that 60 per cent of glaucoma sufferers in Tasmania had a family history of glaucoma, with two-thirds of them involving a first-degree relative.[4] This suggests that specific gene mutations may contribute to the pathogenesis of glaucoma.

Glaucoma genetics has rapidly evolved and it is important to recognise that glaucoma can be inherited in an autosomal dominant or recessive fashion or as a complex multifactorial trait.[5] There are several forms that have been linked to specific genes and susceptibility loci.[5]

Genetic testing

Genetic testing has many uses and can be classified according to the specific purpose.[6]

Diagnostic

Genetic testing can be used to confirm or exclude a genetic disease in individuals who are symptomatic.[7] It can be used to help estimate specific inheritance patterns and recurrence risks, and provide more information about likely prognosis.[6] In glaucoma, certain mutations have been associated with particular aspects of the disease phenotype and this has been demonstrated in Australian myocillin (MYOC) glaucoma families.[8,9] The development of genotype-phenotype databases for glaucoma genes and mutations will be an important step towards clinically useful DNA-based diagnostic testing for glaucoma.[5]

Predictive

The outcome of a diagnostic genetic test for glaucoma is of great relevance not only for the patient but also for first-degree relatives. If the gene mutation has been identified in a glaucoma patient, all the patient's first-degree relatives may be tested and given an important opportunity for disease prevention. This process is known as cascade screening (Figure right). A relative who carries the mutations should receive more stringent glaucoma surveillance than the general population.

Counselling

Patients should be given detailed genetic counselling before undergoing genetic testing to ensure that they understand and can weigh up factors such as benefits, risks, limitations, potential for discrimination and implications of a particular test before making an informed decision.[10]

Because appropriate treatment may slow the progression of glaucoma in many cases, predictive DNA testing for this disease differs considerably from conditions such as retinitis pigmentosa for which there is no treatment. It is beneficial to diagnose glaucoma as early as possible before irreversible damage has occurred. This process has been shown to be acceptable and is considered good practice by most patients and their relatives.[11]

The interpretation of genetic testing can be either straightforward or complex. Very careful counselling is warranted in patients who are offered predictive DNA testing when a mutation has already been identified in a family member. For example, a negative test result does not mean that they won't develop glaucoma, but their risk is equal to that found in the general population so they should still adhere to routine glaucoma screening guidelines.[12]

Testing services

Despite an increase in the number of genetic tests available, many are not covered by the Medicare Benefits Scheme (MBS). Patients who pursue non-MBS rebated tests are either required to pay for this privately or enrol in research studies.[13,14]

- Although it is not covered under the MBS, it is possible to arrange for myocilin genetic testing through the Australian and New Zealand Registry of Advanced Glaucoma (www.anzrag.org). This is at no

cost to the patient and funded by the Eye Foundation (affiliated with Royal Australian and New Zealand College of Ophthalmologists), Glaucoma Australia, National Health and Medical Research Council and various other research foundations.

The aim of the registry is to provide the world's largest cohort of advanced glaucoma cases with clinical information and DNA to ascertain new glaucoma risk profiles. It offers a clinical service for participants by screening for known gene mutations (such as MYOC and CYP1B1).

Other international laboratories offer glaucoma genetic testing, which can be located by accessing web-based reference databases to select the correct test and laboratory.

- Genetests, (www.genetests.org), supported by the National Institute of Health, is a very useful directory of laboratories that can conduct specific tests and provides reviews on genetic disorders including subtypes of glaucoma and other ophthalmic conditions. The descriptions are searchable by disease name, gene symbol, protein name, feature, author or title. It also provides laboratory-specific information, linking it to the laboratory website, names of laboratory directors, availability of prenatal and carrier testing and certification information.
- Orphanet (http://www.orpha.net) is another database, funded by the European Union, which provides a large directory of research and clinical laboratories. At the time of this submission there was limited information on POAG, yet details were available for developmental glaucomas.

Information in these database resources are linked to the Online Mendelian Inheritance in Man (OMIM) (www.ncbi.nlm.nih.gov/omim/) database, PubMed (www.ncbi.nlm.nih.gov/pubmed/) and other search tools from the National Centre for Biotechnology and Information.

The challenge for practitioners is to translate medical research into clinical care. Work continues to identify new glaucoma genes, and develop sensitivity and specificity parameters, genotype-phenotype correlations, and information on prevalence and penetrance that will provide more accurate genetic counselling for patients and their families to eliminate the world's leading cause of irreversible blindness.

Acknowledgement

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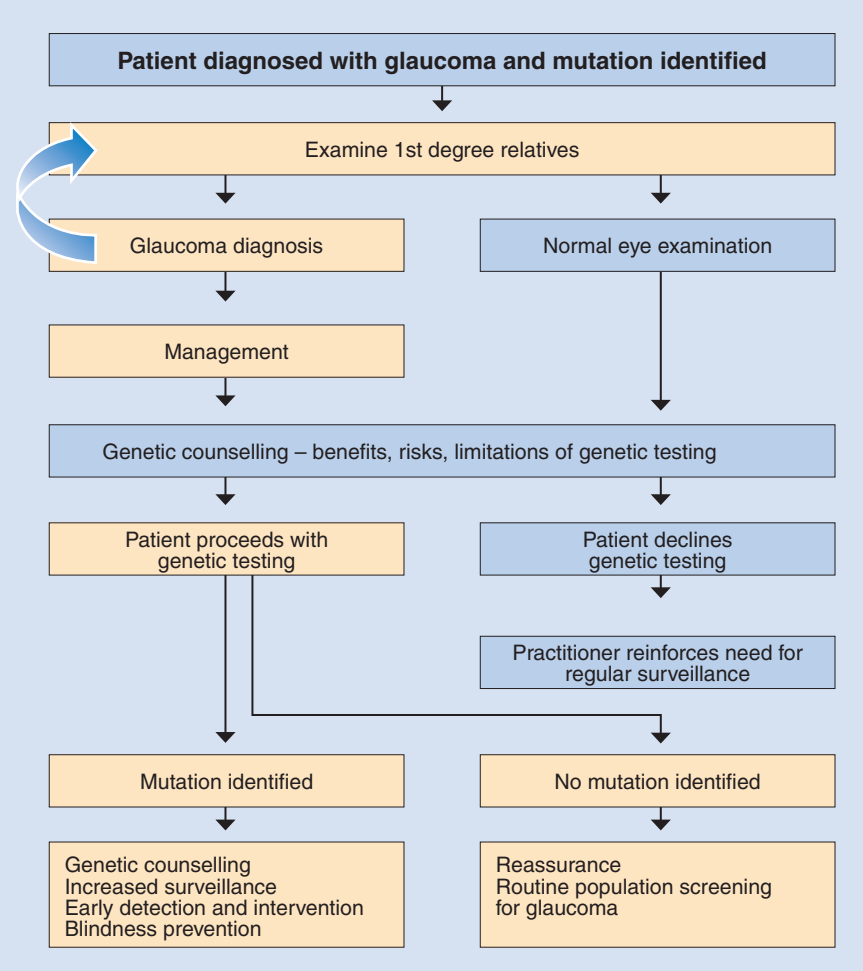

Cascade genetic testing in glaucoma

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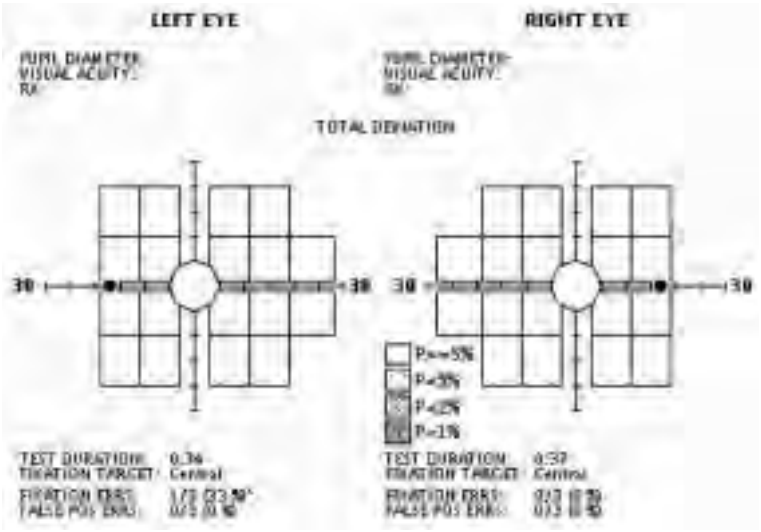


Figure 1

Asymme

Case report

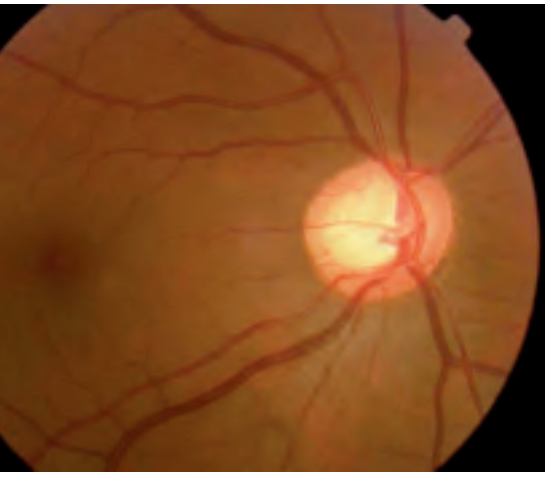


Figure 2

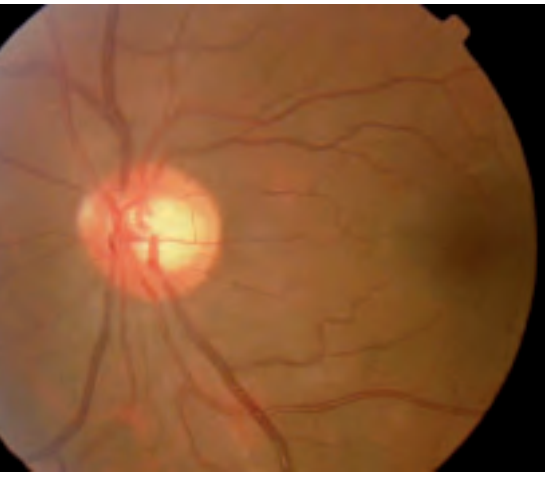


Figure 3

A 48-year-old African American male presented for a comprehensive eye examination. His medical history was pertinent for asthma and hypercholesterolemia, and he was using medications to treat both conditions. His and his family's ocular history were negative. His visual acuity uncorrected was 6/6 in OD and OS, and the pupil examination was negative. His intraocular pressures (Goldmann tonometry) were 19 OD, 17 mmHg OS at 9.30 am. The FDT N 30-5 screening field was full in each eye (Figure 1).

A dilated optic nerve examination took place with the optic disc appraised as being large, the right disc larger than the left (Figures 2 and 3). The ISNT rule was not obeyed in the OD with thinning superiorly. There was no sign of peripapillary atrophy, disc haemorrhage or RNF loss in either eye. The cup/disc ratio was appraised to be 0.7 x 0.7 OD and 0.5 x 0.5 OS. Imaging was performed because the patient was dilated with Heidelberg Retinal Tomography the first time. The HRT images (Figure 4) were of acceptable quality and showed the disc to be large and several sectors flagged at the borderline level in the OD, and two sectors flagged in the OS (one sector was flagged at the highest probability level).

The GDx was also performed and the images were of excellent quality (Figure 5). RNFL loss was seen in both eyes superiorly temporal, with the defect larger in the OD. The TSNIT plots showed asymmetry with greater loss OD, especially inferiorly and the NFI was 33 OD and 12 OS. The GDx was borderline in each eye, with apparent loss OD and suspicious loss OS even though the NFI was in the so-called normal range.

Cirrus OCT was performed and the images were of a very good quality (Figure 6). The images were in focus, centred and evenly illuminated. The superior RNFL was very thin OD, as seen by the quadrant and sector maps, RNFL thickness deviation plot and RNFL TSNIT normative data scales. The OS appeared to be within a normal range and no apparent loss was seen. There was asymmetry with the OD being thinner, especially in the OD. The patient was labelled as a glaucoma suspect due to the suspicious nature of the optic nerves, especially OD and seen with direct dilated examination and confirmed with imaging.

The patient was to return in two to three weeks for pachymetry, gonioscopy, repeat IOP measurement and 24-2 SITA Standard visual fields. The patient returned within the month. IOP measurements were 18/15 mmHg at 9.20 am and pachymetry was 498 µm OD, 501 µm OS. Thin corneas increased the risk for glaucoma developing and gave the impression that IOP was higher than was measured, although how much higher was not clear. Gonioscopy revealed the angles to be wide open with 1+ pigment observed in the trabeculum meshwork. The right visual field was of acceptable reliability (Figure 7). While the field readings showed low test reliability, the fixation loss that triggered this flag occurred at the very onset of the test. Within the first minute the patient's performance steadied (also seen by the gaze tracker at the printout bottom) and overall the performance was more than acceptable.

An inferior partial arcuate scotoma is

tric POAG

Dr Murray Fingeret
OD

present, which correlates with the right optic nerve appearance. The left field's reliability (Figure 8) is very good and the few points flagged are scattered throughout the field with no pattern present. The GHT is within normal limits. The patient was diagnosed with primary open angle glaucoma, based on the optic nerve and visual field results. Before commencing therapy, we took one more IOP measurement and performed selective perimetric tests. When the patient returned a few weeks later, the IOP was 20/15 mmHg at 12 pm. The IOP was always several points higher at each visit in the eye with the greater amount of damage.

HFA 24-2 SITA Standard visual fields were repeated (Figures 9 and 10) with a subtle defect again observed inferiorly OD but not as pronounced as in the initial field test. FDT 24-2 threshold perimetry (Figures 11 and 12) showed an inferior partial arcuate defect, similar to that seen with the HFA perimeter. The OS field showed some scattered points, not necessarily in a cluster or pattern but suspicious nonetheless.

Continued page 24

FDT	frequency doubling technology
GHT	Glaucoma Hemifield Test
HEP	Heidelberg Edge Perimetric
HRT	Heidelberg Retinal Tomograph
IOP	intraocular pressure
ISNT	inferior superior nasal temporal
NFI	Nerve fibre index
OCT	optical coherence tomography
RNF	retinal nerve fibre
TSNIT	temporal superior nasal inferior temporal

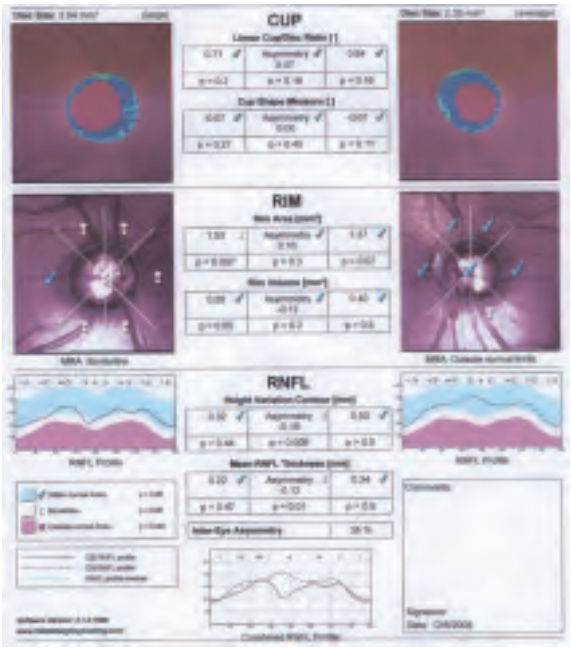


Figure 4

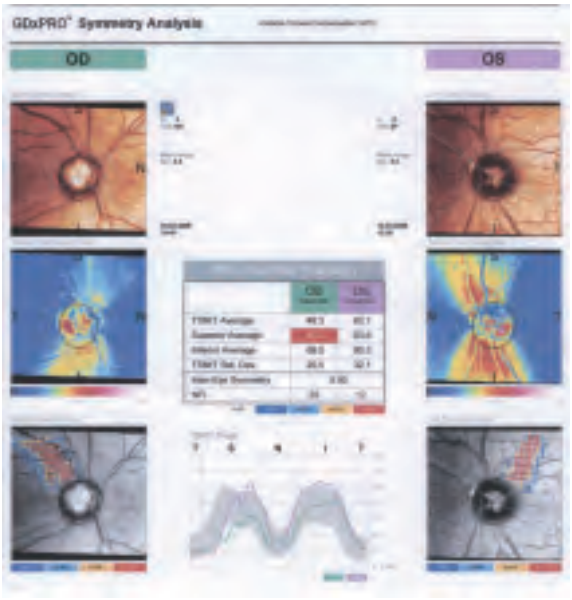


Figure 5

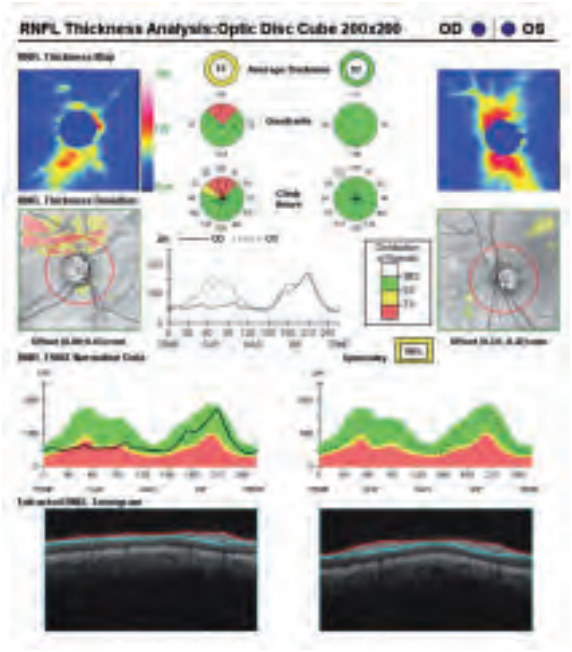


Figure 6

Asymmetric POAG

From page 23

The patient was prescribed prostaglandin in each eye once per day, and told to return in three weeks to assess medication efficacy. A Heidelberg Edge Perimetric visual field was performed (Figure 13) a few months into therapy and the inferior defect was obvious in the right eye. The left eye was clean.

This is an example of early glaucoma with damage present in the right eye as seen by cup/disc asymmetry with the OD being larger and a notch and thinning present superiorly OD. Imaging (GDx, HRT and OCT) confirmed loss OD, with each instrument consistent in their assessment. The GDx also found some loss in the left eye, which is not unusual but no other test confirmed this loss. Visual fields done with HFA, FDT or HEP revealed consistent loss in the right eye that correlated with the mild field damage, with the left eye being full at this time.

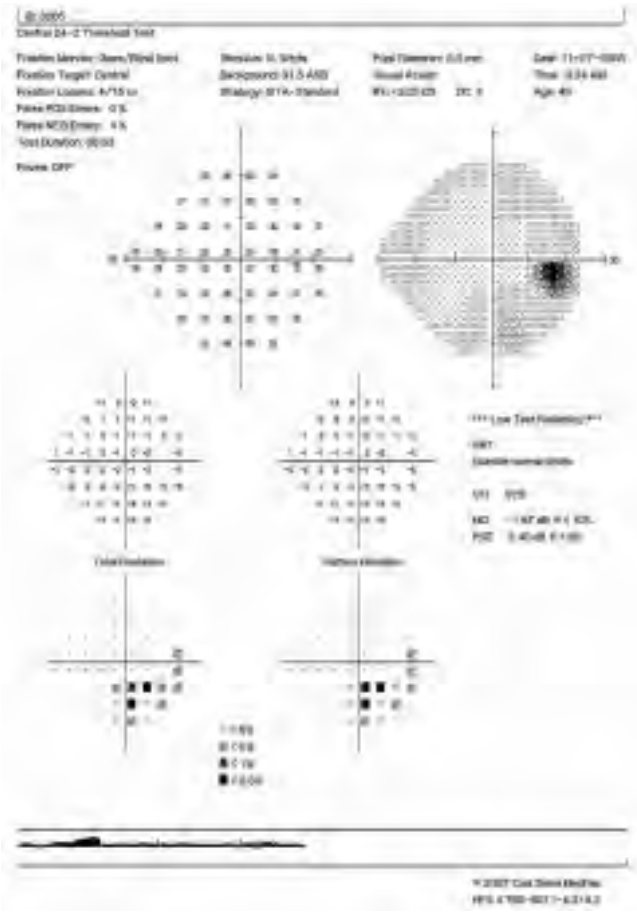


Figure 7

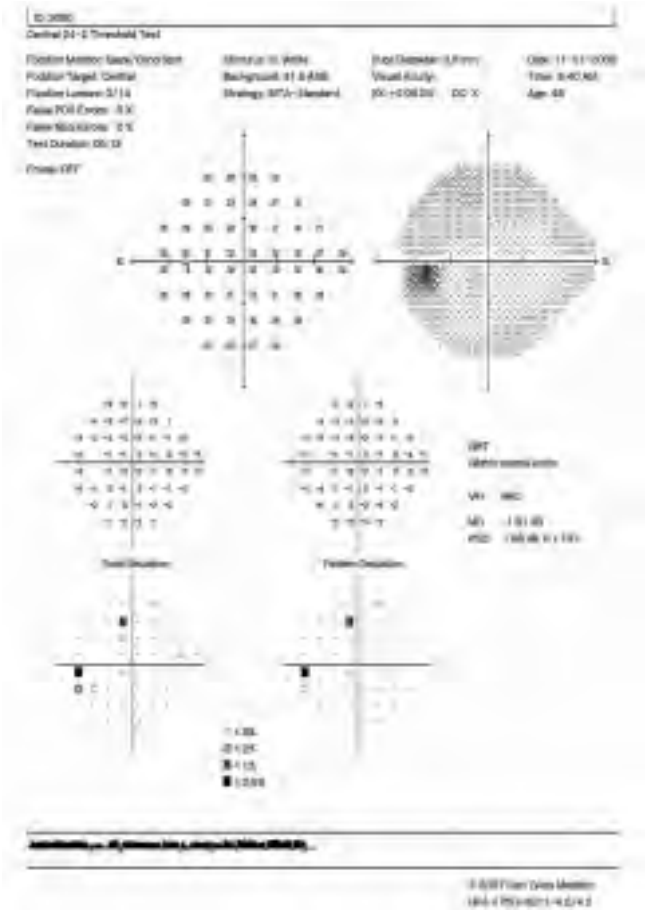


Figure 8

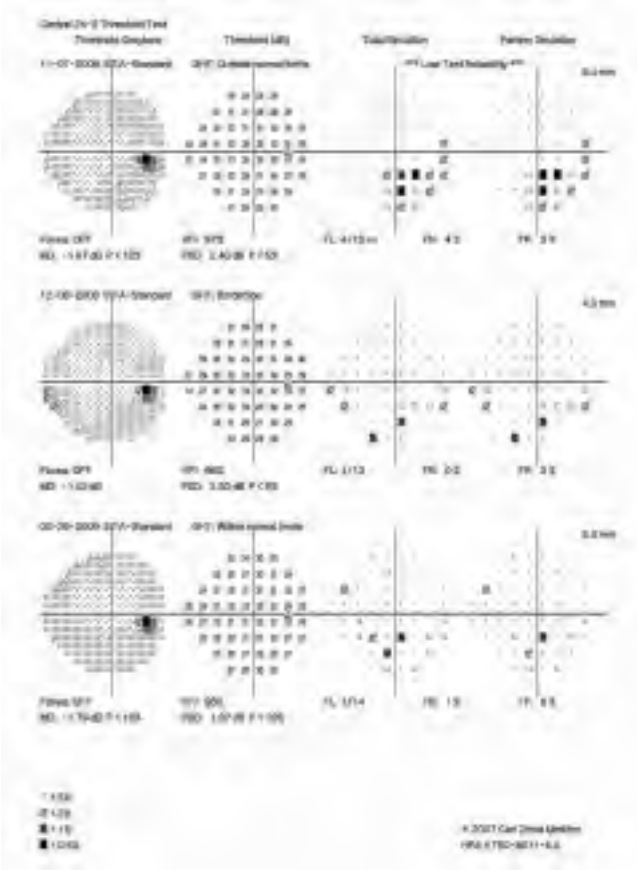


Figure 9

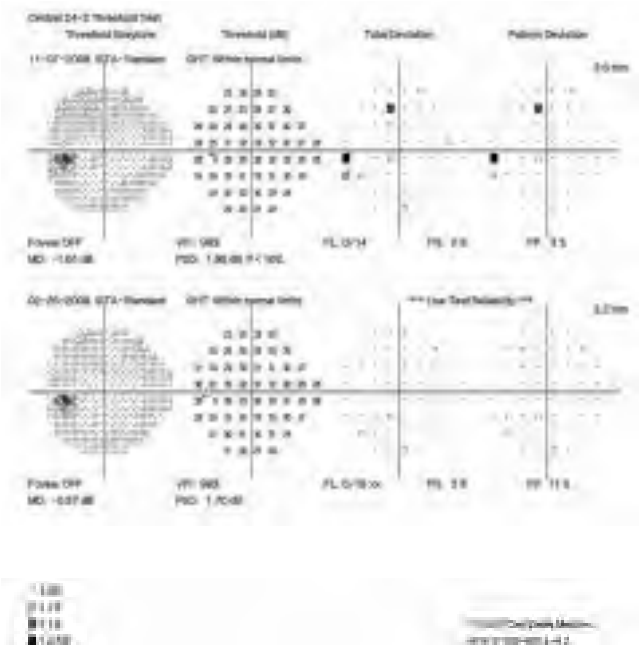


Figure 10

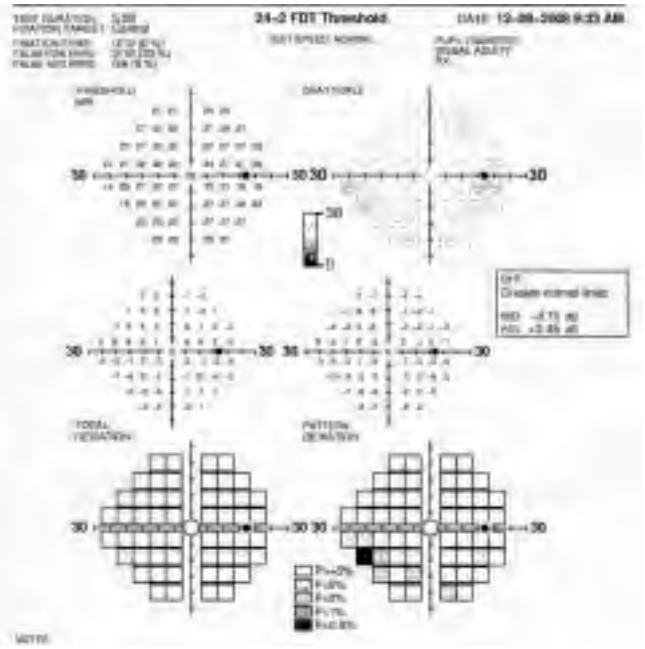


Figure 11

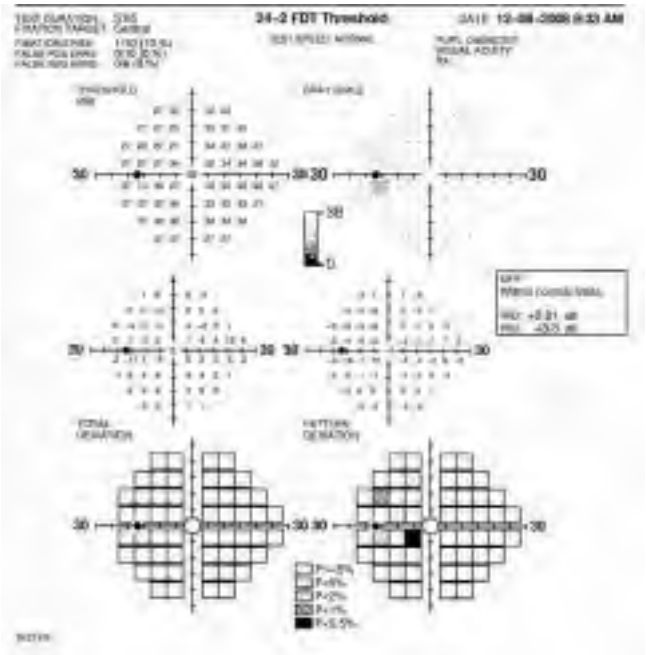


Figure 12

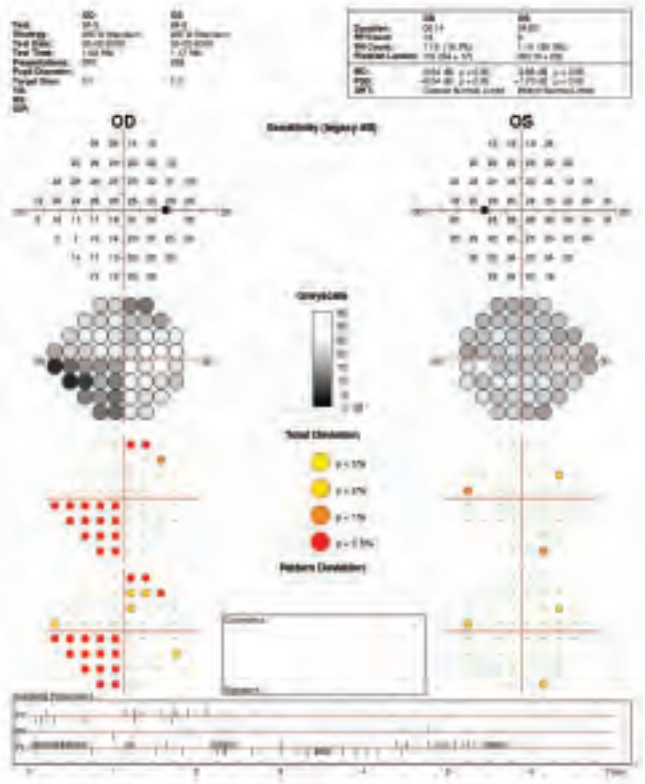


Figure 13

Make it count

After Anna Morse completed her therapeutic endorsement, remote communities across the Northern Territory were winners. **Jennifer Greive** reports

The most satisfying part of Anna Morse's job is being able to see the benefit her work brings to people.

Since becoming therapeutically endorsed two years ago, Morse feels better equipped to provide primary eye care to her patients and says her confidence and accuracy in diagnosing anterior eye diseases have improved.

'Being able to simply prescribe chloramphenicol for a child's bacterial conjunctivitis, or manage a case of recalcitrant allergic conjunctivitis with a short course of FML enhances my clinical scope and job satisfaction,' she said. 'More importantly, it provides a more accessible primary eye-care service to the community.'

Morse is project development officer for the International Centre for Eyecare Education (ICEE) Aboriginal Eye Care Program, and spends half her time providing outreach optometric services to remote Aboriginal communities. She helps teach local health workers the basics of eye care to help strengthen referral pathways.

The rest of Morse's time is spent at Danila Dilba Health Services, Darwin's Aboriginal medical service, where she provides regular consultations and works alongside general practitioners, Aboriginal health workers, nurses, dieticians and other allied and specialist health professionals.

She says by working with local GPs and pharmacists she is helping to provide the local Aboriginal community with accessible eye care. 'GPs or health workers often ask me about a patient they are managing, either referring them to me or asking me to pop in to check a red eye,' she said. 'I have also established a good relationship with the Royal Darwin Hospital ophthalmology clinic.'

Optometrists in the Northern Territory can prescribe ocular therapeutic medicines including anti-glaucoma preparations but patient follow-up can be difficult, especially in remote areas where an optometrist may visit only once or twice a year.

The most commonly prescribed topical ocular drugs are always available at Danila Dilba, and some remote clinics stock prednisolone or dexamethasone for patients who have undergone cataract surgery.

'Cataracts are very common, particularly in remote communities in the Northern Territory where blinding cataracts are not unusual,' Morse said. 'This may be caused by the accumulated UV exposure that comes with living in the Territory. There is a misperception among some people that loss of vision and even blindness is just a normal part of ageing. Some fear cataract surgery, believing that people who go to hospital often don't return.'

Prior to joining ICEE, Morse practised at Laubman & Pank in Alice Springs for four years, participating in regular outreach eye clinics with an ophthalmologist and providing locum service across Australia.

She worked as a locum in Brisbane while studying therapeutics at Queensland University of Technology, having secured a scholarship from Services for Australian Rural and Remote Allied Health, which covered some of the costs involved in undertaking the course.

Although Morse no longer prescribes as often as she did while practising full-time in Alice Springs, she encourages all optometrists working in the Northern Territory to gain endorsement. 'Particularly if you're working in a smaller area, getting endorsed will be beneficial for you and the community,' she said.

'A therapeutically-endorsed optometrist practising in the Northern Territory would certainly never find their prescription pad gathering dust.'

Photo: Dean Saffron, ICEE

Tools of the trade

Matthew Wensor
Product manager
Carl Zeiss Instruments

With an ageing population and early detection of glaucoma critical, much responsibility is placed on optometrists to make a timely and accurate diagnosis. How well are you equipped for the task?

Glaucoma is not a straightforward disease and in many cases its diagnosis is uncertain. Studies have shown that about 50 per cent of glaucoma cases are undiagnosed,[1,2] **and that about half of patients with undiagnosed glaucoma have visited an eye-care professional in the previous 12 months.**[3] **Optometrists play a pivotal role in the diagnosis of glaucoma and are often the first point of contact, so it is crucial that they have the appropriate tools to diagnose this disease.**

In the past few years there have been technological developments in glaucoma detection, particularly in regards to early detection, which is critical.

FDT	frequency doubling technology
GPA	guided progression analysis
NFI	nerve fibre indicator
OCT	optical coherence tomography
RNFL	retinal nerve fibre layer
SAP	standard automated perimetry
SLP	scanning laser polarimetry
SWAP	short wavelength automated perimetry
VFI	visual field index

Perimetry

Perimetry has been part of glaucoma detection for many years but more recently, advances have assisted practitioners in the early detection of glaucoma. Among them, Frequency Doubling Technology (FDT), which is used by the Humphrey Matrix and Humphrey FDT, has gained great acceptance in optometry in Australia.

The FDT stimulus is different from the traditional stimulus in that it consists of vertical black and white bars that flicker at greater than 15 Hz. At this rate, the patient perceives that the stimulus has double the number of stripes than there actually are, hence the name 'frequency doubling'. Research has shown that this stimulus is excellent in detecting glaucoma and, in some instances, up to four years earlier than standard automated perimetry (SAP).[4]

One great advantage of FDT technology is that a screening test can be completed in about 30 seconds per eye, which makes it viable to test more patients at risk.

Short wavelength automated perimetry (SWAP) or blue-yellow perimetry has similarly been shown in the literature to detect glaucoma prior to SAP, in some cases three to five years earlier.[5] It does this by specifically targeting the blue-sensitive cones and excluding the red and the green. In the past, this test has been difficult to use in the clinical setting due to the long test time, but of late SITA SWAP on the Humphrey Field Analyzer has been developed to cut the test time to about four minutes per eye.

Advances in progression software have also been important. Trying to manually differentiate between true progression and normal variability in a glaucoma patient is very difficult, especially because the visual fields of glaucoma patients vary more than those of a 'normal' patient. Progression software uses statistical analysis and predetermined criteria to flag progressing patients in an objective and consistent way.

For example, the Guided Progression Analysis (GPA) software on the Humphrey Field Analyzer compares up to 14 visual fields for a specific patient to a pair of baseline fields and flags progression as defined by the criteria used on the Early Manifest Glaucoma Trial. Additionally, it uses a dedicated index (Visual Field Index or VFI) to determine the rate of progression, which is very important to know for treatment decisions.

Importantly, GPA also projects the analysis five years to give an estimate of the patient's condition if the current rate of progression continues. This analysis is valuable for the practitioner to make decisions on appropriate treatment and can be used as a patient educational tool to promote treatment compliance.

Continued page 28

Tools of the trade

From page 27

Optical coherence tomography

Optical coherence tomography (OCT) has been used for almost 15 years but is only now becoming popular in optometry. Carl Zeiss produced the first three generations of OCT including the Stratus OCT in 2002, which marked the start of its general use in Australia. Since then, spectral domain technology has allowed higher resolution and faster scanning speeds to enable three-dimensional imaging of the retina, including the optic nerve head.

The most established and validated way to use OCT for glaucoma is the measurement of the retinal nerve fibre layer (RNFL) thickness. Depending on the OCT instrument, the RNFL is measured either with a manually-placed circular scan around the optic nerve head or a more comprehensive three-dimensional cube scan that covers the whole peripapillary region including the optic nerve head. The RNFL is then often compared to an age-matched normative database to indicate whether the scanned RNFL lies within or outside normal limits. The right and left eye is also presented on the same page so that the practitioner can assess the eyes for possible asymmetry.

The optic nerve head can also be imaged and the various parameters such as C/D ratio and neuroretinal rim volume may be measured against normative data.

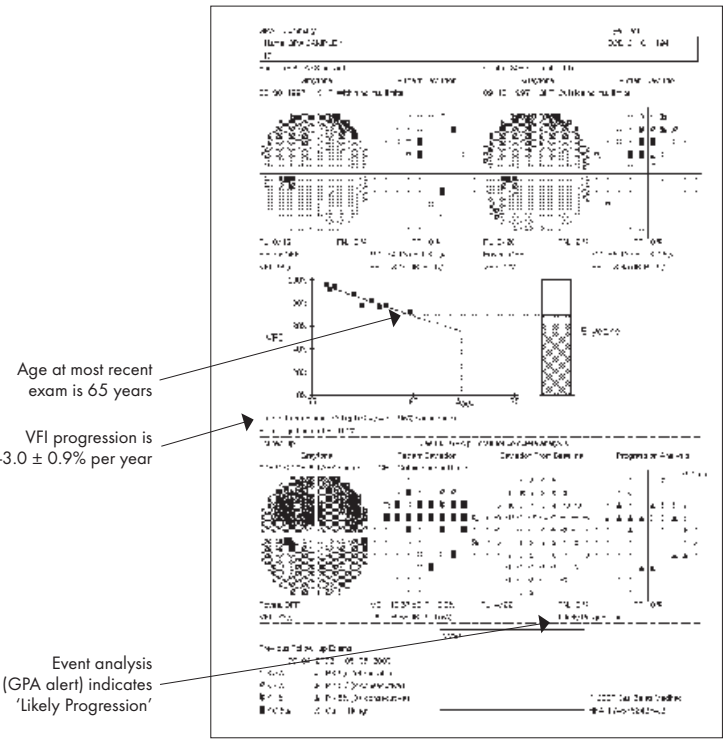


Figure 1. GPA summary report (Humphrey Field Analyzer). The printout is divided into three sections. The top section shows the baseline fields, the middle section shows the rate of progression and the bottom section shows a summary of the most recent field. This patient shows significant and rapid progression.

Like perimetry, OCT also lends itself to progression analysis. For example, the Cirrus HD-OCT features guided progression analysis, which flags scans that progress more than the known test-retest variability of the unit compared to a pair of baseline scans. The software also classes the likelihood of progression using the same categories as the GPA on the Humphrey Field Analyzer so that the practitioner can match their structural and functional testing together.

OCT also offers the possibility of imaging the anterior segment for the assessment of the angle (for closed-angle glaucoma) and central corneal thickness. Most retinal OCTs offer this capability and it is a useful addition, although the wavelength of light that they use is not optimised for this purpose. The best solution is a dedicated anterior segment OCT like the Visante OCT, which uses a longer wavelength of light. This enables it to penetrate opaque tissue such as the sclera to enable imaging and measurement right into the angle, which is otherwise not possible.

Scanning laser polarimetry (SLP)

The only scanning laser polarimeter on the market is the GDxPRO. This instrument projects polarised light into the eye and measures the phase shift of the light as it passes through the RNFL. Due to the way it measures, the resulting scan represents both the thickness and the integrity of the RNFL. The results are then presented against an age-matched normative database for assessment.

The GDxPRO requires no pupil dilation and takes only minutes to perform, so it lends itself to rapid screening of patients at risk.

One useful feature of the GDx is an index called nerve fibre indicator (NFI). NFI is a score that ranges from 1 to 100, with the higher scores representing higher likelihood of glaucoma. Interestingly, it is not based on normative data but uses pattern recognition artificial intelligence and it has been consistently shown in the literature to be the best single indicator on the GDx to differentiate between normal and glaucomatous eyes.

Recently, guided progression analysis has also been added to the GDx. It works in the same way as described above in the OCT section and uses the same progression categories for consistency between platforms.

Fundus photography

Non-mydriatic fundus cameras can be valuable tools for glaucoma. Many fundus cameras offer the ability to create stereo photographs of the optic nerve head for documentation and qualitative optic nerve head assessment. Many models also allow imaging with blue or green filters that help to highlight the RNFL, although this is a qualitative technique only.

As shown above, there are many new tools at optometrists' disposal to assist in the detection of glaucoma. With the growing uptake of such technologies and the move towards ocular therapeutics, the importance of optometry in glaucoma detection and management is growing. With the increasing number of glaucoma patients caused by the ageing population, it will become more important.

1. Weih, LM et al. Prevalence and predictors of open-angle glaucoma: results from the Visual Impairment Project. *Ophthalmology* 2001; 108: 1966-1972.
2. Mitchell et al. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996; 103: 1661-1669.
3. Wong E et al. Detection of undiagnosed glaucoma by eye health professionals. *Ophthalmology* 2004; 111: 1508-1514.
4. Medeiros FA et al. Frequency doubling technology perimetry abnormalities as predictors of glaucomatous visual field loss. *Am J Ophthalmol* 2004; 137: 5: 863-871.
5. Johnson CA et al. Blue-on-yellow perimetry can predict the development of glaucomatous visual field loss. *Arch Ophthalmol* 1993; 111: 645-650.

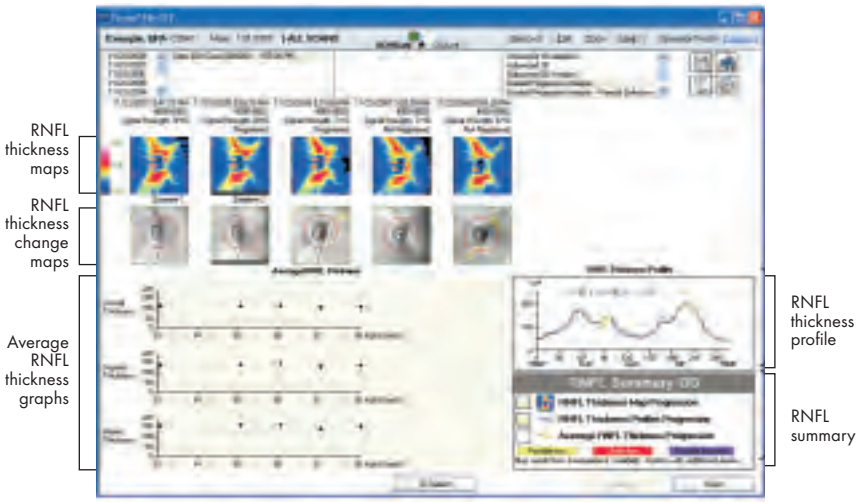


Figure 2. Cirrus HD-OCT (Guided Progression Analysis) display. The RNFL summary in the bottom right corner indicates whether each of the three analyses shows significant change. In this instance, the analysis gives a rating of 'possible loss' for two of the three displays. The RNFL thickness map and RNFL thickness profiles (both significant) are more sensitive to focal RNFL defects, whereas the Average RNFL thickness graphs (not significant in this case) are more sensitive to diffuse defects. The latter will display a trend line only if significant progression is detected.

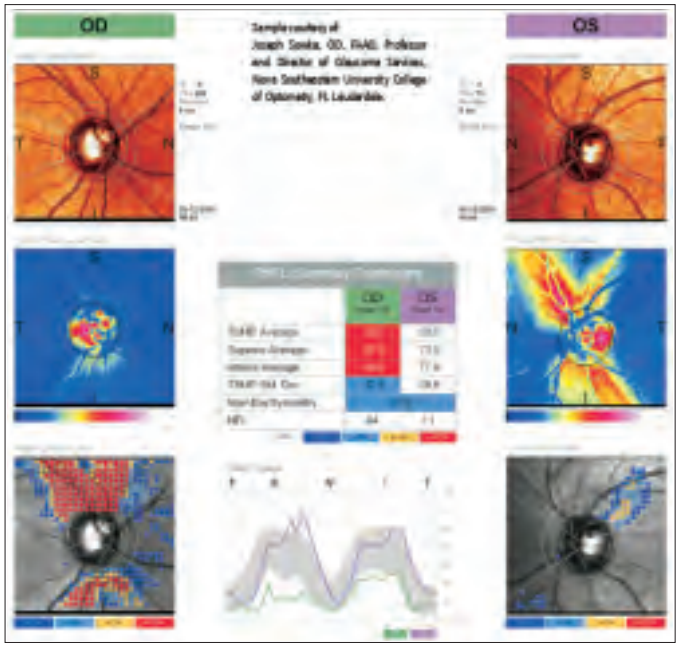


Figure 3. This GDxPRO symmetry analysis print-out shows a patient with significant RNFL loss in the right eye and possible early loss in the left eye. The nerve fibre layer map for the right eye (middle left) shows a lack of 'hot' colours superiorly and inferiorly, thus indicating universally reduced RNFL thickness/integrity. The right eye deviation map (bottom left) shows broad areas of significantly depressed RNFL indicated by the red, yellow and blue pixels. The left eye deviation map (bottom right) shows a possible subtle focal defect (superotemporal region). The TSNIT graph (bottom centre) shows great asymmetry between eyes and the NFI is 94 for the right eye, which indicates that glaucoma is likely.

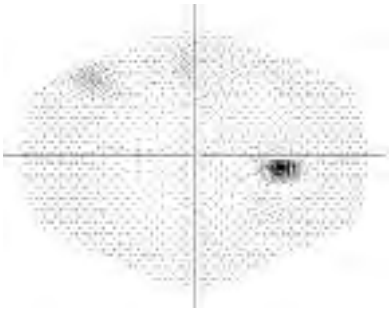
Technology improves patient care

John Warren
BScOptom GradCertOcTherap

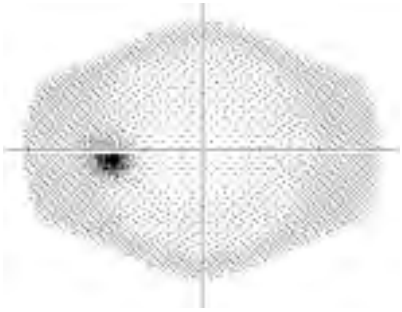
One optometrist demonstrates how technological innovation has revolutionised the way he treats glaucoma patients

Before computerised diagnostic equipment, glaucoma care consisted of measuring IOP, observing the optic nerve head and measuring visual fields. I am dating my time at university when I mention Schiotz tonometry, direct ophthalmoscopy and a Bjerrum screen but that was what most optometrists had available to them in the 1970s. Technology has continued to provide us with quicker, more accurate and more cost-effective methods of assessing visual function, enabling us to provide a higher level of eye care to our patients.

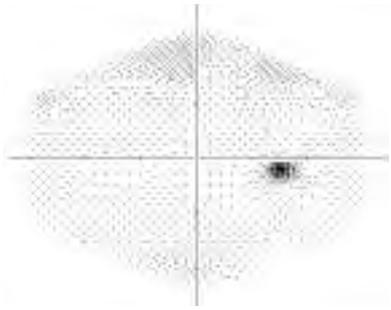
The following is a list of some of the technological advances in the care of glaucoma that have occurred during my career. This list is not intended to be exhaustive but rather just to remind us of the level of improvement and availability of care that has occurred in recent years.



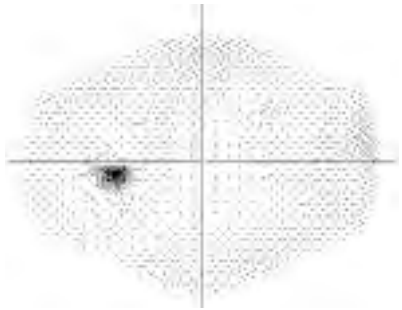
Right eye: 2000



Left eye: 2000



Right eye: 2009



Left eye: 2009

Historical advances

Tonometry has progressed from initial digital palpation to Schiotz, MacKay-Marg, Goldmann, Perkins and Reichart non-contact. The latest generation electronic tonometers include the Tonopen and Icare rebound tonometer.

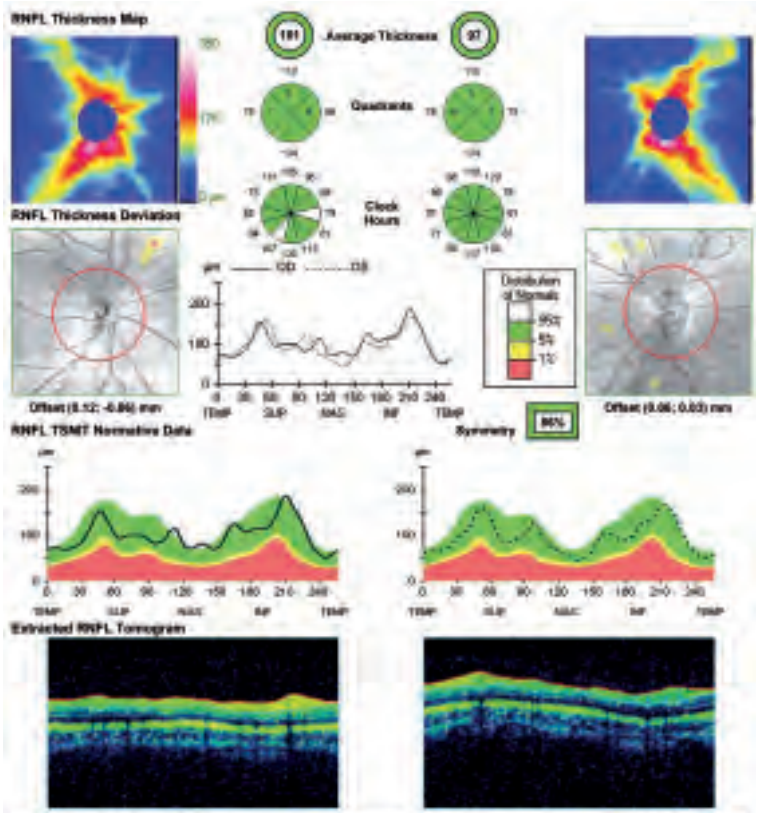
Corneal thickness has long been known to influence IOP measurement by conventional applanation means. Because IOP is the main risk factor for the progression of glaucoma, accurately measuring central corneal thickness is imperative to determining likelihood of disease progression.[1]

Visual fields have progressed from confrontation to kinetic methods, and from Bjerrum and Goldmann to threshold static, Medmont and Humphrey. Recent advances include frequency doubling techniques and short wavelength automated perimetry.

Optic disc assessment has progressed from monocular direct ophthalmoscopes to binocular indirect methods, which are still regarded by many experts as the gold standard. We now use digital imaging, including photography and tomography, such as OCT and HRT.

Studies have shown the detectability of glaucomatous change using various techniques of visual field and disc imaging, including OCT; all are useful methods for discriminating between healthy eyes and eyes with early glaucoma. Among the OCT parameters, nerve fibre layer thickness has the highest sensitivity for detecting early glaucomatous changes in glaucoma suspect patients.[2]

1. Patwardhan A et al. The importance of central corneal thickness measurements and decision making in general ophthalmology clinics: a masked observational study. *BMC Ophthalmology* 2008, 8: 1.
2. Nomoto M et al. Detectability of glaucomatous changes using SAP, FDT, flicker perimetry and OCT. *Br J Ophthalmol* 2009; 93: 139-143.



Case report

March 2000

PC, a 56-year-old white male, presented with a strong family history of glaucoma. Visual acuity was 6/5 R and L with refraction of -0.50 R and -1.0 L. Optic media was clear. IOP was measured at 24 R and L. Optic disc appeared normal with a 0.2 cup disc ratio. Visual field results show no defect. The patient was diagnosed with ocular hypertension as the disc appearance and visual field results were normal. The patient was monitored over time and showed no significant change.

December 2006

There were no signs or symptoms to suggest any change. IOP at this visit was 22 R and L. Additional testing was to measure central corneal thickness at 570 microns R and 560 microns L using a Pachmate pachymeter. This measurement indicated that the measured value of IOP could be lowered by approximately 2 mmHg R and 1 mmHg L due to PC's cornea being slightly thicker than the average of 540 microns. The absence of a thin cornea decreased the risk of glaucoma. Visual field was again unchanged.

April 2009

IOP was measured at 26 R and 24 L. Digital photographic images were taken.

December 2009

IOP was measured at 26 R and 25 L. Additional testing included a Cirrus OCT of the optic nerve head, which showed normal thickness of the retinal nerve fibre layer. The clinical impression was still consistent with a diagnosis of benign ocular hypertension.

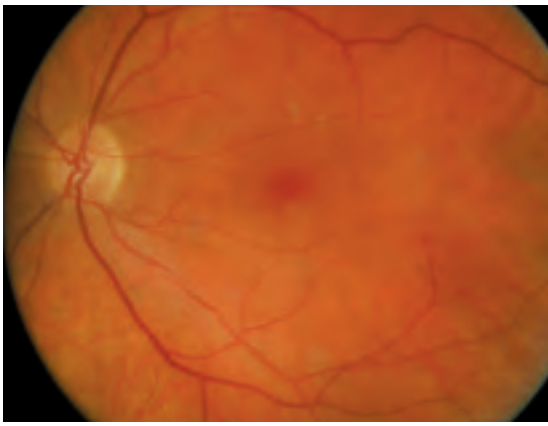
Discussion

Patient monitoring has improved in the past couple of years. Although PC's IOP has fluctuated slightly, it still remains in the mid-20s. The minimum accepted practice standard of care of measuring IOP, visual field and dilated pupil fundus examination all indicate this patient to have ocular hypertension. The additional information of central corneal thickness and OCT scan of the retinal nerve fibre layer reinforce and complement the basic findings.

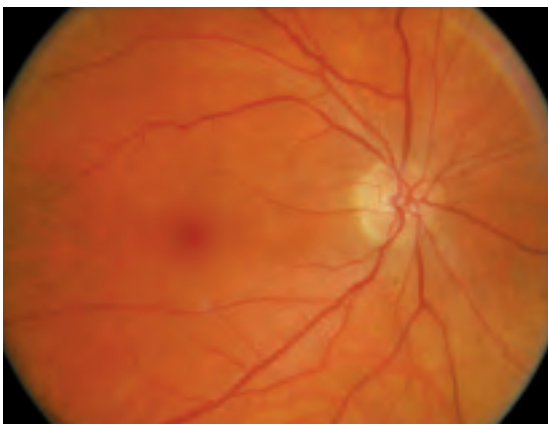
The purchase of a Pachmate pachymeter is a relatively inexpensive addition to the testing regime in glaucoma, allowing the borderline IOP measurements to be fine-tuned up or down as indicated. Low-20s IOP with a thick cornea can be normal, whereas low-20s IOP with a thin cornea can raise concern.

OCTs, used to measure retinal nerve fibre thickness, have become more readily available to optometrists. Being able to make a progression analysis assessment is another way technology assists in providing an increased level of care to the patient.

Using technology to thoroughly examine and monitor your patient's visual status provides continuity of care and is cost-effective, particularly in rural areas where referral for secondary ophthalmological care may not be as easy as in metropolitan areas. ■



Right eye



Left eye

Measure IOP every two hours

Taking IOP measurements over the course of the day can eliminate inaccuracies caused by pressure fluctuations

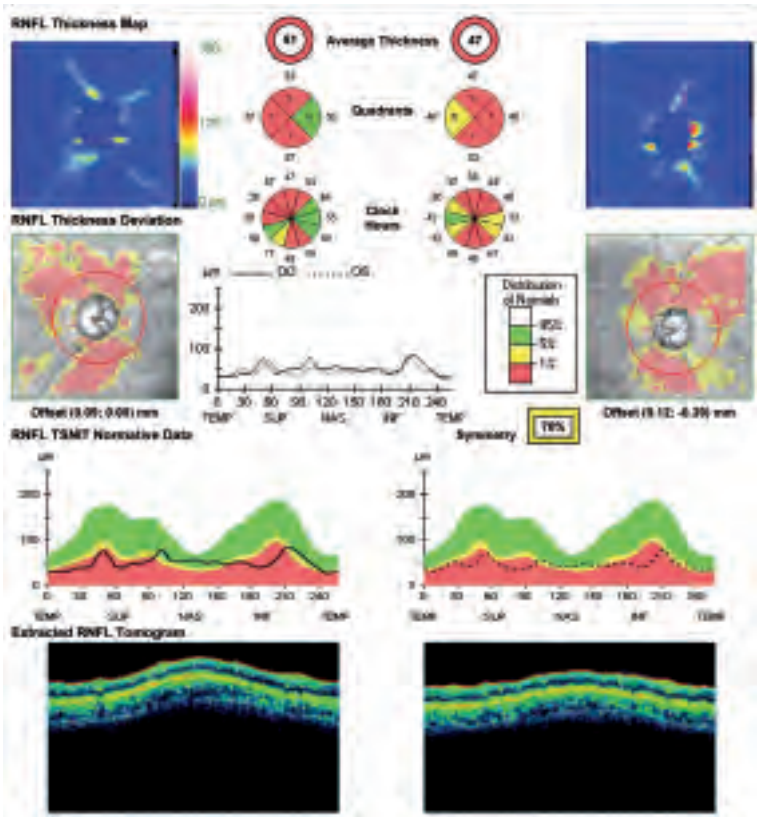
Dr Simon Phipps
MBBS FRANZCO

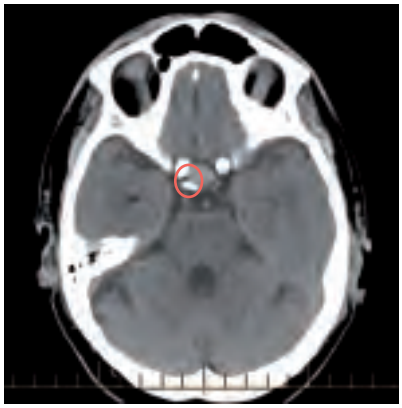
Phasing or diurnal intraocular pressure (IOP) measurements can be a useful tool in glaucoma diagnosis, differentiating normal tension glaucoma from primary open angle glaucoma, and assessing the adequacy of intraocular pressure control in established glaucoma.

Phasing involves the regular measurement (usually every two hours) of IOP over an extended period. Phasing is performed in recognition of the well-established fact that IOPs sometimes vary significantly over a 24-hour period.[1] Ideally, regular IOP measurement should be taken over the full 24 hours, which may be possible once technology for IOP measurement becomes more portable and less labour intensive. My current practise is to check IOPs every two hours over the course of a day, starting between 8 and 9 am and finishing between 3 and 4 pm. I have known other practitioners to simply book a return appointment for an IOP check in the morning if the initial IOP was measured in the afternoon and vice-versa, but in my view this does not reflect 'true' phasing and is less likely to provide useful data.

The case report (right) demonstrates the benefits of phasing as a diagnostic tool. It is also a sombre reminder that occasionally ophthalmic disease can reflect serious systemic illness.

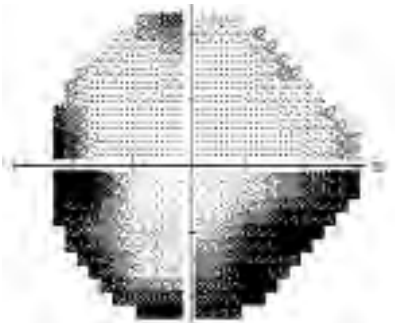
1. Kaufman P, Albert A. Adler's Physiology of the Eye, 10th ed. 2002. Chapter 8.





CT scan showing a pituitary tumour

Right eye



Left eye

Case report

A 47-year-old male courier driver was referred to me by an optometrist due to abnormal visual perimetry in the context of a history of blurry vision, normal intraocular pressures and suspicious optic nerves.

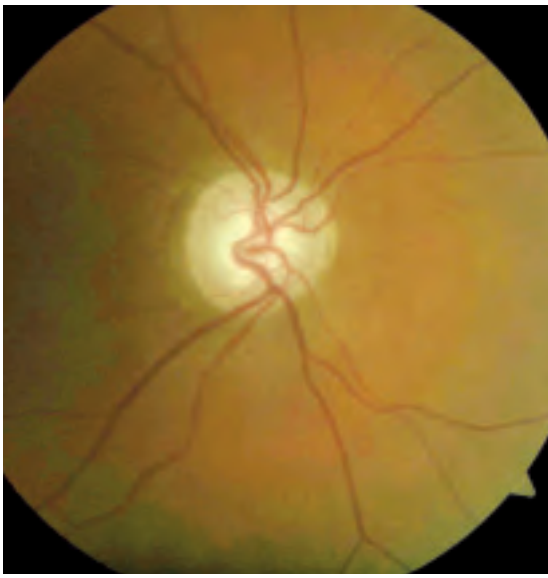
There was a family history of bilateral corneal grafting in the mother. The patient's medical history included type 2 diabetes, hypertension, elevated cholesterol and coronary artery disease. Clinical findings included aided acuities of 6/6 bilaterally (-025/-1.25x80 right eye, -0.50/-0.50x105 left eye). Anterior segments were normal with open angles on gonioscopy and bilateral IOPs of 20 mmHg. Corneal pachymetry was 498 and 500 microns for the right and left eyes, respectively. Dilated examination revealed normal maculae and retinal peripheries. His optic nerves had cup disc ratios of 0.85 bilaterally and looked pale. Visual fields were abnormal, as was the ocular coherence tomography imaging of the peripapillary retinal nerve fibre layers.

Three weeks later the patient underwent phasing: two-hourly IOP checks starting at 9 am and ending at 3 pm. The maximum IOP recording over this period was 18 mmHg for both eyes.

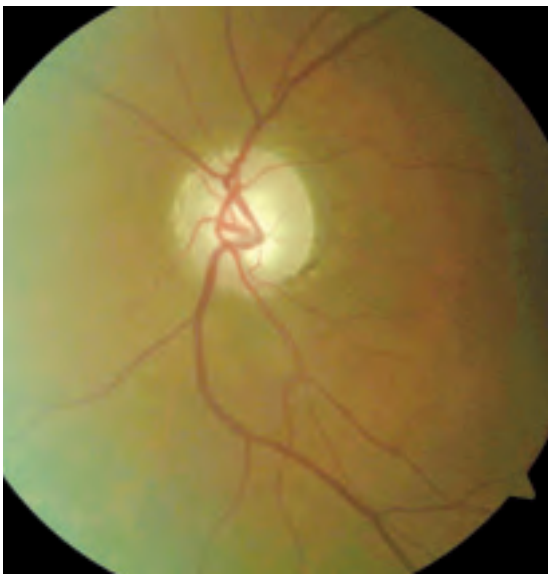
The provisional diagnosis was normal tension glaucoma and he was commenced on latanoprost. In light of the phasing results and optic nerve pallor, a precautionary CT scan of the brain and orbits was performed to exclude a compressive lesion. The CT scan demonstrated a pituitary tumour.

Subsequent referral to an endocrinologist resulted in the diagnosis of hypergonadotropic hypogonadism and anaemia. Referral to a neurosurgeon resulted in the patient undergoing an endoscopic transphenoidal excision of a pituitary macroadenoma. Pathology confirmed a pituitary tumour-basophilic adenoma.

The patient recovered from the surgery but with little improvement to visual perimetry. He is endeavouring to obtain a provisional drivers licence.



Right eye



Left eye

Participating in the GONE project is a great opportunity to assess your dexterity at diagnosing glaucoma through accurate analysis of the optic disc

Hone your skills online

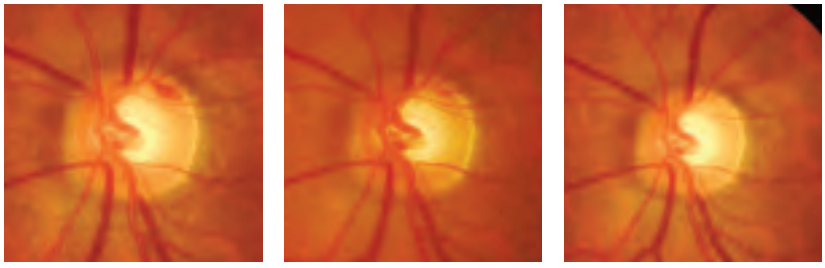
If detected early the effects of glaucoma can be slowed using appropriate treatment, yet in many cases the disease is undiagnosed because key indicators are being overlooked.

Michael Coote is the clinical director at the Royal Victorian Eye and Ear Hospital (RVEEH) and principal researcher in the glaucoma unit at Centre for Eye Research Australia (CERA). He says that to reduce rates of misdiagnosis, it is important that eye-care providers improve their detection skills.

A new online interactive test aims to do just that.

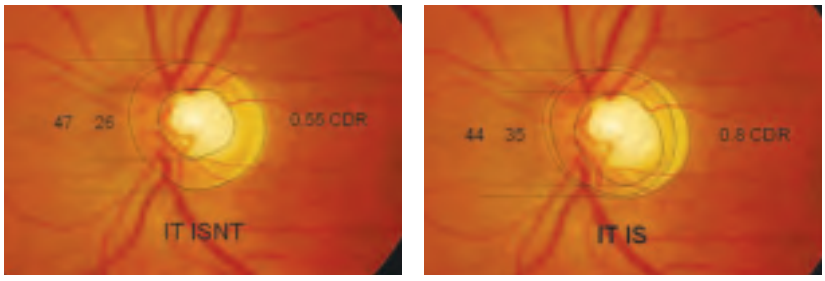
The GONE (Glaucomatous Optic Neuropathy Evaluation) project, a joint initiative of the RVEEH and CERA, is an internet-based system for assessing skills in diagnosing glaucoma. Participants are asked to look at 42 online photographs of the optic disc and assess each photo based on nine characteristics then determine the likelihood of glaucoma. Answers are compared with a group of glaucoma experts and online feedback is provided.

Missing the notch



These are three disc images of the same eye. The disappearance of the nerve fibre layer haemorrhage highlights the rim notch and nerve fibre layer loss, which is frequently missed in the third image.

Margin call



This case illustrates the problem of not accurately defining where the rim and disc margins are. It is easy to mistake the colour changes for the rim and to have the disc fit into the ISNT rule. A more accurate examination shows the rim has eroded and the ISNT rule broken. The patient has glaucoma, which is often missed.

'We have attempted to cover a wide range of disc types and then ask a number of questions on each case,' says Coote. 'From the information provided we have reached a clearer understanding about what commonly goes wrong in disc assessment and how we can improve glaucoma detection in the future.'

Coote says that from the project they have found 'easy' discs and 'hard' discs. Easy discs generally are mid-size, front on, with minimal peripapillary atrophy and a reasonably deep and defined cup/rim.

Conversely, he says that many of the reasons for discs being hard to assess relate to the ability to accurately define where the margins of the disc and rim lie. 'There has been an immense amount of data generated and we are now presenting and publishing this,' he says.

To date 523 optometrists among a total of 957 national and international participants have undertaken the GONE assessment.

The two examples (left) illustrate how the focal rim notch is often missed and how putting the margins in the incorrect place can make a diseased disc appear normal.

Assess your skills in glaucoma detection by visiting www.gone-project.com. For comments, please contact Jess Brennan at Centre for Eye Research Australia at jbrennan@unimelb.edu.au.

This work has been supported by Allergan Australia.

Systematic approach

Clinical optic disc assessment is the cornerstone to diagnosing glaucoma. Glaucoma is an optic neuropathy with characteristic optic disc changes and later, with matching visual field defects. Pre-perimetric (pre-achromatic) glaucoma means that a visual field defect is not required for the diagnosis.

Dr Ridia Lim
MB BS MPH FRANZCO
Cataract and glaucoma specialist

The third prong of the original glaucoma triad, intraocular pressure, is regarded as the most important risk factor and it also is not necessary for the diagnosis. Optic disc and retinal nerve fibre layer (RNFL) imaging devices have assisted but remain problematic for clinically difficult optic discs, the very cases where assistance would be useful.

Consensus among glaucoma specialists is that clinical examination with stereoscopic optic disc photography is still the 'gold standard' for glaucoma diagnosis.[1] Improving skills in clinical optic disc assessment is paramount for all eye-care professionals, and will lead to earlier glaucoma diagnosis and improved outcomes for patients. At present 50 per cent of glaucoma cases remain undiagnosed and therefore untreated.[2]

Efforts have been made to systematise and improve clinical optic disc assessment. The FORGE project[3] (Focusing Ophthalmology on Reframing Glaucoma Evaluation, Allergan, Inc.) and the GONE project[4] (Glaucomatous Optic Nerve Evaluation Project, Centre of Eye Research Australia and Royal Victorian Eye and Ear Hospital) are two projects that are targeting this.

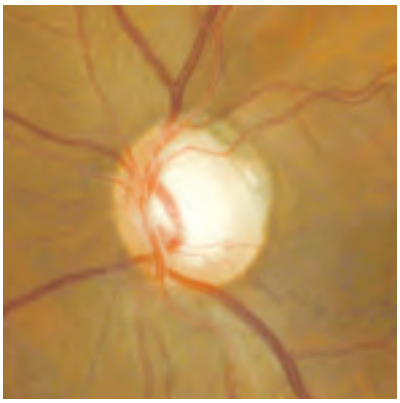
The FORGE disc evaluation emphasises five rules[3] (the five Rs):

1. Observe the scleral **R**ing to identify the limits of the optic disc and its size
2. Identify the size of the **R**im
3. Examine the **R**etinal nerve fibre layer
4. Examine the **R**egion of parapapillary atrophy
5. Look for **R**etinal and optic disc haemorrhages.

Continued page 36

CASE 1. Left optic disc

A 50-year-old man presented with a positive family history, moderate myopia and an IOP of 22 mm Hg with a central corneal thickness (CCT) of 562 µm. The OCT and perimetry support the optic disc assessment. The right eye also has (pre-achromatic) glaucoma. Treatment was started.



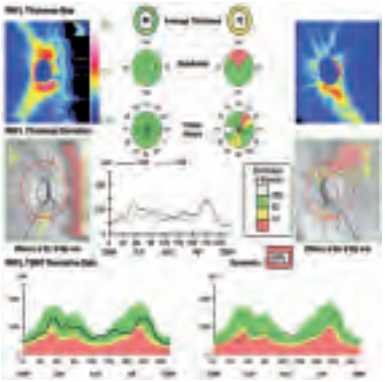
FORGE

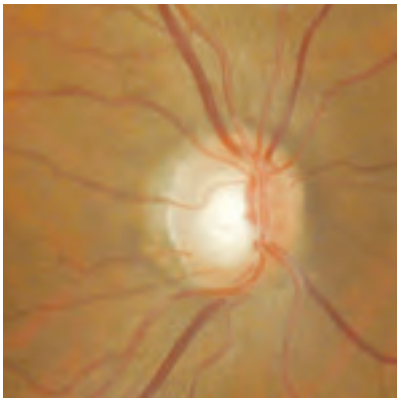
1. Disc size: average
2. ISNT rule: not obeyed. Rim thinning superiorly and inferiorly
3. RNFL loss: localised defect superiorly
4. PPA: localised superiorly
5. Haemorrhage: no

Glaucoma? Yes.

GONE

1. Disc size: average
2. Disc shape: regular shape
3. Disc tilt: tilt horizontal
4. PPA: moderate
5. Cup/disc ratio: 0.8
6. Cup shape: sup rim loss
7. Cup depth: undermined
8. RNFL defect: focal loss superiorly
9. Haemorrhage: absent
10. **Glaucoma: certain**





Systematic approach

From page 35

The GONE project asks 10 questions about the optic disc and gives multiple-choice answers.[4] After answering the first nine questions you should be able reach a conclusion about the probability of glaucoma. The questions are:

1. Disc size: hypo, small, medium, large or macro
2. Disc shape: regular shape, ovoid vertical or ovoid horizontal
3. Disc tilt: no tilt, tilt vertical or tilt horizontal
4. PPA: no PPA, or mild, moderate or extensive PPA
5. Cup/disc ratio: < 0.5, 0.5, 0.6, 0.7, 0.8, 0.9 or > 0.9
6. Cup shape: normal, concentric rim loss, superior rim loss, inferior rim loss or superior/inferior rim loss
7. Cup depth: shallow, moderate, deep or undermined
8. RNFL defect: no NFL loss, focal loss superiorly, focal loss inferiorly or general loss
9. Haemorrhage: absent or present
10. Glaucoma: unlikely, possible, probable or certain.

Test your skills in glaucoma detection by visiting the GONE website. There are 42 'real-life' optic disc photographs and participants can undertake the exercise more than once.

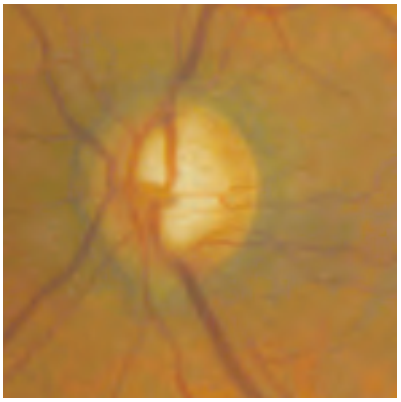
Glaucoma remains a clinical diagnosis and the optic disc examination needs to be seen in the context of the patient. Using systematic methods such as FORGE and GONE to examine the optic disc will improve glaucoma detection by all of us.

In these four case studies the FORGE and GONE process is demonstrated for each optic disc.

1. Association of International Glaucoma Societies. Weinreb RN, Greve EL, eds. Consensus Series 1. Glaucoma diagnosis: Structure and Function. The Hague, The Netherlands: Kugler Publications, 2004.
2. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996; 103: 10: 1661-1669.
3. Susanna R Jr, Vessani RM. New findings in the evaluation of the optic disc in glaucoma diagnosis. *Curr Opin Ophthalmol* 2007; 18: 2: 122-128.
4. Glaucomatous Optic Neuropathy Evaluation Project. www.gone-project.com. Accessed January 2010.

Case 2. Right optic disc

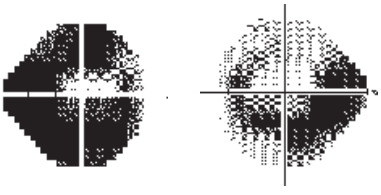
A 59-year-old man presented with cardiovascular risk factors (smoker, diabetes and hypertension) with normal IOP of 20 mm Hg in the right and 16 mm Hg in the left eye with CCT of 530 µm. He was started on topical therapy first but is likely to need surgery.

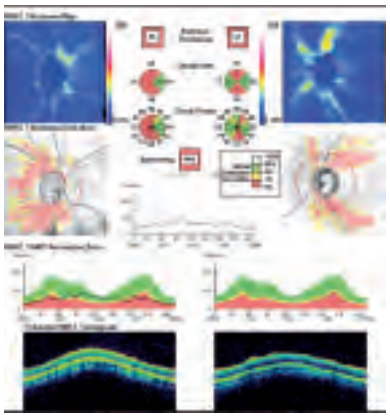


FORGE

1. Disc size: large
2. ISNT rule: not obeyed. Superior and inferior notch
3. RNFL: general loss
4. PPA: no
5. Haemorrhage: no

Glaucoma? Yes

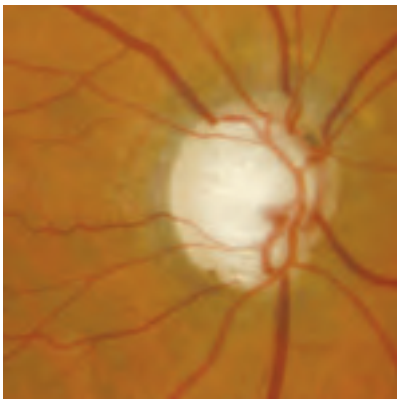




GONE

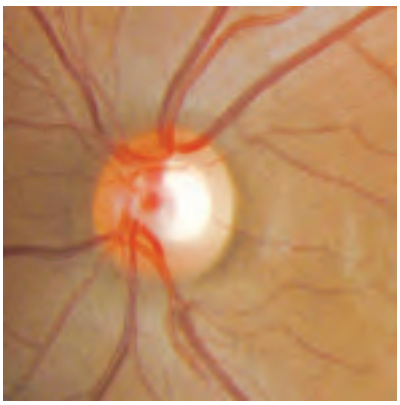
1. Disc size: large
2. Disc shape: regular shape
3. Disc tilt: no tilt
4. PPA: mild or no PPA
5. Cup/disc ratio: 0.9
6. Cup shape: sup/inf rim loss
7. Cup depth: undermined
8. RNFL defect: general loss
9. Haemorrhage: absent

10. Glaucoma: certain



Case 3. Right optic disc

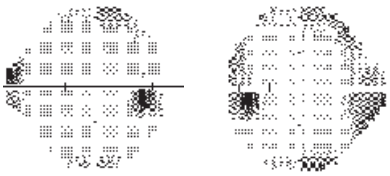
A 26-year-old with no risk factors was referred because of concern about optic disc cupping. The IOP was 14 mmHg with average CCT. OCT is normal and the visual field is a learning field. He has physiological cupping and no treatment is needed.

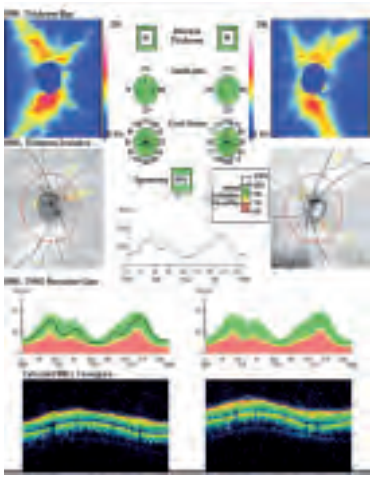


FORGE

1. Disc size: large
2. ISNT rule: obeyed
3. RNFL: normal
4. PPA: no
5. Haemorrhage: no

Glaucoma? No.

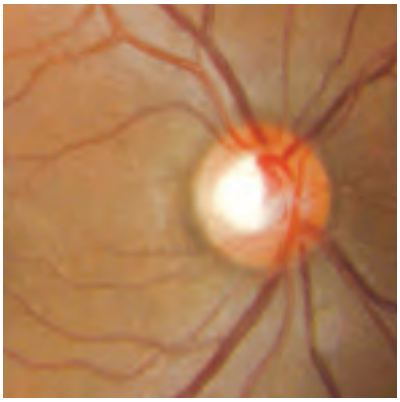




GONE

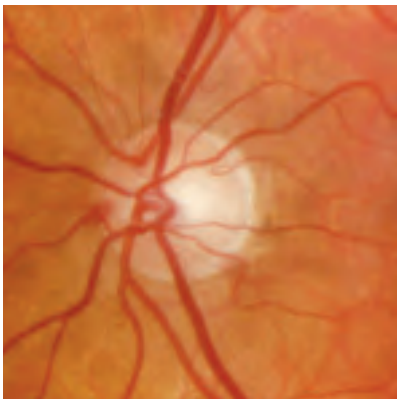
1. Disc size: large
2. Disc shape: regular shape
3. Disc tilt: no tilt
4. PPA: mild or no PPA
5. Cup/disc ratio: 0.6
6. Cup shape: normal
7. Cup depth: moderate
8. RNFL defect: no NFL loss
9. Haemorrhage: absent

10. Glaucoma: unlikely



Case 4. Left optic disc

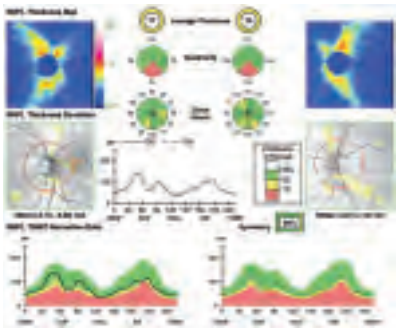
A 38-year-old man presented with moderate myopia and no other risk factor. His peak IOP was 18 mm Hg with CCT of 520 µm and he had a normal visual field. He is a strong glaucoma suspect and treatment initiation is being contemplated.



FORGE

1. Disc size: large disc
2. ISNT rule: not obeyed. Rim thinning present inferiorly
3. RNFL: diffuse loss
4. PPA: moderate
5. Haemorrhage: yes

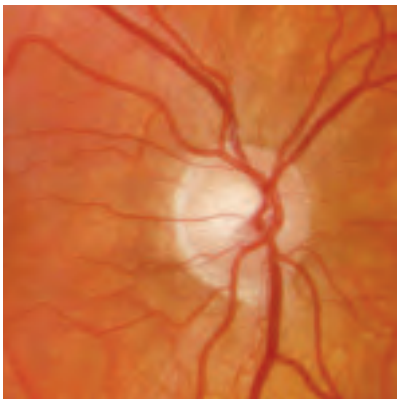
Glaucoma? Likely



GONE

1. Disc size: large
2. Disc shape: regular shape
3. Disc tilt: tilt horizontal
4. PPA- moderate
5. Cup/disc ratio: 0.6
6. Cup shape: concentric rim loss
7. Cup depth: shallow
8. RNFL defect: general loss
9. Haemorrhage: present

10. Glaucoma: probable



Behind every

To ensure their safety and efficacy, drugs are subject to a robust approval process before being released in the market. **Matt Trollope** investigates

Medication may take only seconds to administer but the process involved in bringing each drug to market can take years. This process is essential to ensure that all therapeutic preparations are of the highest quality, have the greatest benefit and adhere to stringent safety guidelines.

The system that exists in Australia for approving drugs closely reflects the process applied in jurisdictions overseas. Before a drug manufacturer can have its product considered by the Therapeutics Goods Administration (TGA), Australia's regulatory agency for medical drugs and devices, it needs to be researched, developed and clinically trialled, first on animals and then humans. The trial length is determined by the nature of the therapy—drugs for chronic conditions require lengthier study periods to determine their longitudinal efficacy.

An application must then be drafted for the medication to be approved as a therapy for patients: this should address administrative and labelling requirements, and manufacturing and quality information, and include non-clinical and clinical data collated throughout the research and trialling process. This application is reviewed by various groups and experts who work within the TGA; the manufacturer is given time to respond to any questions the TGA may raise.

The final step in the process involves determining the pricing and reimbursement that will be attached to the therapy, and assessing its cost-effectiveness. Is the price of the drug justified according to the benefit it will bring to Australia's health system? This step takes into account health economic factors and involves detailed economic modelling.

Once the TGA has determined that all criteria have been met, the drug can be included in the Australian Register of Therapeutic Goods. The manufacturer is not obligated to supply or launch the therapy immediately after approval is given; products have been known to remain unavailable for one or two years after the TGA has approved them.

The time the entire approval process takes can vary significantly depending on the product. When the manufacturer submits a high-quality application and works collaboratively and efficiently with the TGA, the processing period can be reduced. On its website the TGA highlights the anti-cancer drug Glivec (imatinib), which was approved in five months, as an example of how co-operation between parties can accelerate the process.

Consultant's role

The complexities involved with drafting a drug application may extend beyond the expertise of staff at a drug manufacturing company.

Dr Stuart Mudge is general manager of Voisin Consulting Australia, a company that assists biotechnology, pharmaceutical and medical technology companies in the design and implementation of regulatory strategies to expedite product development. He says consultants often assist in this process. 'Drug companies may lack particular knowledge or resources in a particular area, and may wish to seek external input on developing a strategy; they may consider consultants to be more independent and having a higher level of experience,' he says.

'As regulatory consultants, we prepare documents for submission to a regulatory authority, whether it is for a clinical trial, to put a drug on the market, or for a drug that already exists on the market. There is a format for doing this. You need to speak the regulatory language and how you present this information is important. Clients, particularly emerging companies, might not have this expertise.'

Mudge worked for Voisin Consulting in Paris for three years before establishing its Melbourne operations in 2005. His role involves assisting overseas clients to introduce into Australia products that have already been approved overseas or are undergoing the approval process, as well as assisting Australian clients to export products.

There are resources available to guide companies through the process of bringing a drug to market. Mudge says one difficulty for companies with limited experience is anticipating questions the regulatory authority may pose to them relating to their application. 'Voisin was formed primarily to work with smaller and emerging companies, yet there are instances where larger pharmaceutical companies don't have the necessary expertise in a certain area, such as introducing a drug into a market they have never before targeted. We have helped larger Australian companies negotiate with France because our head office is there, even though some of those companies may have more regulatory people than we do,' he says.

Mudge says that many large companies have a clinical or scientific advisory board that they consult during clinical trials, usually comprising four or five members from around the world. Regulatory tasks such as drafting the application will involve another consultant, and some companies may use different consultants in each part of the world where they are submitting a drug application. 'A company could reach double figures in the number of consultants it employs throughout this process. The extent of their consulting activities would vary from just one hour per month to months of full-time work,' he says.

Australia versus overseas

Compared with overseas markets such as the United States or Europe, Australia's drug market is very small. Simone Parkes, who works in business development for Australian biotechnology company HalcyGen Pharmaceuticals, says that companies rarely register a product in Australia alone

drug is a story

because they are unlikely to recoup the costs of registration.

Parkes is a pharmacist who has worked in business development and marketing roles at AstraZeneca Australia, CSL Limited and Clinuvel Pharmaceuticals. At HalcyGen she is working to introduce an oral antifungal medication to the Australian market. Because this product is a reformulation of an established drug that was developed in Adelaide, she says the approval process is less stringent and therefore more viable for the company.

'Drugs introduced to Australia for the first time have often gone through the registration process in the United States or Europe beforehand. The TGA then reviews the dossier of information collated on the drug and employs its own regulatory processes before allowing the drug to be made available,' she says.

Mudge says that introducing drugs into markets other than Australia is often a more attractive option for large pharmaceutical companies. 'These companies are typically headquartered outside of Australia and a large amount of the investment in Australian biotechnology companies comes from the USA. Investors' main concern is approval of the drug in that market. This is one of the main reasons that companies aim there.'

For some companies the converse is true. Mudge says choosing to market a drug in Australia can be a stepping-stone toward applying for its introduction overseas. 'The general consensus is that if a company has gone through the process in Australia, they will have a fairly rigorous package to take into other markets. Of course, the local idiosyncrasies of another country's regulatory process must be considered,' he says.

'There is a perception that America's Food and Drug Administration is a tougher body to deal with than the TGA. Strictly speaking, the data requirements and regulations should be the same in both markets but Australian companies often prefer dealing with the TGA, which can be contacted more easily and is more closely aligned culturally.'

Final approval

Parkes says that the time the TGA takes to review a company's application frequently exceeds expectations because the 'clock stops' every time the company is required to provide the TGA with more information or answer questions relating to its dossier.

Certain therapies have a stronger chance of being approved and the circumstances under which they are being proposed may also have an influence. Review priority is given to products that qualify as new chemical entities or those that are designed to treat serious or life-threatening conditions. The latter, known as 'orphan drugs', are those that meet a medical need for which there is no current satisfactory treatment.

The TGA waives the application fees when there are fewer than 2,000 people within a given year requiring treatment for the condition in question. With such a limited market, there would otherwise be little incentive for companies to develop such a drug.

According to Mudge, the process of approving a drug in Australia might be expedited if the company successfully introduced it elsewhere. 'A company doesn't need to conduct clinical trials in all of the countries where it is applying for drug approval; for example, data collected from American clinical trials will generally be acknowledged in an application to the TGA. If a drug has already been approved in the USA, then the TGA will often be willing to accept the FDA's assessment reports,' he says.

In his former position as a regulatory affairs associate at CSL Limited—CSL was sometimes the local licensor for products approved overseas—Mudge saw examples of the TGA operating contrary to overseas regulatory bodies. 'Even for drug applications that had been approved elsewhere, it was common for the TGA to ask the company for specific information that other agencies had not,' he says.

'Australian labelling requirements for drugs often differ from foreign requirements and can be specific. A common data requirement within drug applications is the storage conditions of products over a certain period; this aims to simulate patients' use of the drug and helps determine its shelf-life. In the USA and Europe, products are traditionally tested at 25 degrees Celsius. Australian labelling policy requires drugs to be indicated for storage at 30 degrees Celsius or below, rendering US and European data inadequate. A company may be able to get away with this elsewhere but the TGA can be stringent.'

A company can suffer if its drug fails to gain approval. Although it can withdraw its submission, appeal against the decision, or choose to collect more data to address the issues before resubmitting, these pathways can be costly and time-consuming. Mudge says that although the majority of drugs are approved, it is less likely that they will be approved to the full extent that the company had originally hoped. 'We recommend to our smaller clients that their application promotes the product to its fullest extent, but that they should be prepared for this scope to be narrowed and should have a lesser position they are willing to accept,' he says.

'Even with an initially restricted indication, the drug is still on the market and generating revenue for the company. With time, the manufacturer can collect data to support the extension of the drug's indications.'

We recommend to our smaller clients that their application promotes the product to its fullest extent, but that they should be prepared for this scope to be narrowed and should have a lesser position they are willing to accept.

Dr Stuart Mudge, Voisin Consulting Australia

Abstracts

Smoking linked to POAG in elderly women

Smoking has been identified as an additional risk factor for glaucoma progression in elderly women. Female patients with established POAG and due to undergo trabeculectomy were allocated to one of three experimental groups: smoker, ex-smoker or non-smoker (n = 40 per group, mean age ~70 years in each group). Samples of aqueous humour and plasma were obtained, with assays taken to measure inflammation and apoptosis. Interleukin-6 (IL-6) levels (an inflammatory marker) and poly (ADP-ribose) polymerase 1 PARP-1 (an apoptosis marker) were found to be significantly higher in the smoking population compared with former and non-smokers.

Zanon-Moreno V et al. Smoking, an additional risk factor in elderly women with primary open angle glaucoma. *Mol Vis* 2009; 15: 2953-2959.

Hair-raising case of inflammation

A pet tarantula has inflicted an injury causing a rare instance of ocular inflammation. A 29-year-old man presented with a three-week history of a unilateral, red, watery and photophobic eye. Topical antibiotics were prescribed for a presumed bacterial conjunctivitis. One week later, after showing no signs of improvement, he presented to his local hospital where biomicroscopy revealed hair-like projections at varying depths within his cornea.

The condition was caused by the patient's pet, a Chilean rose tarantula. Tarantulas have urticating hairs over their bodies. As a defence mechanism they can rub their hind legs against their abdomen to dislodge the hairs into the air.

Doctors noticed that hairs were embedded in the patient's cornea, held in place by small barbs.

The hairs were too fine to be removed from the patient's eye, even with microforceps. The condition required several months of topical steroid treatment to reduce the inflammatory response.

Norris JH, Carrim ZI, Morrell AJ. Case Report. Spiderman's Eye. *The Lancet* 2010; 375: 9708: 92.

Dr Laura Downie
PhD(Melb) BOptom
PGCertOcTher
DipMus(Prac) AMusA

Asthmatics at greater risk of CIN

A study has identified an association between conjunctival intra-epithelial neoplasia (CIN) and the atopic condition asthma in young patients. CIN is typically observed in elderly patients with risk factors including exposure to ultraviolet light and immunodeficiency.

A retrospective case series was conducted from the Royal Hallamshire Hospital, Sheffield UK, ocular oncology database. Seven patients were studied; mean age at presentation with CIN was 44 years (range 36-54 years). Five patients demonstrated unilateral disease, with two showing bilateral CINs. Five patients also showed local recurrence; no metastases were reported.

CIN, particularly the bilateral presentation, in younger immunocompetent individuals was considered highly unusual. As asthma was present in 64 per cent of the patient cohort, it was concluded that it may be a further aetiological factor in the development of this neoplasm.

Rundle P, Mudhar HS, Rennie I. Conjunctival intra-epithelial neoplasia occurring in young patients with asthma. *Eye* (Lond) (advanced online publication, 4 December 2009).

AMD drug costs $155m

Ranibizumab has been named in the list of top 10 drugs by cost to government for the year ending 30 June 2008.

With an annual cost of $155 million, the drug for treating age-related macular degeneration, more commonly known as Lucentis, came in eighth, according to the Australian Statistics on Medicines, an annual publication produced on behalf of the Department of Health and Ageing.

Topping the list was atorvastatin (Lipitor), with a cost to government of $621 million.

CL wear affects meibomian glands

Contact lens wear has been found to be associated with a decrease in the number of functional meibomian glands. In a cross-sectional case series, participants were contact lens wearers (n = 121) and a control group of age-matched, non-contact lens wearers (n = 137). Meibomian glands were assessed using a scoring for each eyelid using four grades (meiboscores), from grade zero (no loss of meibomian glands) to grade three (eyelid area with > 66 per cent measurable meibomian gland drop-out).

Mean meiboscores were significantly higher in contact lens wearers (1.72 vs. 0.96, $p < 0.05$). A positive correlation was observed between the duration of contact lens wear and the meiboscore.

This research provides an insight into one possible mechanism underlying dry eye in contact lens wearers.

Arita R et al. Contact lens wear is associated with decrease of meibomian glands. *Ophthalmology* 2009. 116: 3: 397-384.

Lights, camera ... migraine

New research has provided the first insight into the photoregulation of migraine headache. The perception of head pain in migraine is mediated by noci-ceptive signals transmitted from the cranial dura mater to the brain and is uniquely exacerbated by exposure to light; the neural mechanism for this effect has remained unknown.

Scientists at the Department of Anaesthesia, Boston, USA, found that exacerbation of migraine headache by light is prevalent among blind individuals, who maintain non-image-forming photoregulation in the face of massive photoreceptor degeneration.

Neurons were identified in the thalamus in which activity was distinctly modulated by light, and its axons were projected extensively across the somatosensory, visual and associative cortices. The cell bodies and dendrites of these neurons were apposed by axons originating from retinal ganglion cells.

Noseda R et al. *Nature Neuroscience*. Published online 10 Jan 2010.

photo clinic

Bacterial keratitis

Chris McMahon
BAppScOptom MBCO (Lond) DCLP (Lond)

The patient is 44 years of age, female and wears extended wear silicon hydrogel contact lenses. She has had LASIK surgery. She complains of having had a photophobic, painful red right eye with mildly blurred vision for 12 hours.

On examination, I find a right peripheral epithelial defect with underlying dense infiltrate, ciliary flush, grade 2 cells in the anterior chamber and a miotic pupil. The condition is diagnosed as bacterial keratitis. Ideally, a corneal culture should be done prior to initiation of any antibiotic but this was not possible on this occasion.

Management

I commence the patient on Ciloxan q15 min and refer her for scraping.

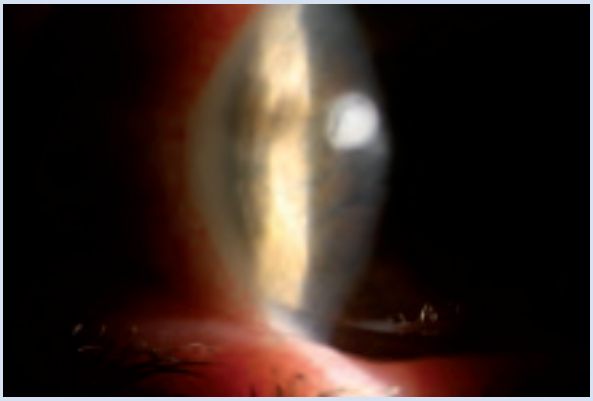
Day 2. *Pseudomonas* is confirmed. Ciloxan q30 min.

Day 3. Ciloxan q1h and Homatropine 2% qid.

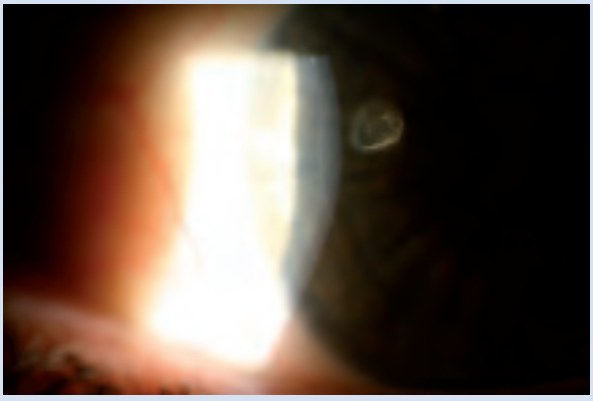
Day 6. Ciloxan q3h, Homatropine 2% qid and Pred Forte qid.

Two weeks. Ciloxane qid and FML qid and Refresh Tears q1h.

Six weeks. Cease all medications; the eye is quiet and VA is normal.



***Pseudomonas* corneal ulcer at presentation**



***Pseudomonas* ulcer and LASIK scar at week six**

Don't delay laser iridotomy

Achieving successful intraocular pressure (IOP) control in patients following acute angle closure glaucoma (AACG) is more likely if laser iridotomy is performed within seven days after the development of symptoms and if an initial IOP reduction of at least 30 per cent is achieved with maximal tolerable medical therapy.

These findings emphasise the need for prompt ophthalmic treatment with appropriate medical IOP control in the long-term management of patients with AACG.

Lee JW et al. Prognostic factors for the success of laser iridotomy for acute primary angle closure glaucoma. *Korean J Ophthalmol* 2009; 23: 4: 286-290.

Marker for wet AMD

A newly-discovered biological marker known as CCR3 may soon point the way for the early detection and preventative treatment of neovascular age-related macular degeneration (AMD).

The CCR3 molecule was identified in the eyes of patients with progressive wet AMD. Experimental blockade of retinal CCR3 receptors was shown to be more effective in reducing neovascularisation than the current gold standard (anti-VEGF therapy) of treatment. A further apparent advantage of CCR3 treatment over VEGF-blocking antibodies was the lack of retinal toxicity. The identification of CCR3 has clinical implications for both the earlier detection and treatment of wet AMD.

Takeda et al. CCR3 is a target for age-related macular degeneration diagnosis and therapy. *Nature* 2009; 9: 460: 7252: 225-230.

Helicobacter pylori infection

A review has surveyed evidence regarding the possible association between infection with the gastric bacteria *Helicobacter pylori* (*H pylori*) and varied eye pathologies including Sjögren syndrome, blepharitis, uveitis and glaucoma.

The authors suggest that *H pylori* infection may influence the pathophysiology of ocular diseases through the release of various pro-inflammatory and vasoactive substances, as well as influence the apoptotic death of neurons. In glaucoma, it was proposed that there may be an increase in oxidative damage that is exported systemically and therefore affect a variety of other tissues and organs including the eye.

Izzoti A et al. Glaucoma and *Helicobacter pylori* infection: correlations and controversies. *Br J Ophthalmol* 2009; 93: 11: 1420-1427.

Eyelash enhancement a new indication

Pharmaceutical companies spend billions of dollars developing new medicines yet few would have imagined the aesthetic benefits of a drug used to treat primary open-angle glaucoma and ocular hypertension

Excessive eyelash growth, known as hypertrichosis, is a well-documented side-effect of topical ophthalmic prostaglandin/prostamide analogs used to treat primary open-angle glaucoma and ocular hypertension.[1-8] These solutions include latanoprost, travoprost and bimatoprost.

Increases in length, thickness, curvature, pigmentation and number, including appearance of additional lash rows, have been reported to occur in both the upper and lower eyelashes with these medications.[1,2,3,8] Prostaglandin/prostamide analogs are the most efficacious topical treatment for ocular hypertension and their systemic profile is very safe.[9] Recently they have gained recognition as a cosmetic treatment for their ability to grow thicker, longer eyelashes.

Bimatoprost is a prostamide analog that functions similarly to its prostaglandin analog counterparts, latanoprost and travoprost.[5] However, bimatoprost has been shown to cause hypertrichosis earlier in treatment and with higher frequency than latanoprost. This is likely to be because it is not a prodrug.[2,10] Latanoprost must undergo conversion into an active metabolite while bimatoprost is already in its active form.[2,10] Therefore, bimatoprost is a prime candidate for cosmetic eyelash enhancement.

Bimatoprost solution 0.03% has recently been approved for cosmetic treatment of reduced eyelash growth, known as hypotrichosis, in the USA.[1] It is marketed under the name Latisse by Allergan Inc. Formulation and dosage of Latisse is identical to those of Lumigan (Allergan Inc, Irvine, California, USA), the bimatoprost solution indicated for treatment of ocular hypertension.[11] Application is the only difference. Lumigan is applied via an eye-drop to the ocular surface. Latisse is applied to the skin of the upper lid near the base of the lashes using a sterile applicator.[1]

Latisse was evaluated for safety and efficacy during a multicentre, double-masked, randomised, vehicle-controlled, parallel study on 278 adults.[1] Within 16 weeks 78 per cent of adults experienced significant eyelash enhancement. Eyelash length increased by an average of 1.4 mm. Pigmentation and thickness also increased significantly (Figure right). Once bimatoprost application was stopped, eyelashes began to return to baseline.[1]

Mechanism of action

Hair follicles cycle through three continuous phases: anagen, catagen and telogen.[12] Hair growth and melanogenesis (pigmentation) occur during anagen. These processes subsequently cease with catagen, when hair remains within the follicle as it undergoes apoptosis. Hair is finally shed during telogen, a rest period at the end of the cycle.[12] Hair length is dependent on the duration of anagen. Scalp follicles remain in anagen for two to eight years; however, eyelashes remain in this stage for only two to three months.[12] Additionally, while 84 per cent of the scalp hairs are in the anagen phase at any one time, a much lower percentage of eyelashes are in the anagen phase simultaneously.[3]

Three types of hair exist: vellus, intermediate and terminal.[12] Vellus hairs are short, soft and unpigmented, whereas terminal hairs are longer, coarser and pigmented. Intermediate hairs lie in between.[12] Eyelashes consist of all three types of hair.[3] The hair follicles that give rise to these hair types are present at birth, and none is additionally formed thereafter, but the size of the follicle and type of hair produced may change, as in puberty.[12]

The mechanism of action of bimatoprost for eyelash enhancement is not fully known. It is thought to be related to stimulation of prostaglandin receptors within the hair follicle, resulting in induction and prolongation of anagen.[3,11] A longer growth stage results in increased hair length and pigmentation. Resultant hyperpigmentation is thought to occur due to increased melanin within melanocytes, not via a direct increase in melanocytes.[13] Additionally, bimatoprost causes vellus eyelash hairs to transition into coarser, longer, terminal hairs.[3] This causes an apparent increase in the number of eyelashes and rows of lashes, while not actually increasing the number of hair follicles.[3]

Indications

Latisse is indicated for cosmetic treatment of reduced eyelash growth.[1] It may be used as a substitute for mascara or eyelash prostheses in patients desiring eyelash enhancement. Because long, thick lashes are often desirable, especially in females, treatment with Latisse is likely to cause a positive psychological effect.[14] Still, it is important to weigh any possible side-effects against the benefit of this treatment.

Latisse should also be considered in patients using a prostaglandin/prostamide analog for monocular treatment of ocular hypertension that has resulted in cosmetic asymmetry. In this case, Latisse should be applied to the lid margin of the non-treated

for bimatoprost

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BA
Dr Leonid Skorin Jr
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eye to restore symmetry without affecting intraocular pressure.

Latisse may also be a future treatment of eyelash loss due to alopecia areata (AA), although it is not currently indicated for AA. Case reports and studies on treatment of AA with bimatoprost are controversial. There are at least two case reports of successful eyelash regrowth in patients with long-standing AA that were treated with cutaneous or ocular application of latanoprost.[15,16] However, two separate studies on subjects with AA-induced eyelash loss of 50 per cent or more showed no clinically significant regrowth of eyelashes with cutaneous application of latanoprost or bimatoprost, or with ocular application of bimatoprost.[17,18]

Within one of these studies, subjects with less than 50 per cent eyelash loss did experience some regrowth.[18] These results suggest that while patients suffering from greater than 50 per cent eyelash loss from AA will not benefit from prostaglandin/prostamide analog treatment, those with less than 50 per cent loss may. This phenomenon would match that of scalp AA, which is typically successfully treated with medication only in those patients with less extensive hair loss.[18] Additional studies on prostaglandin/prostamide treatment for AA are needed to assess efficacy of treatment.

While eyelash follicles are different from scalp follicles, prostaglandin/prostamide analogs like Latisse may be indicated for regrowth of scalp hair in the future. Animal studies on macaque monkeys and mice have demonstrated efficacy of latanoprost for hair regrowth.[19] Latanoprost has been found more effective than topical minoxidil for causing eyelash regrowth, and with longer-lasting results.[19] Minoxidil is used to lengthen and increase thickness of scalp hair.[12] The proposed mechanism of action of minoxidil is stimulation of prostaglandin synethesis,[19] so it makes sense that direct application of a prostaglandin analog has potential to work in a more efficient manner.

Patient instructions for Latisse administration

Patient instructions are included within the package insertion.[1] Make-up and contact lenses must be removed prior to application of Latisse. One drop of Latisse is applied once daily with a special applicator brush to the skin of the upper eyelid, near the lash line. This process is repeated on the other upper eyelid, using a new applicator. Any excess solution that extends past the last line must be blotted away. Latisse is not to be applied to the lower lash line; however the reasoning is not specified within the package insert. Contact lenses may be reinserted 15 minutes after application of Latisse.[1]

Patients should be informed that additional applications of Latisse have not demonstrated increased eyelash growth and therefore are not recommended.[1] They should also be informed of the continual need for treatment. If Latisse is discontinued, they should expect eyelash length, pigmentation and thickness to return to baseline.1

Unwanted side-effects of bimatoprost

Eyelash enhancement from use of prostaglandin/prostamide analogs is desirable to most but not all patients. It can be a nuisance. The lashes can grow so long that they brush against the spectacle lenses and require periodic trimming.[14] The density of lashes may cause a barrier to eye-drop administration, which results in difficult instillation and wastage of medication.[14] Monocular prostaglandin treatment may result in asymmetry, which is not cosmetically pleasing.

Ocular bimatoprost has many additional side-effects, some more or less desirable than

Continued page 44

Eyelash hypertrichosis before and after treatment with Latisse Image: Allergan Inc

Eyelash enhancement

From page 43

others (Table 1). Conjunctival hyperaemia, skin hyperpigmentation, and eyelash growth are the most common side-effects.[1,6,7]

Ocular irritation is usually mild and is likely to be due to the preservative, benzalkonium chloride.[20] Iris darkening may occur due to an increase in melanin in the melanocytes of the iris stroma. Only one to three per cent of patients using ocular bimatoprost report this[11] and no cases have been reported with Latisse.[1] Most side-effects will remit if therapy is discontinued but if iris pigmentation does occur, it is likely to be permanent.[1]

When prescribing Latisse, patients should be warned of possible, undesirable side-effects. Fortunately, less than four per cent of subjects were found to have adverse reactions to Latisse.[1] The most common reactions included conjunctival hyperaemia, dry eye, skin hyperpigmentation, pruritus, ocular irritation, and eyelid erythema.[1] No significant reduction of intraocular pressure was found to occur, nor were any cases of iris darkening reported.[1]

Increased hair length and thickness may also occur in the hair on the eye lids, which is not cosmetically desirable.[21] It is important to blot away excess solution to prevent this.[1] If vellus eyelashes are misdirected prior to treatment, resultant hypertrichosis may result in trichiasis.[13] This can cause significant corneal irritation, keratitis and scarring. Any misdirected lashes may be permanently removed prior to treatment to avoid this adverse effect. Other side-effects seen with ophthalmic instillation of bimatoprost, such as cystoid macular oedema, seem less likely to occur with Latisse. It is applied only to the lid margin and not to the ocular surface, reducing risk of ocular complications.

Side-effects of ocular bimatoprost

- Reduced intraocular pressure
- Increased eyelash length
- Increased eyelash thickness
- Increased eyelash pigmentation
- Increased eyelash curvature
- Allergic conjunctivitis
- Conjunctival hyperaemia & oedema
- Cystoid macular oedema
- Periocular skin hyperpigmentation
- Hypertrichosis of vellus hairs on eyelids
- Superficial punctate keratitis
- Eye discharge
- Ocular irritation/dryness
- Pruritis
- Activation of ocular herpes simplex
- Eye pain/asthenopia
- Blepharitis
- Visual disturbance
- Cataract
- Iris hyperpigmentation
- Tearing
- Photophobia
- Trichiasis
- Poliosis
- Headaches
- Infections
- Anterior uveitis
- Eyelid erythema

Common and rare side-effects reported after instillation of ocular bimatoprost[1,2,3,5,6,8,24,25]

Relative contraindications

Latisse is not for everyone. It should be prescribed with caution to pregnant or nursing women, and children.[1,6] Patients with a history of herpetic eye disease or uveitis should not use Latisse, as it may result in recurrence of these clinical conditions.[6,13] Aphakic individuals, patients with torn posterior capsules, or patients who otherwise demonstrate risk of developing macular oedema should be cautioned against using Latisse.[1,6,13]

Concurrent use of Latisse with prostaglandin analogs for ocular hypertension is contraindicated. Using both medications together may decrease the efficacy of intraocular pressure reduction.[1] Bimatoprost is most effective for lowering intraocular pressures when dosed once daily. Twice daily dosing is no more effective and sometimes even less effective than once daily dosing.[6] Additionally, because these patients already experience the benefit of ocular bimatoprost side-effects, there is no need for additional cosmetic therapy.

Conclusion

Bimatoprost ophthalmic solution 0.03%, now marketed as Latisse in the United States of America, is indicated for the treatment of eyelash hypotrichosis. It may also be indicated for treatment of eyelash AA in the future. Use of bimatoprost for cosmetic purposes is a practical addition to the aesthetics industry. Many patients desire thick, lush eyelashes—mascara and eyelash prostheses generate billion dollar revenues each year.[22] Latisse may be used as a practice builder; the patient base may be increased by offering this additional cosmetic treatment.[23] Eye-care practitioners are in the best position to prescribe Latisse, as most possible side-effects are ocular in nature.

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Eye infections treated OTC

By approving the down scheduling of chloramphenicol eye-drops to schedule 3, the National Drugs and Poisons Schedule Committee (NDPSC) has acknowledged that pharmacists have adequate skills to diagnose and treat minor eye infections such as conjunctivitis.

As pharmacies are often the first point of contact for patients with conjunctivitis, the reclassification of chloramphenicol from prescription medicine to restricted medicine has made effective treatment more readily accessible to the public.

Chloramphenicol, which is also used in the topical treatment of ear and skin infections, is safe and effective and generally well-tolerated, according to an NDPSC report released in October 2009. Adverse side-effects such as hypersensitivity, burning and stinging are rare.

The report states that with sufficient development of guidelines and training materials, pharmacists are capable of differentiating patients with simple eye infections who could be treated with chloramphenicol from those needing to be referred. Pharmacists have experience with diagnosing and treating conjunctivitis, with the provision of propamidine and sulfacetamide preparations for the treatment of acute bacterial conjunctivitis.

They are in a position to obtain information, such as whether the patient has a personal or family history of blood abnormalities, through effective counselling, similarly to other health professionals.

Although conjunctivitis is an easily recognised condition, the report emphasises that training material provided by professional bodies such as the Pharmaceutical Society is essential given that it could be difficult to distinguish between bacterial and viral conjunctivitis, or between conjunctivitis caused by allergy and that caused by irritation.

The decision to down-grade chloramphenicol was passed despite opposition from sceptics who were concerned whether pharmacists could accurately diagnose eye conditions without diagnostic equipment such as a slitlamp, and handle situations in which the condition had not improved within a set time.

PBS list of medicines for optometrists 9 February 2010

	Product	Max qty	Repeats
Antiglaucoma preparations			
Betaxolol eye-drops, suspension, 2.5 mg (as hydrochloride)/mL, 5 mL	Betoptic S	1	5
Betaxolol eye-drops, solution, 5 mg (as hydrochloride)/mL, 5 mL	Betoptic		
	BetoQuin	1	5
Bimatoprost eye-drops 300 mg/mL, 3 mL	Lumigan	1	5
Bimatoprost with timolol eye-drops containing 300 mg bimatoprost with timolol 5 mg (as maleate)/mL, 3 mL	Ganfort 0.3/5	1	5
Brimonidine eye-drops containing brimonidine tartrate 2 mg/mL, 5 mL	Alphagan		
	Enidin	1	5
Brimonidine with timolol eye-drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate)/mL, 5 mL	Combigan	1	5
Brinzolamide eye-drops 10 mg/mL, 5 mL	Azopt		
	BrinzoQuin	1	5
Dorzolamide eye-drops 20 mg (as hydrochloride)/mL, 5 mL	Trusopt	1	5
Dorzolamide with timolol eye-drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate)/mL, 5 mL	Cosopt	1	5
Latanoprost eye-drops 50 micrograms/mL, 2.5 mL	Xalatan	1	5
Latanoprost with timolol eye-drops 50 micrograms latanoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Xalacom	1	5
Pilocarpine eye-drops containing pilocarpine hydrochloride 10 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 20 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 40 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 60 mg/mL, 15 mL	Pilopt	1	5
	PV Carpine		
Timolol eye-drops 2.5 mg (as maleate)/mL, 5 mL	Tenopt		
	Timoptol	1	5
Timolol eye-drops 5 mg (as maleate)/mL, 5 mL	Tenopt		
	Timoptol	1	5
Timolol eye-drops (gellan gum solution) 2.5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5
Timolol eye-drops (gellan gum solution) 5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5
Timolol eye gel 1 mg (as maleate)/g, 5 g	Nyogel	1	5
Travoprost eye-drops 40 micrograms/mL, 2.5 mL	Travatan	1	5
Travoprost with timolol eye-drops 40 micrograms travoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Duotrav	1	5

By writing a PBS prescription for an antiglaucoma agent, the prescriber is certifying that the criteria set out in the PBS guidelines are satisfied

	Product	Restriction	Max qty	Repeats
Anti-viral eye preparations		Restricted:		
Aciclovir eye ointment 30 mg per g (3%), 4.5 g	Zovirax	Herpes simplex keratitis	1	0
Antibiotics		Unrestricted		
Chloramphenicol eye-drops 5 mg/mL (0.5%), 10 mL	Chlorsig		1	2
	Chloromycetin		1	2
Chloramphenicol eye ointment 10 mg/g (1%), 4 g	Chlorsig		1	0
	Chloromycetin		1	0
Framycetin sulfate eye-drops 5 mg/mL (0.5%), 8 mL	Sofracycin		1	2
Sulfacetamide sodium eye-drops 100 mg per mL (10%), 15 mL	Bleph-10		1	2
Anti-inflammatory agents		Unrestricted		
Fluorometholone eye-drops 1mg/mL (0.1%), 5mL	Flucon		1	0
	FML Liquifilm		1	0
Fluorometholone acetate eye-drops 1 mg/mL (0.1%), 5 mL	Flarex		1	0
Flurbiprofen sodium eye-drops 300 µg/mL (0.03%) single dose units 0.4 mL, 5	Ocufen		1	0
Hydrocortisone acetate eye ointment 10 mg/g (1%), 5 g	Hycor		1	0
Anti-allergy agents		Restricted:		
Sodium cromoglycate eye-drops 20 mg/mL (2%), 10 mL	Cromolux	Vernal keratoconjunctivitis	1	5
	Opticrom		1	5

Continued

	Product	Restriction	Max qty	Repeats
Tear supplements		Restricted:		
Carbomer 980 ocular lubricating gel 2 mg/g (0.2%), 10 g	Geltears	Severe dry eye including	1	5
	PAA	Sjögren's syndrome	1	5
	Viscotears Liquid Gel		1	5
Carmellose sodium with glycerin eye-drops 5 mg-9 mg per mL (0.5%-0.9%), 15 mL	Optive		1	3
Carmellose sodium eye-drops 10 mg/mL (1%), 15 mL	Refresh Liquigel		1	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), 15 ml	Refresh Tears plus		1	5
Hypromellose eye-drops 3 mg/mL (0.3%), 15 mL (contains sodium perborate)	In a Wink Moist'ing		1	5
	Genteal		1	5
Hypromellose eye-drops 5 mg/mL (0.5%), 15 mL	Isopto Tears		1	5
	Methopt		1	5
Hypromellose with carbomer 980 ocular lubricating gel 3 mg-2 mg/g (0.3-0.2%), 10 g	HPMC PAA		1	5
	Genteal gel		1	5
Hypromellose with dextran eye-drops 3 mg-1 mg/mL (0.3%-0.1%), 15 mL	Poly-Tears		1	5
	Tears Naturale		1	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); 15 mL	Systane		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	PVA Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	PVA Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	Liquifilm Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	Liquifilm Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil Forte		1	5
Unpreserved tear supplements		Authority required:		
Carbomer 974 ocular lubricating gel 3 mg/g (0.3%), single dose units 0.5 g, 30	Poly Gel	Severe dry eye syndrome in patients sensitive to	3	5
Carbomer 980 eye-drops 2 mg per (0.2%) , single dose units 0.6 mL, 30	Viscotears	preservatives in multi-dose eye-drops	3	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), single dose units 0.4 mL, 30	Cellufresh		3	5
Carmellose sodium eye-drops 10 mg/mL (1%) , single dose unit 0.4 mL, 30	Celluvisc		3	5
Carmellose sodium eye-drops 2.5 mg/mL (0.25%), single dose units, 0.6 mL, 24	TheraTears		4	5
Carmellose sodium ocular lubricating gel 10 mg/mL (1%), single dose 0.6 mL, 28	TheraTears		3	5
Hypromellose with dextran eye-drops 3-1 mg/mL (0.3-0.1%), single 0.4 mL, 28	Bion Tears		3	5
Tamarindus indica seed polysaccharide eye-drops 10 mg/mL, 0.5 mL, 20	Visine Professional		3	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); single dose units 0.8 mL, 28	Systane		2	5
Soy lecithin eye spray 10 mg/mL (1%), 10 mL	Tears Again		2	5
Topical ocular lubricant ointments		Unrestricted		
Paraffin compound eye ointment 3.5 g	Polyvisc		2	5
	Duratears		2	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Polyvisc (2 pack)		1	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Ircal (2 pack)		1	5
	Lacri-Lube (2 pack)		1	5

Commercially available controlled substances that may be used or prescribed by optometrists

9 February 2010

Ocular Medicine	Vic	NT	SA	NSW & ACT	Tas	Qld	WA*	PBS Optometry	PBS Listed
Anti-infectives									
Chloramphenicol	✓	✓	✓	✓	✓	✓	–	✓	✓
Ciprofloxacin	✓	✓	✓	–	✓	✓	–	–	✓
Framycetin	✓	✓	✓	✓	✓	✓	–	✓	✓
Gentamicin sulfate	✓	✓	✓	–	✓	✓	–	–	✓
Ofloxacin	✓	✓	✓	–	✓	✓	–	–	✓
Sulfacetamide	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tetracycline	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Tobramycin	✓	✓	✓	–	✓	✓	–	–	✓
Aciclovir	✓	✓	✓	–	✓	✓	–	✓	✓
Anti-inflammatories									
Dexamethasone	✓	✓	✓	–	✓	◆	–	–	✓
Fluorometholone	✓	✓	✓	✓	✓	✓	–	✓	✓
Fluorometholone acetate	✓	✓	✓	✓	✓	✓	–	✓	✓
Hydrocortisone	✓	✓	✓	✓	✓	✓	–	✓	✓
Prednisolone	✓	✓	✓	–	✓	◆	–	–	✓
Diclofenac	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Flurbiprofen	✓	✓	✓	✓	✓	✓	–	✓	✓
Ketorolac	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Decongestants, anti-allergics and astringents									
Antazoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Ketotifen	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Levocabastine	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Lodoxamide	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Naphazoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Olopatadine	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Pheniramine	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Sodium cromoglycate	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tetrahydrozoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Anti-glaucoma preparations									
Apraclonidine	✓	✓	✓	✓	✓	◆	–	–	✓
Betaxolol	✓	✓	✓	✓	✓	◆	–	✓	✓
Bimatoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Brimonidine	✓	✓	✓	✓	✓	◆	–	✓	✓
Brinzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Dorzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Latanoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Pilocarpine	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol	✓	✓	✓	✓	✓	◆	–	✓	✓
Travoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Bimatoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Brimonidine	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Dorzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Latanoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Travoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Mydriatics and cycloplegics									
Atropine	✓	✓	✓	✓	✓	✓	–	–	✓
Cyclopentolate	✓	✓	✓	✓	D	✓	D	N/L	N/L
Homatropine	✓	✓	✓	✓	✓	✓	–	–	✓
Pilocarpine	✓	✓	✓	–	✓	✓	–	–	✓
Phenylephrine	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Tropicamide	✓	✓	✓	✓	D	✓	D	N/L	N/L
Local anaesthetics									
Amethocaine	✓	✓	✓	✓	D	✓	–	N/L	N/L
Lignocaine	✓	✓	✓	–	D	–	–	N/L	N/L
Oxybuprocaine	✓	✓	✓	✓	D	✓	D	N/L	N/L
Proxymetacaine	✓	✓	✓	✓	D	✓	D	N/L	N/L

◆ The use of these medicines by optometrists is currently being considered
* Optometrists in Western Australia do not have access to the PBS
D Diagnostic use only
N/L Substance is not listed under the PBS

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Guided Progression Analysis (GPA) is software that uses statistical analysis to objectively assist in glaucoma management. GPA assists glaucoma decision making by:

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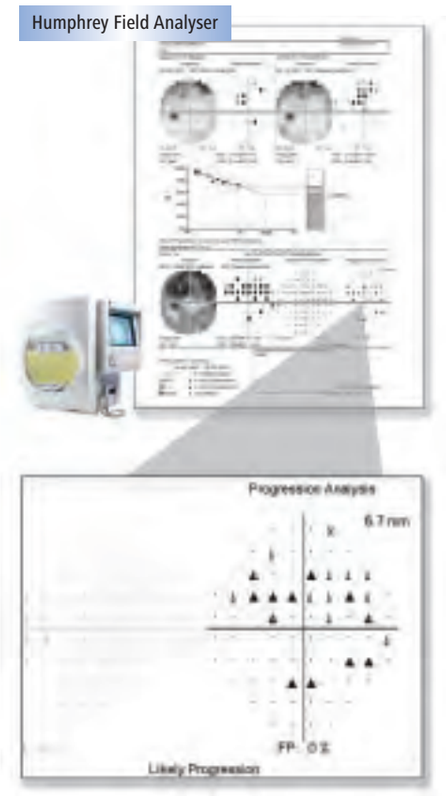
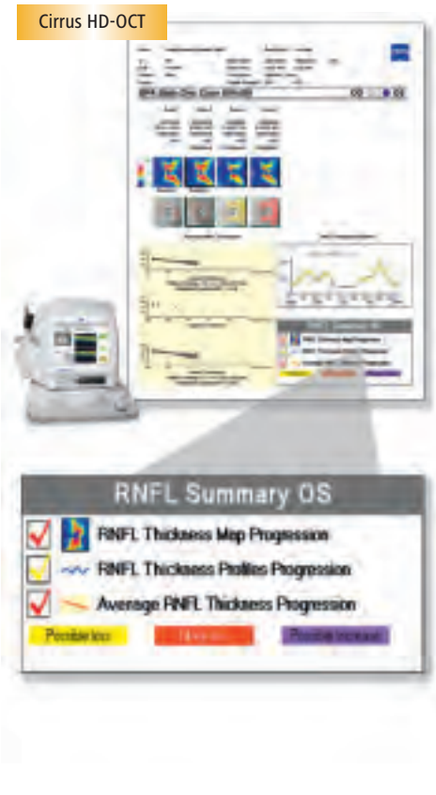


√ Likely Progression

Cirrus HD-OCT



√ Likely Loss

GDxPRO

√ Likely Progression

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Indication: Treatment of neovascular (wet) age-related macular degeneration (AMD). 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month. **Dosage and administration:** Recommended dose is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given monthly. Interval between doses should not be shorter than 1 month. Treatment might be reduced to one injection every 3 months after the first three injections but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly. Must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anaesthetic should be administered prior to injection. Patient should self-administer antimicrobial drops four times daily for 3 days before and after each injection. Not recommended in children and adolescents. **Contraindications:** Hypersensitivity to product components, active or suspected ocular or periocular infections, active intraocular inflammation. **Precautions:** Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must be used. Monitor patients during the week following injection to permit early treatment if an infection occurs. Intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. Safety and efficacy of administration to both eyes concurrently have not been studied. There is a *potential* risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. *A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5mg compared to ranibizumab 0.3mg or control, however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischaemic attack, should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk.* As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. No formal interaction studies have been performed. Should not be used during pregnancy unless clearly needed; use of effective contraception recommended for women of childbearing potential; breastfeeding not recommended. Patients who experience temporary visual disturbances following treatment must not drive or use machines until these subside. **Side effects:** Very common: Conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, *intraocular pressure increased,* vitreous detachment, intraocular inflammation, eye irritation, cataract, foreign body sensation in eyes, lacrimation increased, visual disturbance, blepharitis, subretinal fibrosis, ocular hyperaemia, visual acuity blurred/decreased, dry eye, vitritis, eye pruritis, *nasopharyngitis,* headache, *arthralgia.* Common: Ocular discomfort, eyelid oedema, *eyelid pain,* conjunctival hyperaemia, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, *injection site haemorrhage,* eye haemorrhage, retinal exudates, injection site reactions, conjunctivitis, *conjunctivitis allergic, eye discharge, photopsia,* photophobia, maculopathy, detachment of the retinal pigment epithelium retinal degeneration, retinal disorder, retinal detachment, retinal tear, *retinal pigment epithelium tear,* vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, *cataract subcapsular, influenza, anaemia, anxiety, stroke, cough, nausea, allergic reactions (rash, urticaria, pruritis, erythema).* Uncommon: Keratopathy, *iris adhesions, corneal deposits,* dellen, corneal striae, *injection site pain, injection site irritation, abnormal sensation in eye, hyphema,* cataract nuclear, angle closure glaucoma, endophthalmitis, eyelid irritation, blindness, corneal oedema, hypopyon. Rare but serious adverse reactions related to intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

**Please note changes to Product Information in italics.*

1. Brown MM, et al. Can J Ophthalmol. 2005;40:277-287. 2. Williams RA, et al. Arch Ophthalmol. 1998;116:514-520. 3. Novack GD. Ann Rev Pharmacol Toxicol. 29008:48:61-78. 4. Dalton M. Treatment regimens for AMD focussing on anti-VEGF. EyeWorld January 2007. Available at: http://www.nei.nih.gog/health/maculardegen/armd_facts.asp. Accessed 10 Jan 2008. 5. Rosenfeld PJ, et al. N Engl J Med. 2006;355:1419-1431. 6. Brown DM, et al. N Engl J Med. 2006;355:1432-1444. 7. LUCENTIS Approved Product Information. 8. Brown DM, et al. Ophthalmol. 2009;116:57-65. 9. Chang TS, et al. Arch Ophthalmol. 2007;125:1460-469.

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