World Glaucoma Association

Glaucoma Screening

Robert N. Weinreb, Paul R. Healey and Fotis Topouzis

Consensus Series - 5

Kugler Publications, The Hague, The Netherlands

GLAUCOMA SCREENING

Robert N. Weinreb

Paul R. Healey

Fotis Topouzis

My awareness of constructing an objective truth would never provide me with anything more than an objective truth for me, and my greatest attempt at impartiality would never enable me to prevail over my subjectivity … if I had not, underlying my judgments, the primordial certainty of being in contact with being itself, if, before any voluntary *adoption of a position*, I were not already *situated* in an intersubjective world.

M. Merleau-Ponty

GLAUCOMA SCREENING

Screening for Open Angle Glaucoma,
Primary Angle-Closure and
Primary Angle-Closure Glaucoma

The 5th Consensus Report of the

World Glaucoma Association

edited by

Robert N. Weinreb
Paul R. Healey
and
Fotis Topouzis

Kugler Publications/Amsterdam/The Netherlands

ISBN 10: 90-6299-218-8
ISBN 13: 978-90-6299-218-8

Distributors:

For the USA and Canada:
Pathway Book Service
4 White Brook Road
Gilsum, NH 03448
U.S.A.
email: pbs@pathwaybook.com

For all other countries:
Kugler Publications
P.O. Box 20538
1001 NM Amsterdam, The Netherlands
Telefax (+31.20) 68 45 700

website: www.kuglerpublications.com

This publication is the fifth of a series on Consensus meetings in Glaucoma under the auspices of the World Glaucoma Association

Glaucoma Screening Consensus Meeting participants. Fort Lauderdale, April 26, 2008.

FACULTY

Program Chairs
Robert N. Weinreb, USA
Anne Coleman, USA
Ravi Thomas, India
Fotis Topouzis, Greece
Ningli Wang, China

Section Leaders OAG
Paul R. Healey, Australia
Anders Heijl, Sweden
Linda Zangwill, USA

Section Leaders AC(G)
Tin Aung, Singapore
Paul Foster, UK
David Friedman, USA
Robert Ritch, USA

Participants
Benedictus Ajayi, Nigeria
Douglas Anderson, USA
Makato Araie*, Japan
Yinka Ashaye, Nigeria
Augusto Azuaro Blanco*, UK
Yaniv Barkana, Israel
Khaled Ben Amor, Tunesia
Boel Bengtsson, Sweden
Rupert Bourne, UK
Jennifer Burr, UK
Robert Casson, Australia
Paul Chew, Singapore
Nathan Congdon, Hong Kong
Collin Cook, South Africa
Tanuj Dada, India
P. De Jong, The Netherlands
S. Deokhole, USA
Syril Dorairaj, USA
Amish Doshi, USA
Murray Fingeret, USA
Ronnie George, India
Christopher Girkin, USA
David Greenfield, USA
Daniel Grigera, Argentina
Neeru Gupta, Canada
Paul Harasymowycz, Canada
Mingguang He*, China
David Henson, UK
Aiko Iwase, Japan
Henry Jampel, USA
N. Jansonius, The Netherlands
Kenji Kashiwagi, Japan
Michael Kass, USA
Changwon Kee, South Korea
Dan Kiage,
Elliot Kirstein, USA
Theodore Krupin, USA
Steven Kymes*, USA
Dennis Lam, Hong Kong
George Lambrou, Greece
Paul Lee*, USA
Fabian Lerner, Argentina
Cristina Leske, USA
Christopher Leung, Singapore
Dexter Leung, Hong Kong
Joao Lopes, Chile
Mackey, D, Australia
Baskaran Mani, India
Choka Melamed, Israel
Clive Migdal, UK
Richard Mills, USA
Marcello Nicolela, Canada
Winnie Nolan*, UK
Rajul Parikh, India
Ki-Ho Park, Korea
Michael Patella, USA
Harry Quigley*, USA
R. Ramakrishnan, India
Tony Realini, USA
Prin RojanaPongpun, Thailand
Lisandro Sakata, Brazil
Garudadri Chandra Sekhar,
Ramanjit Sihota*, India
Michael Sinai,USA
Arthur Sit, USA

*Subsection co-chairs

Jim Standefer*, USA
Remo Susanna, Brazil
Celso Tello, USA
Clement Tham*, Hong Kong
Suman Thapa, Nepal
John Thygesen, Denmark
Atsuo Tomidokoro, Japan
Carlo Traverso, Italy
Anja Tuulonen*, Finland
Rohit Varma, USA
Lingam Vijaya, India
Gianmarco Vizzeri, USA
Tsing Hong Wang, Taiwan
Roy Wilson, USA
Tien Wong, Australia
Richard Wormald,UK
Laing Xu, Hong Kong
Tetsuya Yamamoto, Japan
Jennifer Yip, Singapore
Thierry Zeyen, Belgium
Chun Zhang, China
Gerhard Zinser, Germany

Consensus Development Panel
Tin Aung, Singapore
Anne Coleman, USA
Jonathan Crowston, Australia
Paul Foster, UK
David Friedman, USA
Franz Grehn, Germany
Paul R. Healey, Australia
Anders Heijl, Sweden
Robert Ritch, USA
Kuldev Singh, USA
Remo Susanna, Brazil
Ravi Thomas, India
Fotis Topouzis, Greece
Ningli Wang, China
Robert N. Weinreb, USA
Linda Zangwill, USA

Recording Secretaries
A. Doshi
M. Vizzeri

Glaucoma Societies / Sections of the following countries and regions have agreed to review this report:
America, Argentina, Asia-Oceania, Australia and New Zealand, Austria, Azerbaijan, Belgium, Brazil, Bulgaria, Canada, Central America, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Egypt, Estonia, Europe, Finland, France, Georgia, Germany, Ghana, Greece, Hungaria, Iceland, India, Indonesia, Iran, Israel, Italy, Japan, Korea, Latin-America, Lesotho, Lithuania, Mexico, Netherlands, Nigeria, Norway, Pakistan, Pan-America, Pan Arab Africa, Peru, Philippines, Poland, Portugal, Rumania, Russia, Serbia and Montenegro, Slovenia, Spain, South-Africa, South East Asia, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Kingdom and Eire, Glaucoma Research Society, Optometric Glaucoma Society, International Society of Glaucoma Surgery.

* Subsection co-chairs

CONTENTS

Preface xi
Welcome xiii

SCREENING FOR OPEN-ANGLE GLAUCOMA (OAG)

Is OAG an important health problem?
Co-chairs: Anders Heijl, Paul Lee 3
Is there an accepted and effective treatment for patients with the disease that is more effective at preventing morbidity when initiated in the early, asymptomatic stage than when begun in the later, symptomatic stages?
Co-chairs: Makoto Araie, Linda Zangwill 13
Are facilities for diagnosis and treatment available?
Co-chairs: Paul R. Healey, Ramanjit Sihota 25
Is there an appropriate, acceptable, and reasonably accurate screening test?
Co-chairs: Augusto Azuara Blanco, Linda Zangwill 33
Is the natural history of the condition, including development from latent to manifest disease, adequately understood?
Co-chairs: Anders Heijl, Harry Quigley 51
Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditure on medical care as a whole?
Co-chairs: Paul R. Healey, Anja Tuulonen 55

SCREENING FOR PRIMARY ANGLE CLOSURE AND PRIMARY ANGLE-CLOSURE GLAUCOMA

Are angle closure (AC) and angle-closure glaucoma (ACG) important health problems?
Co-chairs: Paul Foster, Mingguang He 65
Is there an accepted and effective treatment for patients with angle-closure glaucoma (ACG) that is more effective at preventing morbidity when initiated in the early, asymptomatic stage than when begun in the later, symptomatic stages?
Co-chairs: Robert Ritch, Clement Tham 79
Are facilities for diagnosis and treatment available?
Co-chairs: Robert Ritch, Jim Standefer 93

Is there an appropriate, acceptable, and reasonably accurate screening test?
Co-chairs: Tin Aung, Winnie Nolan 99
Is the natural history of the condition, including development from latent to manifest disease, adequately understood?
Co-chairs: Paul Foster, Ravi Thomas 111
Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditure on medical care as a whole?
Co-chairs: David Friedman, Steve Kymes 125

Photo Section 136
Index of Authors 145
Summary of Consensus Points 146

PREFACE

This is the fifth glaucoma World Glaucoma Association Consensus. As with other consensus topics, the discussion and conclusions of Glaucoma Screening, the subject for the 2008 consensus, will have broad impact. The global faculty, consisting of leading authorities on various aspects of glaucoma screening, met in Fort Lauderdale on April 26, 2008 to discuss the reports and refine the consensus statements. The Consensus Panel also met at that time, as well as electronically during the subsequent four weeks.

Obtaining consensus on how best to conduct glaucoma screening is quite a challenge, especially since the epidemiology and testing paradigms are so different for open-angle and angle-closure glaucoma. As with the previous WGA consensuses, the Glaucoma Screening consensus was based on the published literature and expert experience. Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, especially when the desired evidence is lacking. The goal of this consensus was to establish the best practice for glaucoma screening, as well as to identify those areas for which we have little evidence and, therefore, need additional research. We hope that this consensus will serve as a benchmark of our understanding, and that it will be revised and improved with the emergence of new evidence.

Robert N. Weinreb
Paul R. Healey
Fotis Topouzis
Anne Coleman
Ningli Wang

Consensus Panel meeting to clarify consensus statements

Consensus Panel deep in thought

WELCOME

For the World Glaucoma Association Consensus V, our topic was Glaucoma Screening, both for open-angle glaucoma and angle-closure glaucoma. Global experts were assembled beginning in January 2008 to participate in the Project Forum E-Room, a unique aspect to facilitate discussion of each of the consensus meetings.

With each of the prior meetings, arriving at the consensus was circuitous and filled with compromises, and this meeting had a similar path. The consensus process provided an excellent opportunity to critically assess the evidence relating to glaucoma screening and develop consensus statements. As with previous ones, the entire process was stimulating, educational, and thought-provoking for all participants and attendees.

Robert N. Weinreb
Erik L. Greve

Anders Heijl presenting Open Angle Consensus

Consensus Panel deliberating

SCREENING
FOR
OPEN-ANGLE GLAUCOMA (OAG)

Sunil Deokhole and Pam Sample

Iwase and Mokoto Araie

IS OAG AN IMPORTANT HEALTH PROBLEM?


Anders Heijl

Co-chairs: Anders Heijl, Paul Lee

Contributors: Makoto Araie, Jennifer Burr, Collin Cook, Daniel Grigera, Aiko Iwase, Dan Kiage, Cristina Leske, Rajul Parikh, Harry Quigley, John Thygesen, Fotis Topouzis, Anja Tuulonen, Rohit Varma, Gerhard Zinser

Consensus points

- Glaucoma is the leading cause of preventable irreversible blindness.
- The goal of glaucoma screening is to prevent visual impairment, preserve quality of life and visual functioning.
- Each society should determine its own criteria, including the stage of disease, for the allocation of an affordable proportion of its resources for glaucoma care and screening.
- The prevalence of open-angle glaucoma has been determined for some populations of European, African and Asian ancestry
  Comment: Prevalence, incidence and severity data are needed still for many regions of the world.
- Long-term data show a substantial frequency of glaucoma blindness in some populations.
  Comment: Additional population based data are needed on the rates and risks of vision loss.

Introduction

To help frame and organize the discussion and our current evidence base, the organizing committee tasked the working group addressing the question 'How much of a burden is the disease?' to assess four specific issues regarding screening for OAG. These issues form the basis for the working group discussion and report: 1) How prevalent is OAG in different parts of the world?; 2) What is its impact on visual impairment and blindness?; 3) What is its economic impact on health care costs?; 4) What is its economic impact on other societal costs/ needs?

Glaucoma Screening, pp. 3-12
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

1. Burden of OAG globally

In order to determine the burden of any disease, including OAG, it is imperative to first define the disease in specific and exclusive terms. Current definitions of OAG vary in different regions of the world with no single, widely accepted set of explicit criteria to clearly define a case of OAG and to exclude a person as NOT having the disease. "There is no general consensus on the specific methods and standards to define glaucomatous optic disc damage or visual field defects, with great variability in OAG classifications among epidemiological studies. An important issue is to develop a consensus on standard criteria for OAG."[1]

Several approaches have been taken in an effort to create a standard definition. Foster *et al.*[2] have suggested an empirical, population-based statistical definition, based on having a cup to disc ratio greater than that of 97.5% of the population, generally combined with a visual field defect. However, patients with small discs may have cup to disc ratios within the 97.5% group but still have glaucoma. Friedman *et al.* combined data from numerous population-based surveys to create consensus estimates of disease prevalence in the United States,[3] which generally require a visual field defect as part of the defining criteria. However, in a third approach, embodied in current clinical definitions of OAG in professional society guidelines in several countries (including the United States),[4] a visual field defect is no longer required as part of the case definition.

With the absence of a commonly accepted definition, the definition chosen will determine the numbers of individuals who have the disease and thus the population at risk (PAR). Based on the definition, the numbers could vary substantially.[5,6] The larger the PAR, the greater the prior probability of the disease on a population basis and thus the better the predictive values of any screening test (through the operation of Bayes' Theorem). In addition, the larger the population affected, the greater the burden of disease is theoretically likely to be. Thus, the decision of any consensus group on what constitutes glaucoma will have significant implications for the performance and perceived value of screening.

One potential approach in assessing the burden of a disease in affected individuals is to evaluate the impact of that disease on an individual and the life-time risk of that disease in causing disability when undetected and left untreated. If a condition does not cause any disability or has a very low likelihood of doing so prior to death or disability from other causes, then the burden of that disease and the importance of its detection through screening is at best low. Thus, in the absence of an agreed upon case definition, the current literature should be assessed (described in section 1-3 below) to determine the burden of different levels of severity of glaucoma on those affected and to use, for the current time, an approach to screening for glaucoma that would detect disease that is severe enough to have a measurable impact (using current knowledge) on functioning of patients during their expected lifetime.

In more clinical terms, it is generally accepted that the goal of glaucoma care is to prevent loss of quality of life during the patient's lifetime.[4,7,8] The European Glaucoma Society formulation goes further to incorporate the societal perspective – to prevent loss of Quality of Life during the patient's lifetime at an affordable cost.[7] Adoption of this goal carries with it the implicit and explicit judgment that what is 'affordable' would vary by society, and that, thus, different societies would choose to screen for different levels of severity of glaucoma damage, as defined by its impact on functioning of individuals within that society.

This is consistent with the approach proposed by the World Health Organization (WHO) (initially for screening for diabetic retinopathy).[9] Each society would have the right to determine the allocation of societal resources for health care and to make choices within its health care system as to which diseases and what level of severity merits societal support for interventions, as well as the means of such intervention. In order to make such decisions, we need to understand the impact of glaucoma associated visual decrements on patient quality of life and to estimate the numbers of people that would be so affected, both at the time of diagnosis and over the course of their lifetimes.

1.1 Prevalence of OAG globally

There is a large and considerable amount of prevalence data from many parts of the world, including European-derived populations, Afro-American populations, and some Asian populations, using a variety of case definitions.[1] However, data are also missing from many important areas, *e.g.,* South America. Published data indicate that regardless of case definition, specific factors are associated with higher rates of OAG on a population basis. Firstly, OAG is more common as individuals age. Secondly, glaucoma prevalence varies by ethnicity. Prevalence data for different regions and ethnicities have been estimated by Quigley and Broman.[10,11] Thirdly, higher levels of intraocular pressure (IOP) in any given population are generally associated with higher risk of developing OAG, even among populations with a high prevalence of 'normal tension' glaucoma. Fourthly, a family history of OAG together with initial evidence from heritability and genetic studies indicate a greater risk for primary relatives in having OAG. Data from North American and European studies also indicate that those with thinner central corneas, lower perfusion pressures, myopia and pseudoexfoliation are also likely to have a greater risk of developing OAG.[12,13] Yet, it is important to note that the majority of patients with OAG may have no risk factors (other than age).

In general, among those aged 40 years and older, OAG occurs in between 1 to 4% of most populations, although African-derived populations may have rates of 8 to 9%.[1] Estimates by Quigley show that OAG will become the most common form of glaucoma in almost all countries within the next 20 years.[10]

While significant and growing data are published and available for the prevalence and incidence of glaucoma, less data are available (due to the limitations of sample sizes in most population-based surveys) as to the age-specific preva-

lence of the levels of damage and undiagnosed damage that exist, for unilateral loss, for best eye, and even potentially for binocular field loss. Data have been published on the distribution of the amount of visual field loss in the Baltimore Eye Study[14] and Malmö, Sweden populations.[15] These data indicate, together with the Olmsted County data from Minnesota, USA,[16] that visual field loss can be significantly advanced if detection of OAG is based on patient presentation for health care. The study by Grødum *et al.*[15] indicates that population-based screening can detect individuals with OAG at considerably earlier stages of visual field loss and with much lower rates of bilateral visual field loss, although the Thessaloniki Eye Study[17] did not find a difference between diagnosed and undiagnosed glaucoma in the community setting.

1.2 Impact on visual impairment and blindness

The WHO notes that glaucoma is the second leading cause of irreversible impairment and *blindness* both in developed and developing countries.[18] In some countries, like Japan, it is the leading cause of authorization of care for low vision or blindness services (private communications, Araie). In analyzing the data, the definitions of blindness and the threshold of visual impairment used in various studies are important. For example, the use of USA definitions would lead to higher estimates of blindness than the more conservative WHO criteria. Rates of blindness based on visual acuity only, which is not uncommon in the literature, are also underestimates because a significant portion of those blind from glaucoma have severely restricted visual fields with visual acuities better than the threshold of legal blindness. Rates of blindness calculated from low vision centres are generally under-estimations, because of under-reporting. As such, it was suggested in the discussion that assembling a data base of legal blindness caused by glaucoma in different countries would be of value.

Incorporation of estimates of *visual impairment* due to glaucoma at different stages of the disease in addition to blindness is vital, because a significant impact on patients' performance of important activities occurs short of blindness. Indeed, in a profound analysis of the actual performance of visually dependent tasks among community dwelling persons aged 65 and older in Salisbury, MD, USA, West *et al.* demonstrated that the ability to perform those tasks varied linearly with visual acuity and contrast sensitivity, suggesting that the use of cutoffs and thresholds was not scientifically based but due to political and economic considerations by policymakers.[19] The study group also demonstrated that visual field loss, as measured by a threshold screening test was also significantly related to task performance. This research group has also more recently reported on the association between glaucoma or visual field loss and *falls, mobility* limitations, and the resulting reductions in independence skills.[20,21] Many other studies have also demonstrated greater rates of falls and injuries among those with visual field loss, a significant finding given the associations between falls and increased morbidity and mortality.[21–25]

Individuals with glaucoma and visual field loss also have higher rates of motor vehicle accidents or restrict their own driving activities and thus limit their degree of independence.[26,27] In those societies where driving is a critical activity to daily living, restriction of driving can have a profound impact on independence and both mental and physical well-being.

With the goal of preventing loss of quality of life (QoL) during patients' lifetimes, the first question is when *clinically meaningful loss of visual functioning* begins to occur. Data analyzed from the Early Manifest Glaucoma Trial (EMGT) indicated that until at least –4.1 decibel (dB) of mean deviation (MD) loss was found on a standard Humphrey achromatic visual field test, no significant patient-reported visual functioning loss could be detected.[28] However, Varma *et al.*,[29,30] in analyzing the data from the Los Angeles Latino Eye Study (LALES) study and correcting for visual acuity, confirmed the initial report by Gutierrez *et al.*[31] that patient reported vision-related QoL as measured by the National Eye Institute Visual Function Questionnaire (NEI-VFQ) declined in a linear relationship to Humphrey achromatic visual field loss (Advanced Glaucoma Intervention Study (AGIS) score in the Gutierrez analysis, MD in the Varma). While VFQ scores declined linearly starting from the earliest amount of field loss, Varma *et al.* also reported that a significant VFQ score decrement of 5 to 7 points (on a 100 point scale) occurred at –3 to –4 dB of MD loss.[29] A second report by Owsley *et al.* among a predominantly black American population also noted the early onset of significant VFQ decrements (on at least some subscales) at or less than this level of VF loss.[32] As such, policymakers can consider using this amount of visual field loss as an initial threshold of a clinically meaningful case of OAG that compromises patient quality of life. However, we must recognize that by the time this amount of visual field loss is developed, patient QoL has already been significantly reduced. Given the chronic progressive nature of the disease and the estimated mean lifespan of 13 (white) to 16 years (black) with the disease,[33] prevention of this QoL loss would require intervention prior to this degree of field loss. Indeed, data from Olmsted County and other investigators show that for those who live 20 years with treated glaucoma (*i.e.*, longer than the average patient), between 20 and 30% of patients will be blind in at least one eye, with an unknown number being significantly visually impaired.[17]

The rationale for such early detection – potentially at the onset of any visual field loss (or contrast sensitivity loss, based on the Salisbury Eye Evaluation

(SEE) results, which can occur early in OAG) – is the likelihood of worsening of OAG among those who have the disease. Annualized event rates of worsening of 8% occurred among those with visual field proven OAG in the untreated arm of the EMGT,[34] and ran as high as 7 to 8% per year in the higher risk groups of the Ocular Hypertension Treatment Study (OHTS) study without VF loss[35] (with the highest risk groups in OHTS arguably being early glaucoma patients without visual field loss at entry). This figure is similar to that in patients with concomitant ocular hypertension and pseudoexfoliation.[12]

Even more importantly, we know that even after detection and treatment, rates of visual field worsening under clinical care, while reduced, remain sig-

nificant. For example, the treatment arm of the EMGT experienced annualized rates of worsening of 5 to 6% per year.[34] Case series from leading academic and glaucoma specialty care centers around the world also demonstrate annualized rates of worsening of 5% or so per year among treated and followed OAG patients.[35,36] Indeed, the best rate (for lowest rate of worsening on an annual basis) is 3% per year in Collaborative Initial Glaucoma Treatment Study (CIGTS).[37] Further, we know from the large recent Randomized Controlled Trials (RCTs) that inter-patient variability of disease progression is very large and can be only poorly predicted from risk factors including IOP levels.[38] Patients going blind or losing QoL will clearly be heavily over-represented among those who have higher progression rates. Risks of blindness or vision loss cannot, therefore, be calculated assuming that all patients progress at the average rate. Instead distributions of progression rates should be used in such risk calculations. There is very little such data in the literature, and almost none for natural untreated progression rates, except for normal tension glaucoma (Collaborative Normal Tension Glaucoma Study (CNTGS)).[39] Thus, since clinical glaucoma care cannot hope to stop disease progression completely, the stage of glaucoma that is important to detect will vary with patient age, being earlier in younger than in elderly patients.

1.3 Impact of glaucoma on health care costs

Several studies in the past ten years have sought to estimate the impact of glaucoma on various aspects and levels of health care costs.[40–42] First, direct costs of glaucoma care have been estimated at both the individual and societal level, using community standards for disease definition in each country.[40–43] All studies on individual or patient level costs show that costs are highest in the first year after diagnosis and that costs increase with the severity of the disease on an annualized basis.[44–46] Traverso *et al.* estimated that the annual per person costs for glaucoma care in European countries varied from €455 to €869,[45] while Lee *et al.* estimated that the costs in the United States varied from $623 to $2511.[46] Medication costs accounted for 42 to 56% of such costs in Europe, compared to 24 to 61% in the USA.[47]

Reports from Australia and USA provide estimates of the annual direct medical costs of glaucoma of $144.2 million[40] and $2.9 billion respectively.[42] Similar data are lacking for other countries and is thus the impetus for an ongoing collaboration to generate such data by the International Agency for the Prevention of Blindness (IAPB) and Association of Research in Vision and Ophthalmology (ARVO).

Recent studies also demonstrate that overall medical costs rise among those diagnosed with glaucoma on a longitudinal basis, even as glaucoma associated costs fall after the first year after diagnosis.[48]

1.4 Impact of glaucoma on other societal costs/needs

Work by Taylor *et al.* in Australia and Rein *et al.* and Frick *et al.* in the USA clearly demonstrates the costs associated with visual impairment in these two countries, together with the direct and indirect costs that can be ascribed to glaucoma.[40,42,43] The higher total costs noted in Australia include a more detailed analysis of social support and opportunity costs by caregivers and informal social support networks, as well as other modeling differences in utility assessment and other factors. What is consistent, is the significant nature of costs associated with visual impairment and glaucoma.

Little data is available on the cost-effectiveness of treatment for OAG. However, two papers have recently demonstrated an acceptable level of incremental cost-effectiveness for the treatment of ocular hypertensives that are at elevated risk for development for OAG, though not necessarily for all ocular hypertensives.[49,50] As such, one can fairly confidently predict that the treatment of those with more severe disease (and thus the prevention of more field loss and loss of associated well-being) will be at least as cost-effective. Indeed, a European study showed that the annual costs for treatment were much smaller than annual community costs for blindness, €885 and €6,097 respectively.[51]

While treatment is thus likely to be appropriately cost-effective, it has been stated by numerous analysts that general screening for OAG is *not* cost-effective, including the important report by Burr and co-workers.[52] However, a Finnish report by Vaahtoranta-Lehtonen *et al.* came to the opposite conclusion.[53] What explains these differences are several variables. Most importantly, screening effectiveness is highly dependent on the predictive value of the screening method employed and the prevalence or prior probability of the disease. The statement that 'screening for glaucoma is only justified in high-risk populations' may be true, but depends on the impact of 'high-risk' criteria on the prevalence of glaucoma in that particular segment of the population. For example, screening for glaucoma in 40-year old persons of Caucasian origin will be very difficult to justify, only because OAG prevalence is so very age-dependent and very low before 50 years of age or so in this ethnic group.

A thorough analysis of age-specific prevalence of glaucoma of defined severity levels should likely precede any large studies of glaucoma screening to determine the prior probability of OAG, or the PAR. Importantly, the use of thresholds of visual field loss such as –4dB or –12 dB MD loss, for example, will lower the prior probability of the condition in the population being screened, compared to one based on any or no visual field loss. This will have the affect of lowering the posterior probability that a positive screening test will represent a true positive (since the prior probability will have been lowered by the simple fact that those with somewhat more severe disease will always be less common than including those with less severe disease).

Possible options for decreasing the costs of detecting a case of OAG through means of screening include adding some form of assessment to an ophthalmic examination that is already paid for or conducted for other reasons, so that

there would be a substantially lower cost to case detection. Available analyses of cost-effectiveness have not evaluated screening for OAG, limited to populations with clinically meaningful visual field loss disease, screened with the goal of detecting this stage of the disease and with screening instruments and interpretation criteria adjusted for this level of ambition.

Topics for future research/further attention

- Prevalence studies are needed in several parts of the world.
- Age-specific distributions of undetected glaucoma stratified according to levels of damage are needed for populations where screening is considered.
- More data are needed on the effects of glaucoma damage at all levels, especially early in the disease, on QoL and performance of everyday tasks.
- Further studies on typical outcomes of glaucoma patients under clinical care are needed, including studies of velocities of progression.

References

1. Leske C. Open-Angle Glaucoma – An Epidemiologic Overview. Ophthalmic Epidemiology 2007; 14: 1566-1572.
2. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. BJO 2003; 86: 238-242.
3. Friedman DS, Wolfs RC, O'Colmain BJ, *et al.* Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 2004; 122: 532-538.
4. American Academy of Ophthalmology. Preferred Practice Pattern: Primary Open-Angle Glaucoma. San Francisco, CA: AAO, 2006.
5. Wolfs RC, Borger PH, Ramrattan RS, *et al.* Changing views on open-angle glaucoma: definitions and prevalences – The Rotterdam Study. Invest Ophthalmol Vis Sci 2000; 41: 3309-3321.
6. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology 1996; 103: 1661-1669.
7. European Glaucoma Society. Terminology and Guidelines for Glaucoma (IInd edition). EGS, 2008.
8. South East Asia Glaucoma Interest Group. Asia Pacific Glaucoma Guidelines. Sydney, Australia: SEAGIG, 2004.
9. World Health Organization. Prevention of Blindness from Diabetes Mellitus. Geneva, Switzerland: 2006.
10. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. BJO 2006; 90: 262-267.
11. Broman AT, Quigley HA, West SK, *et al.* Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. Invest Ophthalmol Vis Sci 2008; 49: 66-76.
12. Grødum K, Heijl A, Bengtsson B. Refractive error and glaucoma Acta Ophthalmolgica 2001; 79: 560-566;
13. Grødum K, Heijl A, Bengtsson B. Risks of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology 2005; 112: 386-390

14. Tielsch JM, Sommer A, Katz J, *et al.* Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA 1991; 266: 369-374.
15. Grødum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine practice. Acta Ophthalmol Scand 2002; 80: 627-631.
16. Hattenhauer MG, Johnson DH, Ing HH, *et al.* The probability of blindness from open-angle glaucoma. Ophthalmology 1998; 105: 2009-2014.
17. Topouzis F, Coleman AL, Harris A, *et al.* Factors associated with undiagnosed open-angle glaucoma: the Thessaloniki Eye Study. Am J Ophthalmol 2008; 145: 327-335.
18. World Health Organization. www.who.int/mediacentre/factsheets/fs282/en/. Accessed April 13, 2008.
19. West SK, Rubin GS, Broman AT, *et al.* How does visual impairment affect performance on tasks of everyday life? The SEE Project. Arch Ophthalmol 2002; 120: 774-780.
20. Friedman DS, Freeman E, Munoz B, Jampel HD, West SK. Glaucoma and mobility performance: the Salisbury Eye Evaluation Project. Ophthalmology 2007; 114: 2232-2237.
21. Feeman EE, Munoz B, Rubin G, West SK. Visual field loss increases the risk of falls in older adults: the Salisbury eye evaluation. Invest Ophthalmol Visc Sci 2007; 48: 4445-4450.
22. Klein BE, Moss SE, Klein KE, Cruickshanks KJ. Associations of visual function with physical outcomes and limitations 5 years later in an older population: the Beaver Dam Eye study. Ophthalmology 2003; 110: 644-650.
23. Ivers RQ, Cumming RB, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains Eye Study. J Am Geriatr Soc 1998; 46: 58-64.
24. Coleman AL, Cummings SR, Yu F, *et al.* Binocular visual-field loss increases the risk of future falls in older white women. J Am Geriatr Soc 2007; 55: 357-364.
25. http://www.vhct.org/case4007/index.htm, accessed April 13, 2008.
26. McGwin G, Mays A, Joiner W, *et al.* Is glaucoma associated with motor vehicle collision involvement and driving avoidance. Invest Opthalmol Vis Sci 2004; 45: 3934-3939.
27. Szlyk JP, Mahler CL, Seiple W, Edward DP, Wilensky JT. Driving performance of glaucoma patients correlates with peripheral visual field loss. J Glaucoma 2005; 14: 145-150.
28. Hyman LG, Komaroff E, Heijl A, *et al.* Treatment and vision-related quality of life inthe early manifest glaucoma trial. Ophthalmology 2005; 112: 1505-1513.
29. McKean-Cowdin R, Varma R, Wu J, *et al.* Severity of visual field loss and health-related quality of life. Am J Ophthalmol 2007; 143: 1013-1023.
30. McKean-Cowdin R, Wang Y, Wu J, *et al.* Impact of visual field loss on health-related quality of life in the glaucoma: the Los Angeles Latino Eye Study. Ophthalmology 2007; Nov. 10 (e-pub).
31. Gutierrez P, Wilson MR, Johnson C, *et al.* Influence of glaucomatous visual field loss on health-related quality of life. Arch Ophthalmol 1997; 115: 777-784.
32. Ringsdorf L, McGwin G, Owsley C. Visual field defects and vision-specific health-related quality of life in African-Americans and whites with glaucoma. J Glaucoma 2006; 15: 41-48.
33. Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. Invest Ophthalmol Vis Sci 1997; 38: 83-91.
34. Heijl A, Leske MC, Bengtsson B, *et al.* Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120: 1268-1279.
35. Lee PP, Walt JG, Doyle JJ, *et al.* A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. Arch Ophthalmol 2006; 124: 12-19.
36. Chen PP, Park RJ. Visual field progression in patients with initially unilateral visual field loss from chronic open-angle glaucoma. Ophthalmology 2000; 107: 1688-1692.
37. Lichter PR, Musch DC, Gillespie BW, *et al.* Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001; 108: 1943-1953.
38. Heijl A, Leske MC, Bengtsson B, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial

Group. Measuring visual field progression in the Early Manifest Glaucoma Trial. Acta Ophthalmol 2003; 81: 286-293.
39. Anderson DR, Drance SM, Schulzer M, Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. Ophthalmology 2001; 108: 247-253.
40. Taylor JR, Pzzullo ML, Keeffe JE. The economic impact and cost of visual impairment in Australia. BJO 2006; 90: 272-275.
41. Schmier JK, Halpern MT, Jones ML. The economic implications of glaucoma: a literature review. Pharmacoeconomics 2007; 25: 287-308.
42. Rein DB, Zhang P, Wirthe KE, *et al.* The economic burden of major adult visual disorders in the United States. Arch Ophthalmol 2006; 124: 1754-1760.
43. Frick KD, Gower EW, Kempen JH, Wolff JL. Economic impact of visual impairment and blindness in the United States. Arch Ophthalmol 2007; 125: 544-550.
44. Kobelt-Nguyen G, Gerdtham EG, Alm A. Costs of treating primary open-angle glaucoma and ocular hypertension: a retrospective, observation two-year chart review of newly diagnosed patients in Sweden and the United States. J Glaucoma 1998; 7: 95-104.
45. Traverso CE, Walt JG, Kelly SP, *et al.* Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilization in Europe. BJO 2005; 89: 1245-1249.
46. Lee PP, Walt JG, Doyle JJ, *et al.* A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. Arch Ophtahlmol 2006; 124: 12-19.
47. Lee PP, Kelly SP, Mills RP, *et al.* Glaucoma in the United States and Europe: predicting costs and surgical rates based upon stage of disease. J Glaucoma 2007; 16: 471-478.
48. Lee PP, Levin LA, Walt JG, *et al.* Cost of patients with primary open-angle glaucoma: a retrospective study of commercial insurance claims data. Ophthalmology 2007; 114: 1241-1247.
49. Kymes SM, Kass MA, Anderson DR, *et al.* Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. Am J Ophthalmol 2006; 141: 997-1008.
50. Stewart WC, Stewart JA, Nassar QJ, Mychaskiw MA. Cost-effectiveness of treating ocular hypertension. Ophthalmology 2008; 115: 94-98.
51. Thygesen J, Aagren M, Arnavielle S, Bron A, Fröhlich SJ, Baggesen K, Azuara-Blanco A, Buchholz P, Walt JG. Late-stage, primary open-angle glaucoma in Europe: social and health care maintenance costs and quality of life of patients from 4 countries. Current Medical Research and Opinion, 2008. Accepted for publication.
52. Burr JM, Mowatt G, Hernandex R, *et al.* The clinical effectiveness and cost-effectiveness of screening for open-angle glaucoma: a systematic review and economic evaluation. Health Technol Assess 2007; 11: 1-190.
53. Vaahtoranta-Lehtonen H, Tuulonen A, Aronen P, *et al.* Acta Ophthalmol Scand 2007; 85: 508-518.

IS THERE AN ACCEPTED AND EFFECTIVE TREATMENT FOR PATIENTS WITH THE DISEASE THAT IS MORE EFFECTIVE AT PREVENTING MORBIDITY WHEN INITIATED IN THE EARLY, ASYMPTOMATIC STAGE THAN WHEN BEGUN IN THE LATER, SYMPTOMATIC STAGES?

Makoto Araie

Co-chairs: Makoto Araie, Linda Zangwill

Contributors: Doug Anderson, Collin Cook, Tanuj Dada, Daniel Grigera, Aiko Iwase, Michael Kass, Changwon Kee, Dan Kiage, Fabian Lerner, Joao Lopes, Choka Melamed, Clive Migdal, Richard Mills, Rajul Parikh, GC Sekhar, Remo Susanna, Ningli Wang, Tsing Hong Wang, Thierry Zeyen, Gerhard Zinser

Consensus points

- High-quality randomized trials (treatment vs. no treatment) and meta-analyses have shown that topical ocular hypotensive medication is effective in delaying onset and progression of open-angle glaucoma (OAG).
- Treatments are effective, easy to use, and well tolerated.
- It is not known whether postponing ocular hypotensive therapy affects the rate of subsequent conversion from ocular hypertension to OAG or the rate of progression of visual field loss once OAG has developed.
- It is not known whether the reduction in progression rate from intraocular pressure (IOP) lowering therapy varies according to disease stage.
  Comment: Asymptomatic disease may include early, moderate, or at times severe stages of OAG.
- Current evidence suggests that glaucoma therapy itself is not associated with a measurable reduction of quality of life.
- Patients' perceived vision-related quality of life (VRQOL) and visual function is correlated with visual field loss, especially binocular visual field loss, in OAG.
  Comment: the greater the visual field loss, or the later the stage of the disease, the more symptomatic the disease.

Glaucoma Screening, pp. pp. 13-22
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

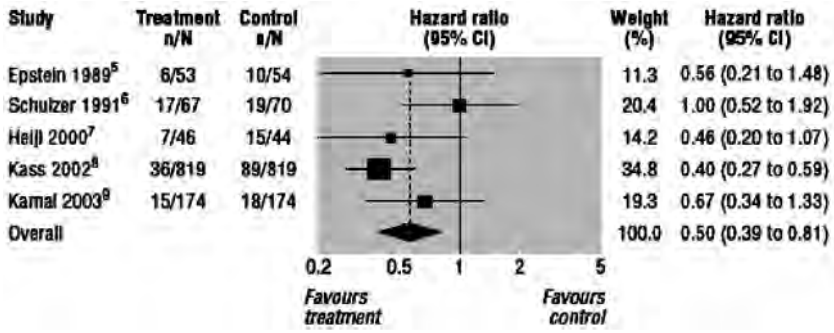

Fig. 1. Visual field loss or deterioration of optic disc, or both, among patients randomised to pressure lowering treatment *V* no treatment in ocular hypertension. Hazard ratios of less than 1.0 favour pressure lowering treatment. Boxed area is proportional to weight given to each trial in the statistical model. Heterogeneity: χ^2=6.2 (P=0.185); I^2=35.4% (95% confidence interval 0 to 75.8%).

Introduction

OAG is generally a slowly progressing disease. However, a significant portion of the glaucoma eyes will reach the end of the visual field damage scale 15-20 years after the diagnosis.[1–9] Because peripheral visual field loss usually progresses gradually in OAG, patients rarely report serious ocular symptoms in the early stages of disease.[10–23]

Strong evidence that IOP lowering therapy is effective at all stages of disease

There is consistent evidence from good quality randomized clinical trials that lowering IOP in patients with ocular hypertension, and early to advanced glaucoma prevents or delays visual field loss. Specifically, the evidence for treating ocular hypertension has been pooled in a systematic review based on five randomized trials of treated versus untreated patients with ocular hypertension (Fig. 1),[24–30] reporting that topical ocular hypotensive medication significantly delays the development of optic disc and visual field damage due to primary open angle glaucoma (POAG). The pooled hazard ratio (95% CI) from this systematic review was 0.56 (95% CI: 0.39 to 0.81), and the number needed to treat (NNT) to prevent the first glaucomatous visual field defect or definite glaucomatous disc change within five years of treatment was 12 (95% CI: 9 to 29)(Fig. 1).[30] It should be noted that the European Glaucoma Prevention Study (EGPS),[31] which did not show a beneficial effect of ocular hypotensive treatment compared to a placebo, was not included in this pooled analysis, because it was published after the systematic review was completed. A more recent systematic review[32] included EGPS in a pooled analysis comparing IOP-lowering medications to no

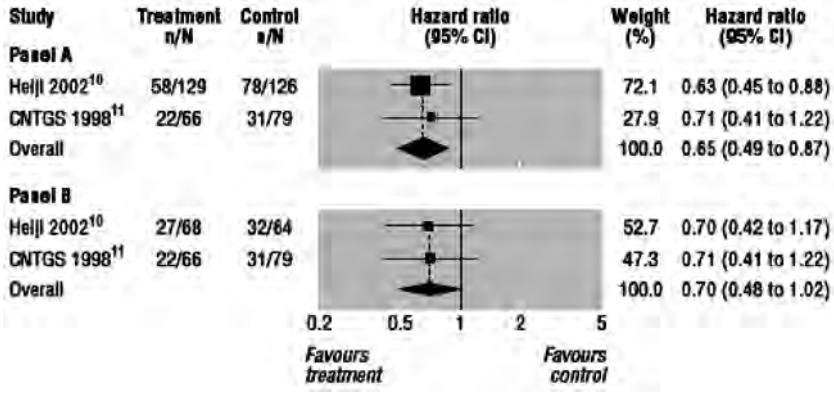

Fig. 2. Visual field loss or deterioration of optic disc, or both, among patients randomised to pressure lowering treatment *V* no treatment in open angle glaucoma (panel A). Panel B shows subgroup analysis of data in normal tension glaucoma. Hazard ratios of less than 1.0 favour pressure lowering treatment. Boxed area is proportional to weight given to each trial in the statistical model. Heterogeneity: χ^2=0.13 (P=0.72) for open angle glaucoma and χ^2=0.001 (P=0.97) for normal tension glaucoma.

treatment or placebo in both ocular hypertension and glaucoma subjects, and found a significant reduction in the incidence of visual field defects.

The Early Manifest Glaucoma Trial (EMGT) revealed that ocular hypotensive therapy of OAG eyes with relatively early stage of glaucomatous damage (median of mean deviation (MD) value by Humphrey Visual Field Analyzer of around –4 dB), which reduced IOP by 25%, significantly slowed further progression of visual field loss compared to untreated eyes.[33] Effects of treatment of elevated IOP by topical medication, laser trabeculoplasty, and/or surgery on further progression of visual field loss have been also demonstrated in OAG eyes with intermediate stage of damage (average MD values between –8 and –11 dB) by the Advanced Glaucoma Intervention Study (AGIS), Collaborative Normal Tension Glaucoma Study (CNTGS), and Collaborative Initial Glaucoma Treatment Study (CIGTS).[34–39] There are however, no randomized clinical trials evaluating the effectiveness of ocular hypotensive treatment in eyes with IOP of less than 15 mmHg. The effectiveness of treating this level of IOP is important in some countries such as Japan where the mean IOP in glaucoma cases identified in a population-based screening was 15.2 mmHg.[40]

Data from two of these randomized clinical trials that included an untreated arm also were pooled in a systemic review.[30] The EMGT and the CNTGS both reported benefits of IOP lowering treatment (topical medication, laser trabeculoplasty and/or surgery) compared to an untreated group in preventing or delaying visual field or optic disc progression with pooled hazard ratio of 0.65 (95% CI: 0.49 to 0.87), and the NTT to prevent visual field deterioration within five years of treatment of seven (95% CI: 4 to 20)(Fig. 2).[30] Subgroup

analysis showed a larger effect in OAG with elevated IOP and a reduced effect in OAG with normal IOP.[30]

In summary, data from good-quality clinical studies show that ocular hypotensive therapy is effective at delaying or preventing glaucomatous changes at different stages of disease, from ocular hypertension to moderate visual field loss.[24,31–35,37,39]

Is there evidence that treatment is more effective in the asymptomatic than symptomatic stages?

There is no direct evidence from randomized clinical trials that ocular hypotensive therapy is more effective in delaying further progression of visual field loss when initiated in the asymptomatic stage rather than in the later, symptomatic stage of OAG. The effect of treatment delay in ocular hypertensive subjects will be investigated in the Ocular Hypertension Treatment Study II (OHTSII). In OAG patients with structural damage or manifest visual field loss, it will be impossible to prospectively investigate whether delaying ocular hypotensive therapy affects future progression rate of visual field loss, since beneficial effects of ocular hypotensive therapy are now well established.

The effect of delaying treatment on future glaucomatous progression may be indirectly assessed from studies: 1) estimating the rate of progression at various stages of glaucoma in treated and untreated groups of patients, and 2) evaluating whether baseline visual field or optic disc status is predictive of future visual field loss.

Burr *et al.*[9] used two approaches to estimate the rate of progression in eyes with varying stages of glaucoma. The first approach, based on two Randomized Controlled Trials (RCTs), CNTGS and EMGT, estimated the annual rate of progression in treated and untreated glaucoma eyes in mild to moderate glaucoma as 0.2 and 0.25, respectively, in moderate to severe glaucoma as 0.07 and 0.11, respectively, and in severe to visually impaired as 0.06 and 0.10, respectively. The second approach included two other RCTs (CIGTS and a sub-study of AGIS) and seven cohort studies to estimate the median yearly probability of progressing from mild to moderate disease as 0.066 (range: 0.028 to 0.11), from moderate to severe disease as 0.087 (range: 0.04 to 0.12), and from severe to visual impaired disease as 0.1 (range: 0.03 to 0.16). These data may be used to indirectly infer the relationship between the effect of treatment and the stage of OAG.

The data on whether baseline severity of disease (based on visual field and optic disc indices) increases the likelihood of future progression is more difficult to interpret. In OHTS,[41] EMGT[42] and CIGTS,[39] worse baseline visual field indices were found to be associated with increased risk of progression, suggesting that delaying treatment or initiating treatment at later stage unfavorably affects the future prognosis of visual field. However, the results of CNTGS, a study of OAG patients with IOP $\leq$ 24 mmHg[43] and re-analysis of EMGT data with longer

follow-up[44,45] showed that contribution of the baseline visual field status to the risk of future progression of visual field loss was relatively small, especially in OAG with lower IOP. Furthermore, the result of AGIS showed that the better baseline visual field status is a risk factor for future progression of visual field loss,[46] suggesting that initiating ocular hypotensive therapy at later stage may not unfavorably affect the visual prognosis of OAG.

Results of retrospective studies also indicate inconsistent results with respect to the effect of severity of damage on future visual field progression; some suggested that later stage progresses more rapidly than earlier stage, while others suggested the opposite.[47–56] Progression of visual field loss of treated OAG was reportedly rather slower in the end stage than in the less-advanced stages.[54,55,57] Thus, there is not consistent evidence showing a relationship between the severity of glaucomatous damage and the effect of ocular hypotensive therapy on the rate of future visual field loss.

It should be noted that there are several methodological issues that make it difficult to find an association between severity of damage and likelihood of progression. Firstly, it may be more difficult to detect glaucomatous visual field progression in eyes with more severe damage at study entry as areas with visual field damage are shown to be more variable than those with less damage.[58] Secondly, the treatment of individuals may be more aggressive in patients with more severe visual field damage thereby lowering the rate of progression in these individuals. Thirdly, those with more advanced visual field loss may represent a group where initiation of ocular hypotensive therapy was delayed due to some reason, or a group with more serious type of OAG that may be less responsive to treatment.[59] This implies that comparing the rate of progression of visual field loss between those with earlier stage and later stage of damage, that is, between two groups with inherently different seriousness of OAG may be methodologically questionable. Finally, it is difficult to draw conclusions from the results of these prospective and retrospective studies because of differences in the severity of the damage of the study populations, methods of staging visual field damage, and effects of confounding factors.

In summary, there is no direct evidence demonstrating that delaying ocular hypotensive therapy unfavorably affects the rate of future progression of visual field loss in OAG. With regards to the progression rate in delaying treatment of ocular hypertension, OHTS II will provide answer to this question in the future, as mentioned above.

The relationship between glaucomatous visual field loss and symptoms

Since central vision, most important for VRQOL, is usually maintained until the late stage of the disease, OAG remains relatively asymptomatic until the disease reaches the advanced stage. Central visual acuity, however, is not an accurate predictor of visual function status,[60,61] and in fact morbidity performance

as measured by percentage of preferred walking speed (PPWS) or automobile crash involvement is not associated with central visual acuity, but visual field loss.[62,63] Consistent with these results, recent evidence suggests that glaucoma patients with slight to moderate visual field loss are more likely to fall and be involved in motor vehicle collisions than normal vision subjects.[64] In addition, glaucoma patients with better residual visual fields performed better on an on-road driving test than those with poorer visual field results.[65]

Clinical studies using various kinds of vision-related quality-of-life questionnaires[66] revealed that OAG patients with mild to moderate visual field loss usually report some visual function symptoms[10–23] and these findings were also confirmed in subjects who participated in a RCT or a population-based study.[67–70] According to these previous studies, a VRQOL score given by a VRQOL questionnaire gradually decreases along with increase in the overall extent of visual field loss,[13,21,69,70] but they found no apparent inflection point in the plot of the VRQOL score versus extent of visual field loss.

These results suggest that it is difficult to determine a critical amount of visual field loss that can sharply discriminate between glaucoma patients who are more likely to complain of visual function symptoms from those who do not. Since visual perception in daily life depends on input from both eyes, binocular visual field results may be more directly related to patients' VRQOL, and integrated binocular visual field was reported to better predict patients' perceived visual disability than mono-ocular visual field or result of binocular visual field test of Esterman.[71–73] Future studies using binocular visual field may shed more light on this problem.

With regards to the effect of glaucoma treatment on patients' perceived QOL, CIGTS demonstrated that there is little difference between medically and surgically treated patients, although increased impact of local eye symptoms and cataract progression were encountered in the latter group.[74] A questionnaire to compare the tolerability of topical ophthalmic medications used in the treatment of glaucoma was proposed,[75], but whether QOL differs between treated and untreated OAG patients is still unknown.[76]

In summary, patients' perceived vision-related quality of life is correlated with visual field loss. The greater the visual field loss, the more symptoms are reported. However, it is difficult to determine how much visual field loss is required before patients initiate the reporting of symptoms.

Topics for future research/further attention

- Effects of ocular hypotensive therapy in OAG eyes with late stage of damage.
- Effects of ocular hypotensive therapy in OAG eyes with lower IOP (≤ 15 mmHg).

- Relationship between VRQOL and extent of damage in binocular subfields at various stages of OAG.
- Difference in VRQOL or QOL between treated and untreated OAG patients.

References

1. Hattenhauer MG, Johnson DH, Ing HH, *et al.* The probability of blindness from open-angle glaucoma. Ophthalmol 1998; 105: 2099-2104.
2. Rasker MTD, van den Enden A, Bakker D, Hoyng PHJ. Rate of visual field loss in progressive glaucoma. Arch Ophthalmol 2000; 118: 481-488.
3. Oliver JE, Hattenhauser MG, Herman D, *et al.* Blindness and glaucoma: A comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol 2002; 133: 764-772.
4. Kwon YH, Kim C-S, Zimmerman MB, *et al.* Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. Am J Ophthalmol 2001; 132: 47-56.
5. Pereira MLM, Kim C-S, Zimmerman MB, *et al.* Rate and pattern of visual field decline in primary open-angle glaucoma. Ophthalmol 2002; 109: 2232-2240.
6. Chen PP. Blindness in patients with treated open-angle glaucoma. Ophthalmol 2003; 110: 726-733.
7. Eid TM, Spaeth GL, Bitterman A, Steinmann WC. Rate and amount of visual loss in 102 patients with open-angle glaucoma followed up for at least 15 years. Ophthalmol 2003; 110: 900-907.
8. Broman AT, Quigley HA, West SK *et al.* Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from corss-sectional data. Invest Ophthalmol Vis Sci 2008; 49: 66-76.
9. Burr JM, Mowatt G, Hernandez R, *et al.* The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess 2007; 11: iii-iv, ix-x, 1-190.
10. Mills RP, Drance SM. Esterman disability rating in severe glaucoma. Ophthalmol 1986; 93: 371-378.
11. Wandell PE, Lundstrom M, Brorsson B, Aberg H. Quality of life among patients with glaucoma in Sweden. Acta Ophthalmol Scand 1997; 75: 584-588.
12. Parrish RK, Gedde SJ, Scott IU, *et al.* Visual function and quality of life among patients with glaucoma. Arch Ophthalmol 1997;115:1447-1455.
13. Gutierrez P, Wilson MR, Johnson C, *et al.* Influence of glaucomatous visual field loss on health-related quality of life. Arch Ophthalmol 1997; 115: 777-784.
14. Lee BL, Gutierrez P, Gordon M, *et al.* The glaucoma symptom scale. A brief index of glaucoma-specific symptoms. Arch Ophthalmol 1998; 116: 861-866.
15. Sherwood MB, Garcia-Siekavizza A, Meltzer MI, *et al.* Glaucoma's impact on quality of life and its relation to clinical indicators. A pilot study. Ophthalmol 1998; 105: 561-566.
16. Wilson MR, Coleman AL, Yu F, *et al.* Functional status and well-being in patients with glaucoma as measured by the medical outcomes study short form- 36 questionnaire. Ophthalmol 1998; 105: 2112-2116.
17. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. Br J Ophthalmol 1999; 83: 546-552.
18. Turano KA, Rubin GS, Quigley HA. Mobility performance in glaucoma. Invest Ophthalmol Vis Sci 1999; 40: 2803-2809.
19. Viswanathan AC, McNaught AI, Poinoosawmy D, *et al.* Severity and stability of glaucoma. Patient perception compared with objective measurement. Arch Ophthalmol 1999; 117: 450-454.

20. Jampel HD, Schwartz A, Pollack I, *et al.* Glaucoma patients' assessment of their visual function and quality of life. J Glaucoma 2002; 11: 154-163.
21. Nelson P, Aspinall P, Papasouliotis O, *et al.*, Quality of life in glaucoma and its relationship with visual function. J Glaucoma 2003; 12: 139-150.
22. Sumi I, Shirato S, Matsumoto S, Araie M. The relationship between visual disability and visual field in patients with glaucoma. Ophthalmol 2003; 110: 332- 339.
23. Cypel MC, Kasahara N, Atique D, *et al.* Quality of life in patients with glaucoma who live in a developing country. Int Ophthalmol 2004; 25: 267-272.
24. Kass MA, Heuer DK, Higginbotham EJ, *et al.*, for the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study. A randomaized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120: 701-713.
25. Gordon MO, Kass MA, for the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: design and baseline description of the study participants. Arch Ophthalmol 1999; 117: 573-583.
26. Epstein DL, Krug JH, Jr, Hertzmark E,*et al.* A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. Ophthalmology 1989; 96: 1460-1467.
27. Schulzer M, Drance SM, Douglas GR. A comparison of treated anduntreated glaucoma suspects. Ophthalmology 1991; 98: 301-307.
28. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocularhypertension: a double-masked, randomised trial. Graefes Arch Clin Exp Ophthalmol 2000; 238: 877-883.
29. Kamal D, Garway-Heath D, Ruben S, *et al.* Results of the betaxolol versus placebo treatment trial in ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2003; 241: 196-203.
30. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. BMJ 2005; 331: 134.
31. Miglior S, Zeyen T, Pfeiffer N, *et al.* Results of the European Glaucoma Prevention Study. Ophthalmology 2005; 112: 366-375.
32. Vass C, Hirn C, Sycha T, Findl O, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension. Cochrane Database Syst Rev 2007: CD003167.
33. Heijl A, Leske MC, Bengtsson B, *et al.* Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120: 1268-1279.
34. Collaborative Normal-tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998; 126: 487-497.
35. Collaborative Normal-tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126: 498-505.
36. The Advanced glaucoma intervention study (AGIS): 3. baseline characteristics of black and white patients. The AGIS Investigators. Ophthalmol 1998; 105: 1137- 1145.
37. The Advanced Glaucoma Intervention Study (AIGS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000; 130: 429-440.
38. Musch DC, Lichter PR, Guire KE, *et al.* The collaborative initial glaucoma treatment study. Study design, methods, and baseline characteristics of enrolled patients. Ophthalmol 1999; 106: 653-662.
39. Lichter PR, Musch DC, Gillespie BW, *et al.* Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. Ophthalmol 2001; 108: 1943-1953.

40. Iwase A, Suzuki Y, Araie M, *et al.* The prevalence of primary open-angle glaucoma in Japanese. The Tajimi Study. Ophthalmology 2004; 111: 1641-1648.
41. Gordon MO, Beiser JA, Brandt JD, *et al.*, for the Ocular Hypertension Treatment Group. The Ocular Hypertension Treatment Study. Baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120: 714-720.
42. Leske MC, Heijl A, Hussein M, *et al.* Factors for glaucoma progression and the effect of treatment. Arch Ophthalmol 2003; 121: 48-56.
43. Drance S, Anderson DR, Schulzer M, for the Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol 2001; 131: 699-708.
44. Bengtsson B, Leske MC, Hyman L, Heijl A, Early Manifest Glaucoma Trial Group. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. Ophthalmol 2007; 114: 205-209.
45. Leske MC, Heijl A, Hyman L, *et al.* Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmol 2007; 114: 1965-1972.
46. The Advanced Glaucoma Intervention Study (AIGS):12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. The AGIS Investigators. Am J Ophthalmol 2002; 134: 499-512.
47. Chandler PA. Long term results in glaucoma therapy. The Stanford R. Gifford lecture. Am J Ophthalmol 1960; 49: 221-246.
48. Lee PF. Importance of status of visual field and optic disc in management of open-angle glaucoma. Am J Ophthalmol 1962; 53: 435-442.
49. Quigley HA, Maumenee AE. Long-term follow-up of treated open-angle glaucoma. Am J Ophthalmol 1979; 87; 519-525.
50. Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. Am J Ophthalmol 1986; 101: 1-6.
51. O'Brien C, Schwartz B, Takamoto T, Wu DC. Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma. Am J Ophthalmol 1991; 111: 491-500.
52. Araie M, Sekine M, Suzuki Y, Koseki N. Factors contributing to the progression of visual field damage in eyes with normal-tension glaucoma. Ophthalmol 1994; 101: 1440-1444.
53. Ishida K, Yamamoto T, Kitazawa Y. Clinical factors associated with progression of normal-tension glaucoma. J Glaucoma 1998; 7: 372-377.
54. Suzuki Y, Shirato S, Adachi M, Hamada C. Risk factors for the progression of treated primary open-angle glaucoma: a multivariate life-table analysis. Graefe's Arch Clin Exp Ophthalmol 1999; 237: 463-467.
55. Spaeth Gl, Hwang S, Gomes M. Disc damage as a prognostic and therapeutic consideration in the management of patients with glaucoma. In: Gramer E, Grehn F (Eds.), Pathogenesis and risk factors of glaucoma. Heidelberg: Springer 1999.
56. Nakagami T, Yamazaki Y, Hayamizu F. Prognostic factors for progression of visual field damage in patients with normal-tension glaucoma. Jpn J Ophthalmol 2006; 50: 38-43.
57. Much JW, Liu C, Piltz-Seymour JR. Long-term survival of central visual field in end-stage glaucoma. Ophthalmology 2008; 115: 1162-1166.
58. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. Am J Ophthalmol 1989; 108: 130-135.
59. Spaeth GL. Reader's comments. Prognostic factors for progression of visual field damage in patients with normal-tension glaucoma. Jpn J Ophthalmol 2007; 51: 156-157.
60. Bernth-Petersen P. Visual functioning in cataract patients. Methods of measuring and results. Acta Ophthalmol 1981; 59: 198-205.
61. Mangione CM, Phillips RS, Lawrence MG, *et al.* Improved visual function and attenuation of declines in health-related quality of life after cataract extraction. Arch Ophthalmol 1994; 112: 1419-1425.
62. Patel I, Turano KA, Broman AT, *et al.* Measures of visual function and percentage of preferred walking speed on older adults: The Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci 2006; 47: 65-71.

63. Rubin GS, Ng ESW, Bandeen-Roche K, *et al.* A prospective, population-based study of the role of visual impairment in motor vehicle crashes among older drivers: The SEE Study. Invest Ophthalmol Vis Sci 2007; 48: 1483-1491.
64. Haymes SA, Leblanc RP, Nicolela MT, *et al.*. Risk of falls and motor vehicle collisions in glaucoma. Invest Ophthalmol Vis Sci 2007; 48: 1149-1455.
65. Haymes SA, Leblanc RP, Nicolela MT, *et al.* Glaucoma and On-Road Driving Performance. Invest Ophthalmol Vis Sci 2008 (in print).
66. Spaeth G, Walt J, Keener J. Evaluation of quality of life for patients with glaucoma. Am J Ophthalmol 2006; 141: S3-S14.
67. Janz NK, Wren PA, Lichter PR, *et al.* Quality of life in newly diagnosed glaucoma patients. The collaborative initial glaucoma treatment study. Ophthalmol 2001; 108: 887-898.
68. Jampel HD, Frick KD, Janz NK, *et al.* Depression and mood indicators in newly diagnosed glaucoma patients. Am J Ophthalmol 2007; 144: 238-244.
69. McKean-Cowdin R, Varma R, Wu J, *et al.* Severity of visual field loss and health-related quality of life. Am J Ophthalmol 2007; 143: 1013-1023.
70. McKean-Cowdin R, Wang Y, Wu J, *et al.* Impact of visual field loss on health-related quality of life in glaucoma the Los Angeles Latino Eye Study. Ophthalmology 2008; 115: 941-948.
71. Viswanathan AC, McNaught AI, Poinoosawmy D, *et al.* Severity and stability of glaucoma. Arch Ophthalmol 1999; 117: 450-454.
72. Jampel HD, Friedman DS, Quigley H, Miller R. Correlation of the binocular visual field with patient assessment of vision. Invest Ophthalmol Vis Sci 2002; 43: 1059-1067.
73. Crabb DP, Viswanathan AC. Integrated visual fields: a new approach to measuring the binocular field of view and visual disability. Graefe's Arch Clin Exp Ophthalmol 2005; 243: 210-216.
74. Janz NK, Wren PA, Lichter PR, *et al.* The collaborative initial glaucoma treatment study. Interim quality of life findings after initial medical or surgical treatment of glaucoma. Ophthalmol 2001; 108: 1954-1965.
75. Barber BL, Strahlman ER, Laibovitz R, *et al.* Validation of a questionnaire for comparing the tolerability of ophthalmic medications. Ophthalmol 1997; 104: 334-342.
76. Hyman LG, Komaroff E, Heijl A, *et al.* Treatment of vision-related quality of life in the Early Manifest Glaucoma Trial. Ophthalmology 2005; 112: 1505-1513.

Consensus Panel discussions

Linda Zangwill

Carlo Traverso

Break, Clive Migdal, Franz Grehn and John Thygesen

ARE FACILITIES FOR DIAGNOSIS AND TREATMENT AVAILABLE?

Paul Healey

Co-chairs: Paul R. Healey, Ramanjit Sihota

Contributors: Khaled Ben Amor, Rupert Bourne, Jennifer Burr, Collin Cook, Tanuj Dada, Daniel Grigera, Mingguang He, Dan Kiage, Clive Migdal, Marcello Nicolela, Rajul Parikh, Ki Ho Park, R. Ramakrishnan, Jim Standefer, Suman Thapa, Ravi Thomas, Atsuo Tomidokoro, Fotis Topouzis, Lingam Vijaya, Ningli Wang, Gerhard Zinser

Consensus points

- The resources for diagnosis and treatment of glaucoma vary worldwide. *Comment: Many countries have insufficient facilities to provide care at present practice standards relative to developed countries. There is a need to identify areas without facilities to help plan resource allocation.*
- Fewer resources are required to diagnose glaucoma at moderate to advanced asymptomatic stages compared to very early stages.
- Treatment of glaucoma requires facilities for regular long-term monitoring.
- There is a need to study barriers to access for glaucoma care so that available facilities can be used optimally

Introduction

The diagnosis and treatment of glaucoma are critical in the effective prevention of disability from this disease. The required facilities for glaucoma care comprise human, teaching and material resources. All these need to be present and available in appropriate levels to effectively and efficiently provide healthcare to this important cause of worldwide blindness. Epidemiological studies consistently report under-diagnosis of glaucoma.[1–16] One reason for this may be a lack of adequate facilities or a lack of access to them. There are relatively few published reports with most data residing in reports from eye disease surveys, particularly in the developing world.[17–24] The existing literature confirms anecdotal data suggesting an enormous variation in facilities between regions

Glaucoma Screening, pp. pp. 25-32
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

across the world. The causes for this variation are unknown, but appear to be strongly associated with economic inequality. Beyond this, there are a number of other potentially important factors that may influence facilities availability and their usage.

The ideal standards of diagnosis and treatment of open-angle glaucoma (OAG) are universally acknowledged. Local variations in standards may be due to a lack of knowledge or acceptance of the ideal. Further, decisions about acceptable standards for diagnosis and treatment are societal and political, as well as medical. These are more likely to affect regions and whole countries.

The diagnosis of OAG is quite different from successful screening. The critical component of screening is to clear unaffected individuals (specificity at the expense of sensitivity). In contrast, diagnosis requires a high degree of accuracy for the state of the disease required to be diagnosed (sensitivity at the expense of specificity).

The resources required for diagnosis vary with stage. The earlier the diagnostic stage, the more uncertain it is.

Table 1. Resources required for glaucoma diagnosis by disease stage

Diagnostic stage	Certainty of diagnosis	Facilities required	Example of facilities
Symptomatic	+++++	Few	Visual acuity, confrontation fields, direct ophthalmoscope, general medical training
Advanced pre-symptomatic	++++	Modest	Any visual field test, any disc exam, basic ophthalmic training
Moderate pre-symptomatic	+++	Modest	Visual field and stereoscopic disc exam, basic ophthalmic training
Early pre-symptomatic	+	More	Reliable visual field with statistic analysis and stereoscopic disc photos/clinical disc and nerve fiber layer examination, advanced ophthalmic training
Pre-perimetric, pre-structural	+–	Many	Serial highly reliable optic nerve head imaging/disc and retinal nerve fiber layer (RNFL) photos, serial highly reliable automatic perimetry, Glaucoma Fellowship training

What constitutes an acceptable stage of glaucoma diagnosis for a society depends on diagnostic costs vs. the harm of not diagnosing. In many regions of the world, capital and maintenance costs of imaging and photographic resources as well as automated perimetry are high considering the available health resources. The human and time resources that can be devoted to training may also be limited by knowledge, culture or clinical priority. Acceptable and desirable stages of glaucoma diagnosis will vary across regions as well as institutions. Before appropriate improvements of facilities can be planned or implemented, a thorough

evaluation of these factors is required. To date, very little published literature exists in this area.

OAG treatment involves the removal of risk factors where possible and the preservation of visual function where disability already exists. The treatment for OAG consists of lowering intraocular (IOP) sufficiently to alter the natural history. After IOP reduction, monitoring of the glaucomatous neuropathy, rate of change and risk factors for progression is an essential part of treatment.

The degree of risk factor reduction is limited by cost and the possible harm of treatment. Medical knowledge and cultural imperatives of individual doctors and institutions play a major role in determining glaucoma treatment. Like diagnosis, decisions about what is acceptable treatment are also societal and patient dependent.

The screening process

A person found positive for OAG at screening should have the disease confirmed or excluded as quickly and efficiently as possible. For those whose OAG is confirmed, a management plan should be formulated and implemented. Those who do not have a diagnosis of OAG confirmed should be counseled concerning the implications of positive screening with negative diagnosis and possible future positive screenings.

Non-ophthalmic medical facilities and, in some countries, optometric facilities are readily available and in much greater number than ophthalmic facilities. This makes these groups attractive for glaucoma screening. One study in the UK evaluated the potential role of specifically trained optometrists in the glaucoma detection process and showed promising results.[25] However, opportunistic glaucoma screening is marginal to the core activities of these healthcare providers. In some regions of the world, a pyramidal delivery system for eye care exists, under which symptomatic evaluation and screening are carried out by trained technicians who then refer to a multi-layered ophthalmic medical system. Alternative strategies involve referral from non-ophthalmic medical or technician screening to optometric screening prior to referral for diagnosis. Opticians also play a role in glaucoma screening in some regions.

While a multi-step screening process can minimize load scarce facilities, such strategies require more facilities overall and delay the time from initial positive screen to definitive diagnosis. Unless the screening is performed by a suitably trained ophthalmologist there must be some delay. The harm (economic and emotional) of being screened positive but not having a disease has no corresponding benefit. So the steps between initial screen and definitive diagnosis should be rapid and efficient to minimize the harm from participating in the screening process.

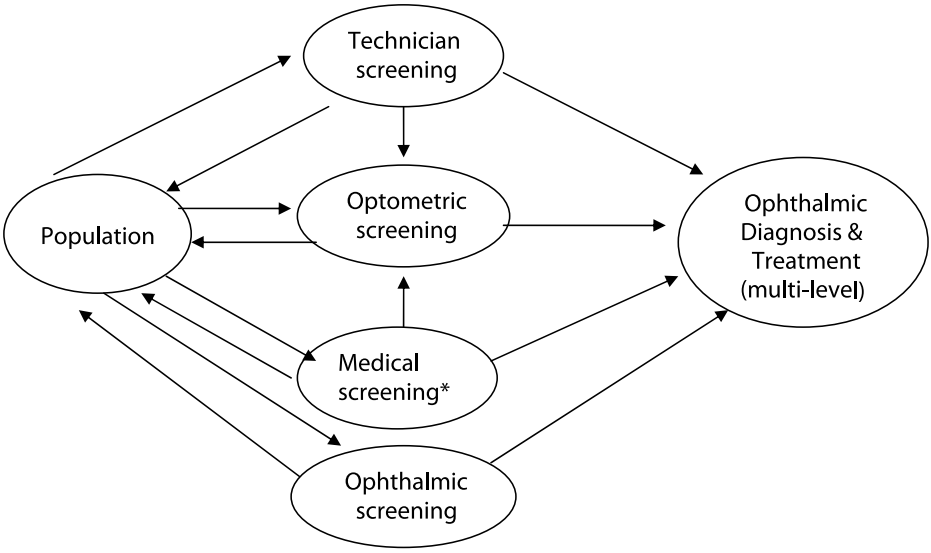

Fig. 1. Alternative screening processes
*Non-ophthalmic medical practitioners

Available facilities for diagnosis and treatment

Human

The ultimate responsibility for OAG diagnosis and comprehensive treatment rests with ophthalmologists. However highly trained ophthalmologists capable of accurately and reliably diagnosing and comprehensively treating glaucoma are a scarce resource in most regions. Even though the large under-diagnosis rate of glaucoma is a powerful motivator for better screening, it is essential that any changes to screening do not result in patient loads that overwhelm the ophthalmic facilities in that region. For this reason, screening solely by ophthalmologists is unlikely to be feasible in most regions.

Material

Available facilities are limited by cost and preferred practice patterns. In many regions throughout the world, ophthalmic equipment or examination methods used routinely in glaucoma diagnosis and monitoring are relatively inaccurate or unreliable. The debate concerning the acceptability of such equipment and methods is as much cultural and political as it is economic and medical.

Table 2. Currently available facilities vary by economic status

	Necessity	Optic nerve head (ONH) evaluation	Tonometry	Occludable angle detection	Perimetry	RNFL/ ONH imaging
Poorer regions	Low cost + independent of electrical supply	Direct ophthalmoscope	Schiotz	Torch light for anterior chamber (AC) depth and iris damage	Kinetic – Bjerrum's	None
Developing regions – rural areas	Low cost + independent of electrical supply + periodic mobile high- tech availability	Direct ophthalmoscope/ Digital, nonmydriatic fundus photography with reading by trained ophthalmologist or optometrist	Schiotz / Perkin's type	Torch light for AC depth and iris damage/ gonioscopy	Kinetic/ Frequency doubling perimetry (FDP)	Camera/Heidelberg retina tomograph (HRT)
Developed regions/ Urban		Digital fundus photography 90D/78D	Applanation	Gonioscopy	Static automated	Camera/HRT/ Optical coherence tomography (OCT)/ scanning laser polarimetry (GDx)

Training

Improved glaucoma screening is worthless if diagnosis and treatment are inaccurate or inappropriate. Levels of expertise in diagnosis and treatment of glaucoma vary considerably across different regions of the world and across different strata of health-care/eye-care providers within any one region.

In general, training is provided by individuals within the same strata and region which delivers the care. This encourages a locally oriented approach, but also entrenchment of teaching styles and treatment approaches and ideas.

Differences of facilities and access across regions and populations

Facilities, including human, material or training, vary widely across regions, due to the nature of government, cost constraints and practice patterns. Decisions concerning what facilities are necessary may be made by governments (national, regional or local), institutional committees or individual practitioners. Constraints in regions where appropriate facilities are not available include capital cost, maintenance facilities, electricity supply, salary, practice patterns, and knowledge and understanding of decision makers. There is little available data as to the primary constraints and therefore the best way to overcome them.

Access is an essential and critical component of healthcare delivery. If a healthcare system can not deliver treatment to its entire population, it is not functioning effectively. Barriers to access can be geographic, financial or cultural. At an individual or institutional level, very high clinical workloads can lead to the erroneous belief that care is being delivered to a whole community. In developed countries in particular, detailed assessment outside of the clinical care delivery system is required to find the significant groups in the population that may not have the opportunity to access clinical services.

Improving available facilities

Although the direct published data are limited, the sub-optimal diagnosis and treatment characteristics of open-angle glaucoma found in many epidemiological studies suggest that facilities for glaucoma diagnosis and treatment should be improved in at least one domain (human, material or training). While many more data are required to make a systematic evaluation of facilities and implement required improvements, anecdotal data suggest that a number of fundamental steps would improve facilities for glaucoma diagnosis and treatment. These include:

1. Educating decision-makers about the increasing burden of blindness due to glaucoma and the appropriate facilities necessary;
2. Training all ophthalmologists in glaucoma diagnosis and treatment to a world-wide standard;

3. Training all primary care non-ophthalmic doctors, optometrists, opticians and other eye care technicians to screen for OAG by examining the optic disc for moderate to advanced OAG, assessing vision and evaluating risk factors;
4. Advocating for the provision of glaucoma resources within the total framework of eye care.

Topics for future research/further attention

- Development of a world-wide staging system for glaucoma to facilitate targeting of diagnosis and treatment.
- Systematic evaluation of diagnostic and screening algorithms for specified glaucoma stages using population-based samples.
- Development of an ongoing database of available facilities for glaucoma screening, diagnosis and treatment; including human, material and teaching resources. Such a database would also include ophthalmic and non-ophthalmic medical practitioners, ophthalmic assistants and technicians, optometrists and opticians.
- Systematic identification of barriers to accurate and timely glaucoma diagnosis and treatment. These include resources, societal preferences and healthcare culture.

References

1. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology 1996; 103: 1661-1669.
2. Dielemans I, Vingerling JR, Wolfs RC, *et al.* The prevalence of primary open-angle glaucoma in a population- based study in The Netherlands. The Rotterdam Study. Ophthalmology 1994; 101: 1851-1855.
3. Coffey M, Reidy A, Wormald R, *et al.* Prevalence of glaucoma in the west of Ireland. Br J Ophthalmol 1993;77:17-21.
4. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol 1994; 112: 821-829.
5. Sommer A, Tielsch JM, Katz J, *et al.* Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 1991; 109: 1090-1095.
6. Wong EY, Keeffe JE, Rait JL, *et al.* Detection of undiagnosed glaucoma by eye health professionals. Ophthalmology 2004; 111: 1508-1514.
7. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966; 50: 570-586.
8. Bengtsson B. The prevalence of glaucoma. Br J Ophthalmol 1981; 65: 46-49.
9. Iwase A, Suzuki Y, Araie M, *et al.* The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 2004; 111: 1641-1648.
10. Nizankowska MH, Kaczmarek R. Prevalence of glaucoma in the Wrocław population. The Wrocław epidemiological study. Ophthalmic Epidemiol 2005; 12: 363-371.
11. Sakata K, Sakata LM, Sakata VM, *et al.* Prevalence of glaucoma in a South Brazilian population: Projeto Glaucoma. Invest Ophthalmol Vis Sci 2007; 48: 4974-4979.

12. Topouzis F, Coleman AL, Harris A, *et al.* Factors associated with undiagnosed open-angle glaucoma: the Thessaloniki Eye Study. Am J Ophthalmol 2008; 145: 327-335.
13. Varma R, Ying-Lai M, Francis BA, *et al.* Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology 2004; 111: 1439-1448.
14. Vijaya L, George R, Paul PG, *et al.* Prevalence of open-angle glaucoma in a rural south Indian population. Invest Ophthalmol Vis Sci 2005; 46: 4461-4467.
15. Vijaya L, George R, Baskaran M, *et al.* Prevalence of Primary Open-angle Glaucoma in an Urban South Indian Population and Comparison with a Rural Population The Chennai Glaucoma Study. Ophthalmology 2008; 115: 648-654.
16. Bourne RR, Sukudom P, Foster PJ, *et al.* Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. Br J Ophthalmol 2003; 87: 1069-1074.
17. Cook CD, Knight SE, Crofton-Briggs I. Prevalence and causes of low vision and blindness in northern KwaZulu. S Afr Med J 1993; 83: 590-593.
18. Graf HP. [Eye surgery in Sudan]. Klin Monatsbl Augenheilkd 1990; 196: 438-441.
19. Huang JT, Rhemtulla F, Huang PT. Glaucoma screening by primary care physicians in southern Alberta: patterns, methods and deficiencies. Can J Ophthalmol 2003; 38: 279-284.
20. Melka F, Alemu B. The pattern of glaucoma in Menelik II Hospital Addis Ababa, Ethiopia. Ethiop Med J 2006; 44: 159-165.
21. Mengesha AY. Spectrum of eye disorders among diabetes mellitus patients in Gaborone, Botswana. Trop Doct 2006; 36: 109-111.
22. Onwasigwe EN, Ezegwui IR, Onwasigwe CN, Aghaji AE. Management of primary congenital glaucoma by trabeculectomy in Nigeria. Ann Trop Paediatr 2008; 28: 49-52.
23. Ramke J, Brian G, du TR. Eye disease and care at hospital clinics in Cook Islands, Fiji, Samoa and Tonga. Clin Experiment Ophthalmol 2007; 35: 627-634.
24. Thomas R, Paul P, Muliyil J. Glaucoma in India. J Glaucoma 2003; 12 :81-87.
25. Azuara-Blanco A, Burr J, Thomas R, *et al.* The accuracy of accredited glaucoma optometrists in the diagnosis and treatment recommendation for glaucoma. Br J Ophthalmol 2007; 91: 1639-1643.

Paul Healey, Linda Zangwill and Anders Heijl

IS THERE AN APPROPRIATE, ACCEPTABLE, AND REASONABLY ACCURATE SCREENING TEST?

Augusto Azuara Blanco

Co-chairs: Augusto Azuara Blanco, Linda Zangwill

Contributors: Khaled Ben Amor, Jennifer Burr, Collin Cook, Murray Fingeret, David Friedman, Chris Girkin, David Greenfield, Daniel Grigera, Paul Harasymowycz, Paul Healey, David Henson, Chris Johnson, Michael Kass, Dan Kiage, Elliot Kirstein, George Lambrou, Chris Leung, Tony Realini, Rajul Parikh, Lisandro Sakata, G.C. Sekhar, Ravi Thomas, Fotis Topouzis, Rohit Varma, Marco Vizzeri, Gerhard Zinser

Consensus points

- The best single test or group of tests for open-angle glaucoma screening is yet to be determined.
- Optimal screening test criteria are not yet known.
  Comment: Screening test criteria depend upon health care system, location, and prevalence of open-angle glaucoma (OAG).
  Comment: The sensitivity and specificity of tests for population-based screening are unknown, as most have been tested only on selected groups, not populations.
- Diagnostic test accuracy may vary according to the severity of the disease.
- The tests available and effective for case-finding are not necessarily the same as those for population- based glaucoma screening which requires a very high specificity to be cost-effective.
  Comment: Screening requires a test with a high specificity. Diagnosis requires a test with a high sensitivity.
  Comment: Individuals at high risk require highly accurate tests.

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide[1,2] with OAG the most common form of the disease. Late presentation is a major risk factor

Glaucoma Screening, pp. pp. 33-50
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

for glaucoma blindness.[3] It is estimated that, in developed countries, current methods of case finding miss about 65% of detectable disease.

Population screening programs for OAG have not been adopted in any country. In view of the public health importance of OAG, and recent evidence which suggests that treatment is effective at delaying progressive visual field loss,[4,5] the question of whether a population-based screening program of OAG would be clinically and cost-effective is under consideration. For screening to be considered, several criteria need to be met regarding the condition, the test and the screening program.

Ideally, a screening test for OAG should be safe, easy to administer and interpret, portable, quick, acceptable to the people who are to be tested, able to obtain results in the majority of tested individuals, and sufficiently valid to distinguish between those who do and do not have OAG.

A number of potential screening tests exist for detecting open-angle glaucoma, including tests of structure and visual function. The level of the intraocular pressure (IOP) provides useful clinical information but it is not a suitable diagnostic test. The accuracy of diagnostic tests has been assessed on an individual test basis, mainly in hospital-based studies and there are high quality studies providing important information. However, little is known about the comparative accuracy of candidate screening tests for detecting OAG in population-based studies. To date no single test or combination of tests has been identified as an optimal screening 'test' for glaucoma.

Potential biases to evaluate the performance of a screening test

Screening tests for low prevalence diseases should have high specificity. To compare diagnostic performances of different tests, several factors would need to be taken into account such as differences in populations, study design, setting, prevalence and severity of glaucoma within studies (*e.g.*, in general, tests become more sensitive as the disease becomes more severe. Hence, a study including participants with advanced disease should report better sensitivity. Definition of the severity stages of glaucoma may use structural or functional damage). Other factors include differences in reference standard, and in tests included within the same category (*e.g.*, different types of perimetry and ophthalmoscopy have a large number of variants, potentially leading to heterogeneity in discriminatory power across studies reporting those tests), and the extent to which studies were affected by other potential biases.[6] Additionally, if an adequate sample size for sub-groups is not achieved, within study comparisons of test performance may result in a loss of power to detect significant differences.

It has been suggested that inclusion of any optic disc criteria in the reference standard when evaluating another optic disc test (*e.g.*, Heidelberg Retina Tomograph (HRT)) introduces incorporation bias. In such studies it may seem logical to use only visual field examination as a reference standard test. This, however, assumes that structural (*e.g.*, optic disc) and functional (*e.g.*, visual field) damage occur simultaneously in glaucoma pathogenesis, whereas there

is evidence that either disc damage or visual field damage can be the first sign of glaucomatous progression. Hence, using visual field assessment alone as a reference standard may report an unfairly low accuracy of an imaging test, especially if more people with early glaucoma are included in the study.[6]

The accuracy of a test may vary according to the population in which it is performed. Although absolute sensitivity and specificity of a diagnostic test are independent of the prevalence of a disease, a diverse spectrum of the disease is encountered in different prevalence levels. With increasing prevalence, more cases of moderate to severe disease are expected, and since it is easier to differentiate between severely diseased and non-diseased people, a test would be expected to report improved (apparent) sensitivity and specificity. Therefore studies with a significantly higher prevalence than expected in a screening population should be interpreted with this limitation in mind.

As mentioned above, in contrast to the scarcity of population-based diagnostic performance studies, there are many hospital-based reports evaluating diagnostic outcomes of multiple glaucoma tests. A hospital population is, by nature, an enriched population, and is likely to include a disproportionate number of participants with more severe disease and with previous experience of tests, potentially leading to over-optimistic performance estimates. However diagnostic case-control studies are useful at the initial stages of validating a test. To test the applicability of a new test it should then be applied directly to the population of its intended use. The majority of the hospital-based case-control studies apply stringent criteria for inclusion such as visual acuity of 6/9, or no other ocular disease and as such are highly prone to bias although they may contribute important and useful information on test accuracy in a clinic situation.[6]

Brief description of possible diagnostic tests

Structural tests

Ophthalmoscopy: direct and binocular

Direct ophthalmoscopy is best performed with the pupils dilated and the room darkened, and with both the examiner and the patient in a comfortable setting. The patient should be seated, looking steadily at a fixation target at the same level of the head. The examiner's head also needs to be at the same level of the patients', without obstructing the fixating eye.

The main disadvantage of analyzing the disc with the direct ophthalmoscope is the absence of a stereoscopic view. The examiner has to use indirect tips to allow the interpretation of the disc as a tri-dimensional structure. Furthermore, direct ophthalmoscopy does not yield a permanent record, and the examiner is required to draw the disc to allow subsequent comparisons.

Binocular ophthalmoscopy provides the advantage of stereopsis, allowing a

tri-dimensional observation of the optic disc. Current practice consists of the use of a standard slit-lamp biomicroscope associated with non-contact lenses (60D or 78D). As any indirect ophthalmoscopy system, this technique provides an inverted and reversed image of the optic disc. The possibility of achieving stereopsis depends on the pupil's size, which often needs to be dilated. The patient is positioned at the slit-lamp and asked to look to the examiner's opposite ear. The examiner visualizes the patient's eye through the slit lamp and then positions the objective lens in the line of sight, approximately 10-15 mm away from the patient's cornea. The fundus image is then brought into sharp focus by slow back-and-forth movements of the biomicroscope.

It is also possible to use the slit lamp in association with a contact lens (*e.g.*, the Goldmann lens), but this technique requires the use of a topical anesthetic and a viscoelastic substance between the lens and the cornea. Despite being more uncomfortable, the image provided is excellent with high magnification and is not inverted.

Monoscopic and stereoscopic photographs of the optic disc

A wide variety of digital and non-digital cameras are available to provide color pictures of the optic disc. Monoscopic photography of the optic disc with a digital camera has been used to detect glaucoma. However, monoscopic photography appears to have less reproducibility and diagnostic accuracy than stereoscopic photography. Stereoscopic pictures can be obtained with sequential photographs using a monocular camera by horizontal realignment of the camera base when photographing the same retinal image. Alternatively, simultaneous stereoscopic fundus photographs can be obtained with special cameras that capture two images of the fundus taken simultaneously at a fixed angle between each other.

Retinal nerve fiber layer (RNFL) photography

RNFL may be documented using high-resolution black & white pictures, where the fiber bundles are seen as silver striations that are most visible in the superior and inferior poles of the optic disc. The technique includes the use of a green or blue filter, a high-contrast, fine-grain, black & white film, and a special development method. However, the results of black & white photography of the RNFL are limited in eyes with small pupils and media opacities. Furthermore, the technique is subjective and depends on the examiner's experience.

Quantitative measurement of the optic disc and RNFL

Heidelberg Retina Tomograph (HRT): Confocal laser scanning imaging technology, employed by the HRT (Heidelberg Engineering, Heidelberg, Germany), exploits the principle of confocal laser scanning to allow quantitative structural information. The topographic image is derived from multiple optical sections at consecutive focal depth planes. Each image consists of numerous pixels, with each pixel corresponding to the retinal height at its location. The first model

was marketed in 1991 and a second version (HRT-II) was made available in 1999. It does not require pupil dilation and HRT-II is portable and relatively easy to use.

Scanning Laser Polarimetry (GDx-VCC): GDx-VCC measures the RNFL thickness. It is based on the birefringent properties of the RNFL, which has its neurotubules disposed in an organized, parallel fashion. This peculiar anatomy leads to a change in the state of polarized light as it passes through the RNFL, creating a retardation that is directly proportional to its thickness. The current model (GDx-VCC) introduces variable corneal compensation to enhance the accuracy of the measurements.

Optical Coherence Tomography (OCT): The RNFL thickness can also be assessed through OCT, which is an optical imaging technique capable of providing high resolution, cross-sectional, in vivo imaging of the human retina in a fashion analogous to B-scan ultrasonography but utilizing light instead of sound. In OCT a near infrared (840 nm) light is used. OCT utilizes the principles of low coherence interferometry using light echoes from the scanned structure to determine the thickness of tissues. Bi-dimensional images are created by successive longitudinal scanning in a transverse direction.

Visual function tests

Standard automated perimetry (SAP)

This is the gold standard in visual field examination of glaucomatous patients. SAP estimates the threshold sensitivity of several points within the visual field using white stimuli on a white background. The target locations remain constant and the brightness is increased or decreased until the threshold sensitivity is reached. SAP is able to quantify the reliability, and compare the actual examination to an age-matched normal database. Examination of the visual field in glaucoma is usually limited to the central 30-degree area, since almost all clinically relevant defects fall within this area.

In threshold testing the sensitivity of each location is determined. There are new threshold-related strategies that shorten the testing time (*e.g.*, Swedish Interactive Thresholding Algorithm (SITA) for Humphrey perimeters and Tendency-oriented perimetry (TOP) for Octopus perimeters) and have gained wide acceptance. Supra-threshold testing with automated perimetry involves the use of stimuli that are of greater intensity than the presumed threshold at each location. This test strategy does not quantify the depth of visual field defects, but is much quicker than threshold testing.

Short-wavelength automated perimetry (SWAP)

This technique is a modification of automated static threshold perimetry. SWAP uses a yellow background and large, blue stimuli to test the blue cones. The

blue cone system is slower and has a low visual acuity (about 20/200). As a consequence, the stimulus is perceived as fuzzy, and the test is more difficult and time-consuming. Uncorrected refractive errors have less of an effect on the thresholds determined by SWAP, but lens opacities tend to result in profoundly depressed fields that are difficult to interpret.

Frequency doubling perimetry (FDP)

This portable instrument presents rapid flickering stimuli to the peripheral visual field. In a normal field, patients perceive twice as many bars as actually exist (frequency-doubling illusion). In abnormal fields, the illusion is present only if the bars are at higher-than-normal contrast levels. The clinical test procedure measures contrast threshold in 19 visual field locations within the central 30 degrees. It is faster than conventional perimetry. It has threshold and suprathreshold algorithms (see above SAP).

Oculo-kinetic perimetry (OKP)

OKP with the Damato campimetry is an inexpensive visual field test device that relies on the subject's eye movements to project a central black stimulus on a specific retinal eccentricity. Damato campimetry consists of 20 numbers located on a flat white card within the central 30° of visual field. The subject looks from number to number, sequentially reporting whether the central 1.5-mm black spot is visible. There is a 40-cm hinged piece that serves to maintain the appropriate test distance and occludes the untested eye. Any point missed, other than the physiologic blind spot area, is confirmed once before considering it a true missed point. A modified version is currently available (free of charge) in the Internet: http://www.testvision.org.

Other technologies

There are other visual function tests designed to detect glaucomatous damage, such as flicker perimetry, high resolution ring perimetry (HPRP), isoluminant flicker-contrast-resolution perimetry (PULSAR), Rarebit (microdot perimetry), and motion perimetry. None of these tests has been used in population-based studies.

Methods to measure the intraocular pressure

There is consensus that increased IOP is not diagnostic of glaucoma, and thus measurement of IOP may not be a suitable test for screening. However, the diagnostic performance of IOP has been studied in several reports, and it might be considered as an additional test to be used along with an imaging or visual function diagnostic test as it provides clinically useful information.

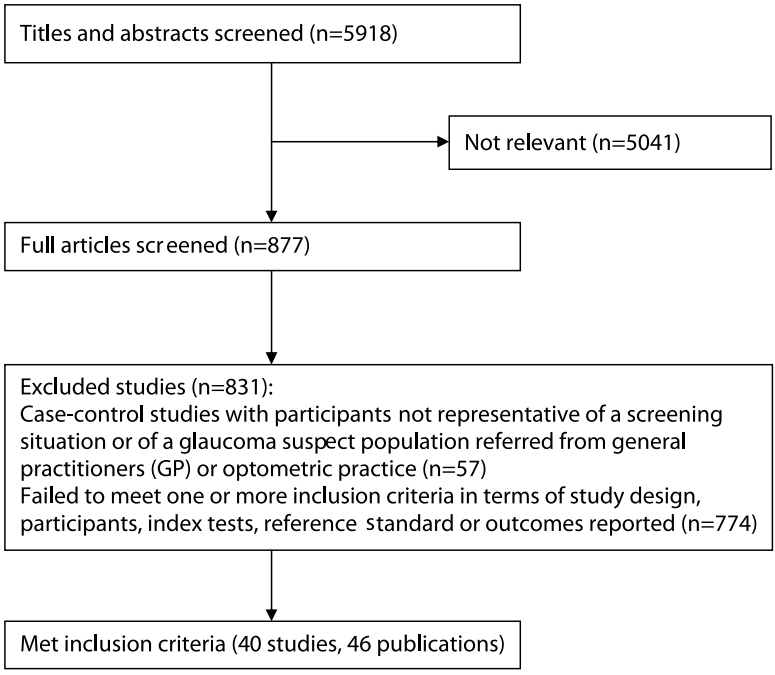

Fig. 1. Flow of studies through review process (Mowatt *et al.*,[6a] reproduced with permission from the Association for Research in Vision and Ophthalmology.)

The most widely used and generally accepted gold standard for measuring the IOP is Goldmann Tonometry, which uses a prism to apply an external force to the cornea to indent and flatten its surface. Interobserver variability of Goldmann tonometry has been estimated at 0-3 mmHg.[7] The two general sources of error with Goldmann tonometry can be categorized as those caused by faults in the application of the technique and those related to biological variability of the human eye and orbit, both normal and pathological. Of particular note is the error induced by variability of the central corneal thickness (CCT). There are new tests to measure IOP that have been introduced recently, but to our knowledge they have not been tested in population-based studies.

Summary of literature of diagnostic performance of tests

In a recent review, Burr *et al.*[6] assessed the comparative accuracy of potential screening tests for detecting OAG. They did a systematic review and meta-analysis from Medline, Embase, Biosis (to November 2005); Medline-In-Process, Science Citation Index (to December 2005); The Cochrane Library (2005; Issue 4), and used quality assessment tool for studies of diagnostic accuracy included in systematic reviews (QUADAS) to evaluate the quality of the diagnostic studies (Fig. 1). Summary receiver operating characteristic (SROC) curves were

Table 1. Characteristics of the included studies

Study id	Index test(s)	Test(s) carried out and interpreted by	Reference Standard	Enrolled (people)	Analysed	Mean age (range)	Gender	Country	Time period
Population-based studies									
Anton 2004	Goldmann applanation tonometry (GAT)	Ophthalmologists	Ophthalmic examination	569	510	(40 to 79)	M: 232; F: 278	Spain (Segovia Study)	N/S
Bengtsson 1980	GAT	Ophthalmologists	Ophthalmic examination	1938	1511	(55 to 69)	N/S	Sweden(Dalby Population Survey)	1977 – 1978
Bonomi 2001	GAT	Ophthalmologists	Follow-up confirmation	5816	4297 eyes of 4297 people	(40 to 80+)	M: 1882; F: 2415	Italy (Egna-Neumarkt Study)	N/S
Christoffersen 1995	OKP	GPs, medical secretaries	Ophthalmic examination	195	187	57 (40 to 84)	M: 51; F: 136	Norway	N/S
Detry-Morel 2004	FDP C-20-5	Residents in training, paramedical staff	Ophthalmic examination	1802	3211 eyes of 1620 people	63 (22 to 97)	M: 680; F: 940	Belgium	October 1999
Harasymowycz 2005	HRT II	Ophthalmic photographer	Ophthalmic examination	303	264 right eyes, 265 left eyes of 271 people	62.2 (SD 11.6)	M: 90; F: 179	Canada	August 2003 – February 2004
Hollows 1966	GAT	Ophthalmologists	Ophthalmic examination	4608	4231	55 (40 to 74)	Approx: M: 3639; F: 592	UK (Rhondda Valley Study)	Summer 1963
Ivers 2001	SAP suprathreshold; GAT	N/S	Ophthalmic examination	4433	3654 (both tests)	(49 to 97)	M: 1582; F: 2072	Australia (Blue Mountains Eye Study)	1992 – 1994
Katz 1991	SAP threshold	N/S	Ophthalmic examination	355	355 eyes of 355 people	Cases: 61; Controls: 53	N/S	USA (Glaucoma Screening Study)	1981 – 1992
Katz 1993	SAP suprathreshold	N/S	Ophthalmic examination	5308	4733	(40 to 80+)	M: 2109; F: 3199	USA (Baltimore Eye Survey)	Jan 1985 – Nov 1988
Kozobolis 2000	GAT	Ophthalmologists?	Ophthalmic examination	1300	1107	(40 to 80+)	M: 463; F: 644	Greece (Crete, Greece Glaucoma Study)	Feb 1993 – June 1998
Mansberger 2005	FDP C-20-5	N/S	Ophthalmic examination	296	251 eyes of 251 people	45 (30 to 65)	M: 117; F: 174	India	N/S

Table 1. Cont.

Study id	Index test(s)	Test(s) carried out and interpreted by	Reference Standard	Enrolled (people)	Analysed	Mean age (range)	Gender	Country	Time period
Mundorf 1989	SAP suprathreshold	N/S	Ophthalmic examination	145	145	71	M: 40; F: 105	USA	N/S
Robin 2005	Ophthalmoscopy; HRT II; SAP threshold; FDP C-20-5	Appropriately trained staff	Ophthalmic examination	704	261 eyes of 261 people (both tests)	65	M: 281; F: 378	Australia	Nov 2001
Vernon 1990	Ophthalmoscopy; SAP suprathreshold; Non-contact pneumo-tonometer (NCT)	Ophthalmoscopy: experienced ophthalmologists; NCT/SAP: non-ophthalmological trained staff	Ophthalmic examination	988	854(ophth); 855 (SAP); 874 (NCT)	65	M: 374; F: 500	UK	N/S
Vitale 2000	Optic disc photography; SAP suprathreshold	Experienced technicians	Follow-up confirmation	249	182 (disc photo); 228 (SAP);	68	M: 100; F: 149	USA (Baltimore Eye Study Follow-up Study)	1994
Wang 1998	Ophthalmoscopy; SAP suprathreshold; GAT [RNFL photography]	N/S	Ophthalmic examination	530	400(ophth); 214 (SAP); 357 (GAT) [136 (RNFL photo)]	(40 to 65+)	M: 111; F: 294	USA	Jul 1991 – Feb 1992
Weih 2001	Ophthalmoscopy	N/S	Consensus by panel of ophthalmologists, based on results of ophthalmic examination	4744	4636	59 (SD 12)	M: 2230; F: 2514	Australia (Visual Impairment Project)	1992 – 1996
Wolfs 1999	Optic disc photography	Technicians	Ophthalmic examination	6777	5143 eyes of 5143 people	(55 and over)	N/S	Netherlands (Rotterdam Study)	N/S
Yamada 1999	OKP; FDP C-20-1	Technicians	Decision of glaucoma specialists, based on ophthalmologic history, examination and Humphrey visual field results	259	175 eyes of 175 people (OKP); 240 eyes of 240 people (FDP)	FDP: 59.6 (SD 14.7); OKP: 58.8 (SD 15.6)	M: 108; F: 135	USA	N/S

Table 1. Cont.

Study id	Index test(s)	Test(s) carried out and interpreted by	Reference Standard	Enrolled (people)	Analysed	Mean age (range)	Gender	Country	Time period
Already suspect population (cohort studies)									
Ekstrom 1993	GAT	N/S	Follow-up confirmation	760	413	(65 to 74)	M: 364; F: 396	Sweden(Tierp Glaucoma Survey)	Mar 1984 – Mar 1986
Hammond 1979	Ophthalmoscopy	Nurses skilled in use of the ophthalmoscope	Ophthalmic examination	219	188	(21 and over)	N/S	USA	N/S
Khong 2001	FDP C-20-5	N/S	Ophthalmic examination	228	113	68.5 (23 to 91)	M: 104; F: 119	Australia	Dec 1999 – Jan 2000
Leibowitz 1980	GAT	Generally performed by 2nd or 3rd year residents in ophthalmology	Follow-up confirmation	2631	574	(<65 to 75+)	M: 272; F: 302	USA (Framingham Eye Study)	Feb 1973 – Feb 1975
Marraffa 1989	SAP suprathreshold	Ophthalmologists	Follow-up confirmation	104	182 eyes of 104 people	54.3 (18 to 76)	M:45; F: 59	Italy	N/S
Schultz 1995	Optic disc photography	Carried out: N/S Interpreted: 3rd year ophthalmology residents	Ophthalmic examination	258	365 eyes of ? people	(<40 to >70)	M: 112; F: 144; Unknown: 2	USA	N/S
Spry 2005	SAP threshold; FDP C-20 matrix	SAP: clinic staff trained in visual field testing; FDP: N/S	Ophthalmic examination	48	48 (both tests)	67.3 (SD 13.5)	M: 24; F: 24	UK	Oct 2003 – Jan 2004
Theodossiades 2001	Ophthalmoscopy	Optometrists	Ophthalmic examination	50	50 eyes of 50 people	N/S	N/S	UK	N/S
Already suspect population (case-control studies)									
Airaksinen 1984	RNFL photography	N/S	Follow-up confirmation	142	132 eyes of 132 people	Glaucoma: 62 (SD 20.5) Normal: 54 (SD 16.9); OHT: 57 (SD 12.7)	N/S	Canada + Finland	N/S

Table 1. Cont.

Study id	Index test(s)	Test(s) carried out and interpreted by	Reference Standard	Enrolled (people)	Analysed	Mean age (range)	Gender	Country	Time period
Anton 1997	SAP threshold	Ophthalmologists?	Ophthalmic examination	180	180 eyes of 180 people	Glaucoma: 61 (SD 8); Normal: 59 (SD 9)	N/S	Spain	N/S
Damato 1989	OKP	Staff experienced in perimetry	Ophthalmic examination	102	102 eyes of 102 people	Glaucoma: 57.3; Normal: 54.4	N/S	UK	N/S
Enger 1987	SAP threshold	N/S	Ophthalmic examination	112	170 eyes of 112 people	Glaucoma: 61 (28 to 80); Normal: 51 (26 to 75)	N/S	USA	N/S
Harper 1994	OKP; SAP suprathreshold	Ophthalmologists?	Ophthalmic examination	212	193 (OKP); 212 (SAP)	Glaucoma: 67.8 (43 to 85); Normal: 61.5 (41 to 85)	N/S	UK	N/S
Heeg 2005	FDP C-20-1; FDP C-20 full threshold	N/S	Ophthalmic examination	1112	208 (FDP C-20-1); 1112 (FDP C-20 full threshold)	Glaucoma: 65 (13 to 91); Normal: 63 (33 to 94)	Eligible: Glaucoma: M: 509; F: 542 Normal: M: 118; F: 119	Netherlands (Groningen Longitudinal Glaucoma Study)	Jul 2000 – Jun 2001
Johnson 1999	FDP C-20-1	N/S	Ophthalmic examination	108	160 eyes of 108 people	Glaucoma: 64 (35 to 85); Normal: 46 (18 to 81)		USA	N/S
Ieong 2003	HRT II; SAP suprathreshold	Optometrists	Ophthalmic examination	66	66 eyes of 66 people (both tests)	Glaucoma: 69; Normal: 60	Glaucoma: M: 16; F: 13 Normal: M: 16; F: 21	UK	N/S

Table 1. Cont.

Study id	Index test(s)	Test(s) carried out and interpreted by	Reference Standard	Enrolled (people)	Analysed	Mean age (range)	Gender	Country	Time period
Quigley 1980	Optic disc photography; RNFL photography	Ophthalmologists	Ophthalmic examination	175	294 eyes of ? people	Readable photos: Glaucoma: 52.7 (SD 2.78); Glaucoma suspect: 45.2 (SD 1.56); Normal: \ 37.9 (SD 2.8) Unreadable photos: Glaucoma: 62.5 (SD 4.0); Glaucoma suspect: 59.6 (SD 6.3); Normal: 50 (SD 12.1)	M: 86; F: 89	USA	Jan 1978 – Apr 1979
Sommer 1979	Optic disc photography; RNFL photography	N/S	Follow-up confirmation	Unclear	223 eyes of ? people (both tests)	N/S	N/S	USA	N/S
Wollstein 2000	Optic disc photography	Photos taken by trained technicians; assessed by glaucoma consultants, glaucoma fellow, clinical glaucoma technician	Ophthalmic examination	123	123 eyes of 123 people	Glaucoma: 65.1 (SD 10.06); Normal: 57.1 (SD 12.52)	N/S	UK	N/S
Wood 1987	Ophthalmoscopy	Ophthalmologists; junior doctors	Ophthalmic examination	22	43 eyes of 22 people	(32 to 75)	N/S	UK	N/S

Notes:
1. N/S, not stated.
2. Numbers analysed are people unless otherwise stated.
3. Study ids in brackets eg [Vernon 1991] are secondary reports that also contribute outcome data.

(From: Mowatt *et al.*,[6a] reproduced with permission from the Association for Research in Vision and Ophthalmology.)

Table 2. Summary of sensitivity, specificity and DOR for tests included in the HSROC meta-analysis models

Test	Number of studies	Sensitivity % (95% CrI)	Specificity % (95% CrI)	DOR (95% CI)	Mean % interpretable results (range)
Ophthalmoscopy	5	60 (34 to 82)	94 (76 to 99)	26 (6 to 110)	98 (86 to 100)
Optic disc photography	6	73 (61 to 83)	89 (50 to 99)	22 (3 to 148)	85 (73 to 100)
RNFL photography	4	75 (46 to 92)	88 (53 to 98)	23 (4 to 124)	80
HRT II	3	86 (55 to 97)	89 (66 to 98)	51 (11 to 246)	94 (91 to 97)
FDP C-20-1	3	92 (65 to 99)	94 (73 to 99)	181 (25 to 2139)	97 (87 to 99)
FDP C-20-5	5	78 (19 to 99)	75 (57 to 87)	10 (0.7 to 249)	92 (86 to 98)
OKP	4	86 (29 to 100)	90 (79 to 96)	58 (4 to 1585)	97 (94 to 98)
SAP suprathreshold	9	71 (51 to 86)	85 (73 to 93)	14 (6 to 34)	81 (60 to 100)
SAP threshold	5	88 (65 to 97)	80 (55 to 93)	30 (6 to 159)	99 (91 to 100)
GAT	9	46 (22 to 71)	95 (89 to 97)	15 (4 to 49)	97 (90 to 100)

Notes:
1. Sensitivity, specificity and DORs are derived from the 40 included studies. The information on interpretable results also includes data, where reported, from 21 additional population-based or prospective cohort studies that did not report useable outcomes in terms of test accuracy but otherwise met the review's inclusion criteria.
2. RNFL photography. One study provided data on interpretable results.[80]
3. DORs are based on all studies using a common cutoff.
(From: Mowatt *et al.*,[6a] reproduced with permission from the Association for Research in Vision and Ophthalmology.)

produced for each test at a common cut-off. Meta-analysis was undertaken using the hierarchical summary receiver operating characteristic (HSROC) model. Forty studies enrolling over 48,000 people were included, reporting nine diagnostic tests (Table 1). Overall the scientific evidence was limited as each test was evaluated by only a few, mostly heterogeneous, studies. In the HSROC meta-analysis models most tests reported a specificity of 85% or higher (Table 2). Diagnostic accuracy improves when a second confirmatory test is used.[8] However it was not possible to identify a single test or group of tests as being clearly superior over all others due to the limited evidence.

Recent large population-based studies (published after the Burr *et al.* report) have evaluated the diagnostic performance of FDP. Iwase *et al.* evaluated 2892 individuals from Japan.[9] Sensitivity and specificity were 55.6 and 92.7%, respectively. The sensitivity was influenced by the severity of glaucomatous visual field loss, ranging form 32.1% to 96% in early and severe glaucoma. Wang *et al.* evaluated 4349 subjects from China.[10] The sensitivity was 64%, and the specificity was 90.8%.

Topics for future research/further attention

Further research is required to explore which of the many potential tests available would be suitable for screening in terms of safety, portability, and acceptability, followed by a cross sectional study of the optimal tests directly comparing their accuracy at different levels of disease severity in populations in whom glaucoma screening is thought to be cost-effective.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006; 90: 262-267.
2. Resnikoff S, Pascolini D, Etayale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82: 844-851.
3. Grant WM, Burke JF, Jr. Why do some people go blind from glaucoma? Ophthalmology 1982; 89: 991-998.
4. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. Br Med J 2005; 331: 134-136.
5. Fleming C, Whitlock E, Biel T, Smit B. Primary care screening for ocular hypertension and primary open-angle glaucoma: Evidence Synthesis No 34 [document on the Internet]. Rockville MD: Agency for Healthcare Research & Quality, US Preventative Services Task Force; 2005 [accessed April 2005]. Available from: URL: http://www.ahrq.gov/clinic/uspstf05/glaucoma/glaucsyn.pdf
6. Burr J, Mowatt G, Hernandez R, Siddiqui MAR, Cook J, Lourenco T *et al*. The clinical and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess. 2007; 11: 1-190.

6a. Mowatt G, Burr JM, Cook JA et al. Screening tests for detecting open angle glaucoma: systematic and meta-analysis. Invest Ophthalmol Vis Sci 2008; in press.

7. Phelps CD, Phelps GK. Measurement of intraocular pressure: a study of its reproducibility. Graefes Arch Klin Exp Ophthalmol 1976; 198: 39-43.
8. Parikh R, Muliyil J, George R, Bhat S, Thomas R. Repeatability of frequency doubling technology perimetry (20-1 screening program) and the effect of pupillary dilatation on interpretation. Ophthalmic Epidemiol 2008; 15: 42-46.
9. Iwase A, Tomidokoro A, Araie M, Shirato S, Shimizu H, Kitazawa Y. Performance of frequency-doubling technology perimetry in a population-based prevalence survey of glaucoma: the Tajimi study. Ophthalmology 2007; 114: 27-32.
10. Wang YX, Xu L, Zhang RX, Jonas JB. Frequency-doubling threshold perimetry in predicting glaucoma in a population-based study: The Beijing Eye Study. Arch Ophthalmol 2007; 125: 1402-1406.

Related References (in alphabetical order)

11. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. Am J Ophthalmol 1984; 98: 566-571.
12. Anderson AJ, Johnson CA. Frequency-doubling technology perimetry. Ophthalmol Clin North Am 2003; 16: 213-225 (Review).
13. Anton A, Maquet JA, Mayo A, Tapia J, Pastor JC. Value of logistic discriminant analysis for interpreting initial visual field defects. Ophthalmology 1997; 104: 525-531.
14. Anton A, Andrada MT, Mujica V, Calle MA, Portela J, Mayo A. Prevalence of primary open-angle glaucoma in a Spanish population: the Segovia study. J Glaucoma 2004; 13: 371-376.
15. Becker K, Semes L. The reliability of frequency-doubling technology (FDP) perimetry in a pediatric population. Optometry 2003; 74: 173-179.
16. Bengtsson B. Findings associated with glaucomatous visual field defects. Acta Ophthalmol (Copenh) 1980; 58: 20-32.
17. Bochmann F, Johnson Z, Azuara-Blanco A. Sample size of studies of diagnostic accuracy in ophthalmology: literature survey. Br J Ophthalmol 2007; 91: 898-900.
18. Bonomi L, Marchini G, Marraffa M, Morbio R. The relationship between intraocular pressure and glaucoma in a defined population. Data from the Egna-Neumarkt Glaucoma Study. Ophthalmologica 2001; 215: 34-38.

19. Brush MB, Chen PP. Test-retest variability in glaucoma patients tested with C-20-1 screening-mode frequency doubling technology perimetry. J Glaucoma. 2004; 13: 273-277.
20. Caprioli J. Clinical evaluation of the optic nerve in glaucoma. Trans Am Ophthalmol Soc 1994; 92: 589-641.
21. Christoffersen T, Fors T, Waage S, Holtedahl K. Glaucoma screening with oculokinetic perimetry in general practice: is its specificity acceptable? Eye 1995; 9: 36-39.
22. Cioffi GA, Mansberger S, Spry P, Johnson C, Van Buskirk EM. Frequency doubling perimetry and the detection of eye disease in the community. Trans Am Ophthalmol Soc 2000; 98: 195-199; discussion 199-202.
23. Damato BE, Ahmed J, Allan D, McClure E, Jay JL. The detection of glaucomatous visual field defects by oculo-kinetic perimetry: which points are best for screening? Eye 1989; 3: 727-731.
24. Detry-Morel M, Zeyen T, Kestelyn P, Collignon J, Goethals M, Belgian Glaucoma Society. Screening for glaucoma in a general population with the non-mydriatic fundus camera and the frequency doubling perimeter. Eur J Ophthalmol 2004; 14: 387-393.
25. Ekstrom C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open angle glaucoma – a population based 5-year follow-up study. Acta Ophthalmol (Copenh) 1993; 71: 189-195.
26. Enger C, Sommer A. Recognizing glaucomatous field loss with the Humphrey STATPAC. Arch Ophthalmol 1987; 105: 1355-1357..
27. FinOHTA. Cost-effectiveness of glaucoma screening (project). Helsinki: Finish Office for Health Technology Assessment; 2005 [accessed April 2007}. Available from: URL: http://finohta.stakes.fi/EN/research/index.htm.
28. Fogagnolo P, Mazzolani F, Rossetti L, Orzalesi N. Detecting glaucoma with frequency-doubling technology perimetry: a comparison between N-30 and C-20 screening programs. J Glaucoma. 2005; 14: 485-491.
29. Gardiner SK, Anderson DR, Fingeret M, McSoley JJ, Johnson CA. http://www.ncbi.nlm.nih.gov/pubmed/16840859?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSumEvaluation of decision rules for frequency-doubling technology screening tests. Optom Vis Sci 2006; 83: 432-437.
30. Garway-Heath D, Hitchings R. Sources of bias in studies of optic disc and retinal nerve fibre layer morphology. Br J Ophthalmol 1998; 82: 986.
31. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003; 56: 1129-1135.
32. Hammond EA, Begley PK. Screening for glaucoma: a comparison of ophthalmoscopy and tonometry. Nurs Res 1979; 28: 371-372.
33. Harasymowycz P, Papamatheakis D, Fansi AK, Gresset J, Lesk MR. Validity of screening for glaucomatous optic nerve damage using confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II) in high-risk populations: a pilot study. Ophthalmology 2005; 112: 2164-2171.
34. Harper RA, Hill AR, Reeves BC. Effectiveness of unsupervised oculokinetic perimetry for detecting glaucomatous visual field defects. Ophthalmic Physiol Opt 1994; 14: 199-202.
35. Heeg GP, Blanksma LJ, Hardus PL, Jansonius NM. The Groningen Longitudinal Glaucoma Study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. Acta Ophthalmol Scand 2005; 83: 46-52.
36. Heeg GP, Stoutenbeek R, Jansonius NM. Strategies for improving the diagnostic specificity of the frequency doubling perimeter. Acta Ophthalmol Scand 2005; 83: 53-56.
37. Heeg GP, Jansonius NM. Influence of test reliability on the screening performance of frequency-doubling perimetry. Am J Ophthalmol. 2006; 141: 585-587.
38. Hollows FC, Graham PA. Intra-ocular pressure glaucoma and glaucoma suspects in a defined population. Br J Ophthalmol 1966; 50: 570-586.
39. Horn FK, Link B, Mardin CY, Jünemann AG, Martus P. Long-term reproducibility of screening for glaucoma with FDP-perimetry. J Glaucoma 2007;16: 448-455.
40. Ieong A, Murdoch I, Cousens S, Healey P, Theodossiades J. Sensitivity and specificity of two glaucoma case-finding strategies for optometrists. Ophthalmic Physiol Opt 2003; 23: 341-346.

41. Ivers RQ, Optom B, Macaskill P, Cumming RG, Mitchell P. Sensitivity and specificity of tests to detect eye disease in an older population. Ophthalmology 2001; 108: 968-95.
42. Johnson CA, Cioffi GA, Van Buskirk EM. Evaluation of two screening tests for frequency doubling technology perimetry. 13th International Perimetric Society Meeting, Garda, Italy, September; 1999. p. 103.
43. Joson PJ, Kamantigue ME, Chen PP. Learning effects among perimetric novices in frequency doubling technology perimetry. Ophthalmology 2002; 109: 757-760.
44. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. Arch Ophthalmol 1991; 109: 1684-1689.
45. Katz J, Tielsch JM, Quigley HA, Javitt J, Witt K, Sommer A. Automated suprathreshold screening for glaucoma: the Baltimore Eye Survey. Invest Ophthalmol Vis Sci 1993; 34: 3271-3277.
46. Katz J, Quigley HA, Sommer A. Repeatability of the Glaucoma Hemifield Test in automated perimetry. Invest Ophthalmol Vis Sci 1995; 36: 1658-1664.
47. Khong JJ, Dimitrov PN, Rait J, McCarty CA. Can the specificity of the FDP for glaucoma be improved by confirming abnormal results? J Glaucoma 2001; 10: 199-202.
48. Kozobolis VP, Detorakis ET, Tsilimbaris M, Siganos DS, Vlachonikolis IG, Pallikaris IG. Crete, Greece glaucoma study. J Glaucoma 2000; 9: 143-149.
49. Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, *et al.* The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. Surv Ophthalmol 1980; 24: 335-610.
50. Mansberger SL, Johnson CA, Cioffi GA, Choi D, Krishnadas SR, Srinivasan M, *et al.* Predictive value of frequency doubling technology perimetry for detecting glaucoma in a developing country. J Glaucoma 2005; 14: 128-134.
51. Mansberger SL, Edmunds B, Johnson CA, Kent KJ, Cioffi GA. Community visual field screening: prevalence of follow-up and factors associated with follow-up of participants with abnormal frequency doubling perimetry technology results. Ophthalmic Epidemiol 2007; 14: 134-140.
52. Mansberger SL, Johnson CA, Cioffi GA. The results of screening frequency doubling technology perimetry in different locations of the community. J Glaucoma 2007; 16: 73-80.
53. Mansberger SL, Johnson CA, Cioffi GA, *et al.* Predictive value of frequency doubling technology perimetry for detecting glaucoma in a developing country. J Glaucoma 2005; 14: 128-134.
54. Marraffa M, Marchini G, Albertini R, Bonomi L. Comparison of different screening methods for the detection of visual field defects in early glaucoma. Int Ophthalmol 1989; 13: 43-45.
55. Matsuo H, Tomita G, Suzuki Y, Araie M. Learning effect and measurement variability in frequency-doubling technology perimetry in chronic open-angle glaucoma. J Glaucoma 2002; 11: 467-473.
56. Medeiros FA, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. Am J Ophthalmol 2005; 139: 1010-1018.
57. Mundorf TK, Zimmerman TJ, Nardin GF, Kendall KS. Automated perimetry, tonometry, and questionnaire in glaucoma screening. Am J Ophthalmol 1989; 108: 505-508.
58. North RV, Jones AL, Hunter E, Morgan JE, Wild JM. Evaluation of the high specificity Screening Program (C-20-1) of the Frequency Doubling Technology (FDP) perimeter in clinical practice. Eye. 2006; 20: 681-7. (Epub 2005 Jun 24)
59. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol 1982; 100: 135-146.
60. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. Arch Ophthalmol 1980; 98: 1564-1571.
61. Quinn LM, Wheeler DT, Gardiner SK, Newkirk M, Johnson CA. Frequency Doubling Technology (FDP) perimetry in normal children. Am J Ophthalmol 2006; 142: 983-989.
62. Robin TA, Muller A, Rait J, Keeffe JE, Taylor HR. Performance of community-based glaucoma screening using frequency doubling technology and Heidelberg retinal tomography. Ophthalmic Epidemiol 2005; 12: 167-178.
63. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias

and variation in diagnostic accuracy studies. Can Med Assoc J 2006; 174: 469-476.
64. Sample PA, Medeiros FA, Racette L, Pascual JP, Boden C, Zangwill LM, Bowd C, Weinreb RN. Identifying glaucomatous vision loss with visual-function-specific perimetry in the diagnostic innovations in glaucoma study. Invest Ophthalmol Vis Sci 2006; 47: 3381-3389.
65. Screening for glaucoma: an update – non-systematic review (project). Quebec: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS); 2007 [accessed April 2007]. Available form: URL: http://www.aetmis.gouv.qc.ca.
66. Schultz RO, Radius RL, Hartz AJ, Brown DB, Eytan ON, Ogawa GSH *et al.* Screening for glaucoma with stereo disc photography. J Glaucoma 1995; 4: 177-182.
67. Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC *et al.* Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol 1991; 109: 77-83.
68. Sommer A, Pollack I, Maumenee AE. Optic disc parameters and onset of glaucomatous field loss. II. Static screening criteria. Arch Ophthalmol 1979; 97: 1449-1454.
69. Stoutenbeek R, Heeg GP, Jansonius NM. Frequency doubling perimetry screening mode compared to the full-threshold mode. Ophthalmic Physiol Opt 2004; 24: 493-497.
70. Spry PG, Sparrow,JM. An evaluation of open-angle glaucoma against the NSC criteria for screening viability, effectiveness and appropriateness [document on the Internet}. UK National Screening Committee; 2005 [accessed September 2005]. Available from: URL: http://rms.nelh.nhs.uk/screening/viewResource.asp?categoryID=1352&dg=107&uri=http://libraries.nelh.nhs.uk/common/resources/?id=61002.
71. Spry PGD, Hussin HM, Sparrow JM. Clinical evaluation of frequency doubling technology perimetry using the Humphrey Matrix 24-2 threshold strategy. Br J Ophthalmol 2005; 89: 1031-1035.
72. Spry PG, Hussin HM, Sparrow JM. Performance of the 24-2-5 frequency doubling technology screening test: a prospective case study. Br J Ophthalmol 2007; 91: 1345-1349. (Epub 2007 Mar 27)
73. Tatemichi M, Nakano T, Tanaka K, Hayashi T, Nawa T, Miyamoto T, Hiro H, Iwasaki A, Sugita M; Glaucoma Screening Project (GSP) Study Group. Performance of glaucoma mass screening with only a visual field test using frequency-doubling technology perimetry. Am J Ophthalmol. 2002; 134: 529-537. Erratum in: Am J Ophthalmol 2003; 136: 592.
74. Theodossiades J, Murdoch I. What optic disc parameters are most accurately assessed using the direct ophthalmoscope? Eye 2001; 15: 283-287.
75. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J *et al.* A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol 1991; 134: 1102-1110.
76. Tóth M, Kóthy P, Vargha P, Holló G. Accuracy of combined GDx-VCC and matrix FDP in a glaucoma screening trial. J Glaucoma 2007; 16: 462-470.
77. Vernon SA, Henry DJ, Cater L, Jones SJ. Screening for glaucoma in the community by non-ophthalmologically trained staff using semi automated equipment. Eye 1990; 4: 89-97.
78. Vernon SA, Jones SJ, Henry DJ. Maximising the sensitivity and specificity of non-contact tonometry in glaucoma screening. Eye 1991; 5: 491-493.
79. Vitale S, Smith TD, Quigley T, Kerrigan-Baumrind TA, Pease TE, Varma R *et al.* Screening performance of functional and structural measurements of neural damage in open-angle glaucoma: a case-control study from the Baltimore Eye Survey. J Glaucoma 2000; 9: 346-356.
80. Wang F, Quigley HA, Tielsch JM. Screening for glaucoma in a medical clinic with photographs of the nerve fiber layer. Arch Ophthalmol 1994; 112: 796-800.
81. Wang F, Tielsch JM, Ford DE, Quigley HA, Whelton PK. Evaluation of screening schemes for eye disease in a primary care setting. Ophthalmic Epidemiol 1998; 5: 69-82.
82. Weih LM, Nanjan M, McCarty CA, Taylor HR. Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. Ophthalmology 2001; 108: 1966-1972.
83. Weinreb RN, Khaw KT. Primary open-angle glaucoma. Lancet 2004; 363: 1711-1720.
84. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003; 3: Nov 10.
85. Wild JM, Kim LS, Pacey IE, Cunliffe IA. Evidence for a learning effect in short-wavelength automated perimetry. Ophthalmology 2006; 113: 206-215.

86. Wood CM. Limitations of direct ophthalmoscopy in screening for glaucoma. Br Med J 1987; 294: 1587-1588.
87. Wolfs RC, Ramrattan RS, Hofman A, de Jong PT. Cup-to-disc ratio: ophthalmoscopy versus automated measurement in a general population: The Rotterdam Study. Ophthalmology 1999; 106: 1597-1601.
88. Wollstein G, Garway-Heath DF, Fontana L, Hitchings RA. Identifying early glaucomatous changes. Comparison between expert clinical assessment of optic disc photographs and confocal scanning ophthalmoscopy. Ophthalmology 2000; 107: 2272-2277.
89. Yamada N, Chen PP, Mills RP, Leen MM, Lieberman MF, Stamper RL *et al.* Screening for glaucoma with frequency-doubling technology and Damato campimetry. Arch Ophthalmol 1999; 117: 1479-1484.
90. Yenice O, Temel A. Evaluation of two Humphrey perimetry programs: full threshold and SITA standard testing strategy for learning effect. Eur J Ophthalmol 2005; 15: 209-212.

Dan Kiage

L. Zangwill, C. Girkin and H. Lemij

IS THE NATURAL HISTORY OF THE CONDITION, INCLUDING DEVELOPMENT FROM LATENT TO MANIFEST DISEASE, ADEQUATELY UNDERSTOOD?

Harry Quigley

Co-chairs: Anders Heijl, Harry Quigley

Contributors: Doug Anderson, Boel Bengtsson, Collin Cook, Daniel Grigera, Mingguang He, Nomdo Jansonius, Paulus de Jong, Michael Kass, Dan Kiage, Paul Lee, Cristina Leske, Rohit Varma, Thierry Zeyen, Gerhard Zinser

Consensus points

- Open-angle glaucoma (OAG) incidence rates are known for untreated and treated patients with ocular hypertension.
- OAG progression rates vary greatly among patients.
  Comment: More research is required to determine the extent and basis of progression rate variation.
- Progression event rates for patients (in clinical trials, under clinical care or observation) in terms of percent of patients/eyes progressing per year are available both for OAG and ocular hypertension.
- Progression data expressed as rate of disease progression (*i.e.*, expressed in dB/year or in % of full field/year) are very sparse.

Introduction

The natural history data for OAG have expanded considerably over the last decade in both population data and from clinical trials, but are still very sparse. We have a reasonably good estimate of incidence, prevalence, and progression rates with and without treatment that can inform the screening process. Population-based data on the incidence of OAG are available from the Dalby, Melbourne, Barbados, St. Lucia, and Rotterdam studies.[1] A meta-analysis and modeling of these data, as well as estimates for European, African, Chinese, and Hispanic ethnicities was published by Broman and Quigley.[2]

Glaucoma Screening, pp. pp. 51-53
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

Clinical trials and cohort data are available that show the incident rate of OAG from ocular hypertension status (Ocular Hypertension Treatment Study (OHTS), European Glaucoma Prevention Study (EGPS), Glaucoma Screening Study,[3] and Collaborative Glaucoma Study). The rate at which persons develop initial damage that matches criteria for crossing the transition from suspect status to glaucomatous optic neuropathy is generally agreed to be 2% per year of follow-up per eye.

The progression rate for visual field damage after the initial injury has also been both studied in clinical trials (Collaborative Normal Tension Glaucoma Study (CNTGS), Early Manifest Glaucoma Trial (EMGT)) and modelled.[2] Depending upon the group selected, its ethinicity and age, the untreated rate of progression is between 0.5 and 1.0 decibels on the field instrument scale per year of observation. If visual field progression is judged as an event, achieving set criteria, many studies can be summarized to indicate that 8% of eyes per year progress untreated, and about 4% per year progress with treatment in standard clinical trials regimens. Progression rate judged by optic disc change is likewise rated as slow.[4]

Clinical trials that show the rate of progression with treatment depend, of course, upon the type and aggressiveness of therapy, but generally show a reduction under ideal conditions in the untreated rate of 50% or more. (Glaucoma Laser Trial (GLT), Advanced Glaucoma Intervention Study (AGIS), Collaborative Glaucoma Treatment Study (CGTS), CNTGS). More data on progression rates obtained in clinical practice are desirable. True progression rates expressed in dB/year or % of full field/year, or rates expressing velocity of disease progression are preferable to progression rates expressed as percentage of patients show to progress per year. The latter rates depend very much on frequency of examinations as well as methods used for follow-up and criteria for defining progression. Velocity rates for untreated glaucoma are very sparse.

The risk factors that affect and modify incidence and progression have been summarized by Boland and Quigley.[5] While it has been suggested that screening yield might be improved by limiting screening to those with risk factors for glaucoma, the Rotterdam group found that only one third of undetected cases had an OAG risk factor. The prevalence of risk factors was much higher among already diagnosed cases. This may vary by region, depending upon the penetration of standard eye care and training levels country by country.

Some population-based studies have spoken to the yield of screening.[6] In a population in the Netherlands screened at a 6.5-year interval, the investigators studied how many new (incident) OAG cases developed overall during the time period. There were two groups among these new cases. Some were detected by regular ophthalmic care (outside the study) between the initial study exam and the second study exam 6.5 years later. The remainder were incident cases that did not know that they had developed glaucoma until the second study exam told them so. From these data, the investigators estimated the number of persons that could be saved from bilateral end stage OAG by screening (assuming that the efficiency of screening was diminished in a developed country by the

typical detection rate of glaucoma). Life expectancy of the undetected incident OAG cases and the amount of damage at the time of detection were used for this estimate. About 1000 OAG screening tests would have to be performed in order to prevent one OAG case from becoming severely visually impaired or blind (about 200 tests if the aim is to prevent unilateral severe impairment). This estimate may be pessimistic compared to other populations due to high rate of eye exams among Dutch adults, 80% of whom visit an eye care practitioner at least once every five years.[7]

Topics for future research/further attention

- There is very little data on the natural history of untreated glaucoma.
- More data on progression rates for glaucoma patient under clinical care are needed, not only average progression rates expressed as progression velocities, but also the distributions around the means.
- Incidence figures need to be studied more in different populations.

References

1. de Voogd S, Ikram MK, Wolfs RC *et al.* Incidence of open-angle glaucoma in a general elderly population : The Rotterdam Study. Ophthalmology 2005; 112:1487-1493.
2. Broman AT, Quigley HA, West SK, *et al.* Estimating the rate of progressive visual field damage among those with open-angle glaucoma from cross-sectional data. Invest Ophthalmol Vis Sci 2008; 49: 66-76.
3. Quigley HA, Enger C, Katz J, Sommer A, Scott R, Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. Arch Ophthalmol 1994; 112: 644-649.
4. Kwon YH, Kim YI, Pereira ML, Montague PR, Zimmerman MB, Alward WL. Rate of optic disc cup progression in treated primary open-angle glaucoma. J Glaucoma 2003; 12: 409-416.
5. Boland MV, Quigley HA. Risk factors and open-angle glaucoma: concepts and applications. J Glaucoma 2007; 16: 406-418.
6. Stoutenbeek R, *et al.* The additional yield of a periodic screening programme for open-angle glaucoma: a population-based comparison of incident glaucoma cases detected in regular ophthalmic care with cases detected during screening. Br J Ophthalmol 2008; 92: 1222-1226.
7. Stoutenbeek R, Jansonius NM. Glaucoma screening during regular optician visits: can the population at risk of developing glaucoma be reached? Br J Ophthalmol 2006; 90: 1242-1244.

Harry Quigley making a point

Douglas Anderson and Murray Fingeret

IS THE COST OF CASE FINDING (INCLUDING DIAGNOSIS AND TREATMENT OF PATIENTS DIAGNOSED) ECONOMICALLY BALANCED IN RELATION TO POSSIBLE EXPENDITURE ON MEDICAL CARE AS A WHOLE?

Anja Tuulonen

Co-chairs: Paul R. Healey, Anja Tuulonen

Contributors: Augusto Azuara Blanco, Rupert Bourne, Jennifer Burr, Collin Cook, Chris Girkin, Daniel Grigera, Neeru Gupta, Mingguang He, Aiko Iwase, Paulus de Jong, Dan Kiage, Steve Kymes, Choka Melamed, Marcello Nicolela, Rajul Parikh, Ki Ho Park, Harry Quigley, Ravi Thomas, Carlo Traverso, Lingam Vijaya, Ningli Wang, Gerhard Zinser

Consensus points

- The best evidence to date, based on two modeling studies, suggests:
  1) Screening of high-risk subgroups may be more cost-effective than screening the entire population.
  2) Screening may be more cost-effective as glaucoma prevalence increases
  3) The optimal screening interval is not yet known
  4) Screening may be more cost-effective when initial assessment is a simple strategy that could be supervised by non-medical technicians.

  Comment: More research is needed for the implementation of the best screening program for glaucoma.

  Comment: Expert consensus is required on how cost data should be collected and reported in glaucoma care. This includes reporting visually relevant outcomes on a per-patient basis.

  Comment: Additional data are required to develop a glaucoma disease staging system based on disability.
- Population-based screening studies are required to determine optimal screening strategies and their cost-effectiveness.
- Multi-eye disease screening needs to be evaluated as to whether it would be more cost-effective than glaucoma-only screening.

Glaucoma Screening, pp. pp. 55-61
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

Introduction

In all parts of the world, health resources are limited and expended in proportion to economic wealth and cultural preferences. The detection and management of disease creates an economic burden, against which is compared the burden of the disease itself.

Open-angle glaucoma (OAG) affects about 60 million people worldwide and is the second most common cause of blindness.[1] Equitable distribution of health resources requires that the cost of case finding, including screening, diagnosis and treatment is economically balanced in relation to the burden of disability from OAG as well as to health expenditure as a whole.

These factors make expenditure decisions concerning glaucoma screening highly dependent on economic capacity and the general level of health care provision within a region. As such, the aim of this subsection is to provide a framework for regionally-oriented assessment.

The economic impact of screening occurs also within the broader aspect of the impact of screening (Table 1). Evaluation of cost-effectiveness is a key part of assessing the impacts of screening.

Table 1. Important considerations in evaluating the impact of screening (adapted from Barrat A *et al.*)[2]

- Values and preferences of screenees and general population
- Benefits and harms of screening strategies
- Impacts of screening on screenees and general population
- Impacts of uncertainty and how to minimize these
- Resource impacts of screening
- Cost effectiveness in the above situations
- Variations across different regions and populations

Limitations in health care delivery and glaucoma practice

There are major shortcomings in delivery of health care worldwide. Access to care is unequal and large variations exist in the distribution of health care services (both between and within countries as well as continents)

The performance of current glaucoma detection and treatment is not optimal. Large epidemiological studies[3–15] consistently report that at least half of glaucoma patients are undiagnosed. Simultaneously, similar numbers of patients currently taking medicines to lower intraocular pressure do not have glaucoma by the study definitions. We do have sufficient data to determine the disease state of those undiagnosed or the incident glaucoma risk of those on treatment whose disease state did not fall into the strict definitions of epidemiological studies. Data from the same studies suggest that more than half of patients with newly diagnosed glaucoma in the study had seen an ophthalmologist (or optometrist)

in prior years, but their disease was not diagnosed.[8,14] Like all chronic diseases, adherence to medical therapy is relatively poor with non-compliance rates of 5-80% commonly reported.[16,17]

Factors limiting cost-effectiveness studies

There is a lack of adequate evidence on the values of most of the important parameters needed for the evaluation of cost-effectiveness of screening. There is no agreement how cost data should be collected and reported in glaucoma care. Reports on utility data in glaucoma are few and mostly based on cross-sectional studies. There are some data available from randomized controlled trials. But, in general, the relatively small sample sizes, restrictive patient selection, protocol driven costs (frequent tests and visits), and relatively short follow-up (considering all costs and outcomes and losses of follow-up) make these studies a limited data source for the economic evaluation of glaucoma.

There are limited diagnostic data available for economic modeling. Most diagnostic studies of glaucoma do not specify a generally approved definition of the disease. The majority of diagnostic studies have been performed on preselected patient populations which may lead to over-optimistic results. High quality diagnostic studies using a randomized design are missing. The estimates of the sensitivity and specificity of diagnostic tests show large variability and are far lower than the thresholds required for screening dominance (screening being less costly and more effective), that is specificity of 98-99% in the age group < 70 years and 94-96% in the age group > 70 years.

Table 2. Thresholds for screening dominance (adapted from Vaahtoranta-Lehtonen H *et al.*)[18]

						Overall specificity of two serial screening tests	
Age cohort	Discount rate	Follow-up cost	Prevalence of glaucoma	Prevalence of suspected glaucoma	Screening cost	Screening doominated	Screening dominant
50-54 years	No	No	No	No	No	< 0.975	> 0.991
55-59 years	No	No	No	No	No	< 0.963	> 0.988
60-64 years	< 0.01	> €371	No	> 0.05	< €23	< 0.954	> 0.983
65-69 years	< 0.095	> €172	< +50%	Yes	< €50	< 0.941	> 0.975
70-74 years	Yes	Yes	< +50%	Yes	< €78	< 0.919	> 0.961
75-79 years	Yes	Yes	< +50%	Yes	Yes	< 0.881	> 0.943

A relatively large amount of data is available from epidemiological studies showing different estimates for prevalence and incidence of glaucoma in different age and ethnic groups. Evidence on the relative proportions of early, moderate and advanced stages of glaucoma in the population-based studies is extremely limited and variable. Data concerning disease staging and progression is limited and varies according to staging definitions. There is little data based on visual endpoints.

High quality data concerning glaucoma progression is available from randomized controlled trials. But progression rates have been reported for one eye only, that is, not per patients' two eyes, which determines both the health related quality of life (HRQoL) and visual disability compared to costs which are driven by the worst eye.

Literature concerning cost-effectiveness of open-angle glaucoma screening

There is very little published literature regarding cost-effectiveness of OAG screening. Six studies reported the cost-effectiveness of various screening tests and treatments for OAG. The first four studies suffered from methodological weaknesses which are generally considered to limit their usefulness for decision making.[19–22] Two economic evaluations of the effectiveness and cost-effectiveness of OAG screening, based on Markov decision analytical modeling, were published more recently. One study was based in Scotland,[23] the other in Finland.[18]

Both studies compared a population-based screening to opportunistic screening (or case finding). It was apparent that opportunistic case finding systems in the two study countries were different, as were the screening strategies and complexity of the models. This highlights the region-specific nature of economic evaluations for disease screening and the critical importance of the cost-effectiveness of the comparator (in these studies, opportunistic screening).

The study by Burr *et al.* (2007) reports that at a threshold of prevalence of around 4%, screening might be considered cost-effective. It found that screening younger people rather than older was more likely to be cost-effective. Their results agreed in with the second study by Vaahtoranta-Lehtonen *et al.* (2007) in four areas in particular:

1) Although untargeted population screening may currently not be cost-effective, screening of some subgroups might be;
2) Screening is more likely to be cost-effective as prevalence increases;
3) Screening is more likely to be cost-effective when screening interval is greater (5-10 years);
4) Screening is more likely to be cost-effective when first assessment is a simple strategy that could be supervised by non medical technicians.

The results of the two studies seemingly disagreed as to whether screening would be cost-effective for 40-60-year olds compared with 75-year olds. The most probable reason for this was the fact that in the Finnish model, patients with a known diagnosis of glaucoma were screened in order to better target the treatment to the 'right' subjects (= manifest glaucoma). This finding emphasizes the great economic burden of false positives and over treatment in health care systems.

In spite of some disparities in these first two screening modeling studies, their main conclusions fully agree in one major aspect: at this stage there is insuf-

ficient evidence to decide whether screening would be cost-effective or not.

The sensitivity analyses of two modeling studies indicated that the results were sensitive to most of the important parameters needed for economic evaluation: costs of visual impairment, specificity of screening tests, screening and follow-up costs and discount rate, prevalence of suspected glaucoma and glaucoma. The Finnish study also reports the threshold values for screening dominance (Table 2) which can be utilized when designing future studies.

Improving the cost effectiveness of OAG screening

There are two approaches when trying to make a health care system more cost-effective. The broader one is concerned with changing the system (in this case initiation of community/population-based screening program) and the narrower one with making the existing system work better (improve opportunistic screening/case-finding).

Both approaches represent new interventions compared to current strategies which universally involve screening or case finding on an opportunistic basis. Improving the current strategy is usually assumed to be cost-effective. However, no intervention is cost-effective in itself. The cost-effectiveness can only be shown in relation to a defined alternative. Before adopting any new interventions it is vital to know their cost-effectiveness. This includes improvement of current case-finding strategies.

Decisions about the cost-effectiveness of population screening are region specific; if opportunistic screening in a country is very poor with many cases of undetected late glaucoma and blindness, a population screening program could be a more cost-effective strategy than expending resources to improve case finding. There is currently insufficient evidence to make a decision in these circumstances as to which is the best way to expend resources.

Topics for future research/further attention

Decisions about the cost-effectiveness of screening are region-specific. Relevant economic modeling has only been reported in two developed European countries. As an initial step for other countries worldwide, existing screening models should be refined and populated with parameter estimates of epidemiology of glaucoma in that setting to determine how a population-based approach to screening compares with an opportunistic screening strategy.

The costs and effectiveness of a testing approach are likely to pick up other treatable eye diseases and could be evaluated in the model or tested in a randomized controlled trial with an economic model running alongside to project what might be the long term costs and benefits of screening.

The ideal study design for economic evaluation would have a randomized design (*e.g.*, population vs opportunistic screening), large sample sizes on both

arms (with 'usual' patients and 'usual' care protocol in the opportunistic arm), long follow-up, follow-up of drop-outs and measures of outcome, QoL and costs.

The two published economic models[18,23] suggest groups where screening might be worthwhile and how screening could be organized. But due to limitations in the data providing the parameter estimates for the models, further research is required to test what appear to be the most effective screening strategies.

A randomized screening trial run in several regions would give the most reliable evidence of both clinical and cost-effectiveness of screening in preventing glaucoma-induced visual disability. Simultaneously, the sensitivity and specificity of diagnostic tests and their combinations could be evaluated in large non-selected populations. Screening involves the systematic identification of those at risk, and therefore the feasibility of inviting the 'at risk' needs to be determined as well as effective interventions to get those invited to participate. In such a study, a standardized definition of glaucoma, its stages and visual impacts is essential, as is prospective data collection and long term follow up. Generic assessment instruments applicable to cost-utility need to be used to measure HRQol associated with different glaucoma stages and in longitudinal studies.

Prior to a trial, further primary research is required to determine the optimal trial design. The Scottish study group[23] has recently received funding from the Medical Research Council for a feasibility study based in the United Kingdom, to develop the intervention and outcome components of a randomized controlled trial of screening for open-angle glaucoma, which addresses the following questions:

- What is the optimal screening strategy (*i.e.*, test; site; target population; provider)?
- The most promising test combinations would then be tested within the randomized control trial (RCT).
- What is the most appropriate unit of clustering for the trial? This will depend on the target population to be screened: the entire population or only subgroups based for example on family history or ethnicity.
- What are the most likely effective interventions for maximizing attendance by the target individuals?
- What are the most appropriate methods for obtaining primary clinical and patient reported outcomes for use in the trial?

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006; 90: 262-267.
2. Barratt A, Irwig L, Glasziou P, *et al.* Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA 1999; 281: 2029-2034.

3. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology 1996; 103: 1661-1669.
4. Dielemans I, Vingerling JR, Wolfs RC, *et al.* The prevalence of primary open-angle glaucoma in a population- based study in The Netherlands. The Rotterdam Study. Ophthalmology 1994; 101: 1851-1855.
5. Coffey M, Reidy A, Wormald R, *et al.* Prevalence of glaucoma in the west of Ireland. Br J Ophthalmol 1993; 77: 17-21.
6. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol 1994; 112: 821-829.
7. Sommer A, Tielsch JM, Katz J, *et al.* Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 1991; 109: 1090-1095.
8. Wong EY, Keeffe JE, Rait JL, *et al.* Detection of undiagnosed glaucoma by eye health professionals. Ophthalmology 2004; 111: 1508-1514.
9. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966; 50: 570-586.
10. Bengtsson B. The prevalence of glaucoma. Br J Ophthalmol 1981; 65: 46-49.
11. Iwase A, Suzuki Y, Araie M, *et al.* The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 2004; 111: 1641-1648.
12. Nizankowska MH, Kaczmarek R. Prevalence of glaucoma in the Wrocław population. The Wrocław epidemiological study. Ophthalmic Epidemiol 2005; 12: 363-371.
13. Sakata K, Sakata LM, Sakata VM, *et al.* Prevalence of glaucoma in a South Brazilian population: Projeto Glaucoma. Invest Ophthalmol Vis Sci 2007; 48:4974-4979.
14. Topouzis F, Coleman AL, Harris A, *et al.* Factors associated with undiagnosed open-angle glaucoma: the Thessaloniki Eye Study. Am J Ophthalmol 2008; 145: 327-335.
15. Varma R, Ying-Lai M, Francis BA, *et al.* Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology 2004; 111: 1439-1448.
16. Schwartz GF. Compliance and persistency in glaucoma follow-up treatment. Curr Opin Ophthalmol 2005; 16: 114-121.
17. Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmology 2005; 112: 953-961.
18. Vaahtoranta-Lehtonen H, Tuulonen A, Aronen P, *et al.* Cost effectiveness and cost utility of an organized screening programme for glaucoma. Acta Ophthalmol Scand 2007; 85: 508-518.
19. Gottlieb LK, Schwartz B, Pauker SG. Glaucoma screening. A cost-effectiveness analysis. Surv Ophthalmol 1983; 28: 206-226.
20. Gooder P. Screening for glaucoma. 38. 1995. Bristol, Research & Development Directorate South and West. Development and Evaluation Committee. (Ref Type: Report)
21. Boivin JF, McGregor M, Archer C. Cost effectiveness of screening for primary open-angle glaucoma. J Med Screen 1996; 3: 154-163.
22. Tuck MW, Crick RP. The cost-effectiveness of various modes of screening for primary open angle glaucoma. Ophthalmic Epidemiol 1997; 4: 3-17.
23. Burr JM, Mowatt G, Hernandez R, *et al.* The clinical effectiveness and cost-effectiveness of screening for open-angle glaucoma: a systematic review and econimic evaluation. Health Technology Assessment 11[41]. 2007. (Ref Type: Report)

Gabor Holló, Lucca Rossetti and Gunilla Norrgren

Paul Healey with Anders Heijl in the background

SCREENING
FOR
PRIMARY ANGLE CLOSURE
AND
PRIMARY ANGLE-CLOSURE GLAUCOMA

Paul Foster presenting

Ningli Wang

ARE ANGLE CLOSURE (AC) AND ANGLE-CLOSURE GLAUCOMA (ACG) IMPORTANT HEALTH PROBLEMS?


Paul Foster

Co-chairs: Paul Foster, Mingguang He

Contributors: Rob Casson, Daniel Grigera, Rajul Parikh, Harry Quigley, R. Ramakrishnan, Lisandro Sakata, Lingam Vijaya, Tetsuya Yamamoto, Laing Xu, Gerhard Zinser

Consensus points

- Primary angle-closure glaucoma (PACG) accounts for approximately 25% of all glaucomatous optic neuropathy worldwide, but 50% of bilateral glaucoma blindness.
- Visual impairment from primary angle closure (PAC) and PACG can result from ocular damage other than glaucomatous optic nerve damage (*e.g.*, corneal decompensation, cataract, ischemic optic neuropathy).
- Some Asian populations have a high prevalence of advanced angle-closure glaucoma.
- PACG is predominantly asymptomatic.
- PACG is a problem of sufficient magnitude that public health intervention should be evaluated.

Terminology

It has been suggested that the development of a meaningful evidence base on diagnosis and management of PAC and PACG has been hindered by inconsistent and inappropriate approaches to defining and classifying the disease. However, there is now broad-based consensus that the term glaucoma should reflect a visually significant optic neuropathy.[1] Approaches for classification include those based on symptomatology, mechanism and natural history. For epidemiological research, the natural history classification[2,3] is now widely used.

Glaucoma Screening, pp. pp. 65-77
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

Three conceptual stages of (AC) are identified; primary angle-closure suspects, primary angle closure and primary angle-closure glaucoma. Primary angle-closure suspects (PACS) or anatomically narrow angles (ANA) (previously identified as occludable angles) are those with an anatomical predisposition to closure, but without any anatomical or physiological damage from irido-trabecular contact (ITC). Some people with anatomically narrow angles develop raised intraocular pressure (IOP) or peripheral anterior synechiae (PAS) as a consequence of ITC. These pathological changes are regarded as defining features of the disease of PAC. If glaucomatous optic neuropathy develops in the setting of PAC, it is termed PACG. One final category that is somewhat different from those discussed above is acute angle 'closure' (AAC). AAC is characterized by sudden, typically painful increases in intraocular pressure. Despite the emphasis placed on AAC in textbooks, recent research indicates that 80% of PAC occurs without an episode of AAC.[4–7] Nonetheless, AAC remains an important manifestation of a condition which can cause severe damage to eyes and vision.

Magnitude of the problem

Hospital-based data

Glaucoma has previously been recognized as a major cause of visual morbidity in Singapore. A retrospective study of 26,900 patients attending clinics at Singapore General Hospital between January 1964 and December 1966 identified 364 people with glaucoma. Of this number, 66.7% had PACG, 14.7% had open-angle glaucoma (OAG), 16.1% were classified as secondary glaucoma and 2.8% as congenital glaucoma. PACG was more common in women (61.1% of total) and people of Chinese origin (91%, compared with 75% of the national population having Chinese parentage).[8] The blind register in Singapore (1953 to 1966) showed a similar pattern. Glaucoma was responsible for 23% of registered blindness, and in the Chinese population, cases of blindness caused by PACG outnumbered OAG by a factor of 2.5:1.[9]

A review of 34,144 hospital records of Alaskan Inuit found that 2.1% of adults aged 40 years and above had been identified as suffering from PACG.[10] Similarly, in Canadian Inuit at Eskimo Point and Coral Harbour, Drance found a PACG prevalence of 2.9% in those aged 40 and above.[11] In Gallup, New Mexico, a hospital-based case note review found that native Americans had quite a different distribution of glaucoma. Twenty-five percent was post-traumatic, 21% was OAG and 18.5% was attributable to AC. However, the cases of AC were split 2:1 phacomorphic to classic pupil block mechanisms.[12]

In San Francisco, an ophthalmological practice retrospectively reviewed the findings of gonioscopic examinations in 482 of their Vietnamese patients. It was found that 29.5% of all patients, and 47.8% of those aged 55 years and older had drainage angles graded 0, 1 or 2 using the Shaffer system. There were 8.5%

among this number who had an angle at high risk of closure (Shaffer grade 0 or 1).[13] The rate of occludable drainage angles increased with age.

It is well recognized that hospital-based studies will not truly reflect population prevalence from glaucoma because of under-detection of early or asymptomatic cases.

Incidence

The incidence of symptomatic AAC has been reported in Finland,[14] Croatia,[15] the United States,[16] Japan,[17] Israel,[18] Thailand,[7] Singapore[19,20] and Hong Kong.[21] Age and gender standardized incidence ranges from 4.7 cases/100,000 population/year in Finland to 15.5 cases/100,000/year among Chinese Singaporeans, East-Asian people (Japanese, and Chinese from Singapore and Hong Kong) having the highest rates. South and Southeast Asians (Indian, Thai and Malay people) have lower rates of AC. It is a recurring theme in these studies that increasing age and female gender are risk factors for AAC. Importantly, these figures must be interpreted in light of the knowledge that only 25-35% of AC in Asian people causes symptoms.[4–6]

Two recent publications from Vellore in Southern India give an important insight into the incidence of different grades of AC. Normal subjects and people with narrow drainage angles were enrolled from a population survey. Among the people with narrow drainage angles 22% (95% CI: 9.8, 34.2) had developed synechial (64%) or appositional AC (36%) over a period of five years.[22] The people with established AC at the time of the population survey were advised to undergo laser iridotomy. Eight of 28 people examined (28%, 95% CI: 12, 45) had progressed to PACG over five years. One of nine who underwent laser peripheral iridotomy (LPI) progressed compared to seven of 19 who refused LPI.[23]

The incidence of ANA has been studied in a high-risk Mongolian population. Six hundred and forty-four participants aged over 50 years with a central anterior chamber depth (cACD) of < 2.53 mm underwent a full slit-lamp (SL) examination. Participants with existing PACS on gonioscopy (ISGEO classification) at baseline were excluded from all further analysis. At follow-up 20.4% (95% CI: 14.8 to 25.7) were diagnosed as having incident PACS. Narrower angles, identified by grading of limbal chamber depth and gonioscopy at baseline, were strongly associated with incident PACS ($p = 0.01$ and $p < 0.01$, respectively). There was weak evidence of an association with change in cACD ($p = 0.05$), and no evidence of an association with age, gender, and baseline cACD for the development of PACS.[24]

Another study of incidence was carried out in Greenland. Seventy five subjects were selected based on either a van Herick score of one or less, or a van Herick score of two with a central ACD<= 2.7 mm (including cornea) by pachymetry. Gonioscopy was performed on 69 participants at baseline. Twenty were considered to have occludable angles. At the ten-year follow-up examination, 7/20 (35%) had developed PACG. Of the 49 subjects without occludable angles at

baseline, only 4/49 (8%) were diagnosed with primary angle-closure glaucoma at follow up.[25]

An interesting change in incidence of angle-closure has been observed in Taiwan. Using eight years of data from the Taiwanese National Health Insurance Research Database (TNHIRD), the authors investigated the relationship between the total number of cataract operations undertaken and admissions for AAC. The 3814 cases of AAC and 503 687 patients who had undergone cataract operations were categorized by age groups (40-49, 50-59, 60-69 and ≥ 70 years) and by gender. Throughout the study period, the admissions for AAC showed a steady decline from 630 cases in 1997 to 351 cases in 2004, while the number of cataract operations revealed a gradual increase from 26 600 in 1997 to 77 924 in 2004. The Spearman rank correlation coefficients showed significant inverse relationships between monthly AAC admission rates and monthly cataract operation rates for the total group ($r = –0.407$, $P < 0.001$), males ($r = –0.330$, $P < 0.001$), females ($r = –0.444$, $P < 0.001$), 40-49 year olds ($r = –0.335$, $P < 0.001$), 50-59 year olds ($r = –0.497$, $P < 0.001$) and 60-69 year olds ($r = –0.417$, $P < 0.001$). No significant inverse relationship was observed for the ≥ 70 age group. It was concluded that a significant inverse relationship between the monthly AAC admission rates and the monthly cataract operation rates existed.[26]

Prevalence

Inuit people of Arctic regions

Studies of the Inuit peoples of Alaska, Canada and, most importantly, Greenland provided important data on the risk factors for PACG, as well as the burden of the disease. In 1971 Clemmesen and Alsbirk recounted the experiences of Danish ophthalmologists visiting Greenland from 1911. They were impressed by the severity of glaucoma they encountered. In 1968 they visited fifteen of the seventeen medical districts of Greenland to examine 109 known cases of glaucoma and found 94 (86%) were caused by PAC, the remaining 15 being classified as OAG. The prevalence of known PACG was 0.9% in men and 2.1% in women aged 40 years and older. The prevalence of OAG was 0.2% and 0.3% in men and women, respectively.[27] Over the next five years, Alsbirk studied the population prevalence of PACG. Based on population surveys of 1,072 people aged 40 years and older in seven medical districts of Greenland, he found rates of 5.1% among women and 1.6% among men in the population aged 40 years and older.[28] Two studies of Alaskan Inuit verified the Greenlandic data. In Kotzebue, Northwest Alaska, Arkell reported 7/60 people aged 70 years and older had glaucoma. Only one of these had OAG.[29] In Norton Sound and the Bering Straits region of Alaska, Van Rens recorded rates of PACG of 2.1% in men, and 5.5% in women aged 40 and over.[30] *Recently, the proportion of blindness due to PACG in Greenland Inuit has been reduced from 64% to 9%*

over 37 years by biometric screening in older people, followed by gonioscopy and prophylactic iridotomy when indicated.[31]

East Asia

In a study in China in 1989, Hu *et al*. reported prevalence of glaucoma in Shunyi County, Beijing. The county had a population of 472,215, from which a sample of 10,851 was drawn. From this number, 10,414 (96%) were examined, 3,147 of whom were aged 40 years and over. Sixty-two cases of glaucoma were identified in all age groups. PACG accounted for 43 of these, of whom 12 were men (0.25%) and 31 women (0.55%). There were 11 cases of OAG, nine men (0.19%) and two women (0.04%). Remarkably, only one of the people suffering OAG was aged over 40 years. The prevalence of primary glaucomas in the over 40 age group was 1.4%, of which 98% was PACG. This unusual pattern of OAG distribution can probably be explained on the basis of the diagnostic criteria used. In this study OAG could have been diagnosed solely on the basis of a raised IOP and a positive water-drinking test. Furthermore, PACG could have been diagnosed in the presence of a partially occluded drainage angle and raised IOP or symptoms consistent with angle closure.[32]

The same group of researchers carried out a similar project in Duilong-Deqing County, a suburb of Lhasa, Tibet, as part of a cataract morbidity study in collaboration with the US National Eye Institute. The study site was at an elevation of around 4,000 m and consisted of 180 villages. The total population was 31,515, of whom 7,028 (22.3%) were aged 40 years and older. Using a randomized sampling strategy, 27 villages were selected. All subjects were aged 20 years and above. From a total of 2,884, 2,665 (92.4%) were examined. Only two cases of PACG were identified among 1,297 people aged 40 and above. After age- and sex-standardization, the prevalence in Tibet was 0.21% compared with a standardized rate of 1.3% in Beijing (this difference was significant, $p < 0.001$). Using the sidelight test, it was felt that anterior chamber depth was significantly deeper in Tibet compared with Beijing. Interestingly, both cases of PACG detected were bilaterally blind.[33]

These two studies in China are clearly worthwhile attempts to assess the level of glaucomatous visual morbidity in East Asians. The drawbacks are that the description of methods and results are not sufficiently clear for the Western reader to clearly discern the exact methods at crucial stages of the examination, such as sampling and diagnostic classification. This limits the inferences that can be drawn, and the validity of comparisons between these studies and others.

The township of Jin Shan in rural Taiwan was the site of a population-based study of screening techniques for ACG. This joint US-Taiwanese project, published in 1996, identified a target population of 5441 people aged 40 years and older. Only 562 (10.3%) were examined. A gonioscopic examination was carried out on all subjects, and a grade of ‘narrow’ allocated if the trabecular meshwork could not be seen in two or more quadrants. PACG was diagnosed in people with a narrow angle and either an IOP > 18 mmHg, an increase in IOP

≥ 8 mmHg on dark-prone provocation test, or a previous episode of AAC with an iridectomy. The diagnosis did not depend on the presence of a visual field defect or structural optic neuropathy. There were 17 people diagnosed as suffering PACG (3.0%). Only 35% of cases gave a history of symptoms characteristic of AAC. Two of these 17 people (12%) were blind in both eyes.[4]

Two population-based studies of glaucoma prevalence in Mongolia and Singapore found rates of PACG of 0.8% (ISGEO Criteria), in people aged 40 years and older. PAC occurred at around 2%, with PACS being present in 6%.[5,6,34] In Mongolia, 91% of glaucoma cases were previously undiagnosed,[5] whereas in Singapore 79% of cases of PACG had been diagnosed before.[6] At the time, population-based prevalence data for glaucoma in China was limited. Available data for OAG and PACG were inconsistent.[32,33] Data from Mongolia[5] and Singapore[6] were used to make a cautious extrapolation to estimate the size of the problem in China. It was estimated that 9.4 million people aged 40 years and older had glaucomatous optic neuropathy. Approximately 5.2 million people (55%) would be blind in at least one eye. Around 1.7 million (18.1%) would be blind in both eyes. These figures suggested that PACG was responsible for the vast majority (91%) of bilateral glaucoma blindness in China. Around 28 million people are thought to have the anatomical trait predisposing to PACG (a narrow drainage angle), and of these nine million have significant AC, indicated by PAS or raised IOP. It is unlikely that this statistical model is entirely accurate. However, it is believed that the visual morbidity from glaucoma in China is considerable.[34] Using comparable (ISGEO) definitions, the prevalence of PACG among Japanese people aged 40 years and older is similar to that seen in Chinese (0.6%).[35] Another study using ISGEO classification recruited 1,504 people (75.3% participation rate) aged 50 years and older in Guangzhou, Guangdong Province in Southern China. The crude prevalence of all glaucoma was 3.8% (95% confidence interval [CI], 2.8%–4.8%). PACG was found in 1.5% (95% CI, 0.8%–2.1%), with age- and sex-standardized rates similar to those reported in Chinese Singaporeans and Mongolians.[36]

In Japan, the results of a nation-wide study of glaucoma prevalence and characteristics were published in 1991. This multi-centre study was carried out in seven prefectures, ranging from Hokkaido island in the north, to Kumamoto Prefecture in the south. A target population of 16,078 people aged 40 years and older was identified. Over a two-year period, 8,126 of this number were examined, giving a response rate of 50.5%. All subjects underwent non-contact tonometry, optic disc photography and a screening examination of the anterior segment at a slit lamp. If the limbal chamber depth was ≤ ¼ peripheral corneal thickness, they were examined with a gonioscope. An IOP ≥ 18 mmHg was confirmed by repeat measurement using applanation tonometry. If a raised IOP (≥ 21 mmHg) or an abnormality of the optic disc or retinal nerve fiber layer (RNFL) was detected, subjects underwent threshold visual field (VF) testing on a Humphrey Field Analyzer (HFA), running the Armaly central 30° three-zone program. Standardized data forms were used, and all photographic grading was carried out by one individual. In contrast to the studies in China, the diagnosis

of glaucoma status in this study was made on uniform criteria using a computer algorithm. Diagnosis of PACG required raised IOP and a narrow drainage angle. Optic disc and VF abnormalities were not required. Prevalence of PACG was 0.21% for men and 0.38% for women (population aged 40 years and older).[37] A further population-based study recruited a random sample of residents 40 years and older from Tajimi, Japan. Each subject underwent a screening program comprising an interview and an ophthalmic examination, including Goldmann applanation tonometry, SL examination, a van Herick test, fundus photography, and a screening VF test using frequency-doubling technology. If glaucoma was suspected, the subject was referred for a definitive examination that included slit-lamp examination, gonioscopy, IOP measurement, a VF test, and optic-disc and fundus examination. A diagnosis of PAC was made when the following criteria were met: at least one eye having a narrow angle of grade 2 or less by Shaffer's classification without other ocular findings that could have caused narrowing of the angle, and the existence of one or more of the following four conditions: IOP > 21 mmHg; a PAS reaching the scleral spur or beyond; < 90° of visibility of the pigmented trabecular meshwork in the primary position; and evidence of a history of an acute IOP rise, including the presence of iris atrophy, glaukomflecken, dilated nonreactive pupil, or a certified medical record of the subject having PAC. A diagnosis of PACG was made based on SL examination, gonioscopy, optic disc appearance, and perimetric results, using ISGEO criteria. Of 3,870 eligible people, 3021 (78.1%) participated in the study. The estimated prevalence of PACG was 0.6% (95% confidence interval [CI], 0.4%–0.9%).[35]

South Asia

On the Indian Subcontinent, it is widely believed that PACG is more common than among European people.[38] However, two recent population surveys have provided conflicting data. In Vellore, Southern India, the prevalence of PACG was 4.3% among people aged 30 to 60 years. All the PACG cases detected were of the chronic type, making PACG about five times as common as OAG.[39] However, in neighboring Hyderabad, PACG and occludable angles without glaucoma were found with prevalence of 0.7% and 1.4% respectively in participants 30 years of age or older. The prevalence of these two conditions considered together increased significantly with age. Only 33% of PACG had been previously diagnosed, and only one of 12 (8%) had a peripheral iridotomy. PACG had caused blindness in at least one eye of 42%. Most (83%) of those with PACG had the chronic form of the disease.[40] The difference in prevalence of PACG between the people of Hyderabad and Vellore may, in part, be explicable on the grounds of differing definitions, although it seems unlikely that this is to sole reason. What can be gleaned from these studies is that PACG is probably more common in Indian than in European people and, as in the rest of Asia, tends to be asymptomatic. In a rural population near Chennai, Southern India, 3,934 people (81.95%) of 4800 enumerated subjects aged 40 years were examined, with cases of glaucoma being classified according to ISGEO

criteria. PACG was diagnosed in 34 subjects (0.87%; 95% confidence interval [CI], 0.58 to 1.16) (27 women, seven men), of whom one (2.9%) was blind. Twenty-eight people (0.71%; 95% CI, 0.45 to 0.98) had PAC (21 women, seven men). Eleven subjects (39.3%) had an IOP greater than 21 mmHg, 13 subjects (46.43%) had PAS, and four subjects (14.29%) had both. Two hundred forty-six subjects (6.3%; 95% CI, 5.5 to 7.0) were classified as PACS (168 women, 78 men). The overall prevalence of all PAC and PACG in this rural population of southern India was 1.6%. There was a female preponderance, and the disease tended to be asymptomatic.[41] A subsequent study of 4,000 people living in an urban Chennai found 34 subjects (17 female, 17 male) had PACG (0.88%; 95% confidence interval [CI], 0.60-1.16). Five subjects (14.7%) had been previously diagnosed with glaucoma, of whom one had undergone glaucoma surgery and two had been classified as OAG. Two subjects (5.9%) were bilaterally and three (8.8%) unilaterally blind. One hundred six subjects (2.75%; 95% CI, 2.01-3.49) were diagnosed with PAC (62 female, 44 male). Thirty-nine subjects (36.8%) had presenting IOP > 24 mmHg, 83 (78.3%) had PAS, and 16 (15.1%) had both. Two hundred seventy-eight subjects (7.24%; 95% CI, 6.38-8.02) had PACS (183 female, 95 male). The prevalence of PACG and PACS were similar in the urban and the previously examined rural population. PAC prevalence was higher in the urban population ($P < 0.0001$).[42] A population-based cross-sectional study of 5150 people aged 40 years and older in Tamil Nadu, southern India identified a total glaucoma prevalence (95% confidence interval, CI) of 2.6% (2.2, 3.0). Of this, OAG accounted for 1.7% (1.3, 2.1), and PACG 0.5% (0.3, 0.7).[43]

South-East Asia

The prevalence, demography, mechanism, and visual morbidity of glaucoma has been studied in Thai people living near Bangkok. Each subject underwent the following investigations: visual acuity (VA), VF testing, slit lamp examination, applanation tonometry, gonioscopy, and an optic disc examination after mydriasis. Glaucoma was diagnosed on the basis of optic disc appearance and visual field defects using ISGEO criteria. Seven hundred and one subjects were examined (response rate 88.7%). Six people had PACG, a prevalence of 0.9% (95% CI: 0.3 to 1.9). Ninety-eight subjects (14%) had occludable angles in either eye, 22 of whom had PAC (prevalence 3.1%, 95% CI: 1.9 to 4.7); 14 had PAS in either eye and eight had ocular hypertension (OHT).[7] Another study in rural Myanmar examined 2,076 (83.7%) people aged 40 years and older. The ophthalmic examination included Snellen VA, SL examination, tonometry, gonioscopy, dilated stereoscopic fundus examination and full-threshold perimetry. Glaucoma was diagnosed using ISGEO criteria. The overall prevalence of PACG was 2.5% (95% CI 1.5 to 3.5). PACG accounted for 84% of all blindness due to glaucoma, with the majority associated with AAC.[44]

People of European origin

PAC has not been recognized as a common condition in Europeans, and typically has a prevalence rate of around 0.1% or less in the population aged 40 years and older.[45–47] A population-based study in northern Italy has recently found a somewhat higher prevalence of 0.6%.[48] However, this study in a rather isolated Italian village may not be fully representative of the general population of Italy. Unpublished data from the Baltimore Eye Survey in the US indicate that 0.4% of whites and 0.6% of blacks over the age of 40 have PACG (Tielsch J, personal communication, 1997). In Europe, it has been estimated that one million people have PACG (Gazzard G, personal communication, 2007). Even though PACG is much less common than OAG among people of European and African decent, it is likely that it accounts for a significant proportion of glaucomatous loss of visual function given the greater severity of the disease. Not only may acute attacks cause severe vision loss, but more chronic forms of the disease also result in severe glaucomatous optic nerve damage.

South America

The prevalence of glaucoma in a South-Brazilian population was assessed in people aged 40 years and older. Participants underwent a screening examination that included a medical interview, SL examination, tonometry, and fundoscopy. Glaucoma was diagnosed based on ISGEO criteria. A total of 1636 subjects were examined (76.5% participation rate); 71% of the study population self-reported their race as white and 24% as non-white (most black and mixed-black/white). Glaucoma was found in 56 subjects (3.4%; 95% CI, 2.5-4.3). PACG was found in 12 (0.7%; 95% CI, 0.3-1.1). Unilateral blindness due to primary glaucoma was observed in two of 12 people with PACG (16%).[49] The Proyecto VER studied the Hispanic population aged 40 years and older living in Nogales and Tucson, Arizona in the United States. Detailed ocular examinations at a local clinic included visual acuity testing, applanation tonometry, gonioscopy, an optic disc evaluation, and a threshold VF test. OAG was defined using a proposed international system for prevalence surveys, including threshold visual field defect and optic disc damage. PACG was defined as bilateral appositional angle closure, combined with optic nerve damage (judged by field and disc as for OAG). Examinations were conducted in 72% (4774/6658) of eligible persons. PACG was detected in five persons (0.10%).[50]

Africa

Africa is home to such a diverse population, that it makes generalizations about the likely pattern of PAC very difficult. A clinic-based study found the rate of PAC (gonioscopically verified closure of the angle with raised IOP) was equal among the black and white populations of Johannesburg. Among the white population 66% of cases were symptomatic, whereas only 31.5% of the black

patients reported symptoms.[51] More recent surveys in Africa with participants of mainly Bantu ethnicity have consistently estimated the prevalence of PACG at 0.5%, much lower than OAG and secondary glaucomas.[52–54] A population-based study of Cape-Malay people (mixed Southeast Asian and African heritage) living in the Western Cape of South Africa found a prevalence of PACG of 2.3% in people aged 40 years and older. In this study of 987 people, all subjects underwent examination including Goldmann applanation tonometry, gonioscopy and examination of the optic disc using a direct ophthalmoscope. If IOP > 21 mmHg, CDR > 0.4 or CDR asymmetry > 0.2 were found subjects underwent a supra-threshold screening VF test using a HFA. The diagnosis of PACG was made on the basis of an angle judged 'occludable' on gonioscopic examination, in conjunction with other features. This may have resulted in an overestimation of PACG prevalence. Three people reported symptoms consistent with intermittent AAC. Asymptomatic PAC was diagnosed in 20 people, eight with glaucomatous optic neuropathy and a further 12 with full VFs but an IOP > 21 mmHg. Therefore, only eight of the 23 (35%) people with PAC had PACG. Three of these were blind in both eyes. In contrast, OAG was diagnosed in 15 people, a prevalence of 1.5%.[55]

Pooled Data

Quigley has used published prevalence data, and rates of blindness to calculate the number of people affected by glaucoma, and those who are blind. The results suggest that glaucoma is the leading cause of irreversible blindness in the world. By 2010, it is projected that 60 million people will have the disease, of whom 8.4 million (14%) will be blind in both eyes. Half this number (3.9 million) will be blinded by PACG. This figures increase to nearly 80 million and 5.3 million by 2020.[56] This manuscript reinforces the findings of previous population-based studies (above) that show people with PACG are more often blind in at least one eye than people with OAG. In hospital settings, people with PACG tend to have more severe loss of visual function than OAG.[57] We therefore believe that, overall, PACG is more visually destructive and rapidly progressive than OAG.

Population attributable risk of primary angle closure

Population attributable risk percentage (PAR %) can help assess whether a disease is a health problem amenable to public health interventions. The PAR% addresses the percentage of risk in a population associated with a risk factor that may potentially be eliminated with treatment. PAR% is based on the fact that risk factors increase the risk of a disease, *over and above* any existing *baseline risk* in the population. By treating a causal risk factor, we can possibly eliminate that portion of the disease caused by the risk factor, but not the baseline risk. One approach to evaluating the size of the problem is to consider PACS. In this situation, PAR% addresses the question: 'if we treat all the PACS in the entire

population, how much PACG in the entire population will we prevent?' For calculation purposes, we use a formula where we need to know the prevalence (P) of the risk factor (PACS) in the population and the relative risk (RR) of developing glaucoma with the risk factor (PACS), *compared to* the baseline risk in the population. The formula used is shown below:

$$PAR\% = \frac{P\,(RR-1)}{P(RR-1)+1} \times 100$$

where P is the prevalence of the risk factor (PACS) in the population and RR is the relative risk of developing PACG from PACS compared to the 'base line' risk in the population.

A PAR% of 20% is something most epidemiologists would be interested in. A PAR% of 40% is associated with interventions like the provision of clean drinking water, sanitation and immunization. Using different values for prevalence of PACS and the relative risk of progression, PAR% for PACS to PACG is 56%. The PAR% of PAC to PACG can be similarly calculated to be 65%. This suggests that AC is an important problem. Other considerations such as the feasibility of testing a population efficiently to detect people at high risk, and the logistics of providing a confirmatory examination and prophylactic treatment need to be considered prior to recommending population-based screening.

References

1. Weinreb RN, Friedman D. Consensus on Angle Closure and Angle-closure Glaucoma. The Hague/Amsterdam: Kugler Publications, 2006.
2. Foster PJ, Buhrmann RR, Quigley HA, *et al.* The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002; 86: 238-242.
3. Foster PJ, Nolan WP, Aung T, *et al.* Defining 'occludable' angles in population surveys: Drainage angle width, peripheral anterior synechiae and glaucomatous optic neuropathy in East Asian people. Br J Ophthalmol 2004; 88: 486-490.
4. Congdon N, Quigley HA, Hung PT, *et al.* Screening techniques for angle-closure glaucoma in rural Taiwan. Acta Ophthalmol Scand 1996; 74: 113-119.
5. Foster PJ, Baasanhu J, Alsbirk PH, *et al.* Glaucoma in Mongolia- A population-based survey in Hövsgöl Province, Northern Mongolia. Arch Ophthalmol 1996; 114: 1235-1241.
6. Foster PJ, Oen FT, Machin DS, *et al.* The prevalence of glaucoma in Chinese residents of Singapore. A cross-sectional population survey in Tanjong Pagar district. Arch Ophthalmol 2000; 118: 1105-1111.
7. Bourne RRA, Sukudom P, Foster PJ, *et al.* Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. Br J Ophthalmol 2003; 87: 1069-1074.
8. Loh RC. The problem of glaucoma in Singapore. Singapore Med J 1968; 9: 76-80.
9. Lim ASM. Primary angle-closure glaucoma in Singapore. Aust J Ophthalmol 1979; 7: 23-30.
10. Cox JE. Angle-closure glaucoma among the Alaskan Eskimo. Glaucoma 1999; 6: 135-137.
11. Drance SM. Angle closure glaucoma among Canadian Eskimos. Can J Ophthalmol 1973; 8: 252-254.

12. Bettman JW. Eye Disease Among American Indians of the Southwest. Arch Ophthalmol 1972; 88: 263-268.
13. Nguyen N, Mora JS, Gaffney MM, *et al.* A high prevalence of occludable angles in a Vietnamese population. Ophthalmology 1996; 103: 1426-1431.
14. Teikari J, Raivio I, Nurminen M. Incidence of acute glaucoma in Finland form 1973 to 1982. Graefe's Arch.Clin.Exp.Ophthalmol 1987; 225: 357-360.
15. Ivanisevic M, Erceg M, Smoljanovic A, *et al.* The incidence and seasonal variations of acute primary angle-closure glaucoma. Coll Antropol 2002; 26: 41-45.
16. Erie JC, Hodge DO, Gray DT. The Incidence of Primary Angle-Closure Glaucoma in Olmstead County, Minnesota. Arch Ophthalmol 1997; 115: 177-181.
17. Fujita K, Negishi K, Fujiki K, *et al.* Epidemiology of acute angle-closure glaucoma. Report I. Jpn J Clin Ophthalmol 1996; 37: 625-629.
18. David R, Tessler Z, Yassur Y. Epidemiology of acute angle-closure glaucoma:incidence and seasonal variations. Ophthalmologica 1985; 191: 4-7.
19. Seah SKL, Foster PJ, Chew PT, *et al.* Incidence of Acute primary angle-closure glaucoma in Singapore. An Island-Wide Survey. Arch Ophthalmol 1997; 115: 1436-1440.
20. Wong TY, Foster PJ, Seah SKL, *et al.* Rates of hospital admissions for primary angle closure glaucoma among Chinese, Malays, and Indians in Singapore. Br J Ophthalmol 2000; 84: 990-992.
21. Lai JS, Liu DT, Tham CC, *et al.* Epidemiology of acute primary angle-closure glaucoma in the Hong Kong Chinese population: prospective study. Hong Kong Med J 2001; 7: 118-123.
22. Thomas R, George R, Parikh R, *et al.* Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. Br J Ophthalmol 2003; 87: 450-454.
23. Thomas R, Parikh R, Muliyil J, *et al.* Five-year risk of progression of primary angle closure to primary angle closure glaucoma: a population-based study. Acta Ophthalmol Scand 2003; 81: 480-485.
24. Yip JL, Foster PJ, Gilbert CE, *et al.* Incidence of occludable angles in a high-risk Mongolian population. Br J Ophthalmol 2008; 92: 30-33.
25. Alsbirk PH. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. Int Ophthalmol 1992; 16: 265-272.
26. Hu CC, Lin HC, Chen CS, *et al.* Reduction in admissions of patients with acute primary angle closure occurring in conjunction with a rise in cataract surgery in Taiwan. Acta Ophthalmol Scand 2007.
27. Clemmesen V, Alsbirk PH. Primary angle-closure glaucoma (a.c.g.) in Greenland. Acta Ophthalmol 1971; 49: 47-58.
28. Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. I. An epidemiologic study in Greenland Eskimos. Acta Ophthalmol 1975; 53: 89-104.
29. Arkell SM, Lightman DA, Sommer A, *et al.* The prevalence of glaucoma among eskimos of Northwest Alaska. Arch Ophthalmol 1987; 105: 482-485.
30. Van Rens GHMB, Arkell SM, Charlton W, *et al.* Primary angle-closure glaucoma among Alaskan Eskimos. Doc Ophthalmol 1988; 70: 265-276.
31. Johnson GJ, Foster PJ. Can we prevent angle-closure glaucoma? Eye 2005; 19: 1119-1124.
32. Hu Z, Zhao ZL, Dong FT. [An epidemiological investigation of glaucoma in Beijing and Shun-yi county]. [Chinese]. Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology] 1989; 25: 115-118.
33. Zhao JL. [An epidemiological survey of primary angle-closure glaucoma (PACG) in Tibet]. [Chinese]. Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology] 1990; 26: 47-50.
34. Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? Br J Ophthalmol 2001; 85: 1277-1282.
35. Yamamoto T, Iwase A, Araie M, *et al.* The Tajimi Study report 2: prevalence of primary

angle closure and secondary glaucoma in a Japanese population. Ophthalmology 2005; 112: 1661-1669.
36. He MG, Foster PJ, Ge J, *et al.* Prevalence and clinical characteristics of glaucoma in adult Chinese: A population-based study in Liwan District, Guangzhou. Invest Ophthalmol Vis Sci 2006; 47: 2782-2788.
37. Shiose Y, Kitazawa Y, Tsukuhara S, *et al.* Epidemiology of glaucoma in Japan- A nationwide glaucoma survey. Jpn J Ophthalmol 1991; 35: 133-155.
38. Congdon N, Wang F, Tielsch JM. Issues in the Epidemiology and Population-Based Screening of Primary Angle-Closure Glaucoma. Surv Ophthalmol 1992; 36: 411-423.
39. Jacob A, Thomas R, Koshi SP, *et al.* Prevalence of primary glaucoma in an urban south Indian population. Ind J Ophthalmol 1998; 46: 81-86.
40. Dandona L, Dandona R, Mandal P, *et al.* Angle-closure glaucoma in an urban population in southern india. The Andhra Pradesh eye disease study. Ophthalmology 2000; 107: 1710-1716.
41. Vijaya L, George R, Arvind H, *et al.* Prevalence of angle-closure disease in a rural southern Indian population. Arch Ophthalmol 2006; 124: 403-409.
42. Vijaya L, George R, Arvind H, *et al.* Prevalence of Primary Angle-Closure Disease in an Urban South Indian Population and Comparison with a Rural Population The Chennai Glaucoma Study. Ophthalmology 2007.
43. Ramakrishnan R, Nirmalan PK, Krishnadas R, *et al.* Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology 2003; 110: 1484-1490.
44. Casson RJ, Newland HS, Muecke J, *et al.* Prevalence of glaucoma in rural Myanmar: the Meiktila Eye Study. Br J Ophthalmol 2007; 91: 710-714.
45. Wensor MD, McCarty CA, Stanislavsky YL, *et al.* The prevalence of glaucoma in the Melbourne Visual Impariment Project. Ophthalmology 1998; 105: 733-739.
46. Hollows FC, Graham PA. Intraocular pressure, glaucoma and glaucoma suspects in a defined population. Br J Ophthalmol 1966; 50: 570-586.
47. Coffey M, Reidy A, Wormald R, *et al.* Prevalence of glaucoma in the west of Ireland. Br J Ophthalmol 1993; 77: 17-21.
48. Bonomi L, Marchini G, Marrafa M, *et al.* Epidemiology of angle-closure glaucoma. Prevalence, clinical types, and association with peripheral anterior chamber depth in the Egna-Neumarkt glaucoma study. Ophthalmology 2000; 107: 998-1003.
49. Sakata K, Sakata LM, Sakata VM, *et al.* Prevalence of glaucoma in a South brazilian population: Projeto Glaucoma. Invest Ophthalmol Vis Sci 2007; 48: 4974-4979.
50. Quigley HA, West SK, Rodriguez J, *et al.* The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol 2001; 119: 1819-1826.
51. Luntz MH. Primary angle-closure glaucoma in urbanized South African caucasoid and negroid communities. Br J Ophthalmol 1973; 57: 445-456.
52. Buhrmann RR, Quigley HA, Barron Y, *et al.* Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci 2000; 41: 40-48.
53. Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. Arch Ophthalmol 2002; 120: 471-478.
54. Rotchford AP, Kirwan JF, Muller MA, *et al.* Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. Ophthalmology 2003; 110: 376-382.
55. Salmon JF, Mermoud A, Ivey A, *et al.* The prevalence of primary angle-closure glaucoma and open angle glaucoma in Mamre, Western Cape, South Africa. Arch Ophthalmol 1993; 111: 1263-1269.
56. Quigley HA, Broman AT. The number of persons with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006; 90: 262-267.
57. Gazzard G, Foster PJ, Viswanathan AC, *et al.* The severity and spatial distribution of visual field defects in primary glaucoma: a comparison of primary open-angle glaucoma and primary angle-closure glaucoma. Arch Ophthalmol 2002; 120: 1636-1643.

Ningli Wang, Anne Coleman, Fotis Topouzis and Robert N. Weinreb

Juan Carlos Rueda, Fabian Lerner, Robert N. Weinreb and Eugenio Maul

IS THERE AN ACCEPTED AND EFFECTIVE TREATMENT FOR PATIENTS WITH ANGLE-CLOSURE GLAUCOMA (ACG) THAT IS MORE EFFECTIVE AT PREVENTING MORBIDITY WHEN INITIATED IN THE EARLY, ASYMPTOMATIC STAGE THAN WHEN BEGUN IN THE LATER, SYMPTOMATIC STAGES?

Robert Ritch

Co-chairs: Robert Ritch, Clement Tham

Contributors: Yaniv Barkana, Paul Chew, Tanuj Dada, Syril Dorairaj, David Friedman, Daniel Grigera, Dexter Leung, Rajul Parikh, Prin RojanaPongpun, Garudadri Chandra Sekhar, Ravi Thomas

Consensus points

- Angle closure is a progressive condition that can lead to glaucoma.
- Iridotomy or iridectomy is the preferred initial treatment for cases of PAC and PACG.
  Comment: Iridotomy or iridectomy eliminates pupillary block.
- There is no evidence to support medical treatment alone for PACG in the absence of iridotomy or iridectomy.
- Medical treatment may be indicated for lowering IOP after iridotomy or iridectomy, following risk assessment.
  Comment: Research is needed to determine whether a residual increase in IOP following iridotomy or iridectomy requires treatment
- Iridotomy or iridectomy will not always alleviate irido-trabecular apposition since mechanisms other than pupillary block may be present, such as plateau iris or phacomorphic angle closure.
  Comment: Peripheral iridoplasty may be effective in further opening the angle and preventing further closure. Unlike iridotomy or iridectomy, peripheral iridoplasty sometimes needs to be repeated.

Glaucoma Screening, pp. pp. 79-91
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

- There is good evidence that preventive iridotomy or iridectomy will eliminate the risk of acute angle closure when performed on the fellow eye of patients who have experienced acute angle closure.
- There is insufficient evidence for deciding which PACG patients should undergo lens extraction alone (without trabeculectomy).
  Comment: Lens extraction alone may be considered in eyes with mild degree of angle closure (less than 180º of PAS), mild optic nerve damage/ visual field damage or those that are not on maximum tolerated medical treatment.
  Comment: There is limited evidence for recommending lens extraction alone in eyes with mild PACG. Similarly there is limited evidence for recommending lens extraction alone in eyes with more advanced PACG.
  Comment: Published studies to date have been non-randomized, with small sample sizes and short follow-up.
- Although commonly performed, there is limited evidence about the effectiveness of combined cataract extraction and trabeculectomy in eyes with PACG.
  Comment: There is a need for studies comparing this form of surgery with separately staged cataract extraction and trabeculectomy.

Introduction – scope of discussion

By medical treatment, we mean conventional anti-glaucoma medications for lowering IOP and/or breaking pupillary block. By primary angle-closure suspect (PACS), we refer to any eye that has a primary, abnormally narrow width of the anterior-chamber angle recess, wherein the peripheral iris is located close to, yet not touching, the posterior pigmented trabecular meshwork.[1] Patients with PACS may be at risk for subsequent PAC, characterized by PAS and/or raised IOP. Patients with PAC can present with either acute or chronic AC features or they may have both of these, presenting with an acute attack superimposed on chronic angle closure.[2] In PAC, the eye is at risk of developing glaucomatous optic disc damage, particularly when associated with elevated IOP. In this case, the eye has progressed from PAC to primary PACG. However, the incidence of conversion from PACS to PAC is yet to be accurately determined.

Asymptomatic stages include PACS and PAC. We also include the preperimetric phase of PACG as asymptomatic. One can argue that established PACG with a visual field deficit may be asymptomatic or symptomatic. Acute angle closure (AAC) is considered symptomatic.

In dealing with the question at hand, then, by asymptomatic stage, we should be considering PACS. However, the question as stated above does not really apply as such to AC, as symptomatic angle closure refers to either an ACC episode or PACG with sufficiently extensive loss of vision to be symptomatic. The question would be better phrased as to whether treatment is indicated prior to the stage at which signs are present. Such signs could include PAS, glaucomatous VF and optic disc damage, or mild intermittent or sub-AAC episodes.

Hence the question becomes: is there any treatment for PACS, PAC or early PACG that is acceptable and effective? If yes, is the treatment more effective when initiated early rather than late? There is no acceptable medical treatment for these conditions, if medications are used alone for those eyes that are obviously at high risk.

The relative lack of data on the natural course of PACS, or clinical course of PACS after receiving either laser or medical treatment, affects our position as to whether to recommend medical or laser treatment as a cost-effective strategy. In one study, the number-needed-to-treat (NNT) for preventing one PACS conversion to PAC was six over five years; the NNT for preventing one PAC conversion to PACG was five over five years.[3] As per personal experience from some of the consensus participants, the rate of conversion from PAC without high IOP into AAC is probably low. With such a low rate of conversion to AAC or IOP rise, the role of chronic use of medication becomes unsure. In addition, the perceived uncertainty in efficacy of medication alone in preventing these late complications, and potential side effects and costs of such chronic medications, makes the use of medication undesirable.

Another situation where the role of medications deserves further evaluation is after aborting an attack of AAC and after LPI. Studies have shown that in these eyes, the incidence of IOP rise can still range from 30.0% to 46.7% at 18 months.[4–6] In a way, these eyes with chronic IOP rise months after the attack of AAC, may return to being 'asymptomatic' until frank optic nerve damage and visual field loss occurs. Most of the IOP rise will occur in the first year after the acute angle-closure attack.[5,7] Whether the chronic use of medications is effective when applied in this 'early asymptomatic' phase in preventing further morbidity requires further studies. One issue that may need to be tackled is to know whether lowering IOP in post-AAC eyes may be effective in halting optic nerve damage and VF progression, in the same way as OAG. While the concept of target pressure (*i.e.*, that IOP at which no further glaucoma progression occurs) is well-defined for OAG[8] no similar data are available for PACG. If the target pressure for PACG is known, one can then study whether medications alone or in fact surgical options are more effective in achieving it, and a cost-effectiveness analysis using tools such as the quality-adjusted-life-years could then be made.

Medical therapy alone is unlikely to be acceptable or effective as far as prevention of AAC is concerned. The use of pressure lowering medications aims mainly to break the cycle of pupillary block, and to clear the cornea to facilitate definitive LPI. Without LPI, even if the IOP is reduced by medication, the pupillary block AAC can easily recur. The use of IOP-lowering medications without laser treatment is not regarded as acceptably safe.

As PACS without IOP rise itself maybe a group of heterogeneous conditions, encompassing those with and without plateau iris configuration[9] with or without a specific iris configuration such as volcano sign, double hump sign, or trabecular meshwork signs such as vertical strips of pigments[10] – more studies are warranted before we can assess whether the role of medical treatment is the

same for all subgroups within PACS. Currently there is not enough evidence to substantiate the role of medication alone as an acceptable and effective treatment for the early phase of this disease.

This discussion does not take into account secondary angle-closure glaucomas or special forms, such as acute phacomorphic AC or aqueous misdirection. In the later scenario, the use of atropine may have a role in preventing attacks, even after laser therapy.

Medical treatment

Prior to the advent of LPI, when surgical iridectomy was the standard treatment, there was more of an argument regarding medical vs. surgical treatment of PACS, PAC and fellow eyes of AAC. In 1957, Bain[11] reported that 78% of untreated and 39% of miotic-treated fellow eyes developed acute attacks within five years after a contralateral attack. Subsequent comparisons of the risk of damage resulting from conservative versus surgical treatment[12–15] showed that the cumulative risks of surgery were less than the risk of damage from angle-closure attacks.[16–19]

Laser treatment

The rationale for laser treatment for PACS or PAC is to prevent AAC and PACG. This is based on observations that suggest that without treatment the disease progresses and that laser treatment can alleviate angle closure and can actually prevent or decrease morbidity when performed early. Early LPI will prevent some cases of PAS and IOP elevation due to damage to the trabecular meshwork from apposition. There may be a huge difference in outcome based on the timing of our interventions. In all populations studied so far, it seems that a substantial proportion of appositional closure is eliminated by LPI, and so PAS should be less likely with early LPI. One question that will ultimately have to be answered is at what cost? When considering a preventive treatment in the early, asymptomatic stage of the disease, we must be sure that the treatment is very safe and is unlikely to cause significant morbidity. LPI and argon laser peripheral iridoplasty (ALPI) have been performed for decades, and reports of serious side effects have been very few.[20–23] There have been reports that cataract progression is more common after LPI over the long term, particularly posterior subcapsular cataract.[23] We will need to balance this with an understanding of what the natural history would have been without LPI.

In clinical practice we encounter eyes with varying extents of reversible iridotrabecular apposition (PACS), fewer eyes in which there is PAC, and still fewer eyes in which there is definite evidence for PACG.[24] In addition, virtually all patients who present with AAC in one eye have an anatomically narrow angle or PAC in the fellow eye. Based on these observations, we presume that angle

closure is a progressive condition that in some eyes will lead from PACS to PAC to PACG or in some eyes to AAC. Although this view is widely and firmly accepted, there is very little published direct evidence to support it. Consequently, the precise incidence and rate of progression, and the factors that determine these parameters, are not known and require further research.

In the study by Wilensky *et al*.[25] glaucoma experts identified on routine examination 129 patients with narrow angles 'believed to be capable of closure' or shallow anterior chamber (less than 2.0 mm central anterior chamber depth (cACD). During an average follow-up of three years, AAC had occurred in eight (6.2%) patients (11 eyes) and PAC, defined as gonioscopic observation of irido-trabecular contact, was observed in 17 (13.2%) patients (27 eyes).

Thomas *et al*.[26] identified 118 subjects with PACS (an angle in which more than 180^0 was not seen, with no PAS or elevated IOP) in one or both eyes. Fifty of these were re-examined after five years. Of these, 11 (22%) progressed to PAC. In seven cases PAS were seen, and in four IOP was > 21 mmHg. Similar progression was observed in one of 110 controls without an anatomically narrow angle (ANA) at baseline, with a calculated relative risk of 24.2 in the eyes with PACS. None of the eyes that progressed showed glaucomatous changes in the optic nerve or VF.

In a subsequent publication based on this cohort, 32 eyes had been diagnosed in 1995 with PAC, with the presence of either PAS and/or IOP > 21 mmHg, but without glaucomatous neuropathy. Five years later, 28 subjects were re-examined, of whom eight (28.5%) had progressed to PACG. All had been advised to undergo LPI in 1995; one of the nine who underwent LPI progressed compared to seven of 19 who refused LPI. Four of those originally diagnosed with PAC without PAS subsequently developed PAS. There was no significant difference in biometric parameters between those who progressed and those who did not. Comparing progression between groups which had an LPI to those which did not, the NNT was only four. This was felt sufficient to suggest LPI in all PAC patients.

Laser treatment to alleviate angle closure

The fundamental idea behind LPI is the understanding that in the presence of relative pupillary block there is resistance to aqueous flow from the posterior chamber to the anterior chamber, increased hydrostatic pressure is created behind the iris, and the iris becomes convex. In eyes with predisposing anatomy (short axial length, shallow anterior chamber), iris convexity leads to narrowing or closure of the iridocorneal angle. LPI creates a bypass to this resistance and allows free flow of aqueous from the posterior chamber to the anterior chamber. The pressure gradient is eliminated, the iris becomes flat, and the angle widens. These anatomic changes can indeed be demonstrated by several imaging modalities, and are seen in most treated eyes.[28–31] In eyes with a plateau iris, the angle can remain narrow even after cataract extraction.[32]

Mechanisms other than pupillary block may cause persistent or progressive PAC despite a patent LPI, most notably plateau iris syndrome and phacomorphic angle closure.[9,10,24–35] ALPI involves the application of contraction burns of low energy, large spot size, and long duration to the peripheral iris. This compacts and contracts the peripheral iris stroma, creating a space between the anterior iris surface and the trabecular meshwork, thus physically opening the angle.[36] Plateau iris syndrome and persistent appositional closure after LPI are more common in eastern Asia than in the West.

Laser treatment to decrease morbidity

Lowe[16] reported retrospectively that after having had an attack of AAC in one eye, in 113 eyes that were treated conservatively there was a 50% chance of a similar episode occurring in the fellow eye; but if preventive (surgical) iridotomy was performed, only one of 54 eyes experienced an attack during the same period. Since it is unlikely that a similar prospective randomized study will be conducted for LPI, mainly due to ethical concerns, we are left to extrapolate Lowe's findings to the use of preventive LPI. However, Lowe's observations on fellow eyes' natural history can be contrasted with other reports on eyes treated with LPI. For example, Ang *et al*.[37] followed 80 fellow eyes that were treated with prophylactic LPI for five years on average, and reported that AAC did not occur in any of the eyes.

There is relatively little published evidence that demonstrates that LPI prevents progression of PAC and ultimately glaucoma. In the study by Thomas *et al*.[26] one of nine who had LPI in 1995 progressed to PACG, compared with seven of 19 who did not have LPI (the procedure had been offered but they refused). Although a small sample, the authors calculated 'number needed to treat' of four suggests justification for preventive treatment with LPI in all PAC patients.

Long-term results of ALPI in plateau iris syndrome were published by Ritch *et al*.[38] In 20 of 23 eyes (87.0%), the angle remained open throughout the entire follow-up period of 72 to 188 months after a single treatment. In three eyes, there was gradual re-closure of the angle five to nine years after initial ALPI, but these were readily re-opened and maintained open by a single repeat treatment. No filtration surgery was necessary in any eye during follow-up. There was no documented progression of PAS in any eye.

Although there is some published evidence that treatment is 'more effective at preventing morbidity when initiated in the early, asymptomatic stage' there is also published evidence that it is *not* effective when initiated late, when glaucomatous damage is already present. In a retrospective analysis of 80 such eyes followed for five years on average, all eyes required IOP-lowering therapy following LPI, 70% with medications with or without laser and 30% with filtration surgery.[39] Similarly in 19 eyes of 16 patients LPI alone did not result in sufficient IOP lowering in any case.[40] Thus, when the patient already has PACG, laser treatment may widen the angle but is not likely to suffice for IOP control.

We can hypothesize that the TM has been irreversibly damaged from years of iris-TM apposition and friction, something that conceptually can be prevented with early LPI and/or ALPI.

Clinical considerations

Considering the statements and evidence above, LPI is indicated for all fellow eyes in patients with AAC. In virtually all cases the anatomy of both eyes is similar, the angle in the fellow eye is very narrow or closed, and as mentioned above is at a significant risk to develop a similar episode. This clinical situation is well defined.

LPI is also indicated in PAC. In these eyes there is either appositional angle closure (PACS) together elevated IOP or the presence of PAS, iris whorling (distortion of the radially oriented iris fibers), 'glaucomfleken' lens opacities, or pigment deposition on the trabecular meshwork and adjacent structures in a distribution and pattern strongly suggesting irido-trabecular contact. PAS are unequivocal evidence for intermittent/chronic touch between the iris and inner eye wall. In most eyes with PAS, the rest of the angle circumference is narrow or appositionally closed, and LPI should be performed in order to cause widening of these parts of the angle, prevent further formation of PAS, and ultimately elevation of IOP and glaucoma. (We refer to eyes with *primary* angle closure, not when PAS are secondary to such conditions as uveitis or anterior segment neovascularization) This category of eyes is also well defined if gonioscopy is performed as part of a routine eye examination. There is some evidence that gonioscopy is not performed frequently enough, even in subjects diagnosed with glaucoma.[41]

By far the largest, and least well defined, group of eyes for which preventive laser treatment is considered, is those eyes with PACS, in which neither of the above two conditions exists and the angle is diagnosed as anatomically narrow or thought to be occludable. We recommend that clinicians attempt to strictly determine whether or not the iris is actually touching the trabecular meshwork. A positive finding provides unequivocal evidence of an abnormal anatomic condition with a potential for TM damage from continued friction with the iris, and irreversible closure if PAS form. This provides clearer indication for treatment. The diagnosis of appositional angle closure relies on correctly performed and interpreted gonioscopy. Imaging instruments such as ultrasound biomicroscopy or anterior segment OCT can provide objective and quantitative assessment of angle anatomy, but do not distinguish appositional from synechial closure and are expensive and consequently not widely available.

Surgical treatment

If despite LPI/ALPI and medical therapy, there is progression from PAC to PACG, or if there is progression of glaucomatous optic neuropathy in PACG,

then surgical therapy, either trabeculectomy alone or phacoemulsification combined with trabeculectomy or goniosynechialysis, is indicated.

The role of the lens in angle closure

The size and position of the lens play a major role in the pathogenesis of PACG.[42–44] With aging, there is an increase in the thickness of the lens and a more anterior lens position.[45] In hyperopic eyes with small anterior segments, this is likely to be accentuated and the result is overcrowding of the angle, a greater predisposition to pupillary block and progression of PAS.[46,47] This perhaps could explain the progressive course of AC seen in certain eyes even after a successful LPI.

Studies on lens extraction for AAC, PAC and PACG

All currently available forms of cataract extraction have been reported to lower IOP in PACG.[48–52] Lens removal relieves pupillary block, reduces iris crowding in the angle and creeping closure by deepening the anterior chamber and widening the angle recess. In addition, it may improve aqueous outflow, lower the IOP and reduce the likelihood of progressive angle closure and chronic rise in IOP.[52] This is especially true in certain instances where the lens plays a role in development of PAC. Lens removal however does not open synechially closed portions of the angle. This requires goniosynechialysis.

A recently published prospective, randomized controlled trial indicated that early phacoemulsification is more effective in preventing an IOP rise than LPI in patients after successful medical relief of AAC.[5] The mean IOP for the phacoemulsification group (12.6 ± 1.9 mmHg) was consistently lower than that of the LPI group (15.0 ± 3.4 mmHg, $P = 0.009$). The mean Shaffer grading for the phacoemulsification group (2.10 ± 0.76) was consistently greater than that of the LPI group (0.73 ± 0.64, $P < 0.0001$). High presenting IOP of > 55 mmHg was an added risk factor for subsequent elevated IOP. For patients with coexisting cataract and presenting IOP of > 55 mmHg, the authors felt that early phacoemulsification should be considered as a definitive treatment to prevent later high IOP.

Lens extraction may be considered in cases of PACG with visually significant cataract and

1. Mild degree of angle closure;
2. Mild to moderate glaucomatous damage;
3. IOP adequately controlled with first line medications.

While any mode of cataract surgery is feasible in eyes with PACG, phacoemulsification has certain distinctive advantages in such eyes, namely

1. The wound is self-sealing and therefore there is better maintenance of the anterior chamber throughout the procedure with less chances of iris prolapse into the wound intraoperatively;
2. Catastrophic complications like suprachoroidal hemorrhage are minimal;
3. If a clear corneal or a sectoral scleral tunnel surgery is performed, it leaves behind enough unscarred conjunctiva for future glaucoma filtration surgery, should a need arise;
4. It has been postulated that during phacoemulsification, the irrigating fluid flushes out the cellular debris from the trabecular meshwork, making it more pliant to aqueous outflow.[53] An IOP-lowering stress response in the trabecular cells due to the release of certain leucotrienes (IL–1) during phacoemulsification by the ultrasonic vibrations has been reported to enhance aqueous outflow and reduce IOP.[54]

Combined lens extraction with trabeculectomy

In patients with PACG and coexistent cataract, surgical treatment for glaucoma is combined with lens extraction and IOL implantation. It is advocated when a patient has moderate to advanced glaucomatous damage and is on multiple or maximum medications. This approach has several advantages:

1. Since the removal of lens is associated with deepening of anterior chamber and long–term decrease in IOP[53], the combined procedure should have a more profound reduction in IOP when compared to trabeculectomy alone;
2. Removal of the cataract improves visual acuity;
3. When trabeculectomy is combined with lens extraction, the replacement of the crystalline lens is with a much thinner IOL. Therefore, postoperative problems of shallow anterior chamber, forward movement of the iris–lens diaphragm and eventual PAS formation and its sequelae are reduced;
4. Any lenticular component responsible for development of PACG is also eliminated.

This procedure prevents IOP spikes in the immediate postoperative period. The combined procedure exposes the patient to a single surgical experience, saving on cost. It is, therefore, suggested that the lens be removed at the time of trabeculectomy, even with a moderate cataract in eyes with recalcitrant ACG.

However, there is limited data on the outcome of such surgery for PACG. A retrospective study from Singapore showed that combined phacoemulsification with posterior chamber IOL implantation and trabeculectomy is associated with good IOP control and visual outcome in patients with PACG. There were no intraoperative complications in this series and the incidence of postoperative complications was also low.[55] Another study found that the complication rates of phacotrabeculectomy were similar in PACG and OAG.[56]

Goniosynechialysis

Goniosynechialysis (GSL) is a surgical technique performed to mechanically reopen areas of angle closed with PAS, so that aqueous can have renewed access to the trabecular meshwork. It can be performed alone or combined with other surgical procedures, such as phacoemulsification. It requires direct intraoperative visualization of the angle after constricting the pupil and deepening of anterior chamber with a viscoelastic agent. GSL involves separating the PAS from the angle wall with a spatula[57] or with forceps to grasp the iris adjacent to the PAS. It is recommended in eyes with minimal to moderate degree of glaucomatous damage and not in eyes with advanced glaucoma with risk of wipe-out. ALPI can be used postoperatively to further flatten the peripheral iris and prevent synechial attachment.[58]

There is limited evidence regarding the effectiveness of GSL in the management of PACG.[59] The procedure is technically difficult and fraught with potential complications. The exact duration of synechial closure within which GSL is successful is still not precisely known. Campbell[57] suggested that the procedure can be successful when the PAS have been present for six months or less. The mere separation of the PAS alone does not obviate or correct all the pathological changes. In an angle that is open following surgical or laser procedures, trabecular dysfunction is sometimes irreversible. There are no clinical studies evaluating recurrence of PAS following GSL.

Goniosynechialysis with cataract extraction

Phacoemulsification combined with GSL can have a successful outcome.[60] Lens removal alone only deepens the peripheral anterior chamber, without actually opening the synechially closed segments of the angle. GSL opens the angle and allows access of aqueous to the meshwork. Therefore, combining GSL with lens extraction has, theoretically, the advantages of noticeable visual improvement after surgery, combined with IOP-lowering effect of these two procedures. However, PAS may form again after the procedure, sometimes accentuated by inflammation or by mere progression of the pathological process.

Topics for future research/further attention

- What is an ‘early’ versus a ‘later’ stage in PAC/PACG?
- What are the criteria for ‘effective’ treatment?
- What morbidity are we attempting to prevent – *i.e.*, what level of damage or disease?

References

1. American Academy of Ophthalmology. Primary Angle-closure, Preferred Practice Pattern. San Francisco: American Academy of Ophthalmology 2005; Available at: www.aao.org/ppp.
2. Ritch R. Argon laser treatment for medically unresponsive attacks of angle-closure glaucoma. Am J Ophthalmol 1982; 94: 197.
3. Thomas R, Sekhar GC, Parikh R. Primary angle closure glaucoma: a developing world perspective. Clin Experiment Ophthalmol 2007; 35: 374-378.
4. Lam DS, Tham CC, Lai JS, Leung D. Current approaches to the management of acute primary angle closure. Curr Opin Ophthalmol 2007; 18: 146-151.
5. Lam DSC, Leung DY, Tham CCY, *et al.* Randomized trial of early phacoemulsification versus peripheral iridotomy to prevent intraocular pressure rise after acute primary angle closure. Ophthalmology 2007; Dec 26 (Epub ahead of print).
6. Lai JSM, Tham CCY, Chua JKH, *et al.* Laser peripheral iridoplasty as initial treatment of acute attack of primary angle-closure: A long-term follow-up study. J Glaucoma 2002; 11: 484-487.
7. Aung T, Ang LP, Chan SP, Chew PTK. Acute primary angle-closure: Long-term intraocular pressure outcome in Asian eyes. Am J Ophthalmol 2001; 131: 7-12.
8. AGIS Investigators. 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130: 429-440.
9. Kumar RS, Baskaran M, Chew PT, *et al.* Prevalence of plateau iris in primary angle closure suspects an ultrasound biomicroscopy study. Ophthalmology 2008; 115: 430-434.
10. Foster PJ, Gazzard GA, Garway-Heath T, R. R. Pattern of trabecular surface pigment deposition in primary angle closure. Arch Ophthalmol 2006; 124: 1062.
11. Bain W. The fellow eye in acute closed angle glaucoma. Br J Ophthalmol 1957; 41: 193.
12. Foster PJ, Oen FTS, Machin D, *et al.* The prevalence of glaucoma in Chinese residents of Singapore. Arch Ophthalmol 2000; 118: 1105-1111.
13. Wang N, Wu H, Fan Z. Primary angle closure glaucoma in Chinese and Western populations. Chin Med J 2002; 115: 1706-1715.
14. Jacob, A., R. T, Braganza A, *et al.* Prevalence of primary glaucomas in an urban South Indian population. Indian J Ophthalmol 1998; 46: 81-86.
15. Foster PJ, Baasanhu J, Alsbirk PH, *et al.* Glaucoma in Mongolia. A population-based survey in Hövsgöl Province, Northern Mongolia. Arch Ophthalmol 1996; 114: 1235-1241.
16. Lowe RF. Acute angle-closure glaucoma – the second eye: and analysis of 200 cases. Br J Ophthalmol 1962; 46: 641.
17. Douglas WHG, Strachan IM. Surgical safety of prophylactic peripheral iridectomy. Br J Ophthalmol 1967; 51: 459.
18. Lowe RF. Primary angle-closure glaucoma: A review 5 years after bilateral surgery. Br J Ophthalmol 1973; 57: 457-463.
19. Ghoshal TK, Blaxter PL. Results of peripheral iridectomy in closed-angle glaucoma. Br J Ophthalmol 1969; 53: 110-115.
20. Espana EM, Ioannidis A, Tello C, *et al.* Urrets-Zavalia syndrome as a complication of argon laser peripheral iridoplasty. Br J Ophthalmol 2007; 91: 427-429.
21. Spaeth GL, Idowu O, Seligsohn A, *et al.* The effects of iridotomy size and position on symptoms following laser peripheral iridotomy. J Glaucoma 2005; 14: 364-367.
22. Dhawahir-Scala FE, Clark D. Neodymium:YAG laser peripheral iridotomy: cause of a visually incapacitating cataract? Ophthalmic Surg Lasers Imaging 2006; 37: 330-332.
23. Lim LS, Husain R, Gazzard G, *et al.* Cataract progression after prophylactic laser peripheral iridotomy. Potential implications for the prevention of glaucoma blindness. Ophthalmology 2005; 112: 1355-1359.
24. Vijaya L, George R, Arvind H, *et al.* Prevalence of Primary Angle-Closure Disease in an Urban South Indian Population and Comparison with a Rural Population The Chennai Glaucoma Study. Ophthalmology 2008; 115: 655-660.

25. Wilensky JT, Kaufman PL, Frohlichstein D, *et al.* Follow-up of angle-closure glaucoma suspects. Am J Ophthalmol 1993; 115: 338-346.
26. Thomas R, George R, Parikh R, *et al.* Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. Br J Ophthalmol 2003; 87: 450-454.
27. Thomas R, Parish R, Muliyil J, Kumar RS. Five-year risk of progression of primary angle closure to primary angle-closure glaucoma: a population-based study. Acta Ophthalmol Scand 2003; 81: 480-485.
28. Hayashi K, Hayashi H, Nakao F, Hayashi F. Changes in anterior chamber angle width and depth after intraocular lens implantation in eyes with glaucoma. Ophthalmology 2000; 107: 698-703.
29. Jin JC, Anderson DR. The effect of iridotomy on iris contour. Am J Ophthalmol 1990; 110: 260-263.
30. Gazzard G, Friedman DS, Devereux JG, Chew P, Seah SKL. A prospective ultrasound biomicroscopy evaluation of changes in anterior segment morphology after laser iridotomy in Asian eyes. Ophthalmology 2003; 110: 630-638.
31. Nonaka A, Kondo T, Kikuchi M, *et al.* Angle widening and alteration of ciliary process configuration after cataract surgery for primary angle closure. Ophthalmology 2006; 113: 437-441.
32. Tran HV, Ritch R, Liebmann JM. Iridociliary apposition in plateau iris syndrome persists after cataract extraction. Am J Ophthalmol 2003; 135: 40-44.
33. Ritch R, Liebmann JM, Tello C. A construct for understanding angle-closure glaucoma: the role of ultrasound biomicroscopy. Ophthalmol Clin N Amer 1995; 8: 281-293.
34. He M, Friedman DS, Ge J, *et al.* Laser peripheral iridotomy in eyes with narrow drainage angles: ultrasound biomicroscopy outcomes. The Liwan Eye Study. Ophthalmology 2007; 114: 1513-1519.
35. Polikoff LA, Chanis RA, Toor A, *et al.* The effect of laser iridotomy on the anterior segment anatomy of patients with plateau iris configuration. J Glaucoma 2005; 14: 109-113.
36. Ritch R, Tham CCY, Lam DSC. Argon laser peripheral iridoplasty (ALPI) – Update 2007. Surv Ophthalmol 2007; 52: 279-88.
37. Ang LP, Aung T, Chew PT. Acute primary angle-closure in an Asian population: long-term outcome of the fellow eye after prophylactic laser peripheral iridotomy. Ophthalmology 2000; 107: 2092-2096.
38. Ritch R, Tham CCY, Lam DSC. Long-term success of argon laser peripheral iridoplasty in the management of plateau iris syndrome. Ophthalmology 2004; 111: 104-108.
39. Rosman M, Aung T, Ang LPK, Chew PTK, Liebmann JM, Ritch R. Chronic angle-closure with glaucomatous damage: Long-term clinical course in a North American population and comparison with an Asian population. Ophthalmology 2002; 109: 2227-2231.
40. Gieser D, Wilensky J. Laser iridectomy in the management of chronic angle-closure glaucoma. Am J Ophthalmol 1984; 98: 446.
41. Coleman AL, Yu F, Evans SJ. Use of gonioscopy in medicare beneficiaries before glaucoma surgery. J Glaucoma 2006; 15: 486-493.
42. Shields MD, Ritch R. Classifications and mechanisms of the glaucomas. In: Ritch R, Shields MB (Eds.) The Secondary Glaucomas. St Louis: CV Mosby, 1982.
43. See JL, Chew PT. Glaucoma in Singapore. J Glaucoma 2004; 13: 417–420.
44. Okabe T, Tomita G, Sugiyama K, Taniguchi T. An epidemiological study on the prevalence of the narrow chamber angle in Japanese. J Jpn Ophthalmol Soc 1991; 95: 279-287.
45. Lai JSM, Liu DT, Tham CCY, Lam DSC. Epidemiology of acute primary angle-closure glaucoma in the Hong Kong Chinese population: prospective study. Hong Kong Med J 2001; 7: 118-123.
46. Dandona L, Dandona R, Mandal P, *et al.* Angle-closure glaucoma in an Urban population in southern India: The Andhra Pradesh eye disease study. Ophthalmology 2000; 107: 1710-1716.

47. Chew PTK, Aung T. Primary angle-closure glaucoma in Asia. J Glaucoma 2001; 10(Suppl 1): S7-S8.
48. Seah SKL, Foster PJ, Chew PTK, *et al*. Incidence of acute primary angle-closure glaucoma in Singapore. An island-wide survey. Arch Ophthalmol 1997; 115: 1436-1440.
49. Ritch R, Lowe RF. Angle-closure glaucoma: epidemiology and mechanisms, 2d ed. In: Ritch R, Shields MB, Krupin T (Eds.) The Glaucomas. St Louis: CV Mosby Co, 1996, pp. 801-819.
50. Ritch R, Lowe RF. Angle-closure glaucoma: clinical types, 2d ed. In: Ritch R, Shields MB, Krupin T (Eds.) The Glaucomas. St Louis: CV Mosby Co, 1996, pp. 823-840.
51. Hung PT, Chou LH. Provocation and mechanism of angle-closure glaucoma after iridectomy. Arch Ophthalmol 1979; 97: 1862-1864.
52. Lowe RF. Anterior lens displacement with age. Br J Ophthalmol 1970; 54: 117-121.
53. Salman HF, Swanevelder SA, Donald MA. The dimensions of eyes with chronic angle closure glaucoma. J Glaucoma 1994; 3: 237
54. Ritch R. Glaucoma secondary to lens intumescence and dislocation. In: Ritch R, Shields MB (Eds.) The Secondary Glaucomas. St Louis: CV Mosby Co, 1982, pp. 131-149.
55. Wishart PK, Atkinson PL. Extracapsular cataract extraction and posteror chamber lens implantation in patients with primary chronic angle-closure glaucoma: Effect on intraocular pressure control. Eye 1989; 3: 706-712.
56. Greve EL. Primary angle closure glaucoma: extracapsular cataract extraction or filtering procedure? Int Ophthalmol 1988; 12: 157-162.
57. Acton J, Salmon JF, Scholtz R. Extracapsular cataract extraction with posterior chamber lens implantation in primary angle closure glaucoma. J Cataract Refract Surg 1997; 23: 930-934.
58. Gunning FP, Greve EL. Lens extraction for uncontrolled angle-closure glaucoma: long-term follow-up. J Cataract Refract Surg 1998; 24: 1347-1356.
59. Meyer MA, Savitt MC, Kopitas E. The effect of phacoemulsification on aqueous outflow facility. Ophthalmology 1997; 104: 1221-1227.
60. Kim DD, Doyle JW, Smith MF. Intraocular pressure reduction following phacoemulsification with posterior chamber intraocular lens implantation in glaucoma patients. Ophthalmic Surg Lasers Imaging 1999; 30: 37-40.

Related references

61. Wang N, Shravan K, Chintala M, Fini E, Schumann JS. Ultrasound Activates the TM ELAM-1/IL-1/NF- B Response: A Potential Mechanism for Intraocular Pressure Reduction after Phacoemulsification. Invest Ophthalmol Vis Sci 2003; 44: 1977-1981.
62. Tow SLC, Aung T, Oen FTS, Seah SKL. Combined phacoemulsification, intraocular lens implantation and Trabeculectomy in Asian patients with chronic angle closure glaucoma. Int Ophthalmol 2001; 24: 283-289.
63. Lai JS, Tham CC, Chan JC, Lam DS. Phacotrabeculectomy in treatment of primary angle-closure glaucoma and primary open-angle glaucoma. Jpn J Ophthalmol 2004; 48: 408-411.
64. Campbell DG, Vela A. Modern goniosynechialysis for the treatment of synechial angle-closure glaucoma. Ophthalmology 1984; 91: 1052-1060.
65. Tanihara H, Nagata M. Argon-laser gonioplasty following goniosynechialysis. Graefes Arch Clin Exp Ophthalmol 1991; 229: 505-507.
66. Weinreb RN, Friedman DS. AIGS Consensus Meeting Statements: Angle-closure and Angle-closure Glaucoma. The Hague, The Netherlands: Kugler Publications 2005.
67. Teekhasaenee C, Ritch R. Combined phacoemulsification and goniosynechialysis for uncontrolled chronic angle-closure glaucoma after acute angle-closure glaucoma. Ophthalmology 1999; 106: 669-675.

David Friedman, Tin Aung and Bob. Ritch

Amish Doshi (consensus scribe)

ARE FACILITIES FOR DIAGNOSIS AND TREATMENT AVAILABLE?

Robert Casson

Co-chairs: Robert Ritch, Jim Standefer

Contributors: Benedictus Ajayi, Yinka Ashaye, Robert Casson, Tanuj Dada, David Friedman, Daniel Grigera, Dennis Lam, Ramanjit Sihota, Celso Tello, Chun Zhang

Consensus points

- There is a need for a systematic assessment of the clinical capacity to identify and treat angle closure (AC).
- Gonioscopy is essential for diagnosis and treatment.
  Comment: Inadequate clinical training and limited use of gonioscopy are major obstacles to successful case finding.

Introduction

The epidemiology of primary angle closure (PAC) and primary angle-closure glaucoma (PACG) suggest that the majority of disease occurs in the developing world. There are many limitations to screening in a population-based fashion in developing countries. Since data on equipment and training are not widely published, this section of the Consensus is largely based on personal experience and reports from local ophthalmologists.

The use of opportunistic screening at clinics is indicated as long as there is the capacity to successfully identify PAC(G). At present, a feasible and sustainable approach to the detection of PAC(G) and/or anatomically narrow angles (ANA) in rural Asia means case-finding in clinics and possibly in some very well-supported cataract outreach programs, and not universal, population-based screening.

It is important to be aware that identification is the beginning and that treatment facilities are necessary to act upon this identification. Based on gonioscopic findings, appropriate surgery, incisional or laser, should be performed. If trabeculectomy is indicated, and the patient comes from a distance, it should be done on the same visit as the diagnosis because follow-up visits are often rare

Glaucoma Screening, pp. pp. 93-98
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

in developing countries where patients have to travel considerable distances to see an ophthalmologist.

Although there are centers in developing areas where proper identification and treatment of AC can and does occur, these are relatively uncommon. There are multiple barriers to successful screening. These can include:

1. Gonioscopy being rarely performed
   Slit lamps not functional outside of major centers
   Limited gonioscopy skills
   Four-mirror lenses not available making gonioscopy more cumbersome
2. Nd:YAG lasers not routinely available
3. Surgical facilities not available in more remote developing country regions

The following information has been assembled from personal anecdote to reflect the situation in some developing countries.

India

A detailed report on problems with training was recently published in the Indian Journal of Ophthalmology.[1] A minority of optometrists and fewer nurses/technicians are trained in gonioscopy, which is not performed routinely even for high risk patients. In many institutions, patients may undergo laser iridotomy based on a shallow anterior chamber detected on penlight examination, while many others with PAC or PACG are medically treated for OAG because gonioscopy has not been performed. Gonioscopic screening and trained ophthalmologists to do this are scarcely available in rural areas.

Unlike the direct ophthalmoscope, the goniolens in not a universal tool of residents and ophthalmologists. Part of the problem is that the standard four-mirror indentation lens costs more than USD $500, making it unaffordable for many. The recent introduction of low-cost indigenous versions may provide a solution. Finally, there is very little practical training on gonioscopy technique and use.

China

Workforce requirements are about two to three ophthalmologists per hospital for 50,000 to 100,000 residents. Different hospitals have different equipment, from flashlights in rural area to ophthalmoscopes, slit-lamps, goniolenses, non-contact tonometry, anterior segment ultrasound or frequency-doubling perimeters in large centers. There are significant differences depending on the public health system, public awareness, equipment budget and doctor training. In rural areas, doctors use flashlights and detect high IOP by finger pressure. Prone testing is often used to make a diagnosis. Patients may be referred to larger hospitals

if feasible. Barriers to screening in China include lack of guidelines, lack of doctors trained in glaucoma, and lack of public awareness.

Mongolia

In 2003, there were no eye surgical facilities outside the capital. One regional center had an operating microscope, but it was not functional at the time. The only lasers (donated by Denmark) were also in the capital. The training facilities are sparse. Good eye care is provided by a private eye hospital which also does offer some training. Supply of basic medication is sporadic. Mongolia relies on overseas visitors for much equipment, consumables, training and consultations regarding difficult cases.

Nigeria and other parts of Africa

Slit-lamps are rare commodities. Where they exist, they often are old, overused and in need of maintenance. Tonometry and gonioscopy are not universally preformed, due to the very large patient load. This is a major militating factor, not only against gonioscopy, but ophthalmological practice and training in general.

Nigeria

There are about 350 ophthalmologists in Nigeria for about 130 million people. Acute angle-closure glaucoma rarely occurs. Olurin found about 20% of chronic glaucoma patients had gonioscopically narrow (Shaffer grade 2) angle.[2] One visiting ophthalmologist recalled seeing about 12 gonioscopically proven cases of AAC in about 20 years. The apparent rarity of AAC may be due to the fact that gonioscopy was rarely performed until about five years ago, when this skill became routinely tested during Residency Examinations of the National Postgraduate Medical College of Nigeria. Gonioscopy is still not widely practiced for several reasons:

1. Goniolenses are not available in every eye clinic managing glaucoma;
2. Functioning slit-lamps are rarely available outside the teaching centers;
3. Where slit-lamps are available, the ratio of users to the slit-lamp could be as high as four to one, creating a disincentive to its usage;
4. There is a high frequency of power failures;
5. The very large volumes of patients that need to be seen require extremely brief consultations. In this context, even an available slit lamp may be seen as slowing down patient flow.
6. Although all ophthalmologists in the country receive gonioscopic training, as few as 20% of ophthalmologists may actually perform it because of lack of

practice or for the reasons mentioned above. Outside the teaching hospitals, the practice of gonioscopy may be less than 10% in other government hospitals. It would be pertinent to conduct an assessment of the use of gonioscopy in the management of glaucoma in Nigeria.

The most pressing problems that stand in the way of adequate detection of PAC(G) for the majority of the population are:

1. Awareness – this has been improved with the publicity of the last World Glaucoma Day. The publicity should be sustained.
2. Lack of adequate numbers of ophthalmologists; inadequate infrastructure such as basic slit-lamp, gonioscope, electricity and appreciation of the importance of gonioscopy by ophthalmologists.

Myanmar

In Myanmar, resources for clinic-based detection of AC are poor or non-existent. Functioning slit lamps are generally only present in major centers. There are almost no gonioscopy lenses in regular use. Nd:YAG lasers are present in major centers (Yangon and Mandalay), but not often used. In contrast, glaucoma surgery rates (principally iridectomy) are very high in some regions.

The Meiktila Eye Study provides some population-based information about the prevalence of PACG and its impact on vision in central Myanmar.[3,4] The prevalence estimate of presenting visual impairment (best eye < 6/18) was 40.4% (95% CI, 36.1-44.7) and of presenting blindness (best eye < 3/60) was 8.1% (95% CI, 6.5-9.9). The age-adjusted prevalence of visual impairment is extremely high compared to other studies. Glaucoma was the cause of 17% of the blindness (39/230) in at least one eye. PACG was the principal form of blinding glaucoma, accounting for 84% of all glaucoma blindness: PACG associated with AAC was the cause in 52% of these eyes and asymptomatic PACG in 32%. Eight participants were bilaterally blind due to AAC associated glaucoma. The overall prevalence of PACG was 2.5% (95% CI 1.5-3.5) and of OAG was 2.0% (95% CI 0.9-3.1). The prevalence of primary angle-glaucoma suspects (PACS) in at least one eye was 5.7% (95% CI 4.72 to 6.62); prevalence increased with age and PACS was more common in women ($p < 0.001$). The prevalence of PAC in at least one eye was 1.50% (95% CI 1.47 to 1.53).

An overview from an ophthalmologist who has spent time in many developing countries

For the past 15 years I have conducted two- to three-week glaucoma workshops in developing countries worldwide. I have done this over 50 times in about 40 training centers in 29 developing countries. I ask for five ophthalmologists (who have completed an ophthalmology residency) from five different training centers

in the host country or from surrounding countries, if necessary. I use the 'trainer of trainers' principle. These five, the core group, are with me about ten hours a day for the duration of the workshop and are expected to return to their home institutions and teach others. The most important part is clinical (I emphasize gonioscopy using a four-mirror gonioprism, which I give to each as a gift) but I also teach trabeculectomy with 5-FU and present about 20 hours of didactic lectures. These ophthalmologists are intelligent, motivated and conscientious. Often neither they nor their regular teachers have had the advantage of good training. A significant handicap is the custom of didactic teaching where questions are not allowed. There is little teaching of either cognitive function nor how to put data together to arrive at a conclusion. Both of these skills would facilitate proper diagnosis and management. The teaching of clinical diagnosis and treatment using an algorithmic approach is essential for the foundation of what is to come.

The number of ophthalmologists in a region does not always correlate with the ability to screen. The designation 'ophthalmologist' varies widely in developing countries. Many are trained at a level of a public health nurse (or less) and others have had five years of training in national ophthalmology centers. The relatively well-trained ophthalmologists practicing comprehensive ophthalmology rarely perform gonioscopy. Iridotomies/iridectomies, when performed, are often based on the finding of shallow anterior chambers with the penlight or slitlamp. Gonioscopy depends on a satisfactory slitlamp. The state of equipment varies widely. When present, it is often in need of repair and shared by many users.

Worldwide, ophthalmologists tend to practice in the large cities. This is especially true in the developing countries. Ophthalmologists, if properly trained, can perform opportunistic screening. However, there are very intelligent technicians, optometrists, nurses, and others who could be trained to screen. In fact, training of ophthalmologists in the developing countries usually starts from scratch, including anatomy and physiology. Just as many selected non-ophthalmologists can be trained in eye procedures; the same would apply to gonioscopy.

Topics for future research/further attention

- There is a need for a systematic assessment of the clinical capacity and skills to identify and treat angle closure in developing countries to determine the training needs.
- Systematic training and facility maintenance.
- Efforts are needed to improve the quality of clinical examination in developing countries, particularly with four-mirror indentation gonioscopy.
- Alternative approaches to screening (including using newer technologies or training non-ophthalmologists in gonioscopy) should be assessed.
- It is desirable to attempt to continue gathering data on the following subjects until broad information is available for countries worldwide.
  1) The number of doctors nationally;

2) The number of ophthalmologists nationally;
3) The number of glaucoma specialists nationally;
4) The number of glaucoma fellowship places per year – domestic (overseas if part of structured training);
5) Glaucoma medications in various urban and rural settings;
6) Laser units for LPI/trabeculoplasty/ALPI.

- Awareness –World Glaucoma Day publicity should be sustained.
- Lack of adequate numbers of ophthalmologists; inadequate infrastructure such as basic slit-lamp, gonioscope, electricity and appreciation of the importance of gonioscopy by ophthalmologists.
- The teaching of clinical diagnosis and treatment using an algorithmic approach is essential.

References

1. Thomas R, Dogra M. An evaluation of medical college departments of ophthalmology in India and change following provision of modern instrumentation and training. Indian J Ophthalmol 2008; 56: 9-16.
2. Olurin O. Anterior chamber depths of Nigerians. Ann Ophthalmol 1977; 9: 315-26.
3. Casson RJ, Newland HS, Muecke J, *et al.* Prevalence and causes of visual impairment in rural Myanmar: the Meiktila Eye Study. Ophthalmology 2007; 114: 2302-2308.
4. Casson RJ, Newland HS, Muecke J, *et al.* Prevalence of glaucoma in rural Myanmar: the Meiktila Eye Study. Br J Ophthalmol 2007; 91: 710-714.

Michael Kass

IS THERE AN APPROPRIATE, ACCEPTABLE, AND REASONABLY ACCURATE SCREENING TEST?

Winnie Nolan

Co-chairs: Tin Aung, Winnie Nolan

Contributors: Nathan Congdon, Ronnie George, Daniel Grigera, Kenji Kashiwagi, George Lambrou, Christopher Leung, Harry Quigley, G.C. Sekhar, John Thygesen, Gerhard Zinser

Consensus points

- There is evidence that limbal anterior chamber depth (LCD) may be an appropriate screening test for angle closure.
  Comment: Using a LCD of 25% corneal thickness as a cut-off all those cases falling below this level would require gonioscopy. Approximately 4% of occludable angles may be missed by this method.
  Comment: More research is required concerning alternative screening tests.
  Comment: A screening test should not be used as a substitute for definitive diagnosis.
- Clinic-based case-detection should target established primary angle closure (PAC) and primary angle closure glaucoma (PACG) as blindness can still be prevented when interventions are implemented at these stages.
- Comment: The evidence supporting early detection and prophylactic treatment of primary angle closure suspects (PACS) is limited at present and cannot be justified where prevalence of PACS is high.
- Gonioscopy is the current gold standard of angle examination and is the appropriate test for diagnosing angle closure.
  Comment: Gonioscopy alone may not be suitable as a screening test.
  Comment: Gonioscopy combined with optic disc examination and intraocular pressure measurement may enable optimum detection of PAC, PACG and open angle glaucoma (POAG) in a clinic setting.
- For accuracy of clinic-based case detection of PAC/G improve, there needs to be a significant increase in the level and use of gonioscopy and disc examination training for ophthalmologists.

Glaucoma Screening, pp. pp. 99-109
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

Introduction

The requirements of a test suitable for use in a screening program were published by Wilson and Jungner[1] for the World Health Organisation (WHO) in 1968. More recently, these criteria were modified and presented in the first report of the UK National Screening Committee.[2] The criteria are listed below.

1. The test should have acceptable validity (sensitivity and specificity);
2. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed;
3. The test should be reliable, *i.e.*, variation between instruments and observers should be minimal;
4. The test should be non-invasive, safe and acceptable to the population being screened. This is important for maximum uptake of a screening program by the population. Any risk to which the subject is being put by the test should be outweighed by the benefits
5. The test should be simple and inexpensive with the capability of being performed by trained non-medical personnel with robust equipment;
6. There must be an agreed policy on the management and further diagnostic investigation of test positive cases.

Definitions

Sensitivity and specificity (validity)

The sensitivity and specificity of a screening test are parameters by which the performance of a test in identifying subjects with and without the disease can be quantified. When calculating these parameters the test being evaluated should be compared with the reference standard diagnostic test for the presence of a disease or risk factor. The sensitivity is the proportion of people with the disease that the test correctly identifies. The specificity is the proportion of disease-free individuals that the test correctly identifies as normal.

Table 1 illustrates the four categories into which individuals subjected to screening are divided. The sensitivity of a test = A/A+C. Specificity = D/B+D.

Table 1. Calculation of sesitivity and specifity of a screening test

	Disease positive	**Disease negative**	**Total**
Test positive	A	B	A+B
Test negative	C	D	C+D
Total	A+C	B+D	A+B+C+D

Sensitivity = A/A+C, Specificity = D/B+D

A graphical representation of the overall performance of a screening test can be constructed by plotting the sensitivity against 1-specificity for a range of cut-off values. This graph is called a receiver operating characteristic (ROC) curve. The area under the curve (AUC) quantifies the overall performance of the test and comparisons between screening tests can be made on comparing the AUC areas plotted on the same graph. The optimum screening test would have an AUC of 1.0 whereas a poor screening test may have an AUC of 0.5.

Positive and negative predictive value

The positive predictive value (PPV) of a screening test is the proportion of individuals testing positive who actually have the disease. Another way of interpreting the PPV is the probability of a test positive subject being a true positive. In reference to table 1 it is calculated as A/A+B. The value of the PPV depends on the sensitivity of the test and the prevalence of the disease in the population. Even when test sensitivity is high, if the prevalence of the disease is low the PPV will also be low. This has particular relevance for population screening.

The negative predictive value (NPV) is the proportion of individuals testing negative on screening who are disease free and is calculated as D/D+C.

At which stage of angle closure process should early detection be aimed?

For the purposes of this document, the different stages of angle closure (AC) are defined according to the ISGEO classification.[3] The aim of any screening program is to detect cases at the pre-symptomatic stage in the natural history and intervene to prevent progression to the stages associated with increased morbidity or mortality. In terms of angle closure, the PACS case is at risk but has not yet developed established disease. The PAC case has established pathology, but no effect on visual function. The PACG case has evidence of structural optic nerve damage which may impair visual function as measured by diagnostic tests including visual field (VF) testing, but the patient may be asymptomatic until the late stages. In advanced PACG the patient may be aware of visual impairment in the form of restricted field of vision or deterioration of visual acuity (VA) (low vision or blindness). The natural history is discussed in more detail in another chapter, but we assume that a proportion of PACS cases will progress to PAC and a proportion of untreated PAC cases will progress to PACG and if left untreated these patients may go blind. The exception to this is acute angle closure (AAC), where a patient may progress from any of the above categories including PACS, to an acute symptomatic stage at which there is a risk of blindness. This does not appear to be the common pattern for PACG in Asia where the chronic form has a greater impact on glaucoma blindness. The stage at which early detection and treatment is targeted has implications for which test or tests are used and has implications for cost effectiveness.

Screening modalities (tests)

The performance of screening tests measured using sensitivity, specificity, PPV) and NPV applies to population-based (universal) and clinic-based (opportunistic) screening. In clinic based case finding the performance of these tests may be different because of the more selected population. It is possible that a higher sensitivity at the expense of lower specificity would be more acceptable for clinic based case detection compared to very high specificity levels required for universal screening.

Gonioscopy

Gonioscopy is the current reference standard for diagnosing AC as it enables visualization of angle. It is most commonly performed using one of the indirect gonioscopy lenses and a slit-lamp. The two types of lenses are the Goldmann type lens with one or two mirrors and the four-mirror lens. The direct Koeppe or Barkan gonioscopy lenses need to be used with magnifying loops or an operating microscope as the patient needs to supine.

Gonioscopic examination is used to estimate the angle width (between trabecular meshwork and peripheral iris) and to look for other signs of angle closure such as pigment or peripheral anterior synechiae (PAS). Goldmann lenses have the advantage of giving a fairly undistorted estimation of angle width but have the disadvantage of requiring a coupling fluid and are less easy to use for indentation. The Sussman and Posner four-mirror lenses do not require a coupling fluid, give a rapid view of the entire angle and can be used for corneal indentation due to having a radius of curvature similar to that of the cornea and a smaller area of contact than the other lenses. But they can inadvertently indent the angle open and distort the view particularly in patients who have difficulty tolerating the lens. Gonioscopy should be performed in dim lighting using a small light beam to avoid constricting the pupil and opening the angle. There are several grading schemes for recording gonioscopy findings of which the most comprehensive and descriptive is the Spaeth system.[4]

One of the limitations of gonioscopy is that it is a subjective examination method. Grading of the angle width is estimated by the observer and is therefore open to a large degree of variability. In addition, the width of the angle may vary according to the position of the pupil, and even a small amount of unintentional manipulation using the contact lenses can inadvertently widen the angle. It can be unpleasant for patients as it requires more than transient contact with the globe.

Due to the time and skill required to perform gonioscopy it is not feasible for population-based screening strategies.

Biometric gonioscopy

In an attempt to measure the angle width more objectively a modified form of gonioscopic examination has been developed by Congdon and Spaeth.[5] This technique involves the use of a specific slit lamp eye piece that has a measuring reticule incorporated into it. Using the reticule and a Goldmann gonioscopy lens, the distance between Schwalbe's line and the apparent iris insertion is measured. The eye piece is calibrated in millimeters but, due to the magnifying effect of the slit lamp and goniolens optics, the measurements are expressed in arbitrary units. Inter-observer agreement for biometric gonioscopy has been reported as good.

Oblique flashlight test

The oblique flashlight (sidelight) test is a simple method of estimating anterior chamber depth (ACD). A pen torch is held at the temporal aspect of the eye parallel to the iris plane and shone towards the nose. Forward curvature of the iris results in a shadow being cast on the nasal iris. The extent of forward curvature, which is related to the depth of the anterior chamber, can be graded according to the amount of nasal iris in the shadow. The problem with this test is the difficulty standardizing it, both in terms of the procedure itself and the interpretation of the result. The pen torch must be held in the correct plane and the area and focus of the light beam should be the same in all cases. Congdon and colleagues reported a sensitivity of 80% and specificity of 69% of oblique flashlight test for the detection of a narrow angle in Taiwan.[6] Recently He and co-workers measured the performance of the standard oblique flashlight test (SOFT) and a slit-lamp simulated flashlight test using a graticule (SSFT) in detecting PACS cases in China.[7] SOFT yielded sensitivity and specificity of 76.3% and 80.7% (AUC = 0.83), respectively, SSFT yielded sensitivity of 84.8% and specificity of 76.7% (AUC = 0.87) and good reproducibility of the test in a sample of patients with occludable angles (180° posterior trabecular meshwork not visible) and equal number of controls.

Limbal anterior chamber depth (LCD)

The technique of using a measurement of peripheral ACD to estimate angle width was initially described by van Herick.[8] Grading of the limbal chamber depth (LCD) requires the optics of a slit lamp. The narrowest, brightest possible vertical beam of light is directed at the temporal limbus with the beam of light perpendicular to the ocular surface, and viewed from the nasal aspect. The peripheral anterior chamber depth at the limbus (corneal endothelium to anterior iris surface) is measured as a percentage fraction of the corneal thickness at that point. Van Herick described five cut-off levels of measurement category; grade 0 for total angle closure, grade 1 = < 1/4, grade 2 = < 1/2 , grade 3 = < 3/4, and grade 4= ≥ full thickness of the peripheral cornea. This grading system of ACD

as a ratio to corneal thickness at the limbus demonstrated good correlation with gonioscopic Shaffer classification of angle width.

A modification of this grading scheme added a number of measurement categories to devise the following system of seven categories; 0%, 5%, 15%, 25%, 40%, 75% and >100%.[9] Using this modified grading scheme, estimated measurements of LCD were directly compared with the 'gold standard' examination of gonioscopy in 1717 Mongolian subjects aged 40 years and older. Sensitivity and specificity parameters for each category limit of LCD were calculated for the detection of occludable angles, PAC and PACG (Table 2). A combination of a van Herick > 1/4 (LCD > 25%) and a negative oblique flashlight test (no shadow) correctly screened out patients with non-occludable angles in a separate study.[10]

LCD has the disadvantage of requiring a slit-lamp. The use of a small hand-held slit-lamp which is portable could overcome this limitation and requires further evaluation.

Central anterior chamber depth by optical pachymetry

Optical pachymetry is a technique where two measuring devices containing a beam splitter are attached to the slit lamp. One of the devices measures the central corneal thickness (CCT). The second measures the axial distance from the corneal epithelium to the anterior lens surface. The true anterior depth is then calculated by subtracting the corneal thickness from the axial ACD.

Alsbirk demonstrated the potential of pachymetry for detecting patients with AC in Greenland. In his population of Eskimos 18% of men and 24% of women with an ACD of less than 2 mm had angle closure.[11]

At a cut-off level of < 2.22 mm optical ACD had a sensitivity of 85% and specificity of 84% for the detection of gonioscopically occludable angles (PACS, PAC and PACG) in Mongolia with a PPV of 28% and a NPV of 98.7%.[12] The sensitivities and specificities for the detection of PAC and PACG only at this level were similar, but the PPV is less due to the lower prevalence of these conditions in the population.

Central anterior chamber depth by ultrasound (biometric ACD)

Central ACD can be measured with the A-mode of the ultrasound (US) biometer. This measurement includes corneal thickness and therefore gives higher readings (approximately 0.5 mm) than those of the ACD measured by the optical method. The performance of this test has been evaluated in rural Taiwan and Mongolia. Sensitivity and specificity for the slit lamp mounted method were 83% and 81% respectively for the detection of occludable angles in Mongolia (See Table 2).[12] The values for the hand held method demonstrated a sensitivity of 86% but a lower specificity of 73% probably due to corneal indentation. Data for Singapore (Table 2) – did not perform as well as in Mongolia.

The role of different mechanisms in the etiology of angle closure in different

Table 2. Comparison of performance of screening tests in previous studies for detecting anatomically narrow angles (PACS, PAC and PACG)

	Alsbirk 1975 [11]	**Congdon *et al.* 1996** [6]	**Devereux *et al.* 2000** [12]	**Devereux et al 2000** [12]	**Devereux *et al.* 2000** [12]	**Foster *et al.*** [9]	**Foster *et al.*** [9]	**Nolan *et al.* 2006** [17]	**Nolan *et al.* 2006** [17]	**Unpublished data courtesy George R**	**Unpublished data courtesy George R**
Location	Greenland	Taiwan	Mongolia	Mongolia	Mongolia	Mongolia	Mongolia	Singapore	Singapore	Chennai South India	Chennai South India
Setting	Community	Community	Community	Community	Community	Population	Population	Population	Population	Population	Population
No. of subjects	1067	562	1717	937	461	1717	1717	1092	1092	7851	1845
Test	Optical ACD	Ultrasound ACD	Optical ACD	Slit-lamp Ultrasound	Hand held Ultrasound	Limbal ACD	Limbal ACD	Ultrasound ACD	Limbal ACD-van Herick grade	Van Herick	Ultrasound ACD
Cut-off ACD	< 2.00 mm	< 2.70 mm	< 2.22 mm	< 2.60 mm	< 2.53 mm	≤ 15 %	≤ 25 %	< 2.53 mm	≤ 15 %	≤ 25%	< 2.7
Sensitivity (%)	86	76.9	85	83	86	83.7	99.2	75.6	83.0	80	78.8
Specificity (%)	88	87.0	84	81	73	85.7	65.5	73.7	88.1	92	77.2
Reference standard	Symptoms and/or tonometry, Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy	Gonioscopy

populations is now better understood due to recent advances in anterior segment imaging.[13,14] This may account for some of the differences in performance of central anterior chamber depth (cACD) as a screening test in different Asian populations.

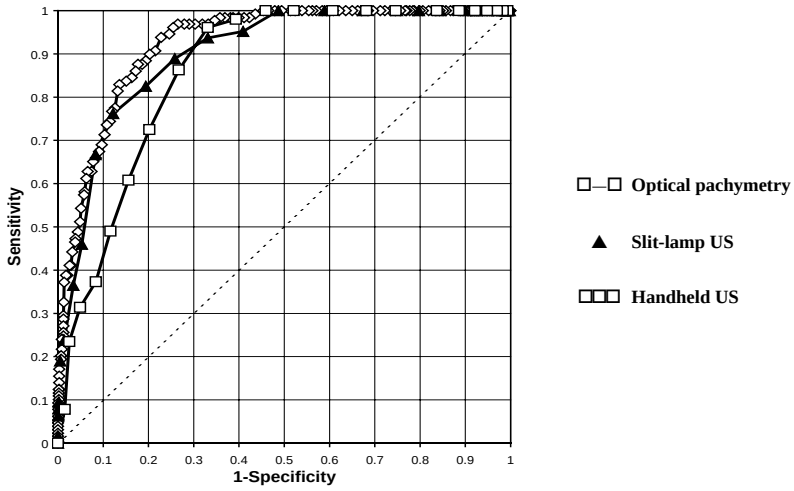

Fig. 1. ROC curve comparing optical pachymetry, slit lamp mounted and hand held ultrasound (US) ACD measurements in the detection of occludable angles

Slit lamp optics are not required for the ultrasound method which gives it an advantage over pachymetry and limbal chamber depth. Figure 1 shows the ROC curves plotted for the performance of ultrasound and pachymetry as screening tests for detection of occludable angles.

New instruments

The following devices that have been recently introduced are non-contact and may be operated by technicians, and may potentially be used for screening for AC.

IOLMaster

The IOLMaster (Carl Zeiss Meditec, Jena, Germany) is a new technique for non-contact ocular biometry of the eye that can be used to measure the axial length of the globe and the central ACD.

Scanning Peripheral Anterior Chamber depth analyzer (SPAC)

The SPAC (Takagi Seiko Co. Ltd, Japan) uses an optical system that allows quantitative measurement of limbal ACD.

Anterior-segment Optical Coherence Tomography (AS-OCT)

Two new anterior segment OCT systems (Visante-OCT, Carl-Zeiss Meditec, Dublin, USA and Slit-Lamp-OCT, Heidelberg Engineering, Heidelberg,Germany) have recently been introduced which use a longer wavelength (1.3 μm), allowing deeper penetration and cross-sectional high-resolution imaging of the anterior chamber and visualization of the angle.

Only one study has evaluated the use of these instruments in screening for AC.[15] In a cross-sectional community-based study, 2,052 phakic subjects aged 50 years and older without ophthalmic complaints were recruited from a community polyclinic in Singapore. All subjects were examined by use of these three instruments and compared to gonioscopy, performed by an ophthalmologist masked to the instruments' findings. The AUC for SPAC using numerical grade ≤ 5 as a cutoff was 0.83 (95% confidence interval (CI): 0.82 to 0.85), with a sensitivity of 90.0% (95% CI: 86.8 to 92.7) and a specificity of 76.6% (95% CI: 74.4 to 78.6); AUC for IOLMaster at a cut-off ACD ≤ 2.87 mm was 0.83 (95% CI: 0.81 to 0.85), sensitivity 87.7% (95% CI: 84.2 to 90.7) and specificity 77.7% (95% CI: 75.6 to 79.7); and AUC of the AS-OCT was 0.76 (95% CI: 0.74 to 0.78), with a sensitivity of 88.4 (95% CI: 84.9 to 91.3) and specificity of 62.9% (95% CI: 60.5 to 65.2). These results suggest that IOLMaster, SPAC and AS-OCT have low specificity when used for screening for narrow angles and this may limit the usefulness of these devices in screening for angle closure. More studies are required to evaluate these instruments for screening for AC.

Detection of angle closure in the clinic setting

The best approach to screening for angle closure has not been the subject of a formal study or modeling. As an alternative to universal or population-based screening, clinic-based case detection may be a more cost-effective method of detecting angle closure in Asia. This has a bearing on which screening or diagnostic test(s) should be employed. Subjects may be attending the clinic for an eye exam and part of the exam could include tests targeted at detecting AC. There are several aspects of delivering eye care in rural Asia which need to be considered in planning either a population-based screening program or a case detection and treatment program for AC:

1. Availability and costs of basic equipment including slit-lamps and lenses. Many clinics do not have slit-lamps at present. In order to run a programme of glaucoma case detection, the minimum requirement for clinics will be the presence of a slit-lamp;
2. Infrastructure with particular respect to stable power supplies for equipment and data storage/analysis. This may rule out more sophisticated tests such as anterior segment OCT;

3. Training of health care workers to perform screening/diagnostic test and interpret the results. This is currently a problem with gonioscopy which worldwide is not performed well (if at all) as part of glaucoma examinations;
4. Facilities and skills for management of test positive cases, *e.g.*, YAG lasers.

These issues are the focus of discussion of other groups for this consensus.

Topics for future research/further attention

- Training of ophthalmologists in gonioscopy and optic disc examination so that the skill levels are present to detect cases of PAC(G). This training needs to be implemented at a junior level and targeted at ophthalmologists in training.
- Evaluation of the performance of surrogate measures of angle width such as LCD and oblique flashlight test in detecting PAC(G) in the population-based/community setting. Combinations of these and other potential screening tests including IOP and optic disc examination need further evaluation.

References

1. Wilson JMG, Jungner G. Principles and Practice of screening for disease. WHO: Geneva, (Public Health Papers No 34) 1968.
2. Health departments of the United Kingdom. First report of the National Screening Committee. Publication of Department of Health 1-4-1998.
3. Foster PJ, Buhrmann R, Quigley HA, *et al.* The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002; 86: 238-242.
4. Spaeth GL. The normal development of the human anterior chamber angle: a new system of descriptive grading. Trans Ophthalmol Soc UK 1971; 91: 709-739.
5. Congdon N, Spaeth GL, Augsburger J, *et al.* A proposed simple method for measurement in the anterior chamber angle: biometric gonioscopy. Ophthalmology 1999; 106: 2161-2167.
6. Congdon NG, Quigley HA, Hung PT, *et al.* Screening techniques for angle-closure glaucoma in rural Taiwan. Acta Ophthalmol Scand 1996; 74: 113-119.
7. He M, Huang W, Friedman DS, *et al.* Slit lamp-simulated oblique flashlight test in detection of narrow angles in Chinese eyes: The Liwan eye study. IOVS 2007; 48: 5459-5463
8. van Herick W, Shaffer RN, Schwartz A. Estimation of the width of the angle of anterior chambers: incidence and significance of the narrow angle. Am J Ophthalmol 1969; 68: 626-629.
9. Foster PJ, Devereux JG, Alsbirk PH, *et al.* Detection of gonioscopically occludable angles and primary angle-closure glaucoma by estimation of limbal chamber depth in Asians. Br J Ophthalmol 2000; 84: 186-192.
10. Thomas R, Thomas George, Andrew B, Jayaprakash Muliyil *et al.* The flash light test and the van Herrick's are poor predictors for occludable angles. Aust N Z J Ophthalmol 1996; 24: 251-256.
11. Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. I. An epidemiologic study in Greenland Eskimos. Acta Ophthalmol 1975; 53: 89-104.
12. Devereux JG, Foster PJ, Baasanhu J, *et al.* Anterior chamber depth measurement as a screen-

ing tool for primary angle closure glaucoma in an East Asian population. Arch Ophthalmol 2000; 118: 257-263.
13. Kumar RS, Baskaran M, Chew PTK, *et al*. Prevalence of Plateau Iris in Primary Angle-closure Suspects An Ultrasound Biomicroscopy Study. Ophthalmology 2008; 115: 430-434.
14. He M, Foster PJ, Johnson GJ *et al.* Angle-closure glaucoma in Asian and European people. Different diseases? Eye 2006; 20: 3-12.
15. Lavanya R, Foster PJ, Sakata LM, *et al.* Screening for narrow angles in the Singapore population: Evaluation of new non-contact screening methods. Ophthalmology (in press).

Related Articles

16. Nolan W, Foster P, Devereux J, *et al.* YAG laser iridotomy treatment for primary angle closure in East Asian eyes. Br J Ophthalmol 2000; 84: 1255-1259.
17. Nolan WP, Aung T, Machin D, *et al.* Detection of narrow angles and established angle-closure in Chinese residents of Singapore. Am J Ophthalmol 2006; 141: 896- 901.

Winnie Nolan presenting

Hans Lemij

Stefano Miglior (rear) and Thierry Zeyen (front)

IS THE NATURAL HISTORY OF THE CONDITION, INCLUDING DEVELOPMENT FROM LATENT TO MANIFEST DISEASE, ADEQUATELY UNDERSTOOD?


Paul Foster

Co-chairs: Paul Foster, Ravi Thomas

Contributors: Tin Aung, Paul Chew, Daniel Grigera, Joao Lopes, Winnie Nolan, Ki Ho Park, Ramanjit Sihota, Tien Wong, Gerhard Zinser

Consensus points

- An episode of symptomatic acute angle closure (AAC) places the unaffected fellow eye at high risk of a similar fate.
- The current best estimate for progression from primary angle closure suspect (PACS) to primary angle closure (PAC) or PAC to primary angle closure glaucoma (PACG) is approximately 20-30% over 5 years.
  Comment: The data on the natural history of PACS/PAC/PACG are sparse and would benefit from confirmation in further studies.
- Asymptomatic angle closure is associated with later presentation and more advanced loss of vision than symptomatic angle closure where facilities for treatment are readily available.

Incidence

Symptomatic AAC

The incidence of angle closure AC has been reported in several countries; Finland,[1] Croatia,[2] the United States,[3] Japan,[4] Israel,[5] Thailand,[4] Singapore,[6,7] and Hong Kong.[8] It is assumed that most of these cases will have been AAC. In Finland, a retrospective review of a national computerized discharge register identified 1,796 cases occurring over a ten year period. Age and gender standardized incidence was 4.7 cases/100,000 population/year. Women accounted for 74% of this number. The Negev region of Israel was the focus of another

Glaucoma Screening, pp. pp. 111-123
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

retrospective case review over a period spanning 12 years. This identified a total of 126 cases of AAC presenting in one practice serving 250,000 inhabitants. Again, women outnumbered men by a ratio of 2:1.[5] Thirty six people treated with a diagnosis of PACG in Olmstead county, Minnesota were identified during the period from January 1980 to December 1992 by retrospective review of the medical diagnostic index of the Mayo Clinic, and data drawn from the Rochester Epidemiology Project. The mean annual incidence (of all AC) was calculated as 8.3/100,000 (95% confidence interval (CI), 5.6 to 11.0) after correction for age and sex. The probability of monocular blindness associated with PACG at the time of diagnosis was 14%. Among patients not blind at diagnosis, the probability of becoming blind in one eye with PACG was 4% after five years.[3]

The highest incidence rates have been reported in East Asia. In Hong Kong, patients with newly presenting AAC, presenting between 1 March 1998 and 29 February 2000 were prospectively registered. Seventy-two cases (72 eyes of 72 patients) of AAC were identified. Crude incidence was 10.4 per 100,000 per year in the population aged 30 years and older. Patients at higher risk of attacks were those aged 70 years or older (age-specific incidence, 58.7/100,000/year) and females, who had a relative risk of 3.8 compared with males (95% CI, 1.7-8.4). Only four (5.6%) patients had a positive family history of AAC. Seventeen (23.6%) patients were noted to have an upper respiratory tract infection before the attack, and 25 (34.7%) patients had taken anti-tussive agents. There was a statistically significant inverse correlation between the monthly attack rate and the monthly rate of influenza ($P = 0.031$).[8]

A prospective, island-wide incidence study, covering all government and private ophthalmological practices in Singapore was carried out over a 1 year period. One hundred eighty-nine people (208 eyes) were seen with AAC for the first time during the one-year period. These new cases represent an incidence of 12.2 per 100,000 per year (95% CI, 10.5-13.9) in those aged 30 years and older. Major risk factors identified were female sex (Relative Risk (RR), 2.4), Chinese ethnic origin (RR, 2.8), and age of 60 years or older (RR, 9.1). Half of those affected were seen three days or more after the onset of symptoms. The incidence among Chinese Singaporeans was 15.5 cases/100,000/year.[6] South and Southeast Asians (Indian and Malay people) living in Singapore have lower rates of AC: A population-wide hospital discharge database in Singapore was used to identify all hospital admissions with a primary discharge diagnosis of PACG (International Classification of Disease CM code: 365.2). Between 1993 and 1997 there were 894 hospital admissions for PACG. The mean annual rate of PACG admissions was 11.1 per 100 000 (95% CI, 10.4, 11.8) among people aged 30 years and over. Again, the annual rate was highest for Chinese (age and sex adjusted rate: 12.2 per 100 000), which was twice that of Malays (6.0 per 100 000) and Indians (6.3 per 100 000).[7] It is a recurring theme in these studies that increasing age and female gender are risk factors for AAC. Importantly, these figures must be interpreted in light of the knowledge that only 25-35% of AC in Asian people causes symptoms.[9–11] Retrospective studies of incidence of symptomatic PAC, drawn from hospital records, are also available for regions

of Thailand and Japan.[4] It remains unclear what proportion of PAC disease is symptomatic in Europeans and Africans. Symptoms appear to have a poor specificity in identifying cases of AC (Ong E, ARVO Abstract 2008).

Incidence of angle-closure disease as a whole

The incidence of PACS has been studied in a high risk Mongolian population. Six hundred and forty-four participants aged 50 years with a central anterior chamber depth (cACD) of < 2.53 mm underwent a full slit lamp (SL) examination. People meeting PACS status on gonioscopy (ISGEO classification) at baseline were excluded from all further analysis. At follow-up after six years, 20.4% (95% CI: 14.8 to 25.7) were diagnosed as having incident PACS. Narrower angles, identified by grading of limbal chamber depth and gonioscopy at baseline, were strongly associated with incident PACS ($p = 0.01$ and $p < 0.01$, respectively). There was weak evidence of an association with change in cACD ($p = 0.05$), and no evidence of an association with age, gender, and baseline cACD for the development of PACS.[12]

Two recent publications from Vellore in southern India using the ISGEO classification give an important insight into the incidence of different grades of AC. Normal subjects and people with anatomically narrow drainage angles were enrolled from a population survey. Five years later, 82 of 118 PACS who could be contacted and 110 randomly selected normals from a population based survey were invited for a follow-up examination. Progression to PAC was based on the development of raised IOP or PAS in PACS. Fifty of the 82 PACS contacted were examined. Eleven people (22%; 95% CI 9.8 to 34.2) developed PAC (seven synechial and four appositional); all were bilateral PACS. Two of 50 people previously diagnosed as PACS were reclassified as normal. One person among the 110 normals progressed to PAC. The relative risk of progression among PACS was 24 (95% CI 3.2 to 182.4). In this small series, there was no significant difference in axial length, ACD, or lens thickness between those who progressed and those who did not. None of the patients developed optic disc or field damage attributable to AC. One subject with PACS was diagnosed subsequently as normotensive glaucoma (NTG).[13] Follow-up of the people with established PAC at the time of the population survey who were advised to undergo laser iridotomy was also carried out five years after the initial survey. In all, 28 of 32 PAC subjects who could be contacted presented for examination. Eight of 28 people examined (28%, 95% CI: 12, 45) had progressed to PACG over five years, two of seven with appositional and six of 21 with synechial closure. One of nine who underwent laser peripheral iridotomy (LPI) progressed compared to seven of 19 who refused LPI. Four of those originally diagnosed with appositional closure developed peripheral anterior synechiae (PAS). One eye of a person previously diagnosed with appositional PAC was reclassified as a PACS. In this small series, there was no significant difference in biometric parameters between those who progressed and those who did not. None developed acute PACG or blindness due to glaucoma.[14]

Wilensky and colleagues enrolled 129 mostly European-derived subjects with 'occludable' angles and cACD (measured by optical pachymetry) less than 2.0 mm in a prospective study over a five-year period at five separate centers. Eight patients (6.2%) developed AAC and 17 (13.2%) developed PAC (either appositional closure or PAS in at least 0.5 clock hours of the superior quadrant) after a median follow-up 2.7 years. Dark room prone provocative testing did not consistently predict who would develop PAC or an acute attack during follow-up. This study in European-derived individuals demonstrates that a combined screening strategy using ACD and gonioscopy had a relatively low positive predictive value for the development of AAC and/or PAC. Furthermore, no comparison group was studied to assess the benefit of prophylactic LPI to this population.[15] Alsbirk examined 75 Greenland Eskimos with shallow cACD and a van Herick score of two or less ten years after a baseline examination. He had performed gonioscopy on 69 of these individuals at baseline. Of the 20 individuals felt to have 'occludable' angles at baseline, seven (35%) developed PACG, as opposed to four of 49 (8%) felt to be non-occludable. However, of these 11 cases, two were acute attacks, and only one other had PAS associated with elevated eye pressure. The remainder had either intermittent symptoms or synechiae on gonioscopy. Of the 69 individuals felt to be at high risk, three (4.3%) developed optic nerve damage or visual field loss over a ten-year period. This study shows that the ability to predict correctly who with narrow angles is at risk of suffering adverse consequences is poor.[16]

It has been noted that people with asymptomatic PACG often present to hospital with severe to end-stage visual field loss. In contrast, most PACG eyes with previous AAC present with mild or moderate field defects. An asymptomatic disease course is probably a risk factor for blindness.[17]

Evidence from studies of medical intervention

Prophylaxis in the fellow eye

It is widely believed that AAC can be avoided in the vast majority of susceptible eyes by performing laser iridotomy or surgical iridectomy. Cases of plateau iris syndrome may not respond to peripheral iridotomy/iridectomy.[18] Several papers have been published examining the contra-lateral eye in individuals suffering an acute attack.[19,20] Although these publications date back to the time when iridectomies had to be performed surgically, they offer insight into the natural history of the disease and the benefit of LPI. Lowe documented that acute attacks developed in the untreated contra-lateral eyes of 58 of 113 patients (51%). While a third of these occurred in the first year, attacks were still occurring after 15 years in some patients. Of the 64 patients treated contralaterally with surgical iridectomy only one went on to have an attack in the other eye, and there were concerns that the iridectomy was not patent in this individual.

The principle that laser iridotomy is an effective prophylactic measure in fellow eye, applies to Asian patients as well as Caucasians. In Singapore, a study with mean follow-up of 51 months (range, 9-99 months) studied 80 fellow eyes. No cases of AAC developed after prophylactic LPI. Seventy-one fellow eyes (88.8%) were successfully treated with LPI alone without the need for additional glaucoma treatment in the long term. Seven eyes (8.8%) had IOPs of 21 mmHg or less on presentation, but a rise in IOP developed on follow-up despite the presence of a patent LPI. Two fellow eyes (2.5%) had signs of pre-existing PACG at presentation and required further glaucoma treatment even after LPI. There were no significant complications from the procedure in any of the fellow eyes studied. Because a small proportion of fellow eyes did experience a rise in IOP within the first year, despite the presence of a patent LPI, close monitoring is still advised in the follow-up of fellow eyes of patients with AAC.[21] There is good evidence that laser iridotomies are as effective as surgical iridectomies. A recent randomized clinical trial comparing laser iridotomy to surgical iridectomy in the fellow eye of patients suffering an acute attack found no difference in outcome.[22]

Treatment of eyes following acute episodes

Theoretically, LPI should prevent the onset of PACG as well as AAC, although once trabecular damage is established, LPI may be insufficient to control intraocular pressure. The outcome after laser iridotomy in affected eyes of patients included in the Singapore study outlined above[21] was also examined (111 eyes of 96 consecutive patients). The mean presenting IOP was 53 mmHg (range, 28 to 80 mmHg). Only 46 eyes (41.8%) were successfully treated with LPI alone in the long term. Sixty-four eyes (58.1%) developed an increase in IOP (requiring treatment) on follow-up, of which 49 eyes developed an increase in IOP within the first six months after acute PAC. Thirty-six eyes (32.7%) eventually underwent trabeculectomy because of uncontrolled IOP despite laser and medical therapy.[23]

Management of chronic, asymptomatic disease

A detailed study of 140 eyes of 104 people with PAC and PACG in Japan treated by argon laser iridotomy found 67% of eyes (73/109) had a cup:disc ratio (CDR) of ≥ 0.7 prior to treatment. The CDR enlarged in 28% (31) and remained unchanged in 59% (64); mean follow-up 1.7 and 2.7 years (in two groups). Visual Field (VF) defects were minimal or absent in 81% (96/118), moderate in 16% (19/118) and advanced in 3% (3/118). The defects progressed in only three patients (all with initially mild changes). IOP < 21 mm Hg (with or without medication) after PI was achieved in 94%. IOP control was more likely to be successful if there were < 180° PAS. There was no significant change in the amount of PAS during the follow-up period. Loss of visual acuity (VA) by more than three lines occurred in 19%. It was stated that this was

due to progression of lens opacities, although this was not quantified.[24] The use of 180 degrees of PAS as a guide to the likely success or failure of PI has been supported by other studies. Salmon identified a triad of features linked with failure of laser iridotomy to control the condition, and that were linked with the eventual need to perform a trabeculectomy.[25] A subsequent study in Mongolia supported these findings.[26] If we accept that the literature suggests an 80% success of LPI in these cases, the posterior probability of success after these findings is 90%.[27]

Table 1. Long-term IOP control* in PAC by LPI and topical medication

Location	Eyes (Patients)	Acute/ Fellow eyes/ Chronic	Successful without Rx *	Successful with Rx *	Follow-up	Design
Israel	53 (34)	20/15/18	15/15/0	16/15/?	2 years	Case series
Baltimore (US)	98 (54)	28/20/50	50 total	21/20/46	Mean: 4.4 years	Case series
Chicago (US)	19 (16)	0/0/19	0	12	Mean: 1.3 years	Case series
South Africa	78 (52)	0/0/78	7	40	Mean: 1.8 years	Case series
Scotland	27 (27)	27/0/0	19	23	3 years	Prospective RCT

* Success defined as IOP ≤ 21 mmHg
RCT: Randomised, controlled trial
Source data: Israel,[28] Baltimore,[29] Chicago,[30] South Africa,[25] Scotland.[22]

Lens extraction

There is a growing body of literature showing that lens extraction is a highly effective method of controlling AC disease. Because the position of the lens determines the iris profile, and therefore the angle configuration, lens extraction is a logical choice for surgical management of raised IOP in cases of PAC with visual impairment due to cataract. Extracapsular cataract extraction was used in the management of PAC in 21 eyes of 20 patients (two with raised IOP alone, five symptomatic and 14 asymptomatic).[31] In 14 cases, lens extraction was performed in place of filtering surgery, where peripheral iridectomy or previous filtering surgery had failed. The mean IOP was reduced from 31 to 16 mmHg after surgery. Seventy-six percent (16/21) of eyes did not require further medication (follow-up: six to 42 months). It was noted that the IOP was reduced even if there were extensive previous PAS. In six patients with previous failed filtering surgery, lens extraction gave a median IOP reduction of 17.5 mm Hg (range five to 30).

A second study examining the IOP control achieved by cataract extraction in 17 patients (19 eyes – nine symptomatic and ten asymptomatic) found post-operative IOP < 22 mmHg without medication was achieved in 68%. With medication, IOP was < 22 mmHg in 94%. In nine eyes with a CDR ≥ 0.7, median IOP after surgery was 17.5 (range: 14 to 21) mmHg, on a median of 0 medications (0 to

2). The authors of both studies concluded that combined cataract extraction and trabeculectomy may not be necessary in PACG.[32]

Indirect support for the theory that lens extraction is highly effective in controlling AC is given by data from Taiwan. Using eight years of data from the Taiwanese National Health Insurance Research Database (TNHIRD), the authors investigated the relationship between the total number of cataract operations undertaken and admissions for AAC. The 3814 cases of AAC and 503 687 patients who had undergone cataract operations were categorized by age groups (40-49, 50-59, 60-69 and ≥ 70 years) and by gender. Throughout the study period, the admissions for AAC showed a steady decline from 630 cases in 1997 to 351 cases in 2004, while the number of cataract operations revealed a gradual increase from 26 600 in 1997 to 77 924 in 2004. The Spearman rank correlation coefficients showed significant inverse relationships between monthly AAC admission rates and monthly cataract operation rates for the total group ($r = –0.407$, $P < 0.001$), males ($r = –0.330$, $P < 0.001$), females ($r = –0.444$, $P < 0.001$), 40-49 year olds ($r = –0.335$, $P < 0.001$), 50-59 year olds ($r = –0.497$, $P < 0.001$) and 60-69 year olds ($r = –0.417$, $P < 0.001$). No significant inverse relationship was observed for the ≥ 70 age group. It was concluded that a significant inverse relationship between the monthly AAC admission rates and the monthly cataract operation rates existed.[33]

Damage by AC disease to ocular tissues

There have been several descriptions of the pattern of AC and the formation of synechial damage. Phillips gave anecdotal descriptions of his observations in European people.[34] Irido-corneal contact in the superior half of the angle was found in individuals without symptoms. It was stated that closure of the angle progresses to the nasal and temporal sectors as age (and lens size) increases. It was suggested that pathological AC is an evolving process that starts with intermittent, appositional contact which gradually becomes permanent with the formation of synechiae. Several possible explanations were cited for the finding of sectorial variations in angle-width.

1. Sectorial differences in the origin of iris from the ciliary body;
2. Unequal differentiation of sectors of the angle during development;
3. Orientation of the lens;
4. Decentration of the pupil;
5. Uneven flattening of the cornea by the eyelids.

In a later, more thorough study, 20 subjects with PAC were examined. Inclusion criteria were: a vague history of transient blurring of vision; no corneal oedema; IOP greater than 21 mmHg and less than 51 mmHg; disc and field examination being normal or showing early glaucomatous changes; gonioscopic examination showing a partially or completely occluded drainage angle and partial or complete reversal of apposition with instillation of pilocarpine. Of these 20 patients,

19 met inclusion criteria for both eyes, although only one eye of each patient was used in the analysis. In every case, the area of irido-trabcular contact was continuous, and extended for at least three clock hours. The superior area from 11 to 1 o'clock was closed in all cases. The 6 o'clock position was closed in only one person. Areas that remained closed after instillation of pilocarpine hydrochloride (1 or 2%) were said to have goniosynechiae, although dynamic gonioscopy was not used. The proportion of individuals with closure of the angle reduced in all sectors after pilocarpine was introduced.[35]

A similar study in Japan used dynamic gonioscopy to assess the morphology and distribution of PAS in 171 eyes of 101 people with PAC.[36] In this study, the inclusion criteria were a closed or partially closed drainage angle with an IOP > 21 mmHg or a narrow angle in the fellow eye once IOP had been effectively controlled. The eyes were sub-divided into those with signs and symptoms of sudden pressure elevation ('acute'), asymptomatic people with narrow angles and either PAS or IOP > 21 mmHg ('chronic'), and 'fellow eyes'. Indentation gonioscopy was carried out, with areas of PAS graded according to height (posterior, mid- or anterior trabecular meshwork) and width (narrow < 15º, medium 15-30º and broad > 30º). Clock hours 11-12 and 12-1 were termed superior, with 5-6 and 6-7 being inferior. The intervening four 'hour' sectors were termed nasal and temporal. PAS were found in 87% of the 'acute' group, 84% of the 'chronic' group and 51% of the 'fellow eyes'. The classification of PAS width was narrow: 44.7%, medium: 15.6%, broad: 39.7%. Interestingly the morphology of PAS varied with clinical type of PAC. In 'chronic' cases, narrow PAS were most common (53%), whereas 'acute' cases had more broad PAS (74%). This difference was highly significant. Broad PAS were also more common in the fellow eye group (52%). PAS of all types were most common in the superior sector and least common in the inferior sector. Table 2 shows the distribution of height of PAS. No narrow PAS reached Schwalbe's line. Ninety-four percent of broad PAS reached the anterior or mid-trabecular meshwork. In the symptomatic 'acute' cases, there was a correlation between the width of PAS and the duration of symptoms.

Table 2. Height of PAS and symptoms of PAC

	Height of synechiae on the trabecular meshwork		
PAS level	Posterior	Middle	Anterior
Acute	3.4 %	68.7 %	27.9 %
Fellow eyes	15.5 %	80.3 %	4.2 %
Chronic	26.5 %	70.2 %	3.3 %

These data are drawn from publications by Inoue *et al*.[36]

As long ago as 1960, Gorin suggested two possible modes by which closure of angle may occur.[37] Firstly, that there was contact between Schwalbe's line and the peripheral iris. Synechiae then form in an anterior-to-posterior direction. Sec-

ondly, he suggested that peripheral anterior synechiae may form initially in the periphery of the angle. The first suggestion (initial contact between Schwalbe's line and the peripheral iris) has subsequently been verified by ultrasound biomicroscopy.[38] Ritch has subsequently called these two patterns 's' (for closure at Schwalbe's line) and 'b' (from bottom of the angle) types respectively. Inoue *et al*.[36] argue that their data support the case for the second mechanism (posterior-to-anterior development of PAS), although it is not clear how it was possible to determine that high PAS have not developed by adhesion of the peripheral iris to Schwalbe's line. On balance, it seems likely that both mechanisms occur. Pathological studies of primates show that IOP 15 mmHg below ophthalmic artery perfusion pressure is sufficient to cause ischaemic necrosis of the iris. This was associated with formation of a fibrinous clot and fibro-vascular proliferation in the drainage angle. This presumably acts as a foundation for the formation of high, broad PAS.[39]

Corneal damage

Observational studies by Lowe[40] suggested that symptomatic PAC may produce several changes in the cornea, beginning with pressure-related epithelial oedema, followed by folds in Decemet's membrane. Prolonged central oedema with Descemet's folds was thought to occur if the endothelium was damaged. Later changes include vascularization, lipoid infiltration and band-type degeneration. In a quantitative study in China, corneal endothelia of 87 cases of unilateral glaucoma were studied with a specular microscope, with healthy fellow eyes used as controls. The endothelial cell density was found to be decreased in the majority of glaucomatous eyes. The reduction was 13% in eyes with symptomatic PAC (34 cases), by 5% in asymptomatic PAC (23 cases), and by 12% in glaucoma cyclitic syndrome (30 cases). In comparison, the mean fall in endothelial cell densities after filtering operations in 16 eyes was 10%, and 5% after Nd:YAG laser iridotomy.[41]

Lens damage

The characteristic lens change in PAC is the formation of 'glaucomflecken'. These were initially described by Vogt in 1930.[42] There is considerable variation in the formation and extent of these opacities. They form in the anterior subcapsular region. It is believed that they are areas of denatured lens protein, and reflect a reduced ability of the terminal areas of transparent lens fibres to withstand physiological stress. With the passage of time they descend deeper into the lens as more fibres are formed on top. They do not form at the posterior pole of the lens, and are said to be restricted to the sutural areas of the lens. Other lens changes include fibrosis of the lens capsule, cortical opacities and dense nuclear sclerosis.[40]

Uveal and retinal damage

Studies of primates (owl monkeys) suggest that the first permanent lesions to occur with acute elevation of IOP are partial necrosis of the iris stroma and ciliary body, associated with microscopic lesions of the photoreceptors and retinal pigment epithelium around the optic disc and in the retinal periphery. These changes occurred at an IOP 15 mmHg below perfusion pressure. At higher levels of pressure (IOP 5 mmHg below perfusion pressure) damage to the retinal nerve-fibre layer and optic disc was observed, together with more diffuse retinal damage. It was suggested that the more pressure-sensitive nature of uveal tissue may result in ciliary body shut-down, and halt any further pressure rise. The retina and optic nerve have a higher IOP threshold for damage, and hence their function is preserved in many cases of symptomatic IOP rises.[39] AAC may be accompanied by substantial inflammation, and hypopyon formation has been reported.[43] Iridoschisis is also reported to be associated with PAC.[44] Light and transmission electron microscopy show that during an attack of AAC, the anterior border layer of the iris became thickened. Following the symptomatic episode, the iris becomes structurally disrupted and the stromal cells degenerate markedly. In end-stage disease the stromal cells were atrophic.[45]

Disc damage

Sudden rises in IOP to near perfusion pressure are associated with atrophy of retinal, pre- and retro-laminar ganglion cell fibres. Remarkably, the glial cells remain almost completely unaffected. The changes in the retro-laminar portion of the optic nerve are identical to an ascending optic neuropathy. Cavernous optic atrophy was not seen.[39] Changes in optic disc morphology in the first four months after an episode of AAC were studied in 47 Asian subjects with unilateral AAC who were successfully treated with LPI. In AAC eyes from week two to week 16, the mean CDR increased from 0.56 ± 0.05 to 0.59 ± 0.03 ($P < 0.001$), and the mean neuroretinal rim area decreased from 1.74 ± 0.31 mm^2 to 1.59 ± 0.27 mm^2 ($P < 0.001$). Quadrantic and sector analysis showed preferential loss of neuro-retinal rim area at the supero-temporal and infero-temporal areas. There was no significant change in optic disc parameters in the fellow eyes over the study period. The authors concluded that changes in optic disc morphology after AAC were comparable with those seen in OAG and experimental glaucoma models.[46]

Visual field loss

Descriptions of the characteristics of VF loss in PAC are scarce and contradictory (probably as a result of inconsistency in nomenclature). One description of subjects with primary and secondary AC found that most (9/11) subjects with chronic disease had VF loss in a nerve fiber bundle pattern. Conversely, 11/18 subjects who had suffered from AAC had no impairment of the VF. The

remaining 7/18 showed typical nerve-fiber bundle VF loss.[47] Another study of 25 cases of unilateral AAC described a 'significant' field defect in over half this group, usually characterized by constriction of the upper field (not felt to be typically 'glaucomatous' in nature). Ten of these 25 subjects did exhibit a blue-yellow dyschromatopsia.[48] In Japan, a study of 110 subjects with glaucoma arising from acute (42 subjects) or chronic (68 subjects) PAC using Goldmann kinetic perimetry concluded that the pattern of VF loss in PACG was similar to that in OAG.[49] In Singapore, the presenting features were studied retrospectively in 50 patients with PAC. VF loss was more common and severe in patients with chronic disease than in AAC. Field loss in chronic PACG was more severe in eyes with higher IOP. Among 20 symptomatic cases, 15 had a full field, three had a nerve fiber bundle pattern of damage and two had gross field constriction. There were 30 subjects with chronic disease; two had full fields, two had generalized constriction (most marked on nasal side), large nasal sectoral defects were found in five people while gross loss with central or paracentral islands were present in 15. Six people had total field loss.[50] A subsequent Singaporean study drawing data from 234 subjects assessed (129 OAG, 105 PACG) indicated more severe visual loss in subjects with PACG (OAG –13.3 dB; PACG –18.0 dB). In subjects with OAG, the superior hemifield was more severely affected than the inferior. This was less pronounced in subjects with PACG. Following stratification by MD, the difference between hemifields was marked in the mild (-10 dB < or = MD) and moderate (-20 dB < or = MD < –10 dB) subgroups but was not present in the severe (MD < –20 dB) subgroup. Differences between OAG and PACG in retinal sensitivity between the superior and inferior hemifields were detected, independent of severity of damage.[51]

References

1. Teikari J, Raivio I, Nurminen M. Incidence of acute glaucoma in Finland form 1973 to 1982. Graefe's Arch Clin Exp Ophthalmol 1987; 225: 357-360.
2. Ivanisevic M, Erceg M, Smoljanovic A *et al.* The incidence and seasonal variations of acute primary angle-closure glaucoma. Coll Antropol 2002; 26: 41-45.
3. Erie JC, Hodge DO, Gray DT. The Incidence of Primary Angle-Closure Glaucoma in Olmstead County, Minnesota. Arch Ophthalmol 1997; 115: 177-181.
4. Fujita K, Negishi K, Fujiki K, *et al.* Epidemiology of acute angle-closure glaucoma. Report I. Jpn.J Clin Ophthalmol 1996; 37: 625-629.
5. David R, Tessler Z, Yassur Y. Epidemiology of acute angle-closure glaucoma:incidence and seasonal variations. Ophthalmologica 1985; 191: 4-7.
6. Seah SKL, Foster PJ, Chew PT, *et al.* Incidence of Acute primary angle-closure glaucoma in Singapore. An Island-Wide Survey. Arch Ophthalmol 1997; 115: 1436-1440.
7. Wong TY, Foster PJ, Seah SKL, *et al.* Rates of hospital admissions for primary angle closure glaucoma among Chinese, Malays, and Indians in Singapore. Br J Ophthalmol 2000; 84: 990-992.
8. Lai JS, Liu DT, Tham CC, *et al.* Epidemiology of acute primary angle-closure glaucoma in the Hong Kong Chinese population: prospective study. Hong Kong Med J 2001; 7: 118-123.
9. Congdon N, Quigley HA, Hung PT, *et al.* Screening techniques for angle-closure glaucoma in rural Taiwan. Acta Ophthalmol Scand 1996; 74: 113-119.

10. Foster PJ, Baasanhu J, Alsbirk PH, *et al.* Glaucoma in Mongolia- A population-based survey in Hövsgöl Province, Northern Mongolia. Arch Ophthalmol 1996; 114: 1235-1241.
11. Foster PJ, Oen FT, Machin DS, *et al.* The prevalence of glaucoma in Chinese residents of Singapore. A cross-sectional population survey in Tanjong Pagar district. Arch Ophthalmol 2000; 118: 1105-1111.
12. Yip JL, Foster PJ, Gilbert CE, *et al.* Incidence of occludable angles in a high-risk Mongolian population. Br J Ophthalmol 2008; 92: 30-33.
13. Thomas R, George R, Parikh R, *et al.* Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. Br J Ophthalmol 2003; 87: 450-454.
14. Thomas R, Parikh R, Muliyil J, *et al.* Five-year risk of progression of primary angle closure to primary angle closure glaucoma: a population-based study. Acta Ophthalmol Scand 2003; 81: 480-485.
15. Wilensky JT, Kaufman PL, Frohlichstein D, *et al.* Follow-up of angle-closure glaucoma suspects. Am J Ophthalmol 1993; 115: 338-346.
16. Alsbirk PH. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. Int Ophthalmol 1992; 16: 265-272.
17. Ang LP, Aung T, Chua WH, *et al.* Visual field loss from primary angle-closure glaucoma: a comparative study of symptomatic and asymptomatic disease. Ophthalmology 2004; 111: 1636-1640.
18. Wand M, Grant WM, Simmons RJ, *et al.* Plateau iris syndrome. Trans Am Acad Ophthalmol Otol 1977; 83: 122-130.
19. Snow JT. Value of prophylactic peripheral iridectomy on the second eye in angle-closure glaucoma. Transactions of the Ophthalmological Societies of the United Kingdom 1977; 97: 189-191.
20. Lowe RF. Acute angle-closure glaucoma. The second eye: an analysis of 200 cases. Br J Ophthalmol 1962; 46: 641-650.
21. Ang LP, Aung T, Chew PT. Acute primary angle closure in an Asian population: long-term outcome of the fellow eye after prophylactic laser peripheral iridotomy. Ophthalmology 2003; 107: 2092-2096.
22. Fleck BW, Wright E, Fairley EA. A randomised prospective comparison of operative peripheral iridectomy and Nd:YAG laser iridotomy treatment of acute angle closure glaucoma: 3 year visual acuity and intraocular pressure control outcome. Br J Ophthalmol 1997; 81: 884-888.
23. Aung T, Ang LP, Chan SP, *et al.* Acute primary angle-closure: long-term intraocular pressure outcome in Asian eyes. Am J Ophthalmol 2001;131:7-12.24. Yamamoto T, Shirato S, Kitazawa Y. Treatment of primary angle-closure glaucoma by argon laser iridotomy: A long-term follow-up study. Jpn J Ophthalmol 1985; 29: 1-12.
25. Salmon JF. Long-term intraocular pressure control after Nd-YAG laser iridotomy in chronic angle-closure glaucoma. J Glaucoma 1993; 2: 291-296.
26. Nolan WP, Foster PJ, Devereux JG, *et al.* YAG laser iridotomy treatment for primary angle-closure in east Asian eyes. Br J Ophthalmol 2000; 84: 1255-1259.
27. Thomas R, Arun T, Muliyil J, *et al.* Outcome of laser peripheral iridotomy in chronic primary angle closure glaucoma. Ophthalmic Surgery and Lasers 1999; 30: 547-553.
28. Yassur Y, Melamed S, Cohen S, *et al.* Laser iridotomy in closed-angle glaucoma. Arch Ophthalmol 1979; 97: 1920-1921.
29. Robin AL, Pollack IP. Argon Laser Peripheral Iridotomies in the Treatment of Primary Angle-closure Glaucoma. Long-term Follow-up. Arch Ophthalmol 1982; 100: 919-923.
30. Gieser DK, Wilensky JT. Laser iridectomy in the management of chronic angle-closure glaucoma. Am J Ophthalmol 1984; 98: 446-450.
31. Greve EL. Primary angle-closure glaucoma: Extracapsular cataract extraction or filtering procedure? Int Ophthalmol 1988; 12: 157-162.

32. Acton J, Salmon JF, Scholtz R. Extracapsular cataract extraction with posterior chamber lens implantation in primary angle-closure glaucoma. Journal of Cataract & Refractive Surgery 1997; 23: 930-934.
33. Hu CC, Lin HC, Chen CS, *et al.* Reduction in admissions of patients with acute primary angle closure occurring in conjunction with a rise in cataract surgery in Taiwan. Acta Ophthalmol. Scand 2007.
34. Phillips CI. Closed-angle glaucoma. Significance of sectorial variations in angle depth. Br J Ophthalmol 1956; 40: 136-143.
35. Bhargava SK, Leighton DA, Phillips CI. Early angle-closure glaucoma. Distribution of irido-trabecular contact and response to pilocarpine. Arch Ophthalmol 1973; 89: 369-372.
36. Inoue T. [Distribution and morphology of peripheral anterior synechia in primary angle-closure glaucoma]. [Japanese]. Nippon Ganka Gakkai Zasshi – Acta Societatis Ophthalmologicae Japonicae 1993; 97: 78-82.
37. Gorin G. Shortening of the angle of the anterior chamber in angle-closure glaucoma. Am J Ophthalmol 1960; 49: 141-146.
38. Ritch R, Stegman Z, Liebmann J. Mapstone's hypothesis confirmed. Br J Ophthalmol 1995; 79: 300.
39. Anderson DR, Davis EB. Sensitivities of ocular tissues to acute pressure-induced ischaemia. Arch Ophthalmol 1975; 93: 267-274.
40. Lowe RF. Primary acute angle-closure glaucoma damage to cornea and lens. Br J Ophthalmol 1965; 49: 460-465.
41. Zhou WB. [Observations on the corneal endothelium in glaucoma]. [Chinese]. Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology] 1990; 26: 209-212.
42. Vogt A. Klinische Monatsblätter für Augenheilkunde 1930; 586.
43. Au Eong KG, Chua EC, Yip CC, *et al.* Hypopyon – an unusual sign in acute angle-closure glaucoma. Int Ophthalmol 1993; 17: 127-119.
44. Salmon JF, Murray AD. The association of iridoschisis and primary angle-closure glaucoma. Eye 1992; 6: 267-272.
45. Cao JT, Wu L, Liu SY. [Histopathologic and ultrastructural studies of the iris in acute angle-closure glaucoma]. [Chinese]. Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology] 1994; 30: 264-266.
46. Shen SY, Baskaran M, Fong AC, *et al.* Changes in the optic disc after acute primary angle closure. Ophthalmology 2006; 113: 924-929.
47. Douglas GR, Drance SM, Schulzer M. The visual field and nerve head in angle-closure glaucoma. A comparison of the effects of acute and chronic angle closure. Arch Ophthalmol 1975; 93: 409-411.
48. McNaught EI, Rennie A, McClure E, *et al.* Pattern of Visual Damage After Acute Angle-closure Glaucoma. Trans Ophthalmol Soc UK 1974; 94: 406-415.
49. Horie T, Kitazawa Y, Nosé H. Visual field changes in primary angle-closure glaucoma. Jpn J Ophthalmol 1975; 19: 108-115.
50. Dhillon B, Chew PT, Lim ASM. Field loss in primary angle-closure glaucoma. Asia-Pac J Ophthalmol 1990; 2: 85-87.
51. Gazzard G, Foster PJ, Viswanathan AC, *et al.* The severity and spatial distribution of visual field defects in primary glaucoma: a comparison of primary open-angle glaucoma and primary angle-closure glaucoma. Arch Ophthalmol 2002; 120: 1636-1643.

Paul Foster, Ningli Wang, Anne Coleman and Fotis Topouzis

Paul Foster and David Friedman

IS THE COST OF CASE FINDING (INCLUDING DIAGNOSIS AND TREATMENT OF PATIENTS DIAGNOSED) ECONOMICALLY BALANCED IN RELATION TO POSSIBLE EXPENDITURE ON MEDICAL CARE AS A WHOLE?

Steve Kymes

Co-chairs: David Friedman, Steve Kymes

Contributors: Augusto Azuara Blanco, Jennifer Burr, Paul Chew, Daniel Grigera, Paul Harasymowycz, Henry Jampel, Paul Lee, Joao Lopes, Baskaran Mani, Kuldev Singh, Anja Tuulonen, Richard Wormald, Jennifer Yip, Gerhard Zinser

Consensus points

- In assessing the cost-effectiveness of a screening program for angle closure and angle closure glaucoma, we must consider fully the costs and benefits of the program.
- Evaluation must consider the perspective of the decision maker, the incremental cost of the proposed program versus current programs and how we measure effectiveness.
- A thorough cost effectiveness analysis is not possible at present.
  Comment: In order to determine the cost-effectiveness of screening for primary angle closure (PAC)/primary angle closure glaucoma (PACG) we will need to be able to define clearly key elements of the screening process and the potential benefits of screening.

Introduction

Financial strains on the healthcare system in the industrialized world caused by an aging population and increasingly expensive technology have led to a growing share of national economic output devoted to medical care.[1] This trend has spurred an explosion of cost-effectiveness research over the past decade, with

Glaucoma Screening, pp. pp. 125-135
edited by Robert N. Weinreb, Paul R. Healey and Fotis Topouzis
2008 Kugler Publications, Amsterdam, The Netherlands

a search of Medline conducted in January 2007 finding over 28,000 citations between 1996 and 2006 that include the MESH heading of 'cost-benefit' and/or the key word of 'cost-effectiveness'. Use of economic evaluation as a decision tool to assist policy makers, clinicians and patients in weighing options for allocation of scarce health care resources is not new to the medical sciences. Indeed, it has been commonly used in evaluation of health programs for over thirty years, and today is considered to be *de rigueur* in decision making by health policy makers in most industrialized nations considering the adoption of new technologies or drugs.[2] In developing nations economic evaluations of public health interventions such as prevention of blindness have also been conducted.[3–5]

In general, most work that is done in economic evaluation is at the level of the local or national health authority and thus remote from the individual physician/patient encounter. However, it is not uncommon for the physician to be placed in a position where he/she is acting as an advocate for adoption of a medication or equipment with a formulary board, hospital administration, or regional health authority on behalf of patients and colleagues.[6] Thus it is useful for physicians to understand the theories and methods employed by cost-effectiveness practitioners. In addition, properly conducted economic evaluation studies can provide physicians information concerning which patients will most benefit from an intervention or what factors will be most influential in the patient deciding whether a treatment is 'worth it'.[7]

The purpose of economic evaluation in health care is to support efforts by a decision maker to determine if the benefits derived from a particular health program to treat or prevent disease outweigh the costs associated with providing the program. This ultimate product of an economic evaluation is the incremental cost-effectiveness ratio (ICER, see Equation 1.0).

Equation 1.0: Incremental cost-effectiveness ratio (ICER)

$$\frac{\text{Incremental cost of intervention over current practice}}{\text{Incremental effectiveness of intervention over current practice}}$$

When the numerator and denominator of the ICER are stated in the same units (*i.e.*, currency), the ICER may be restated as an inequality:

$$\text{Incremental cost of intervention} < \text{or} > \text{Incremental effectiveness of intervention}$$

Or alternatively:

$$\text{Incremental effectiveness of intervention} - \text{Incremental cost of intervention} > 0$$

The final formulation is a 'decision rule' indicating the circumstances under which the intervention might be adopted (*i.e.*, if the benefits of the intervention exceeded the costs). Formulated in this manner (with costs and benefits in the same units) the method of economic evaluation is referred to as 'cost-benefit analysis'.

Where the denominator of the ICER is in a unit different than the numerator, the method is called cost-effectiveness analysis. For example, if we were comparing two methods of glaucoma screening, we might compare the cost per case of glaucoma identified. In that case, we would count the number of cases of glaucoma identified to determine the value for the denominator. Cost-utility analysis is a particular type of cost-effectiveness analysis frequently used in industrialized nations in which the effectiveness (the denominator) is measured by utility, a metric for quality of life.[2,8]

Constructing an economic evaluation

Note that regardless of whether we are conducting a cost-benefit or cost-effectiveness analyses, the cost and effectiveness that are measured for the ICER are the 'incremental' cost of the new program (*i.e.*, how much more it costs than the current one) and the 'incremental' effectiveness (*i.e.*, how much more effective the new program is compared to the current one). As we are concerned with incremental measures, we must begin by properly stating the clinical alternatives to be considered so as to provide a basis for comparison. In the case of screening for PACG, there are two important questions to be answered at this point:

1. What is the perspective of the decision maker?
2. What is current standard of practice to which the new program will be compared?

It is essential that the perspective of the decision maker be understood, as this determines what costs and benefits are relevant in the analyses. If the decision maker is a hospital administrator, then the costs will be those absorbed by the hospital, and the benefit would be costs avoided (or additional funding streams generated) by case identification. Costs borne by patients, or governmental bodies independent of the hospital would not be considered. Similarly, if the decision maker were the patient, then costs borne (or benefits gained) by other stakeholders would not be considered. This also determines the type of analyses that might be done. If the decision maker is a health system, then it might not be concerned with 'the cost per case of glaucoma identified', as the decision maker will typically be more concerned with the fiscal margin. Consequently, the cost-benefit approach might be of more interest. Conversely, national health authorities are concerned with comparing strategies on a system wide basis, and might have a standard 'willingness to pay' for a case of glaucoma, and therefore might prefer a cost-effectiveness approach.

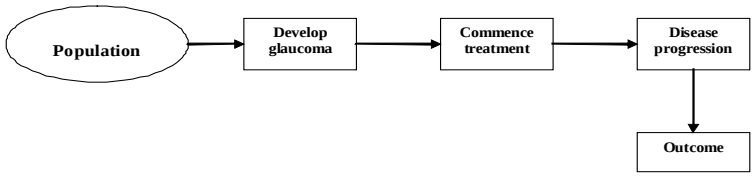

Fig. 1. Schematic of glaucoma management in the absence of a screening strategy.

The second question is essential in determining the basis of calculation of the ICER. Let us assume that a screening program has been proposed in a community in which there is currently no screening for PACG. Thus the current clinical algorithm would resemble that detailed in Figure 1. In this paradigm, people with PACG are only identified once they become symptomatic. Therefore, the costs experienced are those associated with treatment of the disease and its progression. The 'effectiveness' would be the impact of disease progression on visual function (be that measured as impact on quality of life or cases of blindness, visual impairment, etc.).

Now, let us assume that the health authority is considering adoption of a universal screening test. If it is adopted, the new algorithm would resemble that described in Figure 2. Under this paradigm, the population is screened, and depending on the screening result, the patient is referred for definitive evaluation (and if the positive screen is confirmed, treated) or found to not have disease. In this model we must consider a number of new costs and benefits. These include (note that this will vary with the perspective of the decision maker):

1. The cost of conducting the screening
   a. The cost of bringing or attracting patients to the screening location (*i.e.*, transportation vouchers, advertisement, etc.)
   b. The cost of screening equipment
   c. The cost of recruiting and training screeners (note that even if the screening is incorporated into a current exam, the cost of raising awareness among clinicians would need to be considered)
2. Costs associated with the accuracy of the equipment
   d. The cost of a false negative (*i.e.*, the cost of missing a case)
   e. The cost of a false positive (*i.e.*, the cost of unnecessary treatment, including the cost of iatrogenic harm).
3. The cost of missed cases among those people who are not recruited into the screening program.

Questions unique to an evaluation of screening

In most economic evaluations, we deal with an intervention whose costs and benefits are somewhat well defined, or at least can be parameterized within the

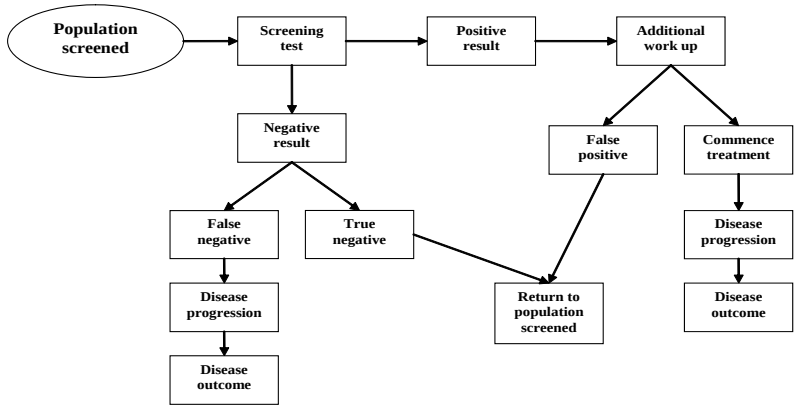

Fig. 2. Schematic of glaucoma screening strategy. At each box there are costs accrued, and affects on quality of life that must be measured to evaluate cost-effectiveness of the screening strategy.

context of the model. For instance, if we are examining the cost-effectiveness of treatment of ocular hypertension (OH)[7] we have good knowledge of the cost of treatment, and its associated side effects. We also have reasonable knowledge of the potential disease progression and its consequences. Given that we have this knowledge, we can build this uncertainty into our model for purposes of evaluation. In the jargon of economic evaluation, we would say that these factors can be made 'endogenous' to our model. This might be done by creation of a microsimulation model[9] or sensitivity analyses.[10]

This is not the case in evaluation of a screening test. Inherent in any diagnostic test is a tension between sensitivity and specificity with a tradeoff occurring between the two (*i.e.*, greater sensitivity being gained only at the cost of worse specificity). This is because sensitivity and specificity of any diagnostic test is a function of the decision threshold chosen on the receiver operating characteristic (ROC) curve that defines the relationship between sensitivity and specificity.[11] Therefore, prior to implementation of the test, the decision must be made concerning where the decision threshold might be set (possibly the optimal operating point on the ROC curve). This is a function of the prevalence of disease in the population and the relationship between the cost of a false positive and a false negative.[12]

Equation 2.0 – Equation for optimal operating point on ROC curve

$$\text{Optimal Operating Point} = \frac{P(D-) * [C_{FP} - C_{TN}]}{P(D+)\,[C_{FN} - C_{TP}]}$$

In this equation P(D–)/P(D+) represent the odds that the person screened does not have the disease, and the next term is the ratio between the net cost of a false positive and a false negative. This yields the optimum operating point on the ROC curve. With the identification of this point, the investigator might then determine the expected distribution of false negative and false positive results that might be included in the algorithm to be costed. However, if a disease is so severe that it would be dangerous to miss many cases, then one might require a very high sensitivity for the test, which would result in lower specificity. No single rule can be applied in all cases.

Estimating Costs in Economic Evaluation

As noted above, the costs to be recognized must be those relevant to the decision maker. Most importantly, 'cost' is properly defined as 'opportunity cost'. That is, the value that would be gained by the next best use of the resource. For instance, suppose that our screening program would be based in a hospital. The hospital must provide space for a waiting area, counseling and equipment. There are many ways we could recognize this cost in our analysis. We could consider what the hospital would charge as rent to a physician or vendor who would want to use that space. We could also consider the cost to the hospital to build and maintain the space. Both of these would be considered costs from a traditional accounting or financial perspective. But what is the purpose of the project? Perhaps it is to add a new source of revenue, or to expand services that are needed in the community, or to support a nearby physician practice. In all cases, we want to take the action that benefits the hospital, or alternatively we want to minimize the harm. In either case, benefit or harm is based upon what we are going to give up in order to do this project.

Suppose that in putting in our screening clinic we make the admittedly absurd decision to take over the waiting area used by patients of our hospital's busiest ophthalmologist? His patients complain to him, he gets angry and takes his clinic to a competing hospital across town which is happy to provide him with a luxurious office suite. Is our cost of doing this project the rent we could charge for the space, or the cost to build and maintain it? No, those costs represent but a fraction of what has been lost when the surgeon left. In this case, our *opportunity cost* is the profit we have lost by losing the surgeon's busy practice. Alternatively, suppose we put the screening program in a long vacant part of our campus. Here again, the cost of doing the project is not properly represented by the rent we would charge (no one was paying rent to us, so how could we lose it?), nor is it the cost of building and maintaining the space (the space already exists and unless we were going to tear it down, we were still going to maintain it). In this case, our opportunity cost associated with this space is zero, because the decision maker is not sacrificing a revenue stream by applying this resource to this use.

Measuring effectiveness with quality adjusted life years (QALYs)

While there are a number of methods for measuring effectiveness, the preferred method in industrialized countries is the 'quality adjusted life year' (QALY). The QALY permits comparison of interventions across disease type and the comparison of an intervention to an external cost-effectiveness threshold (typically $50,000-$100,000 US).[13] QALYs are calculated by weighting a person's remaining years of life by the quality of life expected during those years, as measured by utility, a preference-based measure.

Preference-based measures have their basis in decision theory, where they serve the purpose of clarifying values of the decision maker and the client for whom the decision is being made.[14] In health care, the perspective of the decision to be made is typically considered to be 'society', with the consequence being that all costs and benefits are to be considered in the decision, regardless of whom the burden or benefit falls upon.[15] In most developed nations, with the notable exception of the United States, 'effectiveness' is defined by impact on an individual's quality of life.

The advantage of measuring effectiveness as quality of life should be apparent from our previous discussion of the methods of economic evaluation. Not all benefits of an intervention might be monetized, nor can they be captured in units such as 'cases of blindness avoided'. When the decision is being made from the perspective of a provider of care, this may not be a limitation, but when the perspective being taken is that of the patient, or the broader societal perspective it is problematic. For instance, what is the monetary value of reading a newspaper, a prescription label, or doing the crossword puzzle? How would one characterize in dollars the value of seeing a grandchild or the frustration of no longer being able to drive?

Preference-based measures provide decision makers insight into this problem. The purpose of cost-effectiveness analysis is to insure that scarce resources are optimally distributed to the benefit of the holders of the resource. In the case of most industrialized nations, this means we are seeking to maximize the benefit of society, and according to the principles of health economics, this is achieved (under the theory of welfare economics) when we maximize the preference function of all individuals in society. In the case of the delivery of health care, we assume that the preference being maximized is for quality of life.[15]

The metric of the preference function is a unit typically referred to as the utility.[16] Hence, economic analysis where the preference for quality of life is being maximized is typically referred to as 'cost-utility analysis'.[17] The utility provides a measure of the desirability of a health state against an external metric such as risk, time, or money. When the utility is used to weight the number of years in a person's remaining lifetime, the result is the QALY.[2] To the extent that all health states can be measured according to this common metric, the social value of the prevention or cure of disease can be estimated in terms of improved quality of life. Having established this external metric, health policy makers can then

(in theory) establish the level of payment that will maximize social good. This is the theoretic basis of the oft-cited 'willingness to pay' of $50,000-100,000/QALY as defining a cost-effective program in cost-utility analysis.[18]

Specific issues in the cost-effectiveness of screening for PACG

The natural history, treatment patterns and associated diseases raise some specific economic issues for PACG screening not found in open angle glaucoma (OAG) screening. While screening for PACG can (like OAG) use tests for the optic neuropathy, the close relationship between PAC and PACG may allow potentially easier, cheaper and more reliable risk factor screening (for PAC and raised IOP) to substitute for optic disc and visual function examinations. PAC and PACG are also associated with cataract. Universal and opportunistic screening for cataract is performed in some parts of the world. The feasibility and cost-effectiveness of PAC/G screening may be enhanced by using an opportunistic strategy within a cataract screening program. Given the benefit of cataract extraction on the natural history of angle closure disease, PACG, PAC and in some areas even PACS may be additional indications for cataract extraction. Lastly, PACG causes more blindness and progresses more rapidly than OAG. This will have an effect on the optimal screening frequency for the condition.

Costs of screening for PACG in Mongolia

There are no published economic evaluations of PACG screening. This discussion below is a summary of preliminary results from an economic study performed in conjunction with a randomized controlled trial in screening and prevention of PACG in Mongolia. The intervention was screening for primary angle closure using A-scan central anterior chamber depth (cACD) measurements with prophylactic laser peripheral iridotomy (LPI). The data was provided by one of the consensus participants (Dr Jennifer Yip)

A health services perspective for measurement of costs and benefits is described below. Capital was given a seven-year life span (allowing for two screens of six-year interval as per study), and discounted at 1.3% (discount rate determined from bond rate for Mongolia). Costs of screening and overhead costs were determined from resource use during the study. As this was a study with a baseline screen and six-year follow up, the recall costs have been estimated from costs of tracing subjects in the follow up study. Costs of health care workers were derived from local price salaries. Maintenance required a technician familiar with repairs of all equipment used, this was not available in Mongolia, and therefore we included costs of travel and salary for a British technician. Due to the large distances some patients may have to travel, screening and diagnostic examination were

costed as one visit. Based on our study, screening took place in three different sites; two in Ulaan Baator and one in Bayanhongor, in southwest Mongolia. We calculated screening to take place over six months, after which staff and equipment will return to daily duties. In the baseline study 4725 patients were recruited, and attempts were made to trace all baseline participants. Although some costs were incurred in British pounds, these have been converted in the local currency, Mongolian Tugriks (MNT).

Baseline study

Cost data collected at follow up were inferred to experience at baseline, and therefore will be more representative of a baseline screening carried out in 2005. In brief, 4725 participants were recruited, 128 were diagnosed with glaucoma and were excluded from the study; 4597 were screened, of which 717 were examined, and 158 received LPI.

Estimated cost per glaucoma case detected (including treatment with LPI but not surgery) at first screen = 78339551MNT/128 = 612027MNT (approx. 524 USD).

Estimated cost per AC (PAC and PACG) case detected and treated = 78339551MNT/286 = 273915MNT (approx. 234 USD).

Estimated cost per glaucoma case detected second screen (to follow) will be much higher as this will detect incident cases only, whereas the baseline screen detected prevalent and incident cases. It is likely that all costs are over-estimations of potential true operational costs in a screening program.

Table 1. Annual (full year effect) costs for first screen

Item category	**Cost (MNT)**
Salaries for 3 nurses and 2 doctors	13.758.749
Capital costs	40.838.114
Consumables	2.071.914
Overheads	600.000
Maintenance	16.312.874
Stationary	10.000
Transport equipment and staff	1.282.900
Medicines used	3.465.000
Total	78.339.551

Conclusion and topics for future research and consideration

In assessing the cost-effectiveness of a screening program for PACG, we must consider fully the costs and benefits of the program. The principles of economic evaluation provide us a framework for this by allowing us to fully appraise the

value and significance of a program. Evaluation must consider the perspective of the decision maker, the incremental cost of the proposed program versus current programs and how we measure effectiveness. Recognition of the need for employing rigorous methods to evaluation will ensure credible and replicable results respected by policy makers.

Based on the above, we believe that in order to determine the cost-effectiveness of screening for PACG we will need to be able to define clearly the following elements:

- Who does the screening?
- What are the tradeoffs between cost and accuracy of screening depending on screener?
- What is the sequence of the screening algorithm? (*i.e.*, is there a physician to 'back up' the technician if a technician is used)
- Does the equipment required represent a new purchase for the health system, or is this a new use of equipment that would already be on hand?
- What is the expected incidence of glaucoma among people with PAC?
- What is the expected incidence of an 'AC event' among those who are unscreened?
- What is the sensitivity and specificity of the various screening algorithms?
- What is the cost of treatment of false positive results on screening?
- What is the consequence of a false negative on screening?
- What is the rate of progression among people with PACG?
- What is the incidence of severe visual impairment or blindness among people with PACG?
- What are the costs of treatment of people with PACG and how do these differ by country?
- What is the impact of PACG on quality of life?
- How does the 'willingness to pay' for glaucoma prevention differ among nations where PACG is seen as a major public health issue?

References

1. Anderson GF, *et al.* It's the Prices Stupid: Why the United States is so Different From Other Countries. Health Affairs 2003; 22: 89-105.
2. Drummond MF, *et al.* Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford: Oxford University Press 2005.
3. Frick KD, *et al.* Estimating the burden and economic impact of trachomatous visual loss. Ophth Epidem 2003; 10: 121-132.
4. Frick KD, Colchero MA, Dean D. Modeling the economic net benefit of a potential vaccination program against ocular infection with Chlamydia trachomatis.[see comment]. Vaccine 2004; 22: 689-696.
5. Frick KD, Hanson CL, Jacobson GA. Global burden of trachoma and economics of the disease. Am J Trop Med Hyg 2003; 69: S1-S10.

6. O'Brien B, *et al.* Users' Guides to the Medical Literature: XIII. How to Use an Article on Economic Analysis of Clinical Practice B. What are the Results and Will They Help Me in Caring for My Patients? JAMA, 1997; 277: 1802-1806.
7. Kymes SM, *et al.* Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. Am J Ophthalmol 2006; 141: 997-1008.
8. Torrance GW, Feeny DH. Utilities and Quality Adjusted Life Years. Int J Technnol Assessment in Health Care 1989; 5: 559-575.
9. Weinstein MC. Recent developments in decision-analytic modeling for economic evaluation. Pharmacoeconomics 2006; 24: 1043-1053.
10. Krahn MD, *et al.* Primer on Decision Analysis: Part 4 – Analyzing the Model and Interpreting the Results. Med Dec Making 1997; 17: 142-151.
11. Green DM, Swets JA. Signal Detection Theory and Psychophysics. 1st ed. New York: John Wiley and Sons, Inc. 1966, p. 435.
12. Sox HC, *et al.* Medical Decision Making. 1 ed. Boston: Butterworth-Heinemann 198, p. 406.
13. Kymes SM, Lee BS. Preference-based Quality of Life Measures in People with Visual Impairment. Optom Vis Sci 2007; 84: 809-817.
14. Keeney RL, Raiffa H. Decisions with Multiple Objectives. New York: Cambridge University Press 1993.
15. Gold MR, *et al.* Cost-Effectiveness in Health and Medicine.New York: Oxford University Press 1996, p. 425.
16. Tsevat J. What do Utilities Measure? Medical Care 2000; 38S9: 160-164.
17. Torrance GW. Preferences for Health Outcomes and Cost-Utility Analysis. Am Jf Man Care 1997; 3: S8-S20.
18. Gillick MR. Medicare Coverage for Technological Innovations – Time for New Criteria? New England Journal of Medicine 2004; 350: 2199-2203.

Fig. 1. Chris Girkin (left), Jeff Liebmann and Carlo Traverso

Fig. 2. Chris Leung, Sinee Srisamren, Luceana Alencar and Yi Dai

Fig. 3. Eugenio Maul, T. Wang, Jonathan Crowston and Neeru Gupta

Fig. 4. Jialiang Zhao and Erik Greve

Fig. 5. Clive Migdal and Carlo Traverso

Fig. 6. Luceanar Alencar Sinee Srisamran, Pam Sample, Alberto Gonzalez and Sunil Deokole

Fig. 7. Franz Grehn

Fig. 8. G.C. Sekhar and Syril Dorairaj

Fig. 9. David Friedman

Fig. 10. Doug Anderson

Fig. 11. Linda Zangwill, Gerhard Zinser and Stefano Miglior

Fig. 12. Rupert Bourne

Fig. 13. Jonathan Crowston and Neeru Gupta

Fig. 14. Tony Realini and Sunil Deokhole

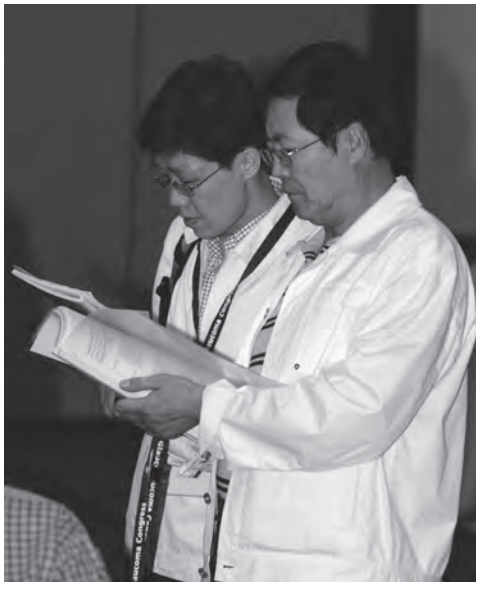

Fig. 15. Huaizhong Wang and Ningli Wang

Fig. 16. Gabor Holló and Ronit Nesher

Fig. 17. Kuldev Singh and Erik Greve

Fig. 18. Thierry Zeyen (left) and Douglas Anderson

Fig. 19. Tony Hommer, Fotis Topouzis, Thierry Zeyen and Clive Migdal (back)

Fig. 20. Ying Xiong and Huaizhong Wang

INDEX OF AUTHORS

Araie, M., 13
Aung, T., 99
Azuara Blanco, A., 33
Coleman, A., xi
Foster, P., 65, 111
Friedman, D., 125
Greve, E.L., xiii
He, M., 65
Healey, P.R., xi, 25, 55
Heijl, A., 3, 51
Kymes, S., 125
Lee, P., 3
Nolan, W., 99
Quigley, H., 51
Ritch, R., 79, 93
Sihota, R., 25
Standefer, J., 93
Tham, C., 79
Thomas, R., 111
Topouzis, F., xi
Tuulonen, A., 55
Wang, N., xi
Weinreb, R.N., xi, xiii
Zangwill, L., 13, 25

SUMMARY CONSENSUS POINTS

Is OAG an important health problem?

- Glaucoma is the leading cause of preventable irreversible blindness.
- The goal of glaucoma screening is to prevent visual impairment, preserve quality of life and visual functioning.
- Each society should determine its own criteria, including the stage of disease, for the allocation of an affordable proportion of its resources for glaucoma care and screening.
- The prevalence of open-angle glaucoma has been determined for some populations of European, African and Asian ancestry
  Comment: Prevalence, incidence and severity data are needed still for many regions of the world.
- Long-term data show a substantial frequency of glaucoma blindness in some populations.
  Comment: Additional population based data are needed on the rates and risks of vision loss.

Is there an accepted and effective treatment for patients with the disease that is more effective at preventing morbidity when initiated in the early, asymptomatic stage than when begun in the later, symptomatic stages?

- High-quality randomized trials (treatment vs. no treatment) and meta-analyses have shown that topical ocular hypotensive medication is effective in delaying onset and progression of open-angle glaucoma (OAG).
- Treatments are effective, easy to use, and well tolerated.
- It is not known whether postponing ocular hypotensive therapy affects the rate of subsequent conversion from ocular hypertension to OAG or the rate of progression of visual field loss once OAG has developed.
- It is not known whether the reduction in progression rate from intraocular pressure (IOP) lowering therapy varies according to disease stage.
  Comment: Asymptomatic disease may include early, moderate, or at times severe stages of OAG.
- Current evidence suggests that glaucoma therapy itself is not associated with a measurable reduction of quality of life.
- Patients' perceived vision-related quality of life (VRQOL) and visual function is correlated with visual field loss, especially binocular visual field loss, in OAG.
  Comment: the greater the visual field loss, or the later the stage of the disease, the more symptomatic the disease.

Are facilities for diagnosis and treatment available?

- The resources for diagnosis and treatment of glaucoma vary worldwide.
  Comment: Many countries have insufficient facilities to provide care at

present practice standards relative to developed countries. There is a need to identify areas without facilities to help plan resource allocation.
- Fewer resources are required to diagnose glaucoma at moderate to advanced asymptomatic stages compared to very early stages.
- Treatment of glaucoma requires facilities for regular long-term monitoring. There is a need to study barriers to access for glaucoma care so that available facilities can be used optimally

Is there an appropriate, acceptable, and reasonably accurate screening test?
- The best single test or group of tests for open-angle glaucoma screening is yet to be determined.
- Optimal screening test criteria are not yet known.
  Comment: Screening test criteria depend upon health care system, location, and prevalence of open-angle glaucoma (OAG).
  Comment: The sensitivity and specificity of tests for population-based screening are unknown, as most have been tested only on selected groups, not populations.
- Diagnostic test accuracy may vary according to the severity of the disease.
- The tests available and effective for case-finding are not necessarily the same as those for population- based glaucoma screening which requires a very high specificity to be cost-effective.
  Comment: Screening requires a test with a high specificity. Diagnosis requires a test with a high sensitivity.
  Comment: Individuals at high risk require highly accurate tests.

Is the natural history of the condition, including development from latent to manifest disease, adequately understood?
- Open-angle glaucoma (OAG) incidence rates are known for untreated and treated patients with ocular hypertension.
- OAG progression rates vary greatly among patients.
  Comment: More research is required to determine the extent and basis of progression rate variation.
- Progression event rates for patients (in clinical trials, under clinical care or observation) in terms of percent of patients/eyes progressing per year are available both for OAG and ocular hypertension.
- Progression data expressed as rate of disease progression (*i.e.*, expressed in dB/year or in % of full field/year) are very sparse.

Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditure on medical care as a whole?
- The best evidence to date, based on two modeling studies, suggests:
  1) Screening of high-risk subgroups may be more cost-effective than screening the entire population.

2) Screening may be more cost-effective as glaucoma prevalence increases
3) The optimal screening interval is not yet known
4) Screening may be more cost-effective when initial assessment is a simple strategy that could be supervised by non-medical technicians.

Comment: More research is needed for the implementation of the best screening program for glaucoma.

Comment: Expert consensus is required on how cost data should be collected and reported in glaucoma care. This includes reporting visually relevant outcomes on a per-patient basis.

Comment: Additional data are required to develop a glaucoma disease staging system based on disability.

- Population-based screening studies are required to determine optimal screening strategies and their cost-effectiveness.
- Multi-eye disease screening needs to be evaluated as to whether it would be more cost-effective than glaucoma-only screening.

Are angle closure (AC) and angle-closure glaucoma (ACG) important health problems?

- Primary angle-closure glaucoma (PACG) accounts for approximately 25% of all glaucomatous optic neuropathy worldwide, but 50% of bilateral glaucoma blindness.
- Visual impairment from primary angle closure (PAC) and PACG can result from ocular damage other than glaucomatous optic nerve damage (*e.g.*, corneal decompensation, cataract, ischemic optic neuropathy).
- Some Asian populations have a high prevalence of advanced angle-closure glaucoma.
- PACG is predominantly asymptomatic.
- PACG is a problem of sufficient magnitude that public health intervention should be evaluated.

Is there an accepted and effective treatment for patients with angle-closure glaucoma (ACG) that is more effective at preventing morbidity when initiated in the early, asymptomatic stage than when begun in the later, symptomatic stages?

- Angle closure is a progressive condition that can lead to glaucoma.
- Iridotomy or iridectomy is the preferred initial treatment for cases of PAC and PACG.

  Comment: Iridotomy or iridectomy eliminates pupillary block.
- There is no evidence to support medical treatment alone for PACG in the absence of iridotomy or iridectomy.
- Medical treatment may be indicated for lowering IOP after iridotomy or iridectomy, following risk assessment.

  Comment: Research is needed to determine whether a residual increase in IOP following iridotomy or iridectomy requires treatment

- Iridotomy or iridectomy will not always alleviate irido-trabecular apposition since mechanisms other than pupillary block may be present, such as plateau iris or phacomorphic angle closure.
  Comment: Peripheral iridoplasty may be effective in further opening the angle and preventing further closure. Unlike iridotomy or iridectomy, peripheral iridoplasty sometimes needs to be repeated.
- There is good evidence that preventive iridotomy or iridectomy will eliminate the risk of acute angle closure when performed on the fellow eye of patients who have experienced acute angle closure.
- There is insufficient evidence for deciding which PACG patients should undergo lens extraction alone (without trabeculectomy).
  Comment: Lens extraction alone may be considered in eyes with mild degree of angle closure (less than 180º of PAS), mild optic nerve damage/ visual field damage or those that are not on maximum tolerated medical treatment.
  Comment: There is limited evidence for recommending lens extraction alone in eyes with mild PACG. Similarly there is limited evidence for recommending lens extraction alone in eyes with more advanced PACG.
  Comment: Published studies to date have been non-randomized, with small sample sizes and short follow-up.
- Although commonly performed, there is limited evidence about the effectiveness of combined cataract extraction and trabeculectomy in eyes with PACG.
  Comment: There is a need for studies comparing this form of surgery with separately staged cataract extraction and trabeculectomy.

Are facilities for diagnosis and treatment available?

- There is a need for a systematic assessment of the clinical capacity to identify and treat angle closure (AC).
- Gonioscopy is essential for diagnosis and treatment.
  Comment: Inadequate clinical training and limited use of gonioscopy are major obstacles to successful case finding.

Is there an appropriate, acceptable, and reasonably accurate screening test?

- There is evidence that limbal anterior chamber depth (LCD) may be an appropriate screening test for angle closure.
  Comment: Using a LCD of 25% corneal thickness as a cut-off all those cases falling below this level would require gonioscopy. Approximately 4% of occludable angles may be missed by this method.
  Comment: More research is required concerning alternative screening tests.
  Comment: A screening test should not be used as a substitute for definitive diagnosis.

- Clinic-based case-detection should target established primary angle closure (PAC) and primary angle closure glaucoma (PACG) as blindness can still be prevented when interventions are implemented at these stages.
- Comment: The evidence supporting early detection and prophylactic treatment of primary angle closure suspects (PACS) is limited at present and cannot be justified where prevalence of PACS is high.
- Gonioscopy is the current gold standard of angle examination and is the appropriate test for diagnosing angle closure.
  Comment: Gonioscopy alone may not be suitable as a screening test.
  Comment: Gonioscopy combined with optic disc examination and intraocular pressure measurement may enable optimum detection of PAC, PACG and open angle glaucoma (POAG) in a clinic setting.
- For accuracy of clinic-based case detection of PAC/G improve, there needs to be a significant increase in the level and use of gonioscopy and disc examination training for ophthalmologists.

Is the natural history of the condition, including development from latent to manifest disease, adequately understood?

- An episode of symptomatic acute angle closure (AAC) places the unaffected fellow eye at high risk of a similar fate.
- The current best estimate for progression from primary angle closure suspect (PACS) to primary angle closure (PAC) or PAC to primary angle closure glaucoma (PACG) is approximately 20-30% over 5 years.
  Comment: The data on the natural history of PACS/PAC/PACG are sparse and would benefit from confirmation in further studies.
- Asymptomatic angle closure is associated with later presentation and more advanced loss of vision than symptomatic angle closure where facilities for treatment are readily available.

Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditure on medical care as a whole?

- In assessing the cost-effectiveness of a screening program for angle closure and angle closure glaucoma, we must consider fully the costs and benefits of the program.
- Evaluation must consider the perspective of the decision maker, the incremental cost of the proposed program versus current programs and how we measure effectiveness.
- A thorough cost effectiveness analysis is not possible at present.
  Comment: In order to determine the cost-effectiveness of screening for primary angle closure (PAC)/primary angle closure glaucoma (PACG) we will need to be able to define clearly key elements of the screening process and the potential benefits of screening.