

PREFERRED PRACTICE PATTERN®



Primary Open-Angle Glaucoma

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GLAUCOMA PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Glaucoma Preferred Practice Pattern® Panel** members wrote the Primary Open-Angle Glaucoma Preferred Practice Pattern® guidelines (“PPP”). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in April 2015. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2015

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The Primary Open-Angle Glaucoma PPP was then sent for review to additional internal and external groups and individuals in July 2015. All those who returned comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the PPP Panel reviewed and discussed these comments and determined revisions to the document.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2015 are available online at www.aao.org/ppp.



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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care**. Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual.

While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Primary Open-Angle Glaucoma PPP are ophthalmologists.



METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network¹ (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation² (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.³

- ◆ All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- ◆ To rate individual studies, a scale based on SIGN¹ is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- ◆ Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE² as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- ◆ Key recommendations for care are defined by GRADE² as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- ◆ The Highlighted Findings and Recommendations for Care section lists points determined by the PPP Panel to be of particular importance to vision and quality of life outcomes.
- ◆ All recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- ◆ Literature searches to update the PPP were undertaken in June 2014 in the PubMed and Cochrane databases. Complete details of the literature searches are available in Appendix 3.



HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Established and important risk factors for primary open-angle glaucoma (POAG) include age, race/ethnicity, level of intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, myopia, and thin central cornea.

Primary open-angle glaucoma with consistently normal IOP is common, especially in certain populations. Lowering pressure in these patients can be beneficial.

Characteristic clinical features of POAG include an open angle on gonioscopy, and glaucomatous optic nerve head (ONH) and retinal nerve fiber layer (RNFL) changes that usually are associated with typical glaucomatous visual field defects.

Computer-based imaging and stereoscopic photography provide different and complementary information about optic nerve status and are useful adjuncts to a good clinical examination.

Adjusting computerized visual field programs (24 degrees, 30 degrees, 10 degrees) and varying stimulus size for patients with advanced glaucoma aid in detecting and monitoring progressive visual field loss.

Clinical trials have shown that lowering IOP reduces the risk of developing POAG and slows the progression of POAG, including normal-tension OAG.

Effective medical, laser, and incisional surgical approaches exist for lowering IOP.

A reasonable initial treatment in a POAG patient is to reduce IOP 20%–30% below baseline and to adjust up or down as indicated by disease course and severity.



INTRODUCTION

DISEASE DEFINITION

Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy.

CLINICAL FINDINGS CHARACTERISTIC OF PRIMARY OPEN-ANGLE GLAUCOMA

Primary open-angle glaucoma is a chronic ocular disease process that is progressive, generally bilateral, but often asymmetric.⁴ It is associated with the following characteristics.

- ◆ Evidence of optic nerve damage from either, or both, of the following:
 - ◆ *Optic disc or retinal nerve fiber layer (RNFL) structural abnormalities*
 - Diffuse or focal narrowing, or notching, of the optic disc rim, especially at the inferior or superior poles, which forms the basis for the ISNT rule⁵ (see subsection on optic nerve head and retinal nerve fiber layer clinical examination in Physical Examination section)
 - Progressive narrowing of the neuroretinal rim with an associated increase in cupping of the optic disc
 - Diffuse or localized abnormalities of the parapapillary RNFL, especially at the inferior or superior poles
 - Disc rim, parapapillary RNFL, or lamina cribrosa hemorrhages
 - Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
 - Large extent of parapapillary atrophy
 - ◆ *Reliable and reproducible visual field abnormality* considered a valid representation of the subject's functional status
 - Visual field damage consistent with RNFL damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites)⁶
 - Visual field loss across the horizontal midline in one hemifield that exceeds loss in the opposite hemifield (in early/moderate cases)
 - Absence of other known explanations (e.g., optic disc drusen, optic nerve pit)
- ◆ Adult onset
- ◆ Open anterior chamber angles
- ◆ Absence of other known explanations (i.e., secondary glaucoma) for progressive glaucomatous optic nerve change (e.g., pigment dispersion, pseudoexfoliation [exfoliation syndrome], uveitis, trauma, and corticosteroid use)

Primary open-angle glaucoma represents a spectrum of disease in adults in which the susceptibility of the optic nerve to damage varies among patients. Although many patients with POAG present with elevated intraocular pressure (IOP), nearly 40% of those with otherwise characteristic POAG may not have elevated IOP measurements.⁷ The vast majority of patients with POAG have disc changes or disc and visual field changes,⁸ but there are rare cases where there may be early visual field changes before there are detectable changes to the optic nerve.

Primary Open-Angle Glaucoma PPP: Background

The severity of glaucoma damage can be estimated according to the following categories:

- ◆ Mild: definite optic disc or RNFL abnormalities consistent with glaucoma as detailed above and a normal visual field as tested with standard automated perimetry (SAP)
- ◆ Moderate: definite optic disc or RNFL abnormalities consistent with glaucoma as detailed above, and visual field abnormalities in one hemifield that are not within 5 degrees of fixation as tested with SAP
- ◆ Severe: definite optic disc or RNFL abnormalities consistent with glaucoma as detailed above, and visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield as tested with SAP
- ◆ Indeterminate: definite optic disc or RNFL abnormalities consistent with glaucoma as detailed above, inability of patient to perform visual field testing, unreliable/uninterpretable visual field test results, or visual fields not performed yet

PATIENT POPULATION

The patient population consists of adults with open anterior chamber angles and with demonstrated optic nerve or RNFL damage, with or without corresponding visual field loss.

CLINICAL OBJECTIVES

- ◆ Document the status of optic nerve structure and function on presentation
- ◆ Estimate an IOP below which further optic nerve damage is unlikely to occur (see discussion of Target Intraocular Pressure for Patients with POAG in the Care Process section)
- ◆ Attempt to maintain IOP at or below this target level by initiating appropriate medical and/or surgical intervention(s)
- ◆ Monitor the structure and function of the optic nerve for further damage and adjust the target IOP to a lower level if deterioration occurs
- ◆ Minimize the side effects of treatment and their impact on the patient's vision, general health, and quality of life
- ◆ Educate and involve the patient and appropriate family members/caregivers in the management of the disease



BACKGROUND

PREVALENCE

Primary open-angle glaucoma is a significant public health problem. It is estimated that 45 million people in the world have open-angle glaucoma (OAG).⁹ Glaucoma (both open-angle and angle-closure) is the second leading cause of blindness worldwide, with approximately 8.4 million people blind from glaucoma.⁹ Overall in 2004, the prevalence of POAG for adults aged 40 and older in the United States was estimated to be about 2%.¹⁰ Open-angle glaucoma affects an estimated 2.2 million people in the United States, and that number is likely to increase to 3.3 million in 2020 as the population ages.^{11,12} However, large differences exist in the prevalence of glaucoma among different ethnoracial groups (see Table 1 and Figure 1). Overall, there appears to be a threefold higher prevalence of OAG in African Americans relative to non-Hispanic whites in the United States.^{10,13} It is also the leading cause of blindness in African Americans.¹³ Further, the prevalence of OAG is even higher in Afro-Caribbeans relative to African Americans. Recent evidence on Hispanics/Latinos suggests that they have high prevalence rates of OAG that are comparable to the prevalence rates for African Americans.¹⁴ An analysis of claims data from a large U.S.-based managed care plan suggests that the prevalence of OAG among Asian Americans is comparable to the prevalence among Latinos and is higher than that of non-Hispanic white Americans.¹⁵

TABLE 1 PREVALENCE (%) OF DEFINITE OPEN-ANGLE GLAUCOMA

Study	Ethnoracial Group	Age-Specific Prevalence					
		Age Groups (yrs)					Total
		40–49	50–59	60–69	70–79	80+	
Baltimore Eye Study ¹⁶	African American	1.3	4.2	6.2	8.9	12.9	5.0
Barbados Eye Study ¹⁷	Afro-Caribbean	1.4	4.1	6.7	14.8	23.2	6.8
Los Angeles Latino Eye Study ¹⁴	Latino	1.3	2.9	7.4	14.7	21.8	4.7
Proyecto Vision Evaluation Research ¹⁸	Latino	0.5	0.6	1.7	5.7	12.6	2.0
Baltimore Eye Study ¹⁶	NHW	0.2	0.3	1.5	3.3	1.94	1.4
Blue Mountains Eye Study ¹⁹	NHW	0.4*		1.3	4.7	11.4	3.0
Visual Impairment Project ²⁰	NHW	0.5	1.5	4.5	8.6	9.9	3.4
Beaver Dam Eye Study ²¹	NHW						
Roscommon ²²	NHW	0.7		1.8	3.2	3.1	1.9

NHW = non-Hispanic white

NOTE: The studies reporting prevalence used different definitions of disease; therefore, caution should be exercised when comparing these studies.

* The study combined ages 40–59 into one group.

Adapted with permission from Varma R, Ying-Lai M, Francis B, et al, Los Angeles Latino Eye Study Group. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology* 2004;111:1445.

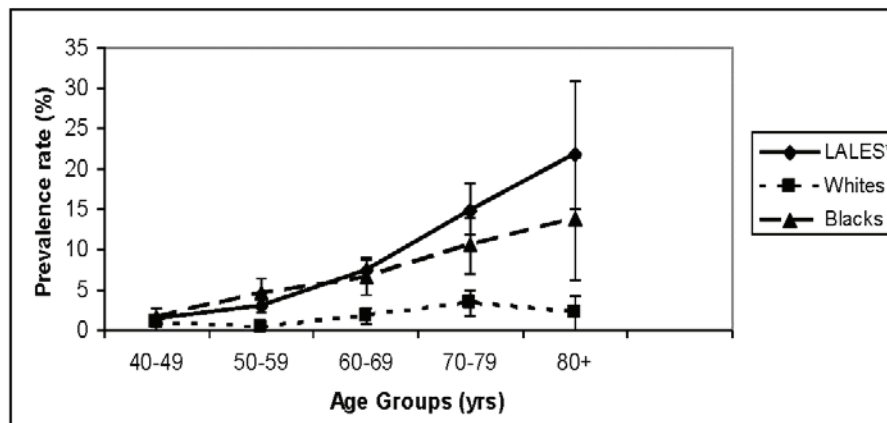


FIGURE 1. Comparison of age-specific prevalence of open-angle glaucoma in Latinos (Los Angeles Latino Eye Study [LALES]), African Americans/blacks and non-Hispanic whites (the Baltimore Eye Study)¹⁶

* The data shown from the Los Angeles Latino Eye Study is from a different study.

Adapted with permission from Varma R, Ying-Lai M, Francis B, et al, Los Angeles Latino Eye Study Group. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology* 2004;111:1446.

RISK FACTORS

The findings of epidemiological investigations and clinical trials provide a framework for assessing the risk factors associated with POAG. Numerous studies have identified risk factors associated with POAG:

- ◆ Higher IOP^{7,8,17-19,21,23-28}
- ◆ Older age^{8,16,23,25,26,29,30}
- ◆ Family history of glaucoma^{26,31}
- ◆ African race or Latino/Hispanic ethnicity
- ◆ Thinner central cornea^{8,23,32}
- ◆ Lower ocular perfusion pressure^{31,33,34}
- ◆ Type 2 diabetes mellitus³⁵⁻³⁸
- ◆ Myopia^{34,39-41}
- ◆ Lower systolic and diastolic blood pressure³¹
- ◆ Disc hemorrhage⁴²⁻⁴⁶
- ◆ Larger cup-to-disc ratio^{8,23}
- ◆ Higher pattern standard deviation on threshold visual field testing^{28,47}

Intraocular Pressure

A number of population-based studies have demonstrated that the prevalence of POAG^{7,17-19,21,24,27,48} increases as the level of IOP increases (see Figure 2). In the Baltimore Eye Survey, at an IOP of 30 mmHg, nearly 7% of Caucasians and 25% of African Americans had POAG.²⁴ These studies provide strong evidence that IOP plays an important role in the optic neuropathy of POAG. Furthermore, studies have demonstrated that reduction in the level of IOP decreases the risk of visual field progression in OAG (see Table 2).^{23,49-54} In addition, treated eyes that have a greater IOP fluctuation may be at increased risk of progression, although this has not been shown consistently.⁵⁵⁻⁶⁰

In spite of the relationship between the level of IOP and POAG, there is great interindividual variation in the susceptibility of the optic nerve to IOP-related damage. Population-based studies indicate that a variable proportion of patients with IOP greater than 21 mmHg (Northern Italy [13%],⁶¹ Los Angeles [18%],¹⁴ Arizona [20%],¹⁸ Blue Mountains [25%],¹⁹ Melbourne [39%],²⁰ Baltimore [45%],¹⁶ Rotterdam [61%],⁷ Barbados [71%]³⁴) have glaucomatous optic nerve damage.²⁴ This suggests that an IOP level of greater than 21 mmHg is an arbitrarily defined level and highlights the poor predictive value of utilizing a specific IOP cutoff as a measure for screening or diagnosis of POAG.

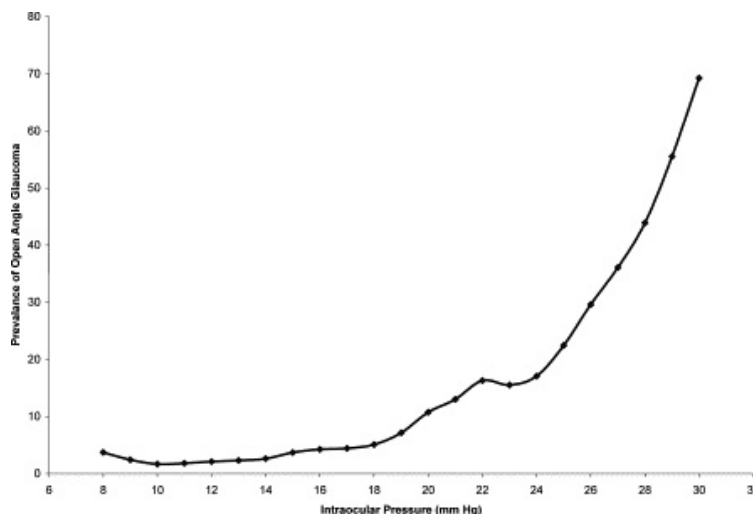


FIGURE 2. The relationship between prevalence of open-angle glaucoma and intraocular pressure (measured using Goldmann applanation tonometry) in Latinos (n=5970) in the Los Angeles Latino Eye Study.

Adapted with permission from Francis B, Varma R, Chopra V, et al, Los Angeles Latino Eye Study Group. Intraocular pressure, central corneal thickness, and prevalence of open-angle glaucoma: the Los Angeles Latino Eye Study. *Am J Ophthalmol* 2008;146:743.

TABLE 2 RELATIONSHIP BETWEEN IOP REDUCTION AND GLAUCOMA PROGRESSION IN MAJOR CLINICAL TRIALS

Study	Study Design	No. of Patients	Follow-up Duration (yrs)	Finding
Scottish Glaucoma Trial, 1988–1989 ^{62,63}	Newly diagnosed POAG: medical therapy vs. trabeculectomy	116	4.6 (mean)	Trabeculectomy lowered IOP (58%) more than medicine (42%); medical therapy group had more deterioration in visual fields than trabeculectomy group.
Moorfields Primary Treatment Trial, 1994 ⁶⁴	Newly diagnosed POAG: medical therapy vs. laser trabeculoplasty vs. trabeculectomy	168	5+	Trabeculectomy lowered IOP the most (60%); laser trabeculoplasty (38%) and medical therapy groups (49%) had more deterioration in visual fields than trabeculectomy group.
Collaborative Normal-Tension Glaucoma Study (CNTGS), 1988 ⁴⁹	POAG in eyes with normal IOP: rate of progression, effect of IOP reduction on progression rate	230	5+	Lowering IOP (37%) slowed the progression rate of visual field loss compared with untreated eyes (1%).
Early Manifest Glaucoma Trial (EMGT), 2002–2007 ^{51,52,58}	Newly diagnosed POAG: medical therapy and laser trabeculoplasty vs. no treatment	255	8 (median)	Lowering IOP with medical therapy and trabeculoplasty (25%) slowed progression of optic disc and visual field damage.
Collaborative Initial Glaucoma Treatment Study (CIGTS), 2001 ⁶⁵	Newly diagnosed POAG: medicine vs. trabeculectomy	607	5+	Lowering IOP with initial filtering as surgery (46%) was as effective as medical therapy (38%) to inhibit progression of visual field damage, though the amount of reduction was slightly greater after surgery.
Advanced Glaucoma Intervention Study (AGIS), 2000, 2004 ^{53,66}	POAG after medical therapy failure with no previous surgery: laser trabeculoplasty first vs. trabeculectomy first	591	10–13	Surgical outcome varied by race; patients of African descent did better with laser trabeculoplasty first (30% IOP), whereas in the longer term (4+ yrs) Caucasian American patients did better with trabeculectomy first (48% IOP). Lowest IOP group during follow-up after surgical interventions (47%) prevented further visual field deterioration in advanced glaucoma patients.
United Kingdom Glaucoma Treatment Study (UKGTS), 2014 ⁵⁴	Newly diagnosed OAG: latanoprost 0.005% vs. placebo	516	2	Patients in the latanoprost group demonstrated a greater mean reduction in IOP (3.8 mmHg vs. 0.9 mmHg), as well as a significantly reduced risk of visual field deterioration (HR=0.44, $P=0.003$), relative to patients in the placebo group.

HR = hazard ratio; IOP = intraocular pressure; POAG = primary open-angle glaucoma

Age

Older age is another important risk factor for the presence and progression of POAG.^{16-20,57,58,67-69} A number of epidemiological studies demonstrate that the prevalence of glaucoma increases dramatically with age, particularly among individuals of Latino/Hispanic and African descent (see Table 1 and Figure 1).

Family History

Family history is a risk factor for glaucoma. In the Rotterdam Eye Study, in which all siblings of glaucoma cases and controls were examined, the odds of having POAG were 9.2-fold higher for individuals who have a first-degree relative (sibling or parent) with confirmed POAG.⁷⁰ Other studies in which family members were not physically examined depend on patient reports of the status of family members, and these are known to be subject to several biases. Nonetheless, they support the concept that first-degree relatives of those with OAG are at greater risk. For example, in the Baltimore Eye Survey and the Los Angeles Latino Eye Study (LALES), the odds were twice as high for individuals with POAG (1.92 and 2.85, respectively) of reporting a first-degree relative (parent, child, or sibling) with glaucoma compared with individuals who did not have glaucoma. However, the odds increased to over three times as high if they reported that they had a sibling with glaucoma (LALES, 3.47⁷¹; Baltimore, 3.7⁷²). Interestingly, the odds rose to fivefold higher if there were two or more siblings who were reported to have a history of glaucoma.

Race or Ethnicity

For POAG, ethnoracial characteristics are an important risk factor (see Figure 1). The prevalence of POAG is higher in individuals of West African, Afro-Caribbean, or Latino/Hispanic origin than of other groups.^{14,16-18,73,74} The prevalence is three times higher in African Americans and Hispanics of Mexican ancestry compared with non-Hispanic whites.^{14,16} Blindness from glaucoma is at least six times more prevalent in African Americans than in Caucasian Americans.¹³

Central Corneal Thickness

Because applanation tonometry measurements are derived from resistance to corneal indentation and corneal stiffness, differences in central corneal thickness (CCT) may introduce artifacts in IOP measurement.^{23,32,75-81} The mean CCT in healthy human eyes varies by ethnoracial characteristics. The average CCT measured ultrasonically in Caucasian Americans is 556 μm ,⁸² in Latinos it is 546 μm ,⁸³ in Asians it is 552 μm ,⁸⁴ in American Indian/Alaskan Natives it is 555 μm ,⁸⁵ and in African Americans it is 534 μm .⁸⁰ If IOP is underestimated in with thinner CCT, the relationship between IOP level and OAG damage may be underestimated, since the IOP is actually higher than measured. Conversely, if IOP is overestimated in with a nonedematous, thicker CCT, the relationship between IOP level and OAG damage may be overestimated, since the IOP is actually lower than measured. Although several tables and figures have been published, no standard nomogram correcting applanation IOP measurements for CCT has yet been validated.^{75,79,86,87} And in all these studies, eyes with forme-fruste keratoconus, Fuchs endotheliopathy, or postkeratorefractive surgery were not considered. Therefore, in such patients it is important to rely on clinical examination of the optic nerve, imaging of the RNFL, and assessment of the visual field to diagnose glaucoma.

A thinner central cornea has been reported as an independent risk factor (independent of IOP) associated with POAG.⁸⁸ In LALES, the risk of having OAG was higher in persons with thinner CCT compared with those with normal or thicker CCT even after adjusting the IOP (see Figure 3).⁸⁹ Corneal biomechanical properties such as hysteresis may also have an impact on IOP measurement and glaucoma risk.⁹⁰⁻⁹³ In particular, in eyes with a thin CCT following keratorefractive surgery, IOP may be significantly underestimated by Goldmann applanation tonometry (GAT). Therefore, true IOP may be determined better by methods less influenced by corneal thickness or hysteresis, such as by pneumatometry, dynamic contour tonometry, or with noncontact differential tonometry (Ocular Response Analyzer®, Reichert, Inc., Depew, NY).⁹⁴⁻⁹⁷

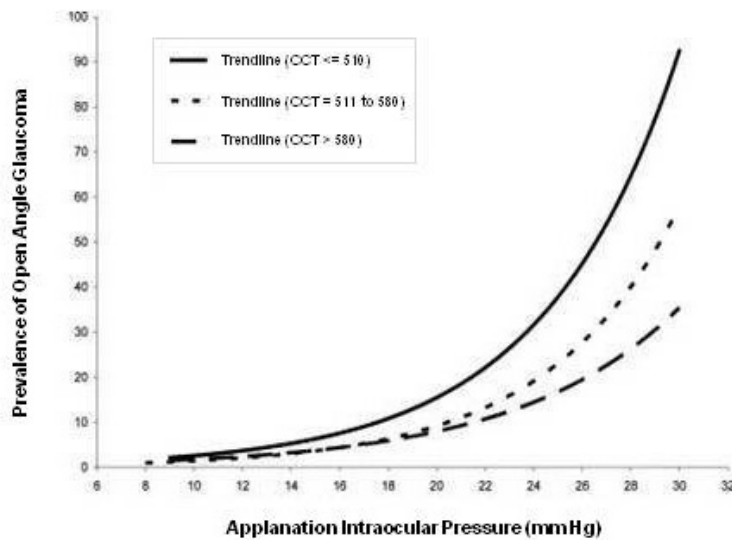


FIGURE 3. The relationship between the prevalence of open-angle glaucoma and applanation intraocular pressure stratified by central corneal thickness (CCT) in micrometers in the Latinos (n=5970) in the Los Angeles Latino Eye Study.

Adapted with permission from Francis B, Varma R, Chopra V, et al, Los Angeles Latino Eye Study Group. Intraocular pressure, central corneal thickness, and prevalence of open-angle glaucoma: the Los Angeles Latino Eye Study. *Am J Ophthalmol* 2008;146:743.

Low Ocular Perfusion Pressure

Ocular perfusion pressure is the difference between blood pressure (at systole or diastole) and the IOP. It has been hypothesized that low ocular perfusion pressures lead to alterations in blood flow at the optic nerve head (ONH) and contribute to progressive glaucomatous optic nerve damage. Population-based studies in African Americans, non-Americans of African descent, Hispanics, and non-Hispanic whites have provided evidence that low diastolic perfusion pressure (<50 mmHg) is associated with a higher prevalence of POAG.^{18,31,33,98,99} In addition, in the Early Manifest Glaucoma Treatment Study, low systolic perfusion pressure (≤ 125 mmHg) was associated with a higher risk of glaucoma progression (relative risk of 1.42) over an 8-year period.⁵⁸ More recent data suggest that nocturnal mean arterial pressure 10 mmHg lower than daytime mean arterial pressure may predict progression of normal-tension glaucoma and increased risk of visual field loss.¹⁰⁰ Recent evidence suggests that low diastolic perfusion pressure is associated with increased risk for glaucoma only in patients taking treatment for systemic hypertension.¹⁰¹ However, statistical analysis is unable to determine whether perfusion pressure is associated with glaucoma because of its individual components (systolic blood pressure, diastolic blood pressure, or IOP), a combination of these components, or an interaction between these components.¹⁰² Further research is needed.

Type 2 Diabetes Mellitus

While there are some conflicting data on the association between type 2 diabetes mellitus and POAG,^{26,35-37,103-108} there is increasing evidence from population-based studies suggesting that type 2 diabetes mellitus is an important risk factor for POAG.^{35-37,104,106} Population-based assessments of Hispanics (in Los Angeles, California),³⁶ non-Hispanic whites (in Beaver Dam, Wisconsin, and Blue Mountains, Australia),^{35,106} and a large cohort enrolled in the Nurses' Health Study¹⁰⁴ have shown that persons with type 2 diabetes mellitus are more likely (40% higher odds in Hispanics, twofold higher odds in non-Hispanic whites) to have POAG. Further, in the LALES,³⁶ longer duration of type 2 diabetes mellitus was associated with a higher risk of having POAG. One explanation for this observation is that microvascular changes in the optic nerve may contribute to the greater susceptibility of optic nerve damage in persons with type 2 diabetes mellitus.¹⁰⁵ A recent meta-analysis of 47 studies concluded that diabetes mellitus is associated with increased risk of glaucoma and may be associated with elevated IOP.³⁸

Myopia

Large cross-sectional epidemiologic studies in Afro-Caribbeans, Hispanics, non-Hispanic whites, Chinese, Asian Indians, and Japanese suggest that persons with myopia have a higher prevalence of OAG than those without myopia.^{34,39-41,109-112} More recently, data from the LALES have provided evidence of an independent relationship between longer axial length (axial myopia) and a higher prevalence of OAG.¹¹³ The underlying hypothesis is that individuals with axial myopia have weaker scleral support at the optic nerve, and this contributes to a greater susceptibility of the optic nerve to glaucomatous damage.

Other Factors – migraine, vasospasm, systemic arterial hypertension, cerebrospinal fluid pressure, and genetic factors

Migraine headache and peripheral vasospasm have been identified as risk factors for glaucomatous optic nerve damage.^{49,114-118} These conditions may decrease autoregulation of optic disc blood flow when compared with patients without this history.¹¹⁹ Although migraine headaches alone may actually decrease visual field sensitivity during the attack,¹²⁰ overall, clinicians should consider migraine and peripheral vasospasm as risk factors for progressive glaucoma.

A number of large population-based studies have noted an association between systemic arterial hypertension and OAG,^{33,98,121-124} though there is also a sizable number of studies reporting no association between these conditions.^{18,34,125-127} A possible explanation for the conflicting findings among these studies may be related to the extent to which the studies adjusted for potential confounding factors. After adjustment for diabetes and hyperlipidemia, one study found that patients with systemic arterial hypertension (and no diabetes or hyperlipidemia) had a 17% increased risk of developing OAG ($P<0.001$) and those with concomitant systemic arterial hypertension and diabetes had a 48% increased risk of glaucoma ($P<0.001$).¹²⁴ The reasons systemic arterial hypertension may increase glaucoma are poorly understood and could be related to increased perfusion of the ciliary body, resulting in increased aqueous production and higher IOP, a known risk factor for glaucoma^{121,128}; decreased perfusion to the optic disc from sclerotic arterioles¹²⁹; or treatment of systemic arterial hypertension with antihypertensives causing systemic hypotension and a reduction in perfusion of the optic nerve.¹³⁰ Interestingly, recent evidence suggests that low diastolic perfusion pressure was found to be associated with increased risk for glaucoma only in patients receiving treatment for systemic hypertension.^{69,101,131} Overall, the association of systemic arterial hypertension with glaucoma is controversial.

Another interesting association may occur between the translaminar pressure gradient (pressure difference between IOP and intracranial pressure) and glaucoma.¹³²⁻¹³⁶ A retrospective study in 30,000 patients who underwent diagnostic lumbar puncture showed lower intracranial pressure in patients with glaucoma compared with age-matched controls.¹³³ Another prospective study demonstrated that patients with POAG had lower intracranial pressure compared with controls.¹³⁵ Follow-up studies from both groups demonstrated that patients with normal-tension glaucoma had even lower levels of intracranial pressure, whereas patients with ocular hypertension had higher levels of intracranial pressure relative to controls without glaucoma.^{134,136} Overall, clinicians need additional research to determine whether intracranial pressure is a risk for glaucoma.¹³⁷

Our understanding of the complex genetic architecture of OAG and how it relates to an increased risk in developing glaucomatous optic neuropathy is rapidly expanding. Traditional linkage methods have identified some genes for some of the heritable forms of glaucoma.¹³⁸⁻¹⁴⁰ Population-based studies have expanded from national consortiums to international collaborations to determine the complex interplay of genetic risk factors for OAG¹⁴¹ and the OAG endophenotypes of IOP,¹⁴²⁻¹⁴⁴ CCT,¹⁴⁵⁻¹⁴⁷ and optic disc parameters.^{148,149} With advances in sequencing technology and reduced costs, there has been a transition to large-scale genome-level interrogation that has led to the identification of the common genetic variants associated with OAG and/or IOP.^{143,149-151} Newer genetic sequencing platforms and large sample sizes of

glaucoma cases and controls will lead to the identification of rare genetic variants associated with OAG. All of these genetic variants, or risk alleles, will require further investigation to determine if the risk alleles are protective, if these alleles are associated with disease progression, or if these alleles are potential new therapeutic targets. At this time, there are genetic tests for select inherited eye diseases,¹⁵² however, routine genetic testing for glaucoma risk alleles is not recommended for patients with POAG.¹⁵³ (III, good quality, strong recommendation)



POPULATION SCREENING FOR GLAUCOMA

Screening for glaucoma in the general population is not cost-effective.^{154,155} Screening is more useful and cost-effective when it is targeted at populations at high risk for glaucoma, such as older adults,¹⁰ those with a family history of glaucoma,^{70,72,156-158} and African Americans and Hispanics.¹⁰

Primary open-angle glaucoma may be an ideal disease to detect by screening because it is often asymptomatic until late in the disease process, it creates significant morbidity, and treatment slows or prevents the progression of visual field loss.¹⁵⁹ Visual field loss in glaucoma decreases health-related quality of life.^{160,161} There are three main approaches to screening patients for POAG: measuring the IOP, assessing the ONH and RNFL, and evaluating the visual field, either alone or in combination.

Measuring IOP is not an effective method for screening populations for glaucoma. Using an IOP above 21 mmHg, the sensitivity for the diagnosis of POAG by tonometry was 47.1% and the specificity was 92.4% in one population survey.¹⁶² Population-based studies suggest that half of all individuals with POAG have IOP levels below 22 mmHg, the usual screening cutoff.^{7,19} Furthermore, half of all individuals with POAG have IOP below 22 mmHg at a single screening.²⁴ Additionally, most individuals with elevated pressures at a screening measurement do not have, and may never develop, optic nerve damage, although risk increases with higher IOP.^{19,24} Studies show that approximately 1 of every 10 to 15 individuals with elevated IOP at screening can have demonstrable optic nerve damage, and half of these (1 in 20 to 30 individuals) may not have been previously diagnosed with glaucoma.^{19,22,24,163}

A second method of screening for glaucoma is to assess the ONH and RNFL. Clinicians can use several techniques to examine the ONH and RNFL. Some techniques, such as ophthalmoscopy and optic disc photography, may require minimal technology but are highly subjective and have poor agreement and high interobserver variation.¹⁶⁴⁻¹⁶⁶ Clinicians can use more technology-dependent objective structural testing (confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography [OCT]) to examine the ONH and/or RNFL. Studies suggest that these have poor to moderate diagnostic precision for glaucoma when used for population-based screening.¹⁶⁷⁻¹⁶⁹

A third method of screening for glaucoma is to evaluate the visual field. Visual field testing has been used in mass screening but may be nonspecific for glaucoma and may show abnormalities in normal eyes because of inexperience with visual field testing, small pupils, inaccuracies due to uncorrected refractive error, and ocular media abnormalities.¹⁷⁰ Frequency doubling technology perimetry does not require correction of moderate refractive error and shows promise as a screening tool to detect moderate to severe glaucomatous damage.^{171,172}

In January 2002, the Centers for Medicare and Medicaid Services initiated coverage for glaucoma examinations by eye care professionals in the office for beneficiaries who have diabetes mellitus, those with a family history of glaucoma, African Americans 50 or older, and Hispanic Americans 65 or older.¹⁷³



CARE PROCESS

PATIENT OUTCOME CRITERIA

- ◆ Preservation of visual function
- ◆ Maintenance of quality of life

DIAGNOSIS

The comprehensive initial glaucoma evaluation (history and physical examination) includes all components of the comprehensive adult medical eye evaluation¹⁷⁴ in addition to, and with special attention to, features that specifically pertain to the diagnosis, course, and treatment of POAG. The examination may require more than one visit. For instance, an individual might be suspected of having glaucoma on one visit but may return for further evaluation to confirm the diagnosis, including additional IOP measurements, gonioscopy, CCT determination, visual field assessment, and ONH and RNFL evaluation and documentation.

History

- ◆ Ocular history (e.g., refractive error, trauma, prior ocular surgery)
- ◆ Race/ethnicity
- ◆ Family history.^{7,70,72} The severity and outcome of glaucoma in family members, including a history of visual loss from glaucoma, should be obtained during initial evaluation.^{70,72}
- ◆ Systemic history (e.g., asthma/chronic obstructive pulmonary disease, migraine headache, vasospasm, diabetes, cardiovascular disease)
- ◆ Review of pertinent records, with particular reference to the past IOP levels, status of the optic nerve, and visual field
- ◆ Current ocular, topical, oral, injected, or inhaled medications (e.g., corticosteroids) and known local or systemic intolerance to ocular or nonocular medications
- ◆ Ocular surgery

A history of LASIK or photorefractive keratectomy is associated with a falsely low IOP measurement due to thinning of the cornea.^{94,96,175-177} Cataract surgery may also lower the IOP compared with the presurgical baseline.^{178,179} A history of prior glaucoma laser or incisional surgical procedures should be elicited. (*good quality, strong recommendation*)

Evaluation of Visual Function

Self-reported functional status or difficulty with vision can be assessed either through patient complaints or by using specific questionnaires, including the National Eye Institute - Visual Function Questionnaire-25 and Glau-QOL.^{160,180-187} Patients who have glaucoma may have sufficient visual field loss to impair night driving, near vision, reading speed, and outdoor mobility.^{161,188-194}

Physical Examination

The ophthalmic evaluation focuses specifically on the following elements in the comprehensive adult medical eye evaluation:¹⁷⁴

- ◆ Visual acuity measurement
- ◆ Pupil examination
- ◆ Anterior segment examination
- ◆ IOP measurement
- ◆ Gonioscopy
- ◆ ONH and RNFL examination
- ◆ Fundus examination

Visual acuity measurement

The best-corrected visual acuity, at distance and at near, should be determined.

Pupil examination

The pupils are examined for reactivity and a relative afferent pupillary defect.¹⁹⁵⁻¹⁹⁸

Anterior segment examination

Slit-lamp biomicroscopic examination of the anterior segment can reveal evidence of physical findings associated with narrow angles, such as shallow peripheral anterior chamber depth and crowded anterior chamber angle anatomy.^{199,200} Secondary mechanisms for elevated IOP may be evident, such as pseudoexfoliation (exfoliation syndrome), pigment dispersion with Krukenberg spindle and/or iris transillumination defects, iris and angle neovascularization, or inflammation.

Intraocular pressure measurement

Clinicians should measure IOP in each eye, preferably by GAT, and before gonioscopy or dilation of the pupil. Recording time of day of IOP measurements may be helpful to assess diurnal variation and its relation to the timing of topical ocular hypotensive agents. The significance of diurnal IOP fluctuation and progression of visual field loss has yet to be fully established in the literature.^{55,57,201-204} Similarly, since IOP may vary within individuals even at the same time of the day, clinicians should consider making therapeutic decisions based on several IOP measurements rather than a single IOP measurement.²⁰⁵

Gonioscopy

The diagnosis of POAG requires careful evaluation of the anterior chamber angle using an indentation gonioscope to exclude the alternative diagnosis of angle-closure glaucoma or secondary causes for IOP elevation, such as angle recession, pigment dispersion, exfoliation syndrome, peripheral anterior synechiae, angle neovascularization, and inflammatory precipitates.²⁰⁶ A useful technique for examining the angle in an eye with a narrow anterior chamber is to have the patient look towards the mirror of the gonio prism into which the examiner is looking.

(See www.gonioscopy.org and Selected Reference Texts section for discussion of the techniques of gonioscopy.)

Optic nerve head and retinal nerve fiber layer clinical examination

Examination of the ONH and RNFL provides valuable structural information about glaucomatous optic nerve damage.^{4,207-210} Physical features that may indicate glaucomatous optic neuropathy include the following:

- ◆ Vertical elongation of the optic cup with associated decrease in neuroretinal rim width
- ◆ Excavation of the cup
- ◆ Thinning of the RNFL
- ◆ Notching of the neuroretinal rim
- ◆ Thinning of the inferior and/or superior neuroretinal rim
- ◆ Disc hemorrhage
- ◆ Large extent of parapapillary atrophy
- ◆ Nasalization of central ONH vessels
- ◆ Baring of the circumlinear vessel
- ◆ Absence of neuroretinal rim pallor

Normally, the neuroretinal rim of the optic nerve is widest inferiorly and narrowest temporally. The abbreviated corollary for this anatomic feature is called the ISNT rule: it is widest at the inferior rim, followed by the superior rim, followed by the nasal rim, and lastly by the temporal rim. In approximately 80% of patients glaucomatous cupping does not follow this rule where both the inferior and superior rims are thinned.^{211,212}

Primary Open-Angle Glaucoma PPP: Diagnosis

Visible structural alterations of the ONH or RNFL and development of parapapillary choroidal atrophy in early glaucoma may precede the onset of visual field defects.^{208,213-215} Other investigations have reported functional deficits occurring in advance of structural change.^{216,217} Careful study of the optic disc neural rim for small hemorrhages is important because these hemorrhages sometimes herald focal disc damage and visual field loss, and they may signify ongoing optic nerve damage in patients with glaucoma.^{46,49-51,58,68,118,218-224} In the Ocular Hypertension Treatment Study (OHTS), the incidence of POAG in eyes with disc hemorrhage was 13.6% compared with 5.2% in eyes without disc hemorrhage over 8 years.⁴⁶ In the Early Manifest Glaucoma Trial, 13% of patients had disc hemorrhages at baseline examination, and hemorrhages were associated with progression.⁵¹

The optic nerve should be carefully examined for the above signs of glaucoma damage, and its appearance should be serially documented.^{4,209,225} (*I+, moderate quality, strong recommendation*) Eye care providers can view the optic disc and RNFL using magnified stereoscopic visualization with the slit-lamp biomicroscope and through a dilated pupil.⁴ (*I+, moderate quality, strong recommendation*) Red-free illumination of the posterior pole by stereobiomicroscopy with an indirect lens at the slit lamp, the direct ophthalmoscope, or with digital red-free photography may aid in evaluating the RNFL.²²⁶ Color stereophotography is an accepted method for documenting qualitative ONH appearance. Computer-based image analysis of the ONH and RNFL is a complementary method for documenting the optic nerve, and is discussed in the Diagnostic Testing section below. Computer-based imaging and stereoscopic photography of the optic nerve provide different information about optic nerve status, and are both useful adjuncts to a good clinical examination.

Fundus examination

Examination of the fundus through a dilated pupil whenever feasible includes a search for other abnormalities that may account for optic nerve changes and/or visual field defects (e.g., disc drusen, optic nerve pits, disc edema or pallor from central nervous system disease or anterior ischemic optic neuropathy, macular degeneration, retinovascular occlusion, or other retinal disease).

Diagnostic Testing

Important diagnostic testing includes the following components:

- ◆ CCT measurement
- ◆ Visual field evaluation
- ◆ ONH and RNFL imaging

Central corneal thickness measurement

Measurement of CCT aids the interpretation of IOP readings and helps to stratify patient risk for ocular damage.^{23,81,88,227} In the OHTS and European Glaucoma Prevention Study trials, the average CCT in the ocular hypertension group was 570 μm , and the risk of developing POAG was greater in eyes with corneal thickness less than 555 μm compared with eyes with corneal thickness 588 μm or greater. (Additional information is available in the Central Corneal Thickness section under Risk Factors.) An overestimation of the real IOP as measured by GAT may occur in eyes with corneas that are thicker than average, whereas an underestimation of the real IOP tends to occur in eyes with corneas that are thinner than average. Several studies have sought to quantify the relationship between measured IOP level and CCT, but there is no generally accepted correction formula. There is a controversy over whether CCT represents a risk factor for glaucoma because of its effect on IOP measurement or whether CCT is a risk factor itself, unrelated to IOP.^{78,228-232} Although it is clear that thinner CCT is a risk factor for the development of POAG when IOP is measured with GAT,²³ studies of progression have had variable findings. Some (but not all) studies found an association with thin CCT (see Table 3).⁶⁸

TABLE 3 SUMMARY OF RESULTS FOR CENTRAL CORNEAL THICKNESS AS A RISK FACTOR FOR PROGRESSION OF GLAUCOMA

Study	No. of Patients	Level of Evidence	Risk	Comments
Early Manifest Glaucoma Trial ⁵⁸	255	I	+	Thin CCT is a risk factor for progression of glaucoma (in those patients with baseline IOP ≥ 21 mmHg)
Kim and Chen ²³³	88	II	+	Thin CCT is associated with visual field progression in glaucoma
Chauhan, et al ²³⁴	54	II	-	CCT did not predict visual field or optic disc progression
Jonas, et al ²³⁵	454	II	-	CCT is not associated with progression of visual field damage
Jonas, et al ²³⁶	390	II	-	CCT is not associated with optic disc hemorrhages
Congdon, et al ⁹¹	230	II	-	CCT is not associated with glaucoma progression (although low corneal hysteresis is associated with glaucoma progression)
Stewart, et al ²³⁷	310	III	+/-	CCT is associated with progression on univariate analysis but is not associated on multivariate analysis

CCT = central corneal thickness; IOP = intraocular pressure

Adapted with permission from Dueker D, Singh K, Lin SC, et al. Corneal thickness measurement in the management of primary open-angle glaucoma: a report by the American Academy of Ophthalmology. *Ophthalmology* 2007;114:1784.

Visual field evaluation

Eye care providers evaluate the visual field using automated static threshold perimetry (SAP) with white-on-white stimuli. It is the gold standard test for comparing other types of visual field testing.²³⁸ (*II, good quality, strong recommendation*) Testing strategies can be tailored to the patient and degree of visual field loss by using specific programs that evaluate the central threshold sensitivity at 24 degrees, 30 degrees, and 10 degrees, and by varying stimulus size. Careful manual combined kinetic and static threshold testing (e.g., Goldmann visual fields) is an acceptable alternative when patients cannot perform automated perimetry reliably or if it is not available. In patients with visual field damage that encroaches upon or involves fixation, use of central 10-degree programs facilitates measurement of this area which is sampled at only four locations using the 24- and 30-degree testing strategies. Before changing glaucoma treatment, repeat and confirmatory visual field examinations are recommended for test results that are unreliable or show a new glaucomatous defect.^{49,239-241} (*III++, good quality, strong recommendation*) It is best to use the same strategy for confirming visual field progression.

Frequency doubling technology and short-wavelength automated perimetry (SWAP) are two of several alternative testing methods shown to be helpful in detecting early visual field damage.²⁴²⁻²⁴⁵ The frequency doubling technology measures contrast sensitivity for a frequency doubling stimulus and has been shown to demonstrate high sensitivity and specificity to detect glaucomatous defects that have later been predictive of functional loss measured by SAP in glaucoma suspect patients.²⁴⁶⁻²⁵⁰ Visual field testing based on SWAP²⁵¹ isolates short-wavelength sensitive cells using a narrow band of blue-light stimulus on a yellow background-illuminated perimeter bowl. See Table 6 in the Follow-up Evaluation section below for recommended guidelines for follow-up timing and frequency for visual field evaluation.²³⁸

Optic nerve head and retinal nerve fiber layer quantitative imaging

Although they are distinctly different methodologies, stereoscopic disc photographs and computerized images of the nerve are complementary with regard to the information they provide the clinician who must manage the patient.²⁵² In the absence of these methodologies, a nonstereoscopic photograph or a drawing of the ONH should be recorded, but this is a less desirable alternative to stereophotography or computer-based imaging.²⁵³⁻²⁵⁶ (*III, insufficient quality, strong recommendation*) In some cases, the topography of the disc is difficult to appreciate on stereo photographs. When the optic disc is saucerized with a paucity of vessels, the topography is often not easily seen on photographs, and a disc drawing obtained by using a narrow slit beam of light moving across the disc may be needed for additional documentation of this anatomic variation. There is limited benefit of using stereophotography or quantitative imaging to identify progressive optic nerve change in patients with advanced glaucomatous optic neuropathy because there is little if any nerve tissue to evaluate or measure.^{257,258}

Computer-based quantitative imaging of the ONH and RNFL is routinely used to provide quantitative information to supplement the clinical examination of the optic nerve. Some patients demonstrate structural alterations in the ONH, parapapillary RNFL, and macular areas of the RNFL before functional change occurs. One rationale for using computerized imaging is to distinguish glaucomatous damage from eyes without glaucoma when thinning of the RNFL is measured, thereby facilitating earlier diagnosis and detection of optic nerve damage.²⁵⁹⁻²⁶¹ There are three types of computer-based optic nerve imaging devices available for glaucoma: confocal scanning laser ophthalmoscopy (CSLO), OCT, and scanning laser polarimetry. The versions of these devices that were studied in a systematic review were similar in their ability to distinguish glaucoma from controls.^{209,262,263} It is important to remember that abnormal results (i.e., results outside of the normative range) from these devices do not always represent disease.²⁶⁴ Criteria used to establish normative databases vary between different imaging devices. Some individual disc findings will not fall into the normative database that is used to establish abnormality, and results should be interpreted cautiously. Therefore, results from these tests must be interpreted in the context of the clinical examination and other supplementary tests in order to avoid falsely concluding that a statistically abnormal result on any quantitative imaging study represents true disease.²⁶⁴ As in these instruments continue to improve, they may become more reliable in helping the clinician diagnose glaucoma and to identify progressive nerve damage.²⁵⁹⁻²⁶¹ Furthermore, progression analysis programs for computer-based imaging devices are evolving to better detect optic nerve and RNFL changes that may be secondary to glaucoma,^{265,266} though these programs are still limited by a lack of longitudinal information on whether these structural changes eventually lead to visual field loss.²⁶⁶

Because some patients show visual field loss without corresponding optic nerve progression,^{8,265-269} both structural and functional assessments remain integral to patient care. Even though quantitative imaging technology is approved as an adjunct to aid in glaucoma diagnosis, the clinician should include all perimetric and other structural information when formulating patient management decisions.²⁵² (*III, insufficient quality, strong recommendation*) As device technology evolves (e.g., specific reference databases, higher resolution spectral domain OCT), the performance of diagnostic imaging devices is expected to improve accordingly.

Differential Diagnosis

Glaucoma is a chronic, progressive optic neuropathy associated with several risk factors, including IOP, that contribute to damage. A characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons result in progressive visual field loss. Other entities associated with optic disc damage or abnormalities of the visual field should be considered prior to accepting the diagnosis of glaucoma. These non-glaucomatous diseases (and examples) are categorized as follows:

- ◆ Optic disc abnormalities
 - ◆ Anterior ischemic optic neuropathies
 - ◆ Optic nerve drusen
 - ◆ Myopic tilted optic nerves
 - ◆ Toxic optic neuropathies
 - ◆ Congenital pit
 - ◆ Congenital disc anomalies (e.g., coloboma, periventricular leukomalacia, Morning Glory syndrome)
 - ◆ Leber hereditary optic neuropathy and dominant optic atrophy
 - ◆ Optic neuritis
- ◆ Retinal abnormalities
 - ◆ Age-related macular degeneration
 - ◆ Panretinal photocoagulation
 - ◆ Retinitis pigmentosa
 - ◆ Retinal arterial and venous occlusions
- ◆ Central nervous system abnormalities
 - ◆ Compressive optic neuropathy
 - ◆ Demyelination from multiple sclerosis
 - ◆ Nutritional optic neuropathy
 - ◆ Dominant optic atrophy

MANAGEMENT

Goals

The goals of managing patients with POAG are as follows:

- ◆ Control of IOP in the target range
- ◆ Stable optic nerve/RNFL status
- ◆ Stable visual fields

Eye care providers can lower IOP with medications, laser therapy, or incisional glaucoma surgery. Results from randomized controlled trials (summarized in Table 2) and other studies provide evidence that these treatments reduce IOP and decrease the rate and incidence of progressive of POAG.^{8,23,49-54,58,64,66,270-283} (*I++*, *good quality*, *strong recommendation*)

Primary open-angle glaucoma is a chronic and usually asymptomatic condition, at least in its early stages, that may require adherence to often multiple and expensive medications,²⁸⁴ which may cause local or systemic side effects. Laser or incisional surgery may also be indicated to manage glaucoma. Visual field loss in glaucoma is associated with a decrease in quality of life measures.^{160,161,285} The effects of treatment, the patient's quality of life, and the patient's life expectancy are to be considered in the decision-making process about therapy. The diagnosis, severity of the disease, prognosis and management plan, and likelihood of long-term therapy should be discussed with the patient. (*good quality*, *strong recommendation*)

Target Intraocular Pressure for Patients with POAG

When deciding to treat a glaucoma suspect patient, it is important to remember that the goal of treatment is to maintain the IOP in a range at which visual field loss is unlikely to significantly reduce a patient's health-related quality of life over his or her lifetime.²⁸⁶ (*II+*, *moderate quality*, *discretionary recommendation*)

Primary Open-Angle Glaucoma PPP: Choice of Therapy

The estimated upper limit of this range is considered the “target pressure.” The initial target pressure is an estimate and a means toward the ultimate goal of protecting the patient’s vision. The target pressure should be individualized and may need adjustment further down or even up during the course of the disease.²⁸⁷ *(III, insufficient quality, discretionary recommendation)*

When initiating therapy, the ophthalmologist assumes that the measured pretreatment pressure range contributed to optic nerve damage and is likely to cause additional damage in the future. Factors to consider when choosing a target pressure include the stage of overall glaucoma damage as determined by the degree of structural optic nerve injury and/or functional visual field loss, baseline IOP at which damage occurred, age of patient, and additional risk factors (e.g., CCT, life expectancy, prior rate of progression). Lowering the pretreatment IOP by 25% or more has been shown to slow progression of POAG.^{49,51-53,65,66} Choosing a lower target IOP can be justified if there is more severe optic nerve damage, if the damage is progressing rapidly, or if other risk factors such as family history, age, or disc hemorrhages are present (see Risk Factors for Progression section below). Choosing a less aggressive target IOP may be reasonable if the risks of treatment outweigh the benefits (e.g., if a patient does not tolerate medical or laser therapy well and surgical intervention would be difficult or if the patient’s anticipated life expectancy is limited). It should be noted, however, that high-quality prospective data comparing different target IOP levels are not currently available; as such, the trade-off between risks and benefits associated with different thresholds is unclear.²⁸⁸

The adequacy and validity of the target pressure are periodically reassessed by comparing optic nerve status (by optic disc appearance and quantitative assessments of the disc and nerve fiber layer) and visual field tests with results from previous examinations. Target IOP may change depending on the results of long-term monitoring. Target pressure is an estimate, and all treatment decisions must be individualized according to the needs of the patient. Although algorithms are useful in clinical practice, no validated algorithm for determining whether to lower or raise any given target IOP currently exists.²⁸⁹

Choice of Therapy

The IOP can be lowered by medical treatment, laser therapy, or incisional glaucoma surgery (alone or in combination). Thorough discussion about the relative risks and benefits of any chosen treatment should be conducted with the patient. *(good quality, strong recommendation)* The patient and ophthalmologist together decide on a practical and feasible regimen to follow in terms of dosing, cost, and adherence in the context of the patient’s age, preferences, and degree of ocular damage.²²⁵ Comorbidities that deserve consideration include asthma/ chronic obstructive pulmonary disease, cardiac arrhythmia, or depression for which patients are using topical ocular hypotensive agents. Patients who are pregnant or nursing also deserve consideration.

Medical treatment

Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of pressure lowering needed (see Table 4 for an overview of options available). If target IOP is not achieved by one medication, then either switching or adding medications should be considered depending on whether the individual patient has responded to the first medication (the first medication should not be kept in the regimen if there is no response in IOP lowering).

Prostaglandin analogs are the most frequently prescribed initial eye drops for lowering IOP in patients with glaucoma because they are most efficacious, well-tolerated, and instilled once daily.^{54,290,291} They are also relatively safe. They are, therefore, often considered as initial medical therapy unless other considerations, such as contraindications, cost, side effects, intolerance, or patient refusal preclude this.²⁹²⁻²⁹⁴ *(I+, good quality, strong recommendation)* Other agents include beta-blockers, alpha₂ adrenergic agonists, parasympathomimetics, and topical and oral carbonic anhydrase inhibitors.^{295,296}

TABLE 4 GLAUCOMA MEDICATIONS

Drug Classification	Methods of Action	IOP Reduction*	Potential Side Effects	Potential Contraindications	FDA Pregnancy Safety Category†
Prostaglandin analogs	Increase uveoscleral and/or trabecular outflow	25%–33%	<ul style="list-style-type: none"> Increased and misdirected eyelash growth Periocular hyperpigmentation Conjunctival injection Allergic conjunctivitis/contact dermatitis Keratitis Possible herpes virus activation Increased iris pigmentation Uveitis Cystoid macular edema Periorbitopathy Migraine-like headache Flu-like symptoms 	<ul style="list-style-type: none"> Macular edema History of herpetic keratitis Active uveitis 	C
Beta-adrenergic antagonists (beta-blockers)	Decrease aqueous production	20%–25%	<ul style="list-style-type: none"> Allergic conjunctivitis/contact dermatitis Keratitis Bronchospasm (seen with nonselective) Bradycardia Hypotension CHF (classic teaching, although cardiologists use beta-blockers as first line treatment in CHF) Reduced exercise tolerance Depression Impotence 	<ul style="list-style-type: none"> Chronic obstructive pulmonary disease (nonselective) Asthma (nonselective) CHF Bradycardia Hypotension Greater than first-degree heart block 	C
Alpha-adrenergic agonists	<p>Nonselective: improve aqueous outflow</p> <p>Selective: decrease aqueous production; decrease episcleral venous pressure or increase uveoscleral outflow</p>	20%–25%	<ul style="list-style-type: none"> Allergic conjunctivitis/contact dermatitis Follicular conjunctivitis Dry mouth and nose Hypotension Headache Fatigue Somnolence 	<ul style="list-style-type: none"> Monoamine oxidase inhibitor therapy Infants and children younger than 2 years 	B
Parasympathomimetic agents	Increase trabecular outflow	20%–25%	<ul style="list-style-type: none"> Increased myopia Decreased vision Cataract Periocular contact dermatitis Allergic conjunctivitis/contact dermatitis Conjunctival scarring Conjunctival shrinkage Keratitis Paradoxical angle closure Retinal tears/detachment Eye or brow ache/pain Increased salivation Abdominal cramps 	<ul style="list-style-type: none"> The need to regularly assess the fundus Neovascular, uveitic, or malignant glaucoma 	C

**Primary Open-Angle Glaucoma PPP:
Choice of Therapy**

TABLE 4 GLAUCOMA MEDICATIONS (CONTINUED)

Drug Classification	Methods of Action	IOP Reduction*	Potential Side Effects	Potential Contraindications	FDA Pregnancy Safety Category†
Topical carbonic anhydrase inhibitors (mainly with systemic use)	Decrease aqueous production	15%–20%	<ul style="list-style-type: none"> • Allergic dermatitis/conjunctivitis • Corneal edema • Keratitis • Metallic taste 	<ul style="list-style-type: none"> • Sulfonamide allergy • Kidney stones • Aplastic anemia • Thrombocytopenia • Sickle cell disease 	C
Oral carbonic anhydrase inhibitors	Decrease aqueous production	20%–30%	<ul style="list-style-type: none"> • Stevens-Johnson syndrome • Malaise, anorexia, depression • Serum electrolyte imbalance • Renal calculi • Blood dyscrasias (aplastic anemia, thrombocytopenia) • Metallic taste • Enuresis • Parasthesia • Diarrhea • Abdominal cramps 	<ul style="list-style-type: none"> • Sulfonamide allergy • Kidney stones • Aplastic anemia • Thrombocytopenia • Sickle cell disease 	C
Hyperosmotic agents	Dehydration of vitreous	No data	<ul style="list-style-type: none"> • Headache • CHF • Nausea, vomiting • Diarrhea • Renal failure • Diabetic complications • Mental confusion 	<ul style="list-style-type: none"> • Renal failure • CHF 	C

CHF = congestive heart failure; IOP = intraocular pressure

* Data from the Heijl A, Traverso CE, eds. Terminology and Guidelines for Glaucoma. European Glaucoma Society. 4th ed. Savona, Italy: PubliComm; 2014:146-51. Available at: www.eugs.org/eng/EGS_guidelines4.asp. Accessed May 29, 2015.

† FDA Pregnancy Category B = Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies on pregnant women. FDA Pregnancy Category C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Adapted with permission from the American Academy of Ophthalmology Practicing Ophthalmologists Curriculum (POC) Panel Chairs and Vice Chairs. Practicing Ophthalmologists Curriculum 2014–2016. Glaucoma. Available at: <http://one.aao.org/POCTopics>. Accessed May 29, 2015.

To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background spontaneous fluctuations of IOP. Though monocular trials have been recommended in the past to determine whether a topical ocular hypotensive agent is effective, recent studies have shown that such trials are not good predictors of long-term efficacy.^{297,298} A monocular trial is defined as the initiation of treatment in only one eye, followed by a comparison of the relative change in IOP in both eyes at follow-up visits to account for spontaneous fluctuations in IOP. However, the trial may not work because the two eyes of an individual may respond differently to the same medication, asymmetric spontaneous fluctuations in IOP may occur, and monocular topical agents may have a contralateral effect.²⁹⁹ A better way to assess IOP-lowering response is to compare the effect in one eye with multiple baseline measurements in the same eye, but the number of necessary baseline measurements will vary among patients.³⁰⁰ (*II+, moderate quality, discretionary recommendation*)

If a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy³⁰¹ or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

The ophthalmologist should assess the patient for local ocular and systemic side effects, toxicity (interactions with other medications), and potential life-threatening adverse reactions. (*good quality, strong recommendation*) To reduce systemic absorption, patients should be educated about eyelid closure or nasolacrimal duct occlusion when applying topical medications (see Related Academy Materials section for public information brochures).³⁰² (*III, good quality, strong recommendation*)

Adequate treatment of glaucoma requires a high level of adherence to therapy. Frequently this is not achieved, and studies indicate relatively poor adherence to therapy.³⁰³⁻³⁰⁶ Multiple dosing requirements or side effects (such as depression, exercise intolerance, and impotence that might occur with topical beta-blockers) may impact adherence to therapy.^{307,308} Even with instruction, free medication, once-daily administration, use of a dosing aid, and electronic monitoring of adherence, nearly 45% of patients in one study took fewer than 75% of their prescribed doses.³⁰⁶ Fixed combinations of two medications may improve patient adherence by reducing the number of drops required for therapy. Instilling eye drops correctly is difficult for many patients, and their ability to do so may worsen with aging, comorbidities, and as glaucoma progresses.^{309,310} Repeated instruction and counseling about proper techniques for using medication, including waiting at least 5 minutes between multiple drop regimens as well as a clearly written medication regimen and follow-up telephone calls or smart phone reminders may improve adherence to therapy.^{306,311,312} At each examination, medication dosage and frequency of use should be recorded. (*good quality, strong recommendation*) Reviewing the time medication was taken may be useful to help patients link eye-drop administration to activities of daily living and to be sure patients are actually using their eye drops. Adherence to the therapeutic regimen and recommendations for therapeutic alternatives or diagnostic procedures should be discussed. (*good quality, strong recommendation*) Cost may be a factor in adherence, especially when multiple medications are used.³¹¹ Patient education through oral, written, and online information and informed participation in treatment decisions may improve adherence³¹¹ and overall effectiveness of glaucoma management. Adherence is also handicapped when patients run out of medication before they are permitted to refill their prescription. However, patients with Medicare insurance may now refill their medication after they have completed at least 70% of the month, or approximately 21 days of therapy.³¹³

Special circumstances in pregnancy and during breast-feeding

Pregnancy

Glaucoma medical management of the pregnant or nursing patient presents challenges with respect to balancing glaucoma progression³¹⁴ against concerns for the safety of the fetus or the infant.³¹⁵⁻³¹⁷ Data on the risks of topical ocular hypotensive agents during pregnancy are limited. The FDA has established drug pregnancy categories of A, B, C, D, and X.³¹⁸

Pregnancy Category A indicates evidence from studies in pregnant women that the drug failed to show fetal risk in any trimester. Category B indicates animal reproductive studies failed to show fetal risk and that there are no well-controlled studies in pregnant women. Category C indicates that animal reproductive studies showed adverse effects on the fetus and that there are no well-controlled studies on pregnant women. Category D indicates evidence of human fetal risk. Category X indicates that animal and human studies showed fetal abnormalities. Brimonidine has a Pregnancy Category B rating. All other topical ocular hypotensive agents have a Pregnancy Category C rating. The beta-blockers tend to be used during pregnancy because there is long-term experience with this drug class. Very few data exist on the risk of taking latanoprost in pregnancy, although a small case series of 11 subjects who took it while pregnant revealed no adverse effects on pregnancy and no birth defects.³¹⁹ In general, most ophthalmologists avoid the use of prostaglandins during pregnancy because of the theoretical risk of premature labor, but these medications may be considered for use in the breast-feeding mother.³¹⁷

Breast-feeding

Some topical glaucoma medications have been detected in breast milk, such as timolol and carbonic anhydrase inhibitors. The data are controversial as to whether timolol poses a threat to the breast-feeding infant. The American Academy of Pediatrics has approved the use of both oral and topical forms of carbonic anhydrase inhibitors during lactation, although the infant should be carefully monitored when the former are used.^{317,320}

Brimonidine is known to cross the blood-brain barrier and can cause apnea in infants. For this reason, it is usually recommended that the medication not be used in mothers who are breast-feeding.³¹⁶ (*III, good quality, strong recommendation*) In summary, managing glaucoma in the pregnant or lactating patient involves an interdisciplinary approach to balance disease progression in the mother while minimizing risks to the fetus and nursing infant.

Laser trabeculoplasty

Laser trabeculoplasty can be considered as initial therapy in selected patients^{272,321,322} or an alternative for patients at high risk for nonadherence to medical therapy who cannot or will not use medications reliably due to cost, memory problems, difficulty with instillation, or intolerance to the medication. (*I+, good quality, discretionary recommendation*) Laser trabeculoplasty lowers IOP by improving aqueous outflow and can be performed using argon, diode, and frequency-doubled neodymium: yttrium-aluminum-garnet (Nd:YAG) lasers.^{323,324}

Argon and diode laser trabeculoplasty

Studies using continuous-wave argon laser with a wavelength spectrum that peaks at 488 nm (argon laser trabeculoplasty [ALT]) found that treatment increases aqueous outflow and provides a clinically significant reduction of IOP in more than 75% of initial treatments on previously unoperated eyes (see Table 5).^{66,272} Since these initial studies were performed, more compact solid-state diode lasers have mostly replaced the original argon laser with equal IOP-lowering efficacy and safety.^{325,326}

For patients initially treated with ALT, the amount of medical treatment required for glaucoma control is often reduced.^{272,327} Results from long-term studies of patients receiving maximum medical therapy who subsequently had laser and incisional surgery indicate that 30% to more than 50% of eyes require additional surgical treatment within 5 years after ALT.^{66,328-331} For eyes that have failed to maintain a previously adequate response, repeat ALT has a low long-term rate of success, with failure occurring in nearly 90% of these eyes by 2 years.³³²⁻³³⁶ Argon laser trabeculoplasty may be performed to 180 degrees or to 360 degrees. After previous applications to the full circumference of the anterior chamber angle, repeat ALT has a lower success rate than initial therapy^{334,335} in eyes that have not had a reduction in IOP for at least a year following the first laser surgery.³³⁵ Compared with initial laser trabeculoplasty, there is an increased risk of complications such as IOP spikes after repeat ALT.^{332,333,336,337}

Selective laser trabeculoplasty

The introduction of selective laser trabeculoplasty (SLT) is most likely responsible for the increase in use of laser trabeculoplasty in 2001 after a previous decline.³³⁸⁻³⁴⁰ Selective laser trabeculoplasty uses a 532 nm, Q-switched, frequency-doubled, Nd:YAG laser that delivers less energy and is selectively absorbed by pigmented cells in the trabecular meshwork.³⁴¹ These attributes produce less thermal damage to the trabecular meshwork compared with ALT.³⁴² However, several prospective and retrospective studies indicate that SLT appears comparable to but not better than ALT in lowering IOP.³⁴³⁻³⁵⁰ Selective laser trabeculoplasty also appears to be comparable in efficacy to medical therapy with prostaglandin analogs,^{321,351} although in one prospective study, SLT was only comparable to latanoprost when 360 degrees of the trabecular meshwork was treated.³⁵¹ In this study, latanoprost had a better IOP-lowering effect compared with 90 and 180 degrees of treatment. A multicenter randomized clinical trial compared SLT and medical therapy as initial treatment for OAG.³²² Similar IOP reduction was seen in the SLT and medication groups after 1 year of follow-up, although this study may have had insufficient statistical power to detect a difference.

It has been suggested that SLT has greater success than ALT with repeated treatments, but no controlled randomized clinical trial has demonstrated this finding. Similar IOP reduction and success rates have been observed with repeat SLT compared with initial SLT in retrospective studies.³⁵²⁻³⁵⁴ The safety profile of SLT appears to be good, with mild anterior chamber inflammation after treatment and less ocular discomfort compared with ALT.³⁴⁶ Intraocular pressure spikes have been noted after SLT in 4.5% to 27% of eyes in various studies,^{343,347,351,355} which are similar to rates observed with ALT.^{343,347} Clinical experience suggests that eyes with more heavily pigmented trabecular meshwork are more prone to IOP spikes.³⁵⁶

TABLE 5 RANDOMIZED CLINICAL TRIALS OF ARGON LASER TRABECULOPLASTY WITH PUBLISHED RESULTS

Study	Study Design	No. of Patients	Follow-up Duration (yrs)	Finding
Glaucoma Laser Trial (GLT), 1990–1995 ^{357,358}	Newly diagnosed POAG: medical therapy vs. laser trabeculoplasty	271	2.5–5.5	Initial laser trabeculoplasty lowered IOP more (9 mmHg) than initial treatment with topical timolol maleate (7 mmHg) over 2 yrs; initial laser trabeculoplasty was at least as effective in preserving visual field and optic disc status over 5.5 yrs.
Glaucoma Laser Trial Follow-up Study, 1995 ³⁵⁸	Participants in the GLT	203	6–9	Longer follow-up reinforced the earlier findings that initial laser trabeculoplasty lowered IOP more (1.2 mmHg) than initial treatment with topical timolol maleate and was at least as effective in preserving visual field and optic disc status.
Moorfields Primary Treatment Trial, 1994 ⁶⁴	Newly diagnosed POAG: medical therapy vs. laser, trabeculoplasty vs. trabeculectomy	168	5+	Trabeculectomy lowered IOP the most (60%). The laser trabeculoplasty (38% IOP reduction) and medical therapy groups (49% IOP reduction) had more deterioration in visual fields than the trabeculectomy group.
Early Manifest Glaucoma Trial, 2002–2007 ^{51,52,58}	Newly diagnosed POAG: medical therapy and laser, trabeculoplasty vs. no treatment	255	4–10	Lowering IOP with medical therapy and trabeculoplasty (25%) slowed progression of optic disc and visual field damage.
Advanced Glaucoma Intervention Study (AGIS), 2000–2004 ^{53,66}	POAG after medical-therapy failure with no previous surgery: laser trabeculoplasty vs. trabeculectomy	591	10–13	Surgical outcome varied by race; patients with African ancestry did better with trabeculoplasty first (30% IOP reduction), whereas in the longer term (4+ yrs) Caucasian American patients did better with trabeculectomy first (48% IOP reduction). Lowest IOP group during follow-up after surgical interventions (47% IOP reduction) protected against further visual field deterioration in advanced glaucoma patients.

IOP = intraocular pressure; POAG = primary open-angle glaucoma

Perioperative care for laser trabeculoplasty

The ophthalmologist who performs the laser surgery has the following responsibilities:^{359,360}

- ◆ To obtain informed consent from the patient or the patient's surrogate decision maker after discussing the risks, benefits, and expected outcomes of surgery
- ◆ To ensure that the preoperative evaluation confirms the need for surgery
- ◆ To perform at least one IOP check immediately prior to surgery and within 30 minutes to 2 hours after surgery³⁶¹
- ◆ To perform a follow-up examination within 6 weeks of surgery or sooner if there is concern about IOP-related damage to the optic nerve during this time^{328,362-364}

Medications that are not being used chronically may be used perioperatively to avert temporary IOP elevations, particularly in those patients with severe disease.^{361,365,366}

Brimonidine has been shown to be as effective as apraclonidine in preventing immediate IOP elevation after laser trabeculoplasty.^{367,368} Treating 180 degrees reduces the incidence and magnitude of postoperative IOP elevation compared with 360-degree treatment.³⁶⁹⁻³⁷¹

Incisional glaucoma surgery

Trabeculectomy

Trabeculectomy is effective in lowering IOP; it is generally indicated when medications and appropriate laser therapy are insufficient to control disease and can be considered in selected cases as initial therapy.^{372,373} (*I+*, *good quality, strong recommendation*)

Trabeculectomy provides an alternative path for the escape of aqueous humor into the subconjunctival space, and it often reduces IOP and the need for medical treatment. Estimates of success rates over time range from 31% to 88% in different populations and with varying definitions of success and failure.³⁷⁴⁻³⁷⁷ The failure rate of trabeculectomy, without the use of adjunctive antifibrotic medications alone or combined with medical therapy, in a previously unoperated eye in the Advanced Glaucoma Intervention Study⁶⁶ reached approximately 30% in African American patients and 20% in Caucasian American patients over a 10-year period.⁶⁶ Even though long-term control is often achieved, many patients require further therapy or additional ocular surgery, with a higher associated long-term failure rate.^{66,378-381} Furthermore, filtering surgery increases the likelihood that phakic eyes may require subsequent cataract surgery.^{65,382,383} A history of glaucoma surgery also increases the risk of corneal graft failure after penetrating keratoplasty.³⁸⁴

In eyes that have undergone previous cataract surgery involving a conjunctival incision, the success rate of initial glaucoma surgery is reduced.^{273,379,385-387} However, a retrospective case comparison study observed a similar success rate of initial trabeculectomy with mitomycin-C (MMC) in phakic eyes and in eyes after clear-corneal phacoemulsification.³⁸⁸

Antifibrotic agents may be used intraoperatively and postoperatively to reduce the subconjunctival scarring after trabeculectomy that can result in failure of the operation. The use of intraoperative-MMC reduces the risk of surgical failure both in eyes at high risk of surgical failure^{389,390} and in eyes that have not undergone previous surgery.³⁹⁰⁻³⁹³ Some studies have demonstrated a benefit of intraoperative 5-fluorouracil^{394,395} and others have not.³⁹⁶ Intraoperative 5-fluorouracil and MMC were found to be equally safe and effective adjuncts to primary trabeculectomy in a multicenter randomized clinical trial.³⁹⁵ The use of postoperative injections of 5-fluorouracil also reduces the likelihood of surgical failure in both high-risk eyes^{273,397-399} and eyes that have not undergone previous surgery.³⁹⁹⁻⁴⁰¹ Aqueous outflow may be enhanced in the early postoperative period with laser suture lysis or removal of releasable sutures.^{402,403} Needling with 5-fluorouracil has been shown to be effective in reviving failing filtering blebs.^{404,405}

The use of an antifibrotic agent carries with it an increased likelihood of complications such as hypotony,⁴⁰⁶⁻⁴⁰⁸ hypotony maculopathy,⁴⁰⁶ late-onset bleb leak,^{399,409} and late-onset infection⁴¹⁰⁻⁴¹² that must be weighed against the benefits when deciding whether to use these agents. These complications may be even more common in primary filtering surgery of phakic patients.⁴¹³⁻⁴¹⁵ A trend toward a lower concentration and shorter exposure time of MMC has been observed over time,⁴¹⁶ and use of a fornix-based conjunctival flap with broad application of MMC has been advocated to avoid bleb-related complications.^{417,418}

The Ex-PRESS shunt (Alcon Laboratories, Fort Worth, TX) is a nonvalved, stainless steel tube originally designed for subconjunctival implantation at the limbus. A high rate of hypotony and device extrusion⁴¹⁹⁻⁴²¹ prompted a modification in surgical technique, which involved placing the device under a partial thickness scleral flap.⁴²² The procedure is similar to trabeculectomy, but sclerostomy and iridectomy are not performed. Retrospective studies⁴²²⁻⁴²⁷ and randomized clinical trials⁴²⁸⁻⁴³⁰ have reported similar IOP reduction and surgical success rates with trabeculectomy and Ex-PRESS. Several studies comparing Ex-PRESS with trabeculectomy found no significant differences in the rates of intraoperative and postoperative complications,^{424,425,427-430} but others have reported a higher incidence of early hypotony following trabeculectomy.^{423,426} Use of the Ex-PRESS implant is associated with greater surgical cost relative to trabeculectomy due to the additional expense of the implant itself.⁴³¹

Aqueous shunts

All aqueous shunts (also known as tube shunts, glaucoma drainage devices, and setons) consist of a tube that diverts aqueous humor to an end plate located under the conjunctiva and Tenon capsule in the equatorial region of the eye. The primary resistance to flow through these devices occurs across the fibrous capsule that develops around the end plate. Aqueous shunts differ in their design with respect to the size, shape, and material composition of the end plate. They may be further subdivided into valved and nonvalved shunts, depending on whether a valve mechanism is present to limit flow through the shunt if the IOP becomes too low. Examples of nonvalved implants are the Baerveldt glaucoma implant (Abbott Medical Optics, Santa Ana, CA) and the Molteno implant (Molteno Ophthalmic Ltd., Dunedin, New Zealand). An example of the valved implants is the Ahmed glaucoma valve (New World Medical, Inc., Rancho Cucamonga, CA).

Aqueous shunts have traditionally been used to manage medically uncontrolled glaucoma when trabeculectomy has failed to control IOP or is deemed unlikely to succeed. This includes eyes with neovascular glaucoma, uveitic glaucoma, conjunctival scarring from previous ocular surgery or cicatrizing diseases of the conjunctiva, and congenital glaucoma in which angle surgery has failed. However, the indications for using aqueous shunts have been broadening, and these devices are being increasingly used in the surgical management of glaucoma. Medicare data show a steady rise in the number of shunts placed from 1995 to 2004, and there has been a concurrent decline in the number of trabeculectomies performed.³³⁹

Several studies have compared aqueous shunts with trabeculectomy. A retrospective study evaluating surgical results in matched patient groups reported similar IOP reduction with the single-plate Molteno implant and trabeculectomy with 5-fluorouracil.⁴³² However, another retrospective case-control study observed a higher 5-year success rate after trabeculectomy with MMC than with Ahmed glaucoma valve implantation.⁴³³ A randomized clinical trial in Sri Lanka comparing the Ahmed implant and trabeculectomy in patients with POAG and angle-closure glaucoma found comparable IOP reduction and success rates, with a mean follow-up of 31 months.⁴³⁴ The Tube Versus Trabeculectomy (TVT) Study is a multicenter prospective randomized clinical trial that compared the safety and efficacy of tube-shunt surgery using the 350-mm² Baerveldt glaucoma implant and trabeculectomy with MMC in patients with previous cataract extraction and/or failed trabeculectomy. Tube-shunt surgery had a higher success rate than trabeculectomy during 5 years of follow-up, but both surgical procedures were associated with similar IOP reduction, use of supplemental medical therapy, serious complications, and vision loss at 5 years.^{435,436}

Numerous studies have compared aqueous shunts that differ in size and design.⁴³⁷⁻⁴⁴⁶ Shunts with larger surface area end plates have been associated with lower levels of IOP⁴³⁷⁻⁴³⁹ and use of fewer topical ocular hypotensive agents^{438,440,441} in several retrospective case series. A randomized clinical trial evaluating the single-plate (135 mm²) and double-plate (270 mm²) Molteno implants observed a higher success rate with the double-plate implant at 2 years.⁴⁴² However, a prospective study of the 350-mm² and 500-mm² Baerveldt implants found a higher success rate with the 350-mm² implant at 5 years.⁴⁴³ A prospective randomized trial comparing the Ahmed glaucoma valve (184 mm²) and single-plate Molteno implant noted similar success with both implants at 2 years.⁴⁴⁴ The Ahmed Baerveldt Comparison (ABC) Study and Ahmed Versus Baerveldt (AVB) Study are both multicenter randomized clinical trials designed to compare the safety and efficacy of the Ahmed glaucoma valve and Baerveldt implant. Greater reductions in IOP and use of glaucoma medical therapy were seen following Baerveldt implantation at 3 months and thereafter, and these differences were statistically significant at multiple time points during 3 years of follow-up in both studies.^{445,446} Serious complications in the ABC Study and hypotony-related vision-threatening complications in the AVB Study occurred less frequently with the Ahmed implant.

Aqueous shunts are associated with intraoperative and postoperative complications that are similar to those that occur with trabeculectomy. In addition, they have unique complications related to implantation of a foreign body. Erosion of the tube may occur through the conjunctiva (5% in TVT Study,⁴³⁶ 1% in ABC Study⁴⁴⁵), and this typically develops a few millimeters behind the limbus following anterior chamber insertion. To prevent tube erosion, patch allografts of sclera, cornea, or pericardium are commonly used. Diplopia may result from extraocular muscle fibrosis or a mass effect of the bleb overlying the end plate (6% in TVT Study,⁴³⁶ 11% in ABC Study,⁴⁴⁵ 4% in AVB Study⁴⁴⁶). Tube-cornea touch can lead to progressive endothelial cell loss and persistent corneal edema (16% in TVT Study,⁴³⁶ 6% in ABC Study,⁴⁴⁵ 11% in AVB Study⁴⁴⁶). Iris, vitreous, blood, or fibrin may obstruct the tube. The risk of postoperative infection appears to be less with aqueous shunts than after trabeculectomy with an antifibrotic agent.

Combined surgeries

Patients with POAG who have a visually significant cataract have a range of options to consider. If IOP control is at target on one or two medications, cataract surgery alone may be adequate, with the additional benefit that it may lower IOP slightly. If IOP is markedly uncontrolled on several medications after laser trabeculoplasty and the patient has a moderate cataract, then glaucoma surgery may be indicated initially, with the plan to perform cataract surgery once IOP is adequately controlled. In between these two extremes, the decision of which procedure(s) to perform first or whether to combine cataract and glaucoma surgery is determined by the ophthalmologist and patient after discussion of the risks and benefits of each course of action.

Cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2 mmHg on average.¹⁷⁸ An average decrease in IOP of 16.5% was observed among patients in OHTS after cataract extraction, which persisted during the 3 years of follow-up postoperatively.¹⁷⁹ Generally, combined cataract and glaucoma surgery is not as effective as glaucoma surgery alone in lowering IOP,^{178,447} so patients who require filtration surgery who also have mild cataract may be better served by filtration surgery alone and cataract surgery later. The use of MMC, but not 5-fluorouracil, results in lower IOP in combined procedures.^{178,390,447} A systematic review published in 2002 found moderate quality evidence that separating the cataract and glaucoma incisions results in lower IOP than a one-site combined procedure, but the differences in outcomes were small.⁴⁴⁷ Subsequent publications have found no difference between the two approaches.⁴⁴⁸⁻⁴⁵⁰

Potential benefits of a combined procedure (cataract extraction with IOL implantation and trabeculectomy) are protection against the IOP rise that may complicate cataract surgery alone, the possibility of achieving long-term glaucoma control with a single operation, and elimination of the risk of bleb failure with subsequent cataract surgery when glaucoma surgery is performed first.⁴⁵¹⁻⁴⁵³ Therefore, an ophthalmologist may reasonably choose to perform a combined surgery because of these perceived advantages to an individual patient.

Other types of glaucoma surgery can also be combined with cataract surgery, such as implantation of aqueous shunts, nonpenetrating glaucoma surgery, minimally invasive glaucoma surgery, and endocyclophotocoagulation.

Other incisional glaucoma surgeries

Several other glaucoma surgeries exist as alternatives to trabeculectomy and aqueous shunt implantation. The precise role of these procedures in the surgical management of glaucoma remains to be determined.

Nonpenetrating glaucoma surgery

The rationale for nonpenetrating glaucoma surgery is that by avoiding a continuous passageway from the anterior chamber to the subconjunctival space, the incidence of complications such as bleb-related problems and hypotony can be reduced. The nonpenetrating procedures have a higher degree of surgical difficulty compared with trabeculectomy and they require special instrumentation.

Deep sclerectomy: Deep sclerectomy involves excision of sclerocorneal tissue under a partial thickness scleral flap, leaving a thin window of trabecular meshwork and Descemet membrane to provide some resistance to aqueous outflow. Antifibrotic agents are frequently used as adjuncts to deep sclerectomy, and it has been suggested that placement of collagen drainage devices under the scleral flap can improve aqueous humor filtration.⁴⁵⁴⁻⁴⁵⁶ One randomized clinical trial found that trabeculectomy was more effective than deep sclerectomy at lowering IOP,⁴⁵⁷ but several others found that the two surgeries were equally effective.⁴⁵⁸⁻⁴⁶¹

Viscocanalostomy: Viscocanalostomy includes deep sclerectomy along with expansion of the Schlemm canal using an ophthalmic viscoelastic device. The procedure is intended to allow passage of aqueous humor through the trabeculodescemet membrane window and into the physiologic outflow pathway through the Schlemm canal. Randomized clinical trials comparing viscocanalostomy with trabeculectomy suggest greater IOP reduction with trabeculectomy but fewer complications with viscocanalostomy.^{463,462-469}

Canaloplasty: In canaloplasty, circumferential viscodilation of the Schlemm canal using a flexible microcatheter is performed in combination with deep sclerectomy. Dilating the entire canal aims to give aqueous humor access to a greater number of collector channels. A 10-0 polypropylene (Prolene) suture is placed with appropriate tension within the Schlemm canal when possible to apply inward directed tension on the trabecular meshwork. The safety and efficacy of canaloplasty alone and combined with phacoemulsification was described in a nonrandomized multicenter clinical trial through 3 years of follow-up.⁴⁷⁰ No randomized clinical trial comparing trabeculectomy and canaloplasty exists. A retrospective case series found lower postoperative IOP with trabeculectomy compared with canaloplasty.⁴⁷¹

Micro-invasive glaucoma surgery

The term micro-invasive or minimally invasive glaucoma surgery (MIGS) refers to a group of newer surgical procedures that are performed by using an ab interno approach and involve minimal trauma to ocular tissues.⁴⁷² Limited long-term data are currently available for MIGS. Modest IOP reduction has been reported following MIGS, and postoperative pressures are typically in the mid to upper teens. Although less effective in lowering IOP than trabeculectomy and aqueous shunt surgery, MIGS appears to have a more favorable safety profile in the short term. It is commonly combined with phacoemulsification.

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Ab interno trabeculectomy: Ab interno trabeculectomy, or Trabectome (NeoMedix Corporation, Tustin, CA), removes a strip of trabecular meshwork and Schlemm canal using high-frequency electrocautery. Reduction in IOP and glaucoma medical therapy has been reported with Trabectome with minimal intraoperative and postoperative complications.⁴⁷³⁻⁴⁷⁷ Case series have described the efficacy of Trabectome combined with phacoemulsification, but no randomized prospective studies have included a comparison group of phacoemulsification alone.^{474,476-481} Therefore, it is unclear how much pressure reduction is provided by the Trabectome and cataract extraction portions of the procedure. Prior laser trabeculoplasty does not appear to significantly affect the results of Trabectome.^{482,483} A failed Trabectome did not affect the success rate of subsequent trabeculectomy in one cohort study.⁴⁸⁴

Trabecular microbypass stent: The trabecular microbypass stent, or iStent (Glaukos Corporation, Laguna Hills, CA), is a snorkel-shaped device manufactured from heparin-coated titanium. A preloaded inserter is used to implant the device into the Schlemm canal under gonioscopic guidance. The iStent has received FDA approval for implantation in combination with cataract extraction in patients with mild to moderate OAG treated with topical ocular hypotensive agents. Several studies have reported a small reduction of IOP and glaucoma medical therapy with the combined phacoemulsification and iStent placement compared with phacoemulsification alone.⁴⁸⁵⁻⁴⁸⁸ A decrease in IOP and topical ocular hypotensive agents has been described with the iStent alone in the treatment of secondary OAG.^{489,490} Recent studies suggest that implantation of multiple stents may provide better IOP lowering than a single stent.^{486,491} Low rates of surgical complications have been reported with the iStent, and most commonly they relate to stent malposition or obstruction.⁴⁸⁵⁻⁴⁹¹

Perioperative care in incisional glaucoma surgery

The ophthalmologist who performs incisional glaucoma surgery has the following responsibilities:^{359,360}

- ◆ Obtain informed consent from the patient or the patient's surrogate decision maker after discussing the risks, benefits, and expected outcomes of surgery⁴⁹²
- ◆ Ensure that the preoperative evaluation accurately documents the findings and indications for surgery
- ◆ Prescribe topical corticosteroids in the postoperative period^{493,494}
- ◆ Perform a follow-up evaluation on the first postoperative day (12 to 36 hours after surgery) and at least once during the first 1 to 2 weeks to evaluate visual acuity, IOP, and status of the anterior segment⁴⁹⁵⁻⁵⁰⁰
- ◆ In the absence of complications, perform additional postoperative visits during a 3-month period to evaluate visual acuity, IOP, and status of the anterior segment⁴⁹⁵⁻⁵⁰⁰
- ◆ Schedule more frequent follow-up visits, as necessary, for patients with postoperative complications such as a flat or shallow anterior chamber or evidence of early bleb failure, increased inflammation, or Tenon's cyst (encapsulated bleb)⁴⁹⁵⁻⁵⁰⁰
- ◆ Undertake additional treatments as necessary to improve aqueous flow into the bleb and lower IOP if evidence of bleb failure develops, including injection of antifibrotic agents, bleb massage, suture adjustment, release or lysis, or bleb needling^{405,501,502}
- ◆ Manage postoperative complications as they develop, such as repair of bleb leak or reformation of a flat anterior chamber
- ◆ Explain that filtration surgery places the eye at risk for endophthalmitis for the duration of the patient's life, and that if the patient has symptoms of pain and decreased vision and the signs of redness and discharge, he or she should notify the ophthalmologist immediately⁵⁰³ (*III, good quality, strong recommendation*)

Cyclodestructive surgery

Cyclodestructive procedures reduce the rate of aqueous production. There are several ways to reduce ciliary body function, including cyclocryotherapy, transscleral and noncontact Nd:YAG laser, and transscleral and noncontact endodiode laser cyclophotocoagulation.^{504,505} Cyclodestructive procedures have traditionally been used for refractory glaucomas, and success rates have been reported in the range of 34% to 94%.⁵⁰⁵ They have been associated with a subsequent decrease of visual acuity^{506,507} and, rarely, cases of sympathetic ophthalmia.^{508,509} Disadvantages of cyclodestructive procedures include postoperative inflammation, pain, hypotony, cystoid macular edema, IOP spike, and the frequent need for repeat treatment weeks or months later.⁵¹⁰ Compared with cyclocryotherapy, laser cyclophotocoagulation causes less postoperative pain and inflammation. Therefore, cyclocryotherapy is now rarely used. Laser cyclodestructive procedures have advantages over filtration surgery that include technical ease, reduced postoperative care, and avoidance of incisional surgery. Transscleral cyclophotocoagulation is a good surgical option for eyes with limited visual potential or are otherwise poor candidates for incisional ocular surgery.

In 2005, 47% of all Medicare cyclophotocoagulation procedures were performed endoscopically; in 2006, 58%; and in 2007, 65%.⁵¹¹ Endoscopic cyclophotocoagulation (ECP) consists of a solid-state 810-nm laser, a video camera, aiming beam, and xenon light source housed together and delivered through a fiberoptic cable⁵⁰⁵ that can be introduced inside the eye for direct visualization and treatment of the ciliary processes. This allows better titration of laser treatment.^{512,513} The efficacy of ECP appears to be good, with IOP reduction reported in the range of 34% to 57%.⁵¹⁴⁻⁵¹⁶ Most studies treat 270 to 360 degrees of the ciliary body.^{514,516} Fibrin exudates, hyphema, cystoid macular edema, vision loss, hypotony, choroidal detachment,⁵¹⁴ and phthisis⁵¹⁷ have been noted after ECP in eyes with advanced glaucoma, but more recent studies involving eyes with less advanced glaucomatous damage seem to report fewer of these complications.⁵¹⁵

Endoscopic cyclophotocoagulation^{514,515,518} may be combined with cataract surgery. One randomized trial comparing cataract surgery combined with either ECP or trabeculectomy suggested that IOP lowering efficacy is similar for both,⁵¹⁹ and another study comparing ECP with the Ahmed drainage implant also showed comparable efficacy in IOP lowering, although the rate of complication with the latter surgery was higher.⁵²⁰

Other therapeutic considerations

Among patients there is a growing interest in complementary and alternative medicinal approaches to the treatment of glaucoma. There is a lack of scientific evidence that herbal medicines or nutritional supplements are beneficial in treating glaucoma.^{521,522} One study based on patient questionnaires found an association between higher intake of certain fruits and vegetables (collard greens, kale, and carrots) and reduced risk of glaucoma.⁵²³ Two reviews of the scientific evidence by the American Academy of Ophthalmology and the American Glaucoma Society found no support for increased benefit or diminished risk with the use of marijuana to treat glaucoma compared with conventional medications.^{524,525}

Follow-up Evaluation

Guidelines for follow-up of patients with POAG are summarized in Table 6. These recommendations apply to ongoing glaucoma management and not to visits for other purposes. Follow-up evaluation includes examination as well as ONH and visual field assessment as indicated.

TABLE 6 CONSENSUS-BASED GUIDELINES FOR FOLLOW-UP GLAUCOMA STATUS EVALUATIONS WITH OPTIC NERVE AND VISUAL FIELD ASSESSMENT*

Target IOP Achieved	Progression of Damage	Duration of Control (mos)	Approximate Follow-up Interval (mos)†
Yes	No	≤6	6
Yes	No	>6	12
Yes	Yes	NA	1–2
No	Yes	NA	1–2
No	No	NA	3–6

IOP = intraocular pressure; NA = not applicable

* Evaluations consist of clinical examination of the patient, including optic nerve head assessment (with periodic color stereophotography or computerized imaging of the optic nerve and retinal nerve fiber layer structure) and visual field assessment.

† Patients with more-advanced damage or greater lifetime risk from primary open-angle glaucoma may require more frequent evaluations. These intervals are the maximum recommended time between evaluations.

History

The following interval history can be elicited at POAG follow-up visits:

- ◆ Interval ocular history
- ◆ Interval systemic medical history
- ◆ Side effects of ocular medications
- ◆ Frequency and time of last IOP-lowering medications and review of medication use

Ophthalmic examination

The following components of the ophthalmic examination should be performed at POAG follow-up visits:

- ◆ Visual acuity measurement
- ◆ Slit-lamp biomicroscopy
- ◆ IOP measurement

Based on the understanding of the effect of CCT on IOP measurements,^{8,23,526} measurement of CCT should be repeated after any event (e.g., refractive surgery⁵²⁷) that may alter CCT.

Gonioscopy

Gonioscopy is indicated when there is a suspicion of an angle-closure component, anterior chamber shallowing or anterior chamber angle abnormalities, or if there is an unexplained change in IOP. Gonioscopy may also be performed periodically.

Optic nerve head and visual field evaluation

Optic nerve head evaluation and documentation by imaging, photography, or drawing^{253,528-530} and visual field evaluation⁵³¹⁻⁵³⁴ should be performed at the recommended intervals listed in Table 6. Periodic photography may also reveal disc hemorrhages not seen on examination⁴⁶ and, in view of the quickly advancing imaging field, may be a more stable baseline for comparison than a new imaging baseline every few years.

Within each of the recommended intervals, factors that determine frequency of evaluations include the severity of damage (mild, moderate, severe, with more frequent evaluations for more severe disease), the rate of progression, the extent to which the IOP exceeds the target pressure, and the number and significance of other risk factors for damage to the optic nerve. In certain cases, follow-up visual field testing may be required more frequently than the recommended intervals (e.g., a second test to establish a baseline for future

comparisons, to clarify a suspicious test result, or to overcome an apparent testing artifact). For example, a patient with glaucomatous damage who has shown long-term stability can be followed every 6 to 12 months, depending on how severe the damage is, whereas a patient with evidence of glaucomatous progression may receive a change in care plan with more frequent follow-up.

Risk Factors for Progression

The risk factors for progression in eyes already diagnosed with OAG are related to the level of IOP and factors independent of IOP:

- ◆ IOP: Several multicenter randomized clinical trials have investigated the relationship between IOP and risk of glaucomatous progression (see Table 2). Higher baseline IOP,⁵¹ higher mean IOP during follow-up,^{53,535} and higher yearly average IOP⁵³⁶ were associated with greater progression of glaucoma as measured by visual field or optic nerve changes. Greater IOP fluctuation in some, but not all studies, has also been shown to be related to visual field progression, but this strongly correlated with absolute IOP level and may not be an independent risk factor.^{55-59,372}
- ◆ Older age^{51,58,372,535,537,538}
- ◆ Disc hemorrhage: Either presence of a disc hemorrhage^{46,537,539-545} or percentage of visits with disc hemorrhage^{51,58} have been associated with progression of visual field defect or optic nerve damage. The association has been reported in both normal-tension and in high-pressure glaucoma.
- ◆ Larger cup-to-disc ratio or small optic nerve rim area^{546,547}
- ◆ Beta-zone parapapillary atrophy: Either the baseline presence^{539,546} or the size^{537,548} of parapapillary atrophy adjacent to the optic nerve (beta zone) has been related to visual field or optic nerve progression in several large prospective and retrospective studies.
- ◆ Thinner central cornea with GAT IOP measurement: Strong evidence exists for thinner central cornea as a risk factor for progression from ocular hypertension to POAG, but evidence is mixed for thinner central cornea as a risk factor for progression in glaucoma.^{81,88,91,233-235,237,526,549,550}
- ◆ Decreased corneal hysteresis: Corneal hysteresis is a measure of the viscoelastic dampening of the cornea and has been shown to be associated with the risk of glaucoma progression.⁹⁰⁻⁹³
- ◆ Lower ocular perfusion pressure^{58,100}
- ◆ Pseudoexfoliation^{51,58,551}
- ◆ Poor adherence with medications⁵⁵²⁻⁵⁵⁴

Damage in one eye is associated with an increased risk of future damage in the other eye.^{58,555,556} A retrospective study in eyes with OAG and severe visual field damage in one eye showed a risk of progression in the other eye (Kaplan Meier estimate of visual field progression = 12.1%).⁵⁵⁷ Risk factors for progression were larger initial cup-to-disc ratio and lower ocular perfusion pressure. In a separate retrospective study, progression in visual field damage between eyes showed a significant correlation.⁵⁵⁶ In a large retrospective study of eyes with normal-tension glaucoma and unilateral visual field damage, the risk factors for progression in the normal eye were greater visual field damage in the eye with glaucoma and smaller neuroretinal rim area.⁵⁵⁸

Adjustment of Therapy

The indications for adjusting therapy are as follows:

- ◆ Target IOP is not achieved and the benefits of a change in therapy outweigh the risks for the patient
- ◆ A patient has progressive optic nerve damage despite achieving the target IOP
- ◆ The patient is intolerant of the prescribed medical regimen
- ◆ The patient does not adhere to the prescribed medical regimen
- ◆ Contraindications to individual medicines develop
- ◆ Stable optic nerve status and low IOP occurs for a prolonged period in a patient on topical ocular hypotensive agents. Under these circumstances, a carefully monitored attempt to reduce the medical regimen may be appropriate.

Downward adjustment of target pressure can be made in the face of progressive optic disc, RNFL, or visual field change.^{553,559-562}

Upward adjustment of target pressure can be considered if the patient has been stable and if the patient either requires (because of side effects) or desires less medication. A follow-up visit in 2 to 8 weeks, depending on disease severity, may help to assess the response and side effects from washout of the old medication or onset of maximum effect of the new medication.

PROVIDER AND SETTING

The performance of certain diagnostic procedures (e.g., tonometry, pachymetry, perimetry, optic disc/RNFL imaging, and photography) may be delegated to appropriately trained and supervised personnel.

However, the interpretation of results and medical and surgical management of the disease require the medical training, clinical judgment, and experience of the ophthalmologist. (*III, good quality, strong recommendation*)

Most diagnostic and therapeutic procedures can be safely undertaken on an outpatient basis. In some instances, however, hospitalization may be required. This includes, for example, patients who have special medical or social needs.

COUNSELING AND REFERRAL

It is important to educate and engage patients in the management of their condition. Patients should be educated through oral, written, and online information about the disease process, the rationale and goals of intervention, the status of their condition, and the relative benefits and risks of alternative interventions so that they can participate meaningfully in developing an appropriate plan of action. (*good quality, strong recommendation*) Patients should be encouraged to alert their ophthalmologists to physical or emotional changes that occur when they are taking topical ocular hypotensive agents. (*good quality, strong recommendation*) The diagnosis of glaucoma can itself lead to negative psychological effects and to fear of blindness.⁵⁶³⁻⁵⁶⁷

Numerous studies have been performed to characterize the psychological profile of the glaucoma patient, and some have shown the prevalence of anxiety to be higher in this population.^{563,566,568} It has been much harder to demonstrate a consistent presence of depression in glaucoma patients; numerous studies have been unable to do so^{183,563,569,570} and only a minority do.^{566,567}

Glaucoma affects the patient's visual and health-related quality of life in many ways,^{161,571} including employment issues (e.g., fear of loss of job and insurance from diminished ability to read and drive), social issues (e.g., fear of negative impact on relationships and sexuality), and loss of independence and activities that require good visual acuity (e.g., sports and other hobbies). The ophthalmologist should be sensitive to these problems and provide support and encouragement. Some patients may find peer-support groups or counseling helpful.

Patients considering keratorefractive surgery should be informed about the possible impact laser vision correction has on reducing contrast sensitivity and decreasing the accuracy of IOP measurements.⁹⁴ (*III, good quality, strong recommendation*) During the LASIK procedure, the IOP will briefly increase from the effect of the suction ring to make the eye rigid during creation of the superficial flap. This effect may cause additional damage in patients whose optic nerves already have advanced damage.⁵⁷² Therefore, LASIK may be relatively contraindicated in such individuals, especially after a trabeculectomy, but photorefractive keratectomy may be possible. In addition, postoperative fluid may develop in the stromal interface and lead to temporary underestimation of the applanation IOP in patients treated aggressively with topical corticosteroids to resolve diffuse lamellar keratitis. These patients may actually have an undetected corticosteroid-induced elevation of IOP.⁵⁷³ Conversely, elevated pressure may be associated with stromal keratitis, a condition known as pressure-induced intralamellar stromal keratitis. This can be caused by corticosteroid-induced IOP elevation, which may be associated with interface fluid accumulation and lead to IOP underestimation.^{574,575} Inflammation subsides as the IOP is reduced using glaucoma medications.

Patients with glaucomatous optic neuropathy considering implantation of a multifocal intraocular lens should be informed of the risk of reduced contrast sensitivity.⁵⁷⁶ (*III, good quality, strong recommendation*) It is important to establish preoperative and baseline documentation of ONH status and visual field to facilitate subsequent glaucoma management.

If the diagnosis or management of POAG is in question, or if the condition is refractory to treatment, consultation with or referral to an ophthalmologist with special training or experience in managing glaucoma should be considered. Patients with substantial visual impairment or blindness can be referred for and encouraged to use appropriate vision rehabilitation and social services.⁵⁷⁷ More information on vision rehabilitation, including materials for patients, is available at www.aao.org/smart-sight-low-vision.

SOCIOECONOMIC CONSIDERATIONS

Presently, there are over 61 million persons with glaucoma worldwide; approximately 45 million with OAG and another 16 million with POAG.⁹ Since the prevalence of glaucoma increases considerably with age and people are living longer, it is estimated that by the year 2020 global glaucoma prevalence will reach nearly 80 million⁹ and 112 million by 2040.⁵⁷⁸ Thus, the burden of disease both to the individual patient and the economic burden to society are substantial.⁵⁷⁹

At the individual patient level, research has demonstrated that glaucoma can have a dramatic impact on quality of well-being. Patients with glaucoma are known to struggle with daily activities such as reading, walking, and driving.⁵⁸⁰ Performance on these activities deteriorates with worsening of glaucoma severity and when both eyes are affected. Studies have reported that patients with glaucoma were three times more likely to experience falls in the past 12 months and 6 times more likely to be involved in motor vehicle collisions over the past 5 years compared with controls.⁵⁸¹ Quality of life is affected for patients with all stages of glaucoma, even those with early disease.⁵⁸²

The costs of managing a chronic disease like glaucoma can be broken down into direct medical costs, direct nonmedical costs, and indirect costs. Direct costs include costs of visits to eye care providers, ancillary testing, and medical and surgical interventions. One study estimated nearly \$3 billion USD a year is spent on direct medical costs.⁵⁸³ Direct nonmedical costs (e.g., costs for transportation to appointments and nursing home care) and indirect costs (e.g., loss of productivity of the patient or caregivers) can be more difficult to quantify but are substantial. Using Medicare claims data and Markov modelling, one study estimated that the average direct and indirect medical costs for patients with glaucoma are \$1688 higher than for other patients without this condition over a lifetime.⁵⁸⁴

Costs of glaucoma are impacted by disease severity. One study determined the average annual direct medical costs for patients with early glaucoma, advanced glaucoma, and end-stage glaucoma were \$623, \$1915, and \$2511, respectively.⁵⁸⁵ Among patients with early glaucoma, most of the costs of care are for medications.⁵⁸⁶ For those with advanced disease, indirect costs such as costs for home health care and rehabilitation predominate.^{587,588}

Several studies have assessed the cost-effectiveness of screening for glaucoma and treating patients with ocular hypertension or glaucoma. One study assessed the cost-effectiveness of treating all patients with ocular hypertension and determined that such a strategy was not cost-effective based on cost-effectiveness standards set by the World Health Organization.⁵⁸⁹ A second study determined that treatment of the subset of patients with ocular hypertension whose IOP was 24 mmHg or greater and those who had at least a 2% annual risk of developing glaucoma was cost-effective.⁵⁹⁰ Using computer modelling, researchers found that treatment of patients who were diagnosed with glaucoma was highly cost-effective when making optimistic assumptions about therapy effectiveness and still reasonably cost-effective when making more conservative estimates of therapy effectiveness.⁵⁹¹ Other studies have compared the cost-effectiveness of using different treatment modalities. One study found use of generic prostaglandin analogues and laser trabeculoplasty to both be cost-effective treatment strategies for patients with early glaucoma.⁵⁹² The use of generic prostaglandin analogues was found to be the more cost-effective treatment option compared with laser trabeculoplasty when assuming optimal medication adherence. However, when assuming less optimistic medication adherence, laser

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trabeculoplasty was found to confer greater value compared with prostaglandin analogues. Ongoing studies are exploring the cost-effectiveness of different incisional surgeries for glaucoma (e.g., trabeculectomy versus glaucoma drainage device implantation) and for some of the newer minimally invasive glaucoma surgical procedures.⁵⁹³

When considering the economic burden of glaucoma, it is important to appreciate that glaucoma affects a disproportionately large number of racial minorities. In fact, glaucoma is the leading cause of blindness among blacks, and studies have demonstrated greater risk of glaucoma among Latinos and Asian Americans relative to non-Hispanic whites as well. Various studies have noted disparities in utilization of eye care services among racial minorities. Studies have demonstrated that blacks are less likely to undergo examinations for glaucoma relative to whites,^{594,595} have lower rates of undergoing visual field testing relative to whites in the year before glaucoma surgery,⁵⁹⁶ and have lower rates of utilization of medical and surgical interventions for glaucoma.⁵⁹⁷ A more recent study found that despite possessing health insurance, Latinos were significantly less likely to undergo monitoring for glaucoma relative to whites.⁵⁹⁸ Fortunately, in 2000, Medicare began providing a benefit for glaucoma screening to individuals with the following risk factors: a family history of glaucoma, a history of diabetes, African American ethnicity and age 50 or older, or Latino ethnicity and age 65 or older.¹⁷³ With the passage of the Affordable Care Act and other recent health care reforms, it will be important to ensure that racial minorities and socioeconomically disadvantaged patients have adequate access to eye care services and receive care that is in line with recommended clinical practice guidelines.



APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

*Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986*

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- ◆ The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- ◆ The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- ◆ The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- ◆ Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
 - ◆ The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
 - ◆ The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
 - ◆ When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
 - ◆ The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.

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Appendix 1. Quality of Ophthalmic Care Core Criteria

- ◆ The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner. The ophthalmologist maintains complete and accurate medical records.
- ◆ On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- ◆ The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- ◆ The ophthalmologist and those who assist in providing care identify themselves and their profession.
- ◆ For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- ◆ Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- ◆ The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- ◆ The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- ◆ The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- ◆ The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- ◆ The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Primary open-angle glaucoma includes the entity of open-angle glaucoma and related entities with the following ICD-9 and ICD-10 classifications:

	ICD-9 CM	ICD-10 CM
Open-angle glaucoma	365.10	H40.10X-
Primary open-angle glaucoma	365.11	H40.11X-
Low-tension glaucoma	365.12	H40.121- H40.122- H40.123-
Residual stage of open-angle glaucoma	365.15	H40.151 H40.152 H40.153
Glaucomatous atrophy of the optic disc	377.14	H47.231 H47.232 H47.233

CM = Clinical Modification used in the United States; (–) = 0, stage unspecified; 1, mild stage; 2, moderate stage; 3, severe stage; 4, indeterminate stage

Additional information for ICD-10 codes:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should be used only when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
 - Right is always 1
 - Left is always 2
 - Bilateral is always 3



APPENDIX 3. LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed and Cochrane databases were conducted in June 2014; the search strategies were as follows. Specific limited update searches were conducted after June 2014.

PubMed Searches

IOP fluctuation & risk of progression (4/29/09 – 6/23/14)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ("Intraocular Pressure"[Mesh] OR "intraocular pressure" OR IOP) AND (fluctuation OR fluctuating OR fluctuates OR fluctu* OR variation* OR varying OR varie* OR variabl*) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 680 references as of 6/23/14.

Primary open-angle glaucoma (POAG) & quality of life (4/29/09 – 6/11/14)

("Quality of Life"[Mesh] OR "quality of life" OR "Sickness Impact Profile"[Mesh] OR "sickness impact" OR "Activities of Daily Living"[Mesh] OR "daily activities" OR "daily activity" OR "Karnofsky Performance Status"[Mesh] OR "Illness Behavior"[Mesh] OR "illness impact") AND ("Glaucoma, Open-Angle"[Mesh] OR "Glaucoma"[Mesh] OR glaucoma OR POAG) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 231 references as of 6/11/14; 230 imported; 1 duplicate.

Stereographic photography of optic nerve head (4/29/09 – 6/11/14)

("Photography"[Mesh] OR stereophotography OR "stereographic photography") AND ("Optic Nerve"[Mesh] OR "Optic Disk"[Mesh] OR "optic nerve") AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 130 references as of 6/11/14.

Nutrition & POAG (4/29/98 – 6/11/14)

("Nutrition Therapy"[Mesh] OR "Nutritional Status"[Mesh] OR nutrition* OR nutrient* OR "Diet"[Mesh] OR "Diet Therapy"[Mesh] OR diet OR "Dietary Supplements"[Mesh] OR "Vitamins"[Mesh] OR vitamin* OR "Antioxidants"[Mesh] OR antioxidant*) AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 254 references as of 6/11/14.

Sleep disturbances & POAG (4/18/09 – 6/11/14)

("Sleep"[Mesh] OR "Sleep Apnea, Central"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Sleep Apnea Syndromes"[Mesh] OR "Sleep Apnea, Obstructive"[Mesh] OR "Sleep Disorders"[Mesh] OR "Sleep Disorders, Intrinsic"[Mesh] OR "Dyssomnias"[Mesh] OR "Sleep Deprivation"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR "sleep disturbance" OR "sleep disturbances" OR "sleep apnea") AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((2009/04/18[EDat]:3000[EDat]) AND (English[lang])): 45 references as of 6/11/14.

Past damage predicts future damage; narrow searches (4/21/09 – 6/11/14)

Weinreb[author] AND glaucoma research community AND 2009/04/21[edat]:3000[edat]: 1 reference as of 6/11/14.

("Intraocular Pressure"[Mesh] OR IOP) AND "Glaucoma"[Mesh] AND "optic nerve damage" AND (past OR future OR predict*) AND (English[lang]) AND 2009/04/21[edat]:3000[edat]: 7 references as of 6/11/14.

("Intraocular Pressure"[Mesh] OR IOP) AND (predict* OR progressive) AND "optic nerve damage" AND (glaucoma OR "Glaucoma"[Mesh]) AND ((English[lang])) AND 2009/04/21[edat]:3000[edat]: 14 references as of 6/11/14.

glaucoma progression index AND ((2009/04/21[PDat]:3000[PDat]) AND (English[lang])): 106 references as of 6/11/14.

multicenter[Title] AND retrospective[Title] AND pilot[Title] AND study[Title] AND resource[Title] AND costs[Title] AND associated[Title] AND severity[Title] AND disease[Title] AND glaucoma.[Title] AND 2009/04/10[edat]:3000[edat]: 0 references as of 6/11/14.

Enhanced Glaucoma Staging System (GSS 2) for classifying functional damage AND 2009/04/21[edat]:3000[edat]: 0 references as of 6/11/14.

Past damage predicts future damage; broad search (4/29/09 – 6/11/14)

("Intraocular pressure"[Mesh] OR IOP) AND "Disease Progression"[Mesh] AND ("Glaucoma"[Mesh] OR glaucoma) AND ((2009/04/29[PDat]:3000[PDat]) AND (Humans[Mesh]) AND (English[lang])): 256 references as of 6/11/14.

Selective laser trabeculoplasty (4/30/09 – 6/11/14)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND "selective laser trabeculoplasty" AND ((2009/04/30[EDat]:3000[EDat]) AND (English[lang])): 90 references as of 6/11/14.

Diode cyclophotocoagulation (4/22/09 – 6/11/14)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND (diode AND cyclophotocoagulation) AND ((2009/04/22[EDat]:3000[EDat]) AND (English[lang])): 43 references as of 6/11/14.

Endoscopic cyclophotocoagulation (4/22/09 – 6/11/14)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND (endoscopic AND cyclophotocoagulation) AND ((2009/04/22[EDat]:3000[EDat]) AND (English[lang])): 22 references as of 6/11/14.

Refractive surgery in patients with POAG or glaucoma suspect (4/29/09 – 6/11/14)

"Refractive Surgical Procedures"[Mesh] AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 649 references as of 6/11/14.

Psychological effects (4/22/09 – 6/11/14)

("Glaucoma"[Mesh] OR glaucoma OR "Glaucoma, Open-Angle"[Mesh]) AND ("Psychology"[Mesh] OR psychology OR psychological OR "Quality of Life"[Mesh] OR "quality of life" OR "Personality"[Mesh]) OR "Glaucoma/psychology"[Mesh] AND ((2009/04/22[EDat]:3000[EDat]) AND (English[lang])): 299 references as of 6/11/14.

Anterior segment imaging (4/29/14 – 6/11/14)

("Tomography, Optical Coherence"[Mesh] OR (ultrasound AND biomicroscopy) OR ("anterior segment" AND imaging) OR ("anterior segment" AND image*)) AND ("Glaucoma"[Mesh] OR glaucoma OR "Glaucoma, Open-Angle"[Mesh]) AND ((2009/04/29[EDat]:3000[EDat]) AND (English[lang])): 1092 references as of 6/11/14; 1091 imported; 1 duplicate.

POAG update (4/29/09 – 6/11/14)

"Glaucoma, Open-Angle"[Mesh] AND (randomized controlled trial [PT] OR controlled clinical trial [PT] OR randomized [TIAB] OR placebo [TIAB] OR drug therapy [SH] OR randomly [TIAB] OR trial [TIAB] OR groups [TIAB]) NOT (animals[MH] NOT (humans [MH] AND animals[MH])) AND ((2009/04/29[PDat]:3000[PDat]) AND (English[lang])): 805 references as of 6/11/14.

"Glaucoma, Open-Angle"[Mesh] AND ((2009/04/29[PDat]:3000[PDat]) AND (English[lang]) AND (Clinical Trial[ptyp])): 284 references as of 6/11/14.

Cochrane Searches

IOP fluctuation & risk of progression (4/2009– 6/2014)

(Glaucoma[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ("Intraocular Pressure"[Mesh] OR "intraocular pressure" OR IOP) AND (fluctuation OR fluctuating OR fluctuates OR fluctu* OR variation OR varying OR varied OR varies OR vary): 3 results in Cochrane Database of Systematic Reviews as of 6/13/14.

POAG & quality of life (4/2009 – 6/2014)

("Quality of Life"[Mesh] OR "quality of life" OR "Sickness Impact Profile"[Mesh] OR "sickness impact" OR "Activities of Daily Living"[Mesh] OR "daily activities" OR "daily activity" OR "Karnofsky Performance Status"[Mesh] OR "Illness Behavior"[Mesh] OR "illness impact") AND ("Glaucoma, Open-Angle"[Mesh] OR "Glaucoma"[Mesh] OR glaucoma OR POAG): 3 results in Cochrane Database of Systematic Reviews as of 6/13/14.

**Primary Open-Angle Glaucoma PPP:
Appendix 3. Literature Searches**

Stereographic photography of optic nerve head (4/2009 – 6/2014)

("Photography"[Mesh] OR photography OR stereophotography OR "stereographic photography") AND ("Optic Nerve"[Mesh] OR "Optic Disk"[Mesh] OR "optic nerve" OR "optic disk") AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma): 14 results in Cochrane Central Register of Controlled Trials as of 6/17/14.

Nutrition & POAG (4/2009 – 6/2014)

("Nutrition Therapy"[Mesh] OR "Nutritional Status"[Mesh] OR nutrition* OR nutrient* OR "Diet"[Mesh] OR "Diet Therapy"[Mesh] OR diet OR "Dietary Supplements"[Mesh] OR "Vitamins"[Mesh] OR vitamin* OR "Antioxidants"[Mesh] OR antioxidant*) AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma): 18 results in Cochrane Central Register of Controlled Trials as of 6/17/14.

Sleep disturbances & POAG (4/2009 – 6/2014)

("Sleep"[Mesh] OR "Sleep Apnea, Central"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Sleep Apnea Syndromes"[Mesh] OR "Sleep Apnea, Obstructive"[Mesh] OR "Sleep Disorders"[Mesh] OR "Dyssomnias"[Mesh] OR "Sleep Deprivation"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR "sleep disturbance" OR "sleep disturbances" OR "sleep apnea" OR "sleep disorder" OR "sleep disorders" OR "sleep deprivation") AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma): 1 result in Cochrane Central Register of Controlled Trials as of 6/18/14.

Selective laser trabeculoplasty (4/2009 – 6/2014)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND "selective laser trabeculoplasty": 3 results in Database of Abstracts of Reviews of Effects as of 6/18/14.

Diode cyclophotocoagulation (4/2009 – 6/2014)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND (diode AND cyclophotocoagulation): 2 results in Cochrane Central Register of Controlled Trials as of 6/18/14.

Endoscopic cyclophotocoagulation (4/2009 – 6/2014)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND (endoscopic AND cyclophotocoagulation): 1 result in Health Technology Assessment Database as of 6/18/14.

Refractive surgery in patients with POAG or glaucoma suspect (4/2009 – 6/2014)

"refractive surgery" OR "Refractive Surgical Procedures"[Mesh] AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma): 2 results in Database of Abstracts of Reviews and Effects as of 6/18/14.

Psychological effects (4/2009 – 6/2014)

("Glaucoma"[Mesh] OR glaucoma OR "Glaucoma, Open-Angle"[Mesh]) AND ("Psychology"[Mesh] OR psychology OR psychological OR "Quality of Life"[Mesh] OR "quality of life" OR "Personality"[Mesh]) OR "Glaucoma/psychology"[Mesh]: 4 results in Cochrane Database of Systematic Reviews" as of 6/18/14.

Anterior segment imaging (4/2009 – 6/2014)

("Tomography, Optical Coherence"[Mesh] OR (ultrasound AND biomicroscopy) OR ("anterior segment" AND imaging) OR ("anterior segment" AND image*)) AND ("Glaucoma"[Mesh] OR glaucoma OR "Glaucoma, Open-Angle"[Mesh]): 1 result in Health Technology Assessments Database as of 6/18/14.

POAG update (4/2009 – 6/2014)

"Glaucoma, Open-Angle"[Mesh] OR POAG or "open-angle glaucoma" OR "open angle glaucoma": 6 results in Cochrane Database of Systematic Reviews as of 6/18/14.



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