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Primary Open-Angle Glaucoma Preferred Practice Pattern®

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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We thank our partners, the Cochrane Eyes and Vision US Satellite (CEV@US), for identifying reliable systematic reviews that we cite and discuss in support of the PPP recommendations.

The Preferred Practice Patterns Committee members reviewed and discussed the document during a meeting in May 2020. The document was edited in response to the discussion and comments.

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The Primary Open-Angle Glaucoma PPP was then sent for review to additional internal and external groups and individuals in June 2020. 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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FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at https://cmss.org/code-signers-pdf/) , relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (57%) of the members of the Glaucoma Preferred Practice Pattern Panel 2019-2020 had no related financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2020 are available online at www.aao.org/ppp.

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Primary Open-Angle Glaucoma Preferred Practice Pattern®

Background:
Primary open-angle glaucoma (POAG) is a chronic, progressive ocular disease causing loss of the optic nerve rim and retinal nerve fiber layer (RNFL) with associated visual field defects. The anterior chamber angle is open, and the disease is generally bilateral. Risk factors for POAG include older age, African race or Latino/Hispanic ethnicity, elevated intraocular pressure (IOP), family history of glaucoma, lower ocular perfusion pressure, type 2 diabetes mellitus, and thin central cornea. It is estimated that 53 million people in the world have POAG in 2020 with a prevalence of 3.0% in the population aged 40 to 80 years.

Rationale for Treatment:
Clinical trials have shown that lowering IOP reduces the risk of developing POAG and slows the progression of the disease. Medical, laser, and incisional surgical approaches exist to effectively lower IOP. Early diagnosis and treatment generally prevent visual disability.

Care Process:
The goals of managing patients with POAG are to control IOP in a target range and to prevent progressive visual field and optic nerve/RNFL damage in order to preserve visual function and quality of life. The initial glaucoma evaluation includes all components of the comprehensive adult medical evaluation focusing on those elements that specifically pertain to the diagnosis and management of POAG. Important diagnostic testing includes central corneal thickness measurement, visual field evaluation, and imaging of the optic nerve head, RNFL and macula. The relative risks and benefits of treatment with medications, laser therapy, or incisional surgery should be discussed with the patient prior to its initiation. The adequacy of treatment is determined during follow-up by regular assessment of the optic nerve appearance and quantitative evaluation with visual field testing and imaging of the optic nerve head, RNFL and macula.

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 Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (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 SIGN[1] 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 GRADE[2] 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 GRADE[2] 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 March 2019 and June 2020 in the PubMed and Cochrane databases. Complete details of the literature searches are available in Appendix 3.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

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

Primary open-angle glaucoma patients often have untreated IOP consistently within the normal range (i.e., normal tension glaucoma). Lowering pressure in these patients is beneficial.

Characteristic clinical features of POAG include an open angle on gonioscopy, and glaucomatous optic nerve head (ONH) and retinal nerve fiber layer (RNFL)/macula imaging 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.

Adjusting computerized visual field programs (24 degrees, 30 degrees, 10 degrees) and stimulus size (III, V) can 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. Effective medical, laser, and incisional surgical approaches exist for lowering IOP.

A reasonable initial treatment goal in a POAG patient is to reduce IOP 20% to 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. Primary open-angle glaucoma is a potentially blinding eye disease, but early diagnosis and treatment can generally prevent visual disability.

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 rule[5] (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 thinning of the parapapillary RNFL, especially at the inferior or superior poles. (Highly myopic individuals without glaucoma may have diffusely thin RNFL.)
    - Optic disc hemorrhages involving the disc rim, parapapillary RNFL, or lamina cribrosa
    - Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
    - Beta-zone parapapillary atrophy
    - Thinning of the RNFL and/or macula on imaging
  - Reliable and reproducible visual field abnormality
    - 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, retinal or neurological pathology)
- 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 syndrome, pseudoexfoliation 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 IOP, nearly 40% of those with otherwise characteristic POAG may not have elevated IOP measurements during office hours.[7] The vast majority of patients with POAG have disc changes or disc and visual field changes,[8] but there are cases where early visual field changes may develop before there are detectable changes to the optic nerve.

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

- Mild: Definite optic disc, RNFL, or macular imaging abnormalities consistent with glaucoma as detailed above and a normal visual field as tested with standard automated perimetry (SAP)
- Moderate: Definite optic disc, RNFL, or macular imaging abnormalities consistent with glaucoma as detailed above, and visual field abnormalities in one hemifield that are not within 5 degrees of fixation

- Severe: Definite optic disc, RNFL, or macular imaging 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, RNFL, or macular imaging 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 yet performed

PATIENT POPULATION

The patient population consists of adults with open anterior chamber angles and demonstrated optic nerve or RNFL damage, and/or visual field loss.

CLINICAL OBJECTIVES

- Document the status of the optic nerve structure at baseline by clinical evaluation and imaging, and document visual function by visual field testing
- Estimate an IOP below which further optic nerve damage is unlikely to occur (see Target Intraocular Pressure subsection in the Care Process section)
- Perform and document gonioscopy
- Attempt to maintain IOP at or below a defined target level by initiating appropriate medical and/or surgical intervention(s) after discussing the options with the patient
- 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
- Maintain quality of vision and preserve quality of life

BACKGROUND

PREVALENCE

Primary open-angle glaucoma is a significant public health problem.[9-17] It is estimated that 76 million people in the world have glaucoma in the year 2020.[10] Glaucoma (both open-angle and angle-closure) is the second leading cause of blindness worldwide.[11] Overall, the prevalence of POAG for adults aged 40 and older was estimated to be about 3.05% in 2013.[10] Prevalence studies suggest that POAG will increase by 50% worldwide from 52.7 million in 2020 to 79.8 million in 2040 as the population ages,[10] and will disproportionally affect African and Asian countries.[9, 10, 12, 13] 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 open-angle glaucoma (OAG) in African Americans relative to non-Hispanic whites in the United States.[14, 15] It is also the leading cause of blindness in African Americans.[15] 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.[16] 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.[17]

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

Study	Ethnoracial Group	Age-Specific Prevalence					
		Age Groups (yrs)					
		40–49	50–59	60–69	70–79	80+	Total
Baltimore Eye Study[18]	African American	1.3	4.2	6.2	8.9	12.9	5.0
Barbados Eye Study[19]	Afro-Caribbean	1.4	4.1	6.7	14.8	23.2	6.8
Los Angeles Latino Eye Study[16]	Latino	1.3	2.9	7.4	14.7	21.8	4.7
Proyecto Vision Evaluation Research[20]	Latino	0.5	0.6	1.7	5.7	12.6	2.0
Baltimore Eye Study[18]	NHW	0.2	0.3	1.5	3.3	1.94	1.4
Blue Mountains Eye Study[21]	NHW	0.4*		1.3	4.7	11.4	3.0
Visual Impairment Project[22]	NHW	0.5	1.5	4.5	8.6	9.9	3.4
Beaver Dam Eye Study[23]	NHW						2.1
Roscommon[24]	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.

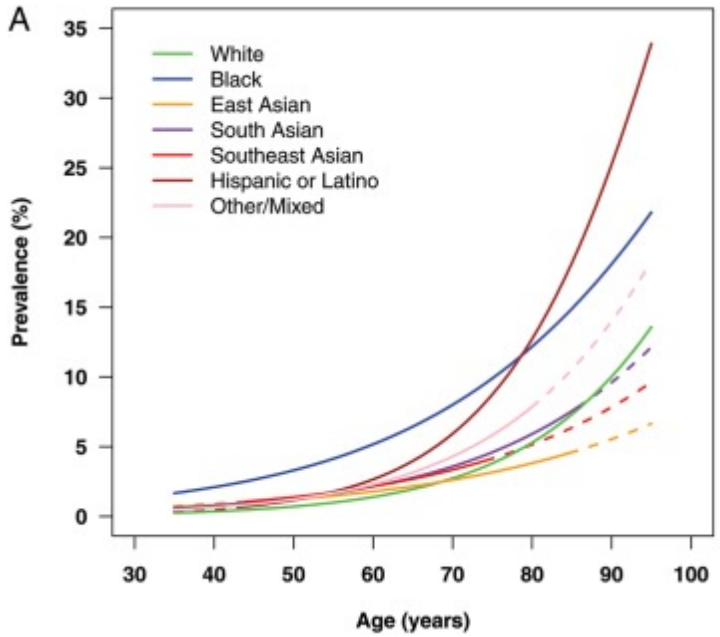

FIGURE 1. Estimated prevalence (%) of primary open-angle glaucoma with age for men and women combined by ethnicity. Colored lines come from regression models adjusting for age, fitted separately for different ethnicities. Solid lines are given across the age range of available data for each ethnic group.

Adapted from Kapetanakis V, Chan M, Foster P, et al. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta analysis. *Br J Ophthalmol.* 2016 Jan;100(1):86-93.

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:

- Elevated IOP[7, 8, 19-21, 23, 25-32]
- Older age[8, 18, 25, 27, 28, 31-34]
- Family history of glaucoma[28, 35-37]
- African race or Latino/Hispanic ethnicity[9, 10]
- Thin central cornea[8, 25, 36, 38]
- Low ocular perfusion pressure[35, 39-41]
- Type 2 diabetes mellitus[42-45]
- Myopia[32, 40, 46-49]
- Low systolic and diastolic blood pressure[35, 41]
- Disc hemorrhage[50-54]
- Large cup-to-disc ratio[8, 25]
- High pattern standard deviation on threshold visual field testing[25, 30, 55]
- Hypothyroidism[56]
- Male sex[9, 31]

Other factors that have been associated with OAG include migraine headache, sleep apnea, peripheral vasospasm (Raynaud's syndrome), cardiovascular disease, low corneal hysteresis, and systemic hypertension.[25, 57-62] However, the association between these factors and the development of glaucomatous optic nerve damage has not been demonstrated consistently.[25, 33, 40, 46, 63-68]

Intraocular Pressure

A number of population-based studies have demonstrated that the prevalence of POAG[7, 19-21, 23, 26, 29, 32, 69] increases as the level of IOP increases (see Figure 2). In the Baltimore Eye Survey, nearly 7% of Caucasians and 25% of African Americans had POAG at an IOP of 30 mmHg.[26] These studies provide strong evidence that IOP plays an important role in the optic neuropathy of POAG. Furthermore, studies have demonstrated that reducing IOP decreases the risk of visual field progression in OAG (see Table 2).[25, 70-75]

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%],[76] Los Angeles [18%],[16] Arizona [20%],[20] Blue Mountains [25%],[21] Melbourne [39%],[22] Baltimore [45%],[18] Rotterdam [61%],[7] Barbados [71%][40]) have glaucomatous optic nerve damage.[26] 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 diagnosing POAG.

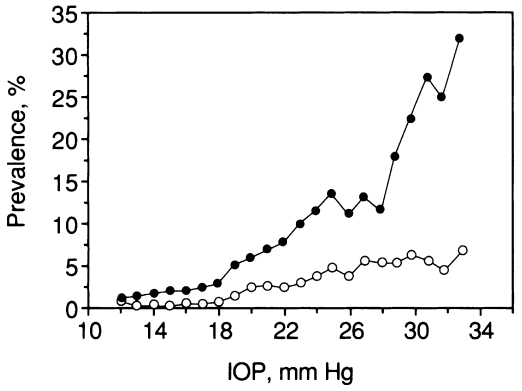

Figure 2: Prevalence of primary open-angle glaucoma in relation to screening intraocular pressure. African American subjects, n = 4,674 eyes (closed circles); Caucasian American subjects, n = 5,700 eyes (open circles).

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[77, 78]	Newly diagnosed POAG: medical therapy vs. trabeculectomy	116	4.6 (mean)	Trabeculectomy lowered IOP (58% IOP reduction) more than medicine (42% IOP reduction); medical therapy group had more deterioration in visual fields than trabeculectomy group.
Moorfields Primary Treatment Trial, 1994[79]	Newly diagnosed POAG: medical therapy vs. laser trabeculoplasty vs. trabeculectomy	168	5+	Trabeculectomy lowered IOP the most (60% IOP reduction); laser trabeculoplasty (38% IOP reduction) and medical therapy groups (49% IOP reduction) had more deterioration in visual fields than trabeculectomy group.
Collaborative Normal-Tension Glaucoma Study, 1998[70]	POAG in eyes with normal IOP: rate of progression, effect of IOP reduction on progression rate	230	5+	Lowering IOP (37% IOP reduction) slowed the progression rate of visual field loss compared with untreated eyes (1% IOP reduction).
Early Manifest Glaucoma Trial, 2002–2007[72, 73, 80]	Newly diagnosed POAG: medical therapy and laser trabeculoplasty vs. no treatment	255	8 (median)	Lowering IOP with medical therapy and trabeculoplasty (25% IOP reduction) slowed progression of optic disc and visual field damage.
Collaborative Initial Glaucoma Treatment Study, 2001[81]	Newly diagnosed POAG: medicine vs. trabeculectomy	607	5+	Lowering IOP with initial filtering surgery (46% IOP reduction) was as effective as medical therapy (38% IOP reduction) to inhibit progression of visual field damage, though the amount of reduction was slightly greater after surgery.
Advanced Glaucoma Intervention Study, 2000, 2004[74, 82]	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 reduction), whereas in the longer term (4+ yrs) Caucasian American patients did better with trabeculectomy first (48% IOP reduction). The lowest IOP group during follow-up after surgical interventions (47% IOP reduction) had no further visual field deterioration in advanced glaucoma patients.
United Kingdom Glaucoma Treatment Study, 2014[75]	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 an important risk factor for the presence and progression of POAG.[18-22, 80, 83-86] A number of epidemiological studies demonstrate that the prevalence of glaucoma increases dramatically with age, particularly among Latinos, Hispanics, and African Americans (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.[87] Other studies in which family members were not examined depended 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, 3.47[88]; Baltimore, 3.7[89]). 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.[16, 18-20, 90, 91] The prevalence is three times higher in African Americans and Hispanics of Mexican ancestry compared with non-Hispanic whites.[16, 18] Blindness from glaucoma is at least six times more prevalent in African Americans than in Caucasian Americans.[15] Systematic reviews and meta-analysis studies suggest that POAG will disproportionally affect African and Asian countries.[9, 10]

Genetic Factors

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 various genes for some of the heritable forms of glaucoma.[92-94] Population-based studies have expanded from national consortiums to international collaborations to determine the complex interplay of genetic risk factors for OAG[95] and the OAG endophenotypes of IOP,[96-98] central corneal thickness (CCT),[99-101] and optic disc parameters.[102, 103] With advances in sequencing technology and reduced costs, studies have utilized large-scale genome-level interrogation that has led to the identification of the common genetic variants associated with OAG and/or IOP elevation.[97, 103-105] Newer genetic sequencing platforms and large sample sizes of glaucoma cases and controls have resulted in the identification of rare genetic variants associated with OAG. Population-based studies suggest that multiple genetic polymorphisms, post-translational, and environmental interactions are associated with the phenotype of POAG.[106-108] These genetic variants, or risk alleles, or gene-environmental interactions will require further investigation to determine if these factors are protective, are associated with disease progression, or represent potential new therapeutic targets. At this time, genetic tests are available for select inherited eye diseases.[109] However, routine genetic testing for glaucoma risk alleles is not recommended for patients with POAG.[110]

Central Corneal Thickness

Because applanation tonometry measurements are derived from resistance to corneal indentation and corneal stiffness, differences in CCT may introduce artifacts in IOP

measurement.[25, 38, 111-117] The mean CCT in healthy human eyes varies with ethnoracial characteristics. The average CCT measured ultrasonically in Caucasian Americans is 556 µm,[118] in Latinos it is 546 µm,[119] in Asians it is 552 µm,[120] in American Indian/Alaska Natives it is 555 µm,[121] and in African Americans it is 534 µm.[116] If IOP is underestimated in eyes 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 eyes 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.[111, 115, 122-124] In all these studies, eyes with forme-fruste keratoconus, Fuchs endotheliopathy, or postkeratorefractive surgery were not considered. Therefore, clinicians diagnose glaucoma using the clinical examination of the optic nerve head (ONH); imaging of the ONH, RNFL, and macula; and assessment of the visual field.

A thinner central cornea has been reported as a risk factor for POAG (see Figure 3).[125-127] Central corneal thickness may be a biomarker for structural or physical factors involved in the pathogenesis of POAG.[125] Corneal biomechanical properties such as hysteresis may also have an impact on IOP measurement and glaucoma risk.[128-131] 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 pneumatonometry, dynamic contour tonometry, or with noncontact differential tonometry. [124, 132-135] Even though controversy exists about CCT as an "independent" risk factor because CCT alters the measurement of IOP and hysteresis, clinicians should measure CCT when evaluating patients with POAG.

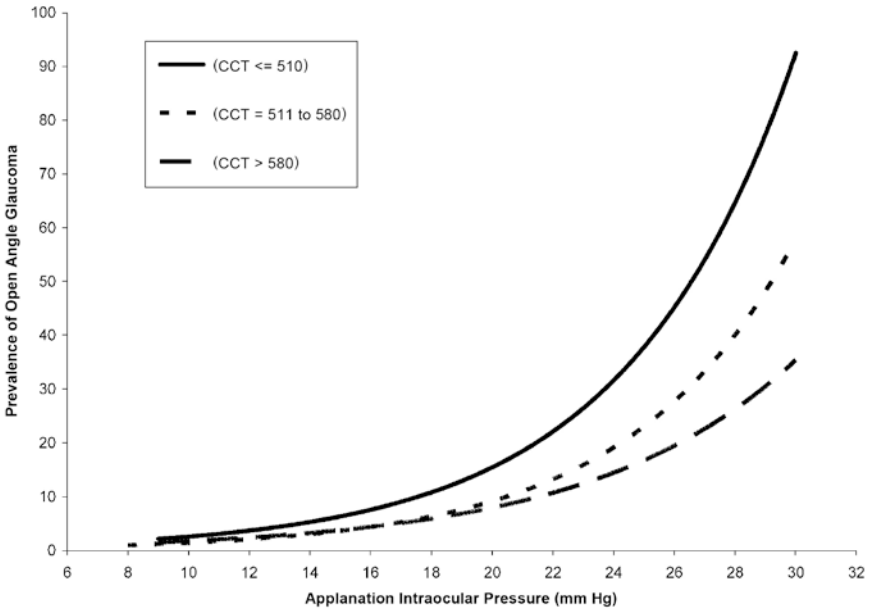

FIGURE 3. Trendlines showing the relationship between the prevalence of open-angle glaucoma and applanation intraocular pressure stratified by central corneal thickness in micrometers in the Latinos (n = 5970) in the Los Angeles Latino Eye Study.

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.

Ocular Perfusion Pressure

Ocular perfusion pressure is the difference between blood pressure (at systole or diastole) and the IOP. Low ocular perfusion pressure may lead to alterations in blood flow and contribute to

progressive glaucomatous optic nerve damage. Population-based studies have provided evidence that low diastolic perfusion pressure (<50 mmHg) is associated with a higher prevalence of POAG.[20, 35, 39, 63, 136] In addition, in the Early Manifest Glaucoma Trial (EGMT), 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.[80] Other 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.[137] Recent evidence suggests that low diastolic perfusion pressure is associated with increased risk for glaucoma only in patients taking treatment for systemic hypertension.[138] 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.[139]

Type 2 Diabetes Mellitus

Even though conflicting data exist on the association between type 2 diabetes mellitus and POAG,[28, 42-44, 140-145] there is increasing evidence from population-based studies suggesting that type 2 diabetes mellitus is an important risk factor for POAG.[42-44, 141, 143] Population-based assessments of Hispanics (in Los Angeles, California),[43] non-Hispanic whites (in Beaver Dam, Wisconsin, and Blue Mountains, Australia),[42, 143] and a large cohort enrolled in the Nurses' Health Study[141] 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,[43] 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.[142] Interestingly, authors have suggested that type 2 diabetes is directly associated with a higher IOP reading, likely related to a change in corneal biomechanics.[146] While this may act as a confounder, 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.[45]

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.[40, 46-48, 147-150] 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.[60] 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 headache and peripheral vasospasm (Raynaud's syndrome) have been identified as risk factors for glaucomatous optic nerve damage.[57, 58, 61, 70, 151-153] These conditions may decrease autoregulation of optic disc blood flow when compared with patients without this history.[154] Although migraine headaches alone may actually decrease visual field sensitivity during the attack,[155] 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,[39, 63, 64, 156-158] though there is also a sizable number of studies reporting no association between these conditions.[20, 40, 159-161] 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 ($P < 0.001$).[158] 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[156, 162]; decreased perfusion to the optic disc from sclerotic arterioles[163]; or treatment of systemic arterial hypertension with antihypertensives causing systemic hypotension and a reduction in perfusion of the optic nerve.[164] 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.[85, 138, 165] 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.[166-170] 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.[167] Another prospective study demonstrated that patients with POAG had lower intracranial pressure compared with controls.[169] Follow-up studies from both groups demonstrated that patients with normal-tension glaucoma had even lower intracranial pressure, whereas patients with ocular hypertension had higher levels of intracranial pressure.[168, 170] Overall, additional research is needed to determine whether intracranial pressure is a risk factor for glaucoma.[171]

Reports suggest that hypothyroidism may be associated with glaucoma. The biologic explanation may include decreased cellular metabolism with increased susceptibility to ganglion cell loss and/or alterations in mucopolysaccharides in the trabecular meshwork that increase IOP.[56, 172, 173] Also, male sex is associated with a higher risk of glaucoma, which may be due to a protective effect of female hormones on ganglion cell loss. However, women have a larger population burden of glaucoma from longer survival.[9, 31]

POPULATION SCREENING FOR GLAUCOMA

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.[174] Visual field loss in glaucoma decreases health-related quality of life.[175, 176] However, screening for glaucoma in the general population is not cost-effective.[177, 178] Screening is more useful and cost-effective when it is targeted at populations at high risk for glaucoma, such as older adults,[14] those with a family history of glaucoma,[87, 89, 179-181] and African Americans and Hispanics.[14]

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.[182] Population-based studies suggest that half of all individuals with POAG have IOP levels below 22 mmHg, the usual screening cutoff.[7, 21,26] 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.[21, 26] 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.[21, 24, 26, 183]

A second method of screening for glaucoma is to assess the ONH and RNFL. Clinicians have used 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.[184-186] Clinicians have used more technology-dependent objective structural testing (confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography [OCT]) to examine the ONH, RNFL, and the macula. Studies suggest that these have poor to moderate diagnostic precision for glaucoma when used for population-based screening.[187-189]

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.[190] Frequency doubling technology perimetry does not require correction of moderate refractive error and is useful as a screening tool to detect moderate to severe glaucomatous damage.[191, 192]

Clinicians and researchers have evaluated telemedicine to screen for glaucoma. Telemedicine uses telecommunication equipment to remotely diagnose and recommend treatment. The same considerations for screening listed above apply to telemedicine, but one of the advantages of this approach is increased access to screening outside of the eye care provider's office and the rapid transfer of information.[193, 194] Another potential tool for population-based screening is artificial intelligence.[195-197] Artificial intelligence is used for multiple purposes, including natural language processing, transportation navigating, and image processing. It uses computer programs for glaucoma screening to provide discrimination of diseased eyes from normal eyes without the restrictions of human graders and conventional statistical techniques, and it has a higher diagnostic performance compared to these methods.[195-197] Limitations include its difficulty understanding the discriminatory factors and generalizability to different patient groups.

The Centers for Medicare and Medicaid Services covers 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 Hispanics who are aged 65 years or older.[198]

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 evaluation[199] and focuses attention on those features that specifically pertain to the diagnosis, course, and treatment of POAG. The evaluation 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, RNFL, and macular imaging evaluation and documentation.

History

- Ocular history (e.g., refractive error, trauma, prior ocular surgery)
- Race/ethnicity
- Family history.[7, 87, 89] The severity and outcome of glaucoma in family members, including a history of visual loss from glaucoma, should be obtained during initial evaluation.[87, 89]
- Systemic history (e.g., asthma/chronic obstructive pulmonary disease, migraine headache, Raynaud's syndrome, diabetes, cardiovascular disease)
- Review of pertinent records, with particular attention to IOP levels, status of the optic nerve, and visual field testing
- Current and prior ocular and nonocular medications (e.g., corticosteroids) and known local or systemic intolerance to ocular or nonocular medications

  Cataract surgery may also lower the IOP compared with the presurgical baseline.[200, 201] A history of laser-assisted in situ keratomileusis (LASIK), small-incision lenticule extraction, (SMILE) or photorefractive keratectomy can be associated with a falsely low IOP measurement due to thinning of the cornea.[132, 134, 202-205] A history of prior glaucoma laser or incisional surgical procedures should be elicited.

Evaluation of Visual Function

Self-reported functional status or difficulty with vision can be assessed either through the patient's description or by using specific questionnaires, such as the National Eye Institute - Visual Function Questionnaire-25 and Glau-QOL.[175, 206-213] Patients who have glaucoma may have sufficient visual field loss to impair driving (especially at night), near vision, reading speed, and outdoor mobility.[176, 214-220]

Physical Examination

The ophthalmic evaluation focuses specifically on the following elements in the comprehensive adult medical eye evaluation:[221]

- Visual acuity measurement
- Pupil examination
- Confrontation visual fields
- Slit-lamp biomicroscopy
- 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.[222-225]

Confrontation visual fields

Confrontation visual fields are evaluated as an adjunct to automated visual field testing.

Slit-lamp biomicroscopy

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.[226, 227] Secondary mechanisms for elevated IOP can be detected on anterior segment examination and can include pseudoexfoliation material on the pupil margin, anterior lens capsule or corneal endothelium (pseudoexfoliation syndrome); pigment dispersion syndrome with spoke-like, mid-peripheral radial iris transillumination defects, Krukenberg spindle, and/or Scheie stripe; iris and angle neovascularization; or inflammation.

Intraocular pressure measurement

Intraocular pressure is measured 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.[80, 86, 228-235] Similarly, since IOP may vary within individuals even at the same time of the day, ophthalmologists should consider making therapeutic decisions based on several IOP measurements rather than on a single measurement.[236] Some patients may benefit from IOP measurement at different times of the day.[237]

Gonioscopy

The diagnosis of POAG requires careful evaluation of the anterior chamber angle to exclude angle-closure glaucoma or secondary causes for IOP elevation, such as angle recession, pigment dispersion, pseudoexfoliation syndrome, peripheral anterior synechiae, angle neovascularization, and inflammatory precipitates.[238] A useful technique to examine a narrow anterior chamber angle is to have the patient look slightly towards the mirror of the gonioprism into which the examiner is looking. The use of a grading system for gonioscopy is desirable. The Spaeth gonioscopy grading system describes with detail the anterior chamber angle anatomy with a high correlation to ultrasound biomicroscopy.[239]

(See www.gonioscopy.org 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 and thinning of the RNFL.[4, 240-243] Physical features that may indicate glaucomatous optic neuropathy include the following:

- Vertical elongation of the optic nerve cup with an associated decrease in neuroretinal rim width
- Enlargement of the optic nerve cup
- Diffuse or focal narrowing of the neuroretinal rim, especially superior and/or inferior
- Optic disc hemorrhages involving the disc rim, parapapillary RNFL, or lamina cribrosa
- Nasalization of central ONH vessels
- Baring of the circumlinear vessel
- Absence of pallor in the neuroretinal rim
- Diffuse or focal thinning of the RNFL
- Beta-zone parapapillary atrophy

The size of the physiologic cup is related to the size of the optic disc. Larger overall disc area is associated with a larger optic nerve cup. Commonly, the neuroretinal rim of the optic nerve is widest inferiorly and narrowest temporally. This anatomic feature is referred to as ISNT: the neuroretinal rim is widest at the inferior rim, followed by the superior rim, followed by the nasal rim, and lastly by the temporal rim.[244-246] In approximately 80% of glaucoma patients, cupping does not follow this rule because both the inferior and superior rims show thinning.[244, 245] However, a recent study has demonstrated that normal eyes follow the ISNT rule less than 45% of the time.[246]

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.[241, 247-249] Other investigations have reported functional deficits occurring in advance of structural change.[250, 251] Careful examination 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.[54, 70-72, 80, 84, 152, 252-258] 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.[54] In the EGMT, 13% of patients had disc hemorrhages at baseline examination, and hemorrhages were associated with progression.[72]

The optic nerve should be carefully examined for the above signs of glaucomatous damage, and its appearance should be documented.[4, 242, 259] The preferred technique for ONH evaluation involves magnified stereoscopic visualization (as obtained with the slit-lamp biomicroscope), preferably through a dilated pupil. In some cases, direct ophthalmoscopy complements magnified stereoscopic visualization, providing additional information of optic nerve detail as a result of the greater magnification of the direct ophthalmoscope. Red-free illumination of the posterior pole may aid in evaluating the RNFL.[260] Color stereophotography is an accepted method for documenting qualitative ONH appearance. Computer-based image analysis of the ONH and RNFL/macula 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 comprehensive 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., optic nerve pallor, disc drusen, optic nerve pits, disc edema or, macular degeneration, retinovascular occlusion, or other retinal disease).

Diagnostic Testing

Important diagnostic testing includes the following components:

- CCT measurement
- Visual field evaluation
- ONH, RNFL, and macular imaging

Central corneal thickness measurement

Measurement of CCT aids the interpretation of IOP readings and helps to stratify patient risk for ocular damage.[25, 38, 117, 126, 261] 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.[25, 262] (Additional information is available in the Central Corneal Thickness section under Risk Factors.) An overestimation of the true IOP as measured by GAT may occur in eyes with corneas that are thicker than average, whereas an underestimation of the true IOP tends to occur in eyes with corneas that are thinner than average. An exception to this is that the measurement of IOP is underestimated in eyes with large amounts of corneal edema.[126] Several studies have sought to quantify the relationship between measured IOP level and CCT, but there is no generally accepted correction formula. The World Glaucoma Association Consensus on IOP suggests that a correction factor should not be used to adjust values measured in individual patients. Although it is clear that thinner CCT is a risk factor for the development of POAG,[25] studies of progression have had variable findings. Some (but not all) studies found an association between glaucoma progression and thin CCT (see Table 3).[80, 263-267] Corneal hysteresis appears to provide additional, independent information associated with the risk of POAG.[62, 268, 269]

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[80]	255	I	+	Thin CCT is a risk factor for progression of glaucoma (in those patients with baseline IOP ≥21 mmHg)
Kim and Chen[263]	88	II	+	Thin CCT is associated with visual field progression in glaucoma
Chauhan, et al[264]	54	II	-	CCT did not predict visual field or optic disc progression

Jonas, et al[266]	454	II	-	CCT is not associated with progression of visual field damage
Jonas, et al[265]	390	II	-	CCT is not associated with optic disc hemorrhages
Congdon, et al[129]	230	II	-	CCT is not associated with glaucoma progression (although low corneal hysteresis is associated with glaucoma progression)
Stewart, et al[267]	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 SAP with white-on-white stimuli.[270] 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 by sampling more points near fixation than do either the 24- and 30-degree testing strategies. Testing with a 10-2 program may also be useful to detect early visual field damage in the central 10 degrees before such abnormalities are obvious in a 24 or 30-degree testing strategy.[271] Before changing glaucoma treatment, repeat and confirmatory visual field examinations are recommended for test results that are unreliable or show a new glaucomatous defect.[70, 272-274] Repeating the same strategy that showed a new glaucomatous defect is best for confirming visual field progression.

Frequency doubling technology and short-wavelength automated perimetry (SWAP) are two alternative testing methods to detect visual field damage.[275-278] Frequency doubling technology measures contrast sensitivity for a frequency doubling stimulus.[279-283] Visual field testing based on SWAP[284] isolates short-wavelength sensitive cells using a narrow band of blue-light stimulus on a yellow background-illuminated perimeter bowl. Despite the existence of frequency doubling technology and SWAP, all of the major glaucoma clinical trials used SAP for detection and progression of glaucoma. See Table 6 in the Follow-up Evaluation section below for recommended guidelines for follow-up timing and frequency for visual field evaluation.[270]

Optic nerve head, retinal nerve fiber layer, and macular imaging

The appearance of the optic nerve and RNFL should be documented for the POAG patient, if possible.[242, 259] The use of an ONH grading system is desirable. The disc damage likelihood scale takes into account the optic disc size and the thickness of the neuroretinal rim.[285] Stereoscopic disc photographs and computerized images of the nerve are complementary with regard to the information they provide to the clinician.[286] In the absence of these methodologies, a nonstereoscopic photograph or a drawing of the optic nerve should be recorded, but this is a less desirable alternative to stereophotography or computer-based imaging.[287-290] 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 in 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 in using stereophotography to identify progressive optic nerve change in patients with advanced glaucomatous cupping because there is little if any nerve tissue to evaluate or measure.[291, 292]

Computer-based digital imaging of the ONH, RNFL, and macula is routinely used to provide quantitative information to supplement the clinical examination of the optic nerve. Some patients demonstrate structural alterations in the ONH and the macular and parapapillary RNFL before functional change occurs. In many, but not all, cases, computerized imaging may be useful to distinguish between glaucomatous and nonglaucomatous RNFL thinning, based on the presence or absence of progression, respectively.[293-295] There are three types of computer-based optic nerve imaging devices that have been used to evaluate glaucoma: confocal scanning laser ophthalmoscopy, OCT, and scanning laser polarimetry. The versions of these devices that were studied in a systematic review were similar in their ability to distinguish glaucomatous eyes from control eyes.[242, 296-298]

Abnormal results (i.e., results outside of the normative range) from these devices do not always represent disease.[299] Criteria used to establish normative databases vary between different imaging devices, and a nerve or RNFL may fall outside normative ranges for reasons other than glaucoma. Their interpretation should include an evaluation of all components of the report and not just their summary statistics, after an adequate assessment of scan quality is performed. 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.[300] As these instruments continue to improve, they may become more reliable in helping the clinician diagnose glaucoma and to identify progressive nerve damage.[293-295] Furthermore, progression analysis programs for computer-based imaging devices are evolving to better detect optic nerve, RNFL, and macular imaging changes that may be secondary to glaucoma.[301, 302]

Because some patients show visual field loss without corresponding optic nerve progression,[8, 301-305] 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.[286] 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. The characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons can result in progressive visual field loss. Other entities associated with optic disc damage or abnormalities of the visual field should be considered prior to confirming the diagnosis of glaucoma. These nonglaucomatous 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 disc anomalies (e.g., congenital pit, coloboma, periventricular leukomalacia in prematurity, morning glory syndrome)
  - Leber hereditary optic neuropathy and dominant optic atrophy
  - Optic neuritis
- Retinal abnormalities
  - Age-related macular degeneration

- Chorioretinal scars from panretinal photocoagulation
- Retinitis pigmentosa
- Retinal arterial and venous occlusions
- Myelinated nerve fibers
- Retinal colobomas

- Central nervous system abnormalities
  - Compressive optic neuropathy
  - Demyelination from multiple sclerosis
  - Nutritional optic neuropathy

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

Ophthalmologists can lower IOP with medications, laser therapy, or incisional 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 POAG.[8, 25, 70-75, 79, 80, 82, 306-319]

Primary open-angle glaucoma is a chronic and usually asymptomatic condition, at least in its early stages. Its medical treatment requires adherence to single or multiple topical medications,[320] which can be expensive and 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.[175, 176, 321] The effects of treatment, as well as, the patient's quality of life, comorbidities, and 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.

Target Intraocular Pressure

When deciding to treat a patient with glaucoma, it is important to remember that the goal of treatment is to maintain the IOP within a range at which visual field loss is unlikely to substantially reduce a patient's health-related quality of life over his or her lifetime.[322]

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.[323]

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 glaucomatous 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 considerations (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.[70, 72-74, 81, 82] 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.[324]

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 ONH, RNFL, and macula) 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.[325]

Choice of Therapy

The IOP can be lowered by medical treatment, laser therapy, or incisional surgery (alone or in combination). Thorough discussion about the relative risks and benefits of a given treatment should be conducted with the patient prior to its initiation. 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 optic nerve damage.[259] Systemic comorbidities that deserve consideration when choosing medical therapy for glaucoma include asthma/chronic obstructive pulmonary disease, cardiac arrhythmia, and depression. Patients who are pregnant or nursing also deserve special consideration.

Medical treatment

Medical therapy is presently the most common initial intervention to lower IOP (see Table 4 for an overview of options available). Prostaglandin analogs are the most frequently prescribed eye drops for lowering IOP in patients with glaucoma because they are most efficacious and well tolerated, and they need to be instilled only once daily.[75, 326-328] Therefore, prostaglandin analogs are often selected as initial medical therapy unless other considerations, such as contraindications, cost, side effects, intolerance, or patient refusal preclude this.[329-331]

Topical beta adrenergic antagonists are commonly prescribed to treat glaucoma and have demonstrated good efficacy and tolerability.[328] Nonselective beta adrenergic antagonists (e.g., timolol) block both beta-1 (primarily cardiac) and beta-2 (primarily pulmonary) receptors. Cardioselective beta-blockers (e.g., betaxolol) target beta-1 receptors and minimize, but do not completely eliminate, the risk of pulmonary adverse effects in patients with obstructive airway disease.[332] Topical beta-blockers may be dosed once or twice daily. However, nighttime dosing of beta-blockers is associated with limited efficacy[333] and may contribute to visual field progression via nocturnal reduction of systemic blood pressure.[334] Other glaucoma medications include alpha$_2$ adrenergic agonists, parasympathomimetics, rho-kinase inhibitors, and topical and oral carbonic anhydrase inhibitors.[335-337]

TABLE 4 GLAUCOMA MEDICATIONS

Drug Classification	Agents	Methods of Action	IOP Reduction*	Potential Side Effects	Potential Contraindications	FDA Pregnancy Safety Category†
Prostaglandin analogs‡	Bimatoprost Latanoprost Latanoprostene bunod Tafluprost Travoprost	Increase uveoscleral and/or trabecular outflow	25%–33%	• 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	• Macular edema • History of herpetic keratitis • Active uveitis	C
Beta-adrenergic antagonists (beta-blockers)	*Nonselective* Carteolol Levobunolol Metipranolol Timolol *Selective* Betaxolol	Decrease aqueous production	20%–25%	• Allergic conjunctivitis/contact dermatitis • Keratitis • Bronchospasm • Bradycardia • Hypotension • CHF • Reduced exercise tolerance • Depression • Impotence	• Chronic obstructive pulmonary disease • Asthma • CHF • Bradycardia • Hypotension • Greater than first-degree heart block	C
Alpha-adrenergic agonists	Apraclonidine Brimonidine	Decrease aqueous production; decrease episcleral venous pressure or increase uveoscleral outflow	20%–25%	• Allergic conjunctivitis/contact dermatitis • Follicular conjunctivitis • Dry mouth and nose • Hypotension • Headache • Fatigue • Somnolence	• Monoamine oxidase inhibitor therapy • Infants and children (for brimonidine)	B
Parasympathomimetic agents	*Cholinergic agonist* Pilocarpine *Anticholinesterase agent* Echothiophate	Increase trabecular outflow	20%–25%	• 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	• Areas of peripheral retina that predispose to breaks • The need to regularly assess the fundus • Neovascular, uveitic, or malignant glaucoma	C

TABLE 4 GLAUCOMA MEDICATIONS (CONTINUED)

Drug Classification	Agents	Methods of Action	IOP Reduction*	Potential Side Effects	Potential Contraindications	FDA Pregnancy Safety Category†
Rho kinase inhibitors	Netarsudil	Increase trabecular outflow Decrease episcleral venous pressure Decrease aqueous production	10%–20%	• Conjunctival hyperemia • Corneal verticillata • Instillation site pain • Conjunctival hemorrhage • Keratitis	• None	---**
Topical carbonic anhydrase inhibitors	Brinzolamide Dorzolamide	Decrease aqueous production	15%–20%	• Allergic dermatitis/conjunctivitis • Corneal edema • Keratitis • Metallic taste	• Sulfonamide allergy • Sickle cell disease with hyphema	C
Oral carbonic anhydrase inhibitors	Acetazolamide Methazolamide	Decrease aqueous production	20%–30%	• Stevens-Johnson syndrome • Malaise, anorexia, depression • Serum electrolyte imbalance • Renal calculi • Blood dyscrasias (aplastic anemia, thrombocytopenia) • Metallic taste • Enuresis • Parasthesia • Diarrhea • Abdominal cramps	• Sulfonamide allergy • Kidney stones • Aplastic anemia • Thrombocytopenia • Sickle cell disease	C
Hyperosmotic agents	Glycerol Mannitol	Dehydration of vitreous	No data	• Headache • CHF • Nausea, vomiting • Diarrhea • Renal failure • Diabetic complications • Mental confusion	• Renal failure • CHF • Potential CNS pathology	C

CHF = congestive heart failure; CNS = central nervous system; FDA = Food and Drug Administration; 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: http://www.icoph.org/dynamic/attachments/resources/egs_guidelines_4_english.pdf Accessed October 16, 2020.

† 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.

‡ Latanoprostene bunod is a new IOP-lowering agent that is rapidly metabolized to latanoprost (a prostaglandin analog) and butanediol mononitrate (a nitric oxide-donating moiety). It enhances aqueous humor outflow through both the uveoscleral and trabecular meshwork pathways.[338-341]

** The FDA replaced the ABCDX drug pregnancy categories with descriptive information regarding medication risks to the developing fetus, breastfed infant, and individual of reproductive potential under the Pregnancy and Lactation Labeling Rule in 2015. Rho-kinase inhibitors are therefore not assigned a pregnancy category. No data exist on the use of netarsudil in pregnant women. Animal studies did not demonstrate adverse effects on the developing fetus with clinically relevant intravenous exposures.[342]

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, studies have shown that such trials are not good predictors of long-term efficacy.[343, 344] 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.[345] 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.[346]

If a drug fails to reduce IOP sufficiently, then either switching to an alternative medication as monotherapy or adding medication is appropriate until the desired IOP level is attained.[259] Since some studies have shown that adding a second medication decreased adherence to glaucoma treatment,[347, 348] fixed combination therapy may improve patient adherence, and reduce exposure to preservatives, although it is not recommended for initial treatment in most circumstances. However, when the necessary reduction of IOP exceeds the expected efficacy of a single drug, combination therapy may be prescribed in selected patients. The patient and the 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 and preferences.[259] The ophthalmologist should assess the patient for local ocular and systemic side effects and toxicity, including interactions with other medications and potential life-threatening adverse reactions. Patients should be educated about eyelid closure or nasolacrimal occlusion to reduce systemic absorption after eye drop instillation (see Related Academy Materials section for patient education brochures).[349]

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.[350-353] 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.[348, 354] 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.[353] 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.[355, 356] 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 smartphone reminders, may improve adherence to therapy.[353, 357] A Cochrane Systematic Review in 2013 found that although complex interventions consisting of patient education combined with personalized behavioral change interventions, including tailoring daily routines to promote adherence to eye drops, may improve adherence to glaucoma medications, overall there is insufficient evidence to recommend a particular intervention. Simplified drug regimens also could be of benefit but again the current published studies do not provide conclusive evidence. Thus, adherence interventions are left to the judgment of the treating ophthalmologist.[358] *(I-, Insufficient Quality, Strong Recommendation)* At each examination, medication dosage and frequency of use should be reviewed and recorded. Reviewing the time medication was taken may help patients link eye-drop administration to common activities of daily living and help to ensure patients are actually using their eye drops. Adherence to the therapeutic regimen and recommendations for therapeutic alternatives should be discussed. Cost may be a factor in adherence, especially when multiple medications are used.[357]

Patient education through oral, written, and online information and informed participation in treatment decisions may improve adherence[357] and overall effectiveness of glaucoma management. Adherence to medical therapy may be handicapped when patients run out of medication, due to inadvertent drop wastage or inability to properly instill eye drops, before they are permitted to refill their prescription. One study found this was more likely for patients who self-administered eye drop medications when visual acuity was worse than 20/70 in either eye.[359] 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.[360]

Multiple drug delivery systems have been developed to address the problems of patient adherence and side effects associated with glaucoma medical therapy. Enhanced drug delivery targets include punctal plugs,[361] rings placed in the fornix,[362] contact lenses,[363] subconjunctival injections[364]/devices,[365] intracameral delivery systems,[366] and drug-eluting intraocular devices.[367] In 2020, a bimatoprost intracameral implant (Allergan, Irvine, CA) received Food and Drug Administration (FDA) approval for use in patients with ocular hypertension and POAG. This biodegradable implant, which is injected with a 28-gauge delivery system, demonstrated noninferiority to twice daily timolol in phase III clinical trials.[368] In phase I/II studies, a single bimatoprost sustained-release (SR) implant showed similar efficacy to topical bimatoprost 0.03% through 4 months of follow-up, and 68% of patients had a persistent effect at 6 months.[366] At 24 months, central endothelial cell density was comparable between eyes that received the bimatoprost implant and those treated topically.

Special circumstances in pregnancy and during breastfeeding

Managing glaucoma in the pregnant or lactating patient involves an interdisciplinary approach to prevent disease progression in the mother while minimizing risks to the fetus and nursing infant. Laser trabeculoplasty may be considered as an alternative or adjunct to medical therapy in select patients during pregnancy and breastfeeding.

Pregnancy

Glaucoma medical management of the pregnant patient presents challenges with respect to balancing the risk of glaucoma progression[369] against concerns for the safety of the fetus.[370-372] Data on the risks of topical ocular hypotensive agents during pregnancy are limited. The FDA established drug pregnancy categories of A, B, C, D, and X in 1979.[373] 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. Beta-blockers, prostaglandin analogs, topical carbonic anhydrase inhibitors, parasympathomimetics, and hyperosmotics have a Pregnancy Category C rating. Beta-blockers tend to be used during pregnancy because there is long-term experience with this drug class. A paucity of data exists 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.[374] 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 breastfeeding mother.[372] Oral carbonic anhydrase inhibitors have been shown to cause teratogenicity when delivered in high doses to animals.[375]

The FDA replaced the ABCDX drug pregnancy categories with descriptive information on medication risks to the developing fetus, breastfed infant, and individual of reproductive potential under the Pregnancy and Lactation Labeling Rule in 2015. Rho-kinase inhibitors are therefore not assigned a pregnancy category. No data exist on the use of netarsudil in pregnant women. Animal studies did not demonstrate adverse effects on the developing fetus with clinically relevant intravenous exposures.[342]

Breastfeeding

Some topical glaucoma medications have been detected in breast milk, such as timolol, carbonic anhydrase inhibitors, and brimonidine. The data are inconsistent as to whether timolol poses a threat to the breastfeeding 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.[372, 376] Brimonidine is known to cross the blood-brain barrier and can cause apnea in infants,

toddlers, and children. For this reason, it is usually recommended that the medication not be used in mothers who are breastfeeding.[371]

Laser trabeculoplasty

Laser trabeculoplasty may be used as initial or adjunctive therapy in patients with POAG.[319, 377-380] Laser trabeculoplasty lowers IOP by improving aqueous outflow and can be performed using argon or solid-state lasers.[381, 382] Laser trabeculoplasty may be performed to 180 degrees or to 360 degrees of the angle. Several randomized clinical trials have evaluated the safety and efficacy of laser trabeculoplasty (see Table 5).

Argon and diode laser trabeculoplasty

The Glaucoma Laser Trial (GLT) as well as other studies using continuous-wave argon laser with a wavelength spectrum that peaks at 488 nm (argon laser trabeculoplasty [ALT]) found that treatment provides a clinically significant reduction of IOP in more than 75% of initial treatments on previously unoperated eyes.[82, 319] More compact solid-state diode lasers have mostly replaced the original argon laser used in these initial studies with equal IOP-lowering efficacy and safety.[383, 384]

For patients initially treated with ALT, the amount of medical treatment required for glaucoma control is often reduced.[319, 385] 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.[82, 386-389] 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.[390-394] Repeat ALT confers an increased risk of complications such as IOP spikes compared with initial ALT.[390, 391, 394, 395]

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.[396-398] 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,[399] producing less thermal damage than ALT.[400] However, several prospective and retrospective studies indicate that SLT appears similar to but not better than ALT in lowering IOP.[401-409] Selective laser trabeculoplasty also appears to be comparable in efficacy to medical therapy with prostaglandin analogs,[377, 380, 410, 411] although in one prospective study, IOP lowering was only similar between treatments when 360 degrees (but not 90 or 180 degrees) of the trabecular meshwork was treated with SLT.[410] A small, multicenter, randomized clinical trial comparing SLT and medical therapy (i.e., prostaglandin analog) as initial treatment for OAG[378] found similar IOP reduction between groups after one year of follow-up. The Selective Laser Trabeculoplasty Versus Eye Drops for First-Line Treatment of Ocular Hypertension and Glaucoma (LiGHT Study) is a larger multicenter, randomized trial comparing initial treatment with 360-degree SLT and medications in patients with OAG and ocular hypertension. Selective laser trabeculoplasty was associated with better cost-effectiveness than medical therapy over 3 years, and resulted in similar IOP lowering and quality of life scores.[379] Rapid visual field progression occurred in more eyes in the medication-treated group than in the SLT-treated group.[412] The West Indies Glaucoma Laser Study (WIGLS) demonstrated safe and effective IOP lowering one year after monotherapy with 360-degree SLT in patients of African descent in St. Lucia and Dominica.[413]

Some studies suggest that SLT has greater success than ALT with repeated treatments, whereas others do not.[414] Studies report varying success rates with repeat SLT compared with initial SLT in retrospective studies.[415-417] The safety profile of SLT appears to be good, with only mild anterior chamber inflammation after treatment and less ocular discomfort compared with ALT.[405] Intraocular pressure spikes have been noted after SLT in 4.5% to 27% of eyes in various studies,[402, 406, 410, 418] which are similar to rates observed

with ALT.[402, 406] Clinical experience suggests that eyes with more heavily pigmented trabecular meshwork are more prone to IOP spikes.[419]

TABLE 5 RANDOMIZED CLINICAL TRIALS OF LASER TRABECULOPLASTY WITH PUBLISHED RESULTS

Study	Study Design	No. of Patients	Follow-up Duration (yrs)	Finding
Glaucoma Laser Trial (GLT), 1990–1995[319, 385]	Newly diagnosed POAG: medical therapy vs. ALT	271	2.5–5.5	Initial ALT lowered IOP more (9 mmHg) than initial treatment with topical timolol maleate (7 mmHg) over 2 yrs; initial ALT was at least as effective in preserving visual field and optic disc status over 5.5 yrs.
Glaucoma Laser Trial Follow-up Study, 1995[319]	Participants in the GLT	203	6–9	Longer follow-up reinforced the earlier findings that initial ALT 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 Therapy Trial, 1994[79]	Newly diagnosed POAG: medical therapy vs. ALT vs. trabeculectomy	168	5+	Trabeculectomy lowered IOP the most (60% IOP reduction). The ALT (38% IOP reduction) and medical therapy groups (49% IOP reduction) had more deterioration in visual fields than the trabeculectomy group.
Early Manifest Glaucoma Trial (EMGT), 2002–2007[72, 73, 80]	Newly diagnosed POAG: medical therapy and ALT vs. no treatment	255	4–10	Lowering IOP with medical therapy and ALT (25% IOP reduction) slowed progression of optic disc and visual field damage.
Advanced Glaucoma Intervention Study (AGIS), 2000–2004[74, 82]	POAG after medical-therapy failure with no previous surgery: ALT vs. trabeculectomy	591	10–13	Surgical outcome varied by race; patients with African ancestry did better with ALT 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.
Selective Laser Trabeculoplasty vs. Medical Therapy as Initial Treatment for Glaucoma (SLT/Med), 2012[378]	POAG and OHTN: initial medical therapy vs. SLT	69	1	Medical therapy with prostaglandin analogs and 360-degree SLT showed similar IOP lowering at 1 year.
West Indies Glaucoma Laser Study (WIGLS), 2017[413]	POAG: immediate medication washout and SLT vs. 3-month delay then washout and SLT vs. 6-month delay then washout and SLT	72	1	360-degree SLT monotherapy reduced IOP by 20% in 78% of patients of Afro-Caribbean descent through 1 year.

Selective Laser Trabeculoplasty Versus Eye Drops for First Line Treatment of Ocular Hypertension and Glaucoma (LiGHT), 2019[379]	POAG and OHTN; initial medical therapy vs. SLT	718	3	Medical therapy resulted in similar IOP lowering and quality of life scores compared with 360-degree SLT at 3 years. SLT was more cost-effective than medication.

ALT = argon laser trabeculoplasty; IOP = intraocular pressure; OHTN = ocular hypertension; POAG = primary open-angle glaucoma; SLT = selective laser trabeculoplasty

Perioperative care for laser trabeculoplasty

The ophthalmologist who performs the laser surgery has the following responsibilities:[420, 421]

- 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 that surgery is indicated
- To perform at least one IOP check immediately prior to surgery and within 30 minutes to 2 hours after surgery[422]
- 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[386, 423-425]

Medications that are not being used chronically may be used perioperatively to avert temporary IOP elevations, particularly in those patients with severe disease.[422, 426, 427] A 2017 Cochrane Systematic Review found that perioperative medications are superior to no medication to prevent the occurrence of spikes in IOP but it was unclear whether one medication was better than other medications in this class of drugs. Therefore, in consultation with the individual patient, treating ophthalmologists should use perioperative medications if temporary IOP elevations are a concern.[428] *(I+, Moderate Quality, Strong Recommendation)* Brimonidine has been shown to be as effective as apraclonidine in preventing immediate IOP elevation after laser trabeculoplasty.[429, 430] Treating 180 degrees reduces the incidence and magnitude of postoperative IOP elevation compared with 360-degree treatment.[431-433]

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.[233, 434] In the Collaborative Initial Glaucoma Treatment Study (CIGTS), initial trabeculectomy was more effective than initial medical therapy in reducing IOP, and it slowed visual field progression among patients who presented with more advanced visual field loss.[233] Patients who underwent primary trabeculectomy in the Moorfields Primary Therapy Trial showed no visual field deterioration over 5 years, in contrast to those treated with medications. Early surgery also resulted in lower IOP than medical and laser therapy did over the same time period.[79]

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.[435-438] 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 Study[82] reached approximately 30% in African American patients and 20% in Caucasian American patients over a 10-year period.[82] Medical treatment with benzalkonium chloride-preserved drugs may be a risk factor for surgical failure.[439] 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.[82,440-443] Furthermore, filtering surgery increases the likelihood that phakic eyes will develop a visually significant cataract.[81, 444, 445] A history of glaucoma surgery also increases the risk of corneal graft failure after penetrating keratoplasty.[446]

In eyes that have undergone previous cataract surgery involving a conjunctival incision, the success rate of initial glaucoma filtering surgery has been reported to be reduced.[308, 441, 447-449] 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.[450]

A 2005 Cochrane Systematic Review concluded that antifibrotic agents may be used intraoperatively and postoperatively to reduce the subconjunctival scarring after trabeculectomy that can result in failure of the operation, and therefore intraoperative MMC should be used.[451] *(I+, Moderate Quality, Strong Recommendation)* Studies confirm this outcome in eyes at high risk of surgical failure[452] and eyes that have not undergone previous surgery.[453-455] A 2015 Cochrane Systematic Review concluded that there is low quality evidence that MMC may be more effective than intraoperative 5-fluorouracil (5-FU) in achieving long-term lower IOP. A 2014 Cochrane Systematic Review reported evidence that intraoperative 5-FU may improve the success rate of lowering IOP compared with no antifibrotic agents but requires multiple injections. Also, 5-FU is increasingly being used on an ad-hoc basis, for which there is no evidence. Therefore, the selection of intraoperative MMC or 5-FU should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient.[456, 457] Intraoperative 5-FU and MMC were found to be equally safe and effective adjuncts to primary trabeculectomy in a multicenter, randomized clinical trial.[458] The use of postoperative injections of 5-FU also reduces the likelihood of surgical failure in both high-risk eyes[308, 459, 460] and eyes that have not undergone previous surgery.[457, 461, 462] A 2014 Cochrane Systematic Review reported that postoperative injections of 5-FU were rarely utilized in postoperative regimens, perhaps because of patient preference and an increased risk of complications. Thus, the routine administration of postoperative 5-FU is not recommended, but should be based on individualized considerations for the patient.[457] *(I++, Moderate Quality, Strong Recommendation)* Aqueous outflow may be enhanced in the early postoperative period with laser suture lysis or removal of releasable sutures.[463, 464] Transconjunctival needling with 5-FU or MMC has been shown to be effective in reviving failing filtering blebs.[465-477] Open trabeculectomy revision with MMC has also demonstrated success in reestablishing aqueous outflow.[478, 479]

The use of an antifibrotic agent carries with it an increased risk of complications such as hypotony,[480-482] hypotony maculopathy,[480] late-onset bleb leak,[457, 483] and late-onset infection[484-486] 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.[487-489] A trend toward a lower concentration and shorter exposure time of MMC has been observed over time,[490] and use of a fornix-based conjunctival flap with broad application of MMC has been advocated to avoid bleb-related complications.[491, 492]

The Ex-PRESS shunt (Alcon Laboratories, Fort Worth, TX) is a nonvalved, stainless steel implant originally designed for subconjunctival insertion at the limbus. A high rate of hypotony and device extrusion[493-495] prompted a modification in surgical technique, which involved placing the device under a partial-thickness scleral flap.[496] The procedure is similar to trabeculectomy, but sclerectomy and iridectomy are not performed. Retrospective studies[496-501] and randomized clinical trials[502-504] have reported similar IOP reduction and surgical success rates with standard trabeculectomy and trabeculectomy with Ex-PRESS. Several studies comparing trabeculectomy with Ex-PRESS with standard trabeculectomy found no significant differences in the rates of intraoperative and postoperative complications,[498, 499, 501-504] but others have reported a higher incidence of early hypotony and cataract progression following standard trabeculectomy.[497, 500, 505] Notably, use of the Ex-PRESS shunt was shown to result in greater endothelial cell loss than standard trabeculectomy in one randomized clinical trial.[505] Use of the Ex-PRESS

implant is associated with greater surgical cost relative to standard trabeculectomy due to the additional expense of the implant itself.[506]

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 within the subconjunctival space 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), ClearPath (New World Medical, Inc., Rancho Cucamonga, CA), and the Molteno implant (Molteno Ophthalmic Ltd., Dunedin, New Zealand). An example of a valved implant 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 1994 to 2012, and there has been a concurrent decline in the number of trabeculectomies performed.[507]

Several studies have compared aqueous shunts with trabeculectomy. A 2017 Cochrane Systematic Review found that there was insufficient information to conclude whether aqueous shunts or trabeculectomy yielded superior results, with heterogenous methodology and data quality across studies. Therefore, the selection of aqueous shunts or trabeculectomy should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient.[508] *(I-, Insufficient Quality, Strong Recommendation).* A retrospective study evaluating surgical results in matched patient groups reported similar IOP reduction with the single-plate Molteno implant and trabeculectomy with 5-FU.[509] However, another retrospective case-control study observed a higher 5-year success rate after trabeculectomy with MMC than with Ahmed glaucoma valve implantation.[510] 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.[511] The Tube Versus Trabeculectomy (TVT) Study is a multicenter, randomized clinical trial that compared the safety and efficacy of tube-shunt surgery using the 350-mm^2 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.[512, 513] The Primary Tube Versus Trabeculectomy (PTVT) Study is an ongoing multicenter, randomized clinical trial comparing 350-mm^2 Baerveldt glaucoma implant surgery versus trabeculectomy with MMC in eyes without previous incisional surgery. At 3 years, rates of surgical success and serious complications were similar between groups, but the trabeculectomy group demonstrated lower IOP with fewer medications than the tube group.[514]

Numerous studies have compared aqueous shunts that differ in size and design.[515-524] Shunts with larger surface area end plates have been associated with lower levels of IOP[515-517] and use of fewer topical ocular hypotensive agents[516, 518, 519] in several retrospective case series. A randomized clinical trial evaluating the single-plate (135 mm^2) and double-plate (270 mm^2) Molteno implants observed a higher success rate with the double-plate implant at 2 years.[520] However, a prospective study of the 350-mm^2 and 500-mm^2 Baerveldt

implants found a higher success rate with the 350-mm^2 implant at 5 years.[521] A prospective randomized trial comparing the Ahmed glaucoma valve (184 mm^2) and single-plate Molteno implant noted similar success with both implants at 2 years.[522] 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 5 years of follow-up in both studies.[523-525] 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 occurring 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,[513] 1%–2.9% in ABC Study,[524] 2%–4% in AVB Study[523]), and this typically develops a few millimeters behind the limbus following anterior chamber insertion. Patch allografts of sclera, cornea, or pericardium are commonly used to prevent tube erosion, and a long scleral tunnel may also mitigate this risk.[526, 527] Diplopia and motility disorders may result from extraocular muscle fibrosis or a mass effect of the bleb overlying the end plate (6% in TVT Study,[513] 11.8%–12.7% in ABC Study,[524] 2%–5% in AVB Study[523]). Progressive endothelial cell loss can produce persistent corneal edema (16% in TVT Study,[513] 11.7%–11.9% in ABC Study,[524] 11%–12% in AVB Study[523]). Potential causes of corneal decompensation include mechanical tube-cornea touch, foreign body reaction to the tube, disruption of the blood-aqueous barrier, and changes in aqueous composition with increased inflammatory mediators.[528] 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 visually significant cataracts have a range of options available. 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 poorly controlled on several medications or there is evidence of glaucomatous progression in a patient with a moderate cataract, 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 intraocular lens (IOL) implantation alone results in a modest reduction in IOP of less than 2 mmHg on average.[201] However, a mean decrease in IOP of 16.5% was observed among patients in the OHTS after cataract extraction, which persisted during 3 years of follow-up postoperatively.[200] Generally, combined cataract and glaucoma surgery is not as effective as glaucoma surgery alone in lowering IOP,[201, 529] so patients who require filtration surgery who also have mild cataract may be better served by filtration surgery alone and cataract surgery later. An evidence-based review of combined cataract and glaucoma surgery concluded that use of MMC, but not 5-FU, results in lower IOP in combined procedures.[529] A 2005 Cochrane Systematic Review concluded that MMC may be used intraoperatively to reduce the subconjunctival scarring after trabeculectomy that can result in failure of the operation, but found no evidence on the use of MMC in combined cataract and glaucoma surgery.[451] *(I+, Moderate Quality, Strong Recommendation)* A 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.[529] Subsequent publications have found no difference between the two approaches.[530-532]

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.[533-535] A 2015 Cochrane Systematic Review identified low quality evidence for better IOP control with combined surgery over cataract surgery alone, and more high quality studies are required with outcomes that are relevant to patients. Therefore, the selection of a combined surgery or cataract surgery alone can be left to the discretion of the treating ophthalmologist in consultation with the individual patient.[536] *(I-, Insufficient Quality, Strong Recommendation)*

Intraocular lens selection merits special consideration in cases where trabeculectomy is performed first and cataract surgery is deferred until optimization of IOP. Myopic surprises have been described following phacoemulsification in patients with prior filtering surgery and lower preoperative IOP,[537-539] even when using fourth-generation formulas and noncontact (laser) interferometry.[538] Multifocal intraocular lenses may have adverse effects on contrast sensitivity[540] and visual field performance[541] in patients with glaucoma. Intraocular lens choices and refractive goals should be individualized in each patient based on history of filtering surgery, IOP level, and severity of glaucomatous damage.

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 (MIGS), and endoscopic cyclophotocoagulation.

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 continues to evolve.

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.[542-544] One randomized clinical trial found that trabeculectomy was more effective than deep sclerectomy at lowering IOP,[545] but several others found that the two surgeries were equally effective.[546-549]

Viscocanalostomy: Viscocanalostomy includes deep sclerectomy along with expansion of Schlemm's canal using an ophthalmic viscoelastic device. The procedure is intended to allow passage of aqueous humor through the trabeculodescemetic membrane window and into the physiologic outflow pathway through Schlemm's canal. Randomized clinical trials comparing viscocanalostomy with trabeculectomy suggest greater IOP reduction with trabeculectomy but fewer complications with viscocanalostomy.[464, 550-557] A 2014 Cochrane Systematic Review found some limited evidence that control of IOP was better with trabeculectomy than with viscocanaloplasty, but conclusions could not be drawn for deep sclerectomy, and quality of life outcomes may be needed to differentiate among procedures. Thus, the selection of viscocanalostomy and deep sclerectomy over trabeculectomy should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient.[558] *(I-, Insufficient Quality, Strong Recommendation)*

Canaloplasty: In canaloplasty, circumferential viscodilation of Schlemm's 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 Schlemm's 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.[559] A retrospective case series found lower postoperative IOP with trabeculectomy compared with canaloplasty.[560] In a randomized clinical trial comparing trabeculectomy and canaloplasty, patients in the trabeculectomy group achieved higher success rates and required fewer medications than those in the canaloplasty group, but they also experienced a higher rate of late hypotony.[561]

Minimally invasive glaucoma surgery

The term minimally invasive glaucoma surgery, or MIGS, refers to a group of surgical procedures that are performed using an ab interno approach and involve minimal trauma to ocular tissues.[562] Limited long-term data are currently available for MIGS, given its relatively recent introduction. Modest IOP reduction has been reported following MIGS, and postoperative pressures are typically in the middle 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. Currently available MIGS includes procedures targeting the trabecular meshwork/Schlemm's canal and the subconjunctival space (Table 6). They are commonly combined with phacoemulsification; some are only FDA approved to be performed concurrently with phacoemulsification.

Trabecular meshwork/Schlemm's canal-based MIGS: Trabecular MIGS includes the excision or cleavage, dilation, or stenting of varying extents of the trabecular meshwork and inner wall of Schlemm's canal under gonioscopic guidance. These procedures enhance aqueous access to collector channels and increase outflow.[563] The IOP-lowering effect of trabecular MIGS is limited by resistance in distal outflow pathways and the episcleral venous pressure.

Ab interno trabeculectomy involves the removal of a strip of trabecular meshwork and inner wall of Schlemm's canal. The Trabectome (NeoMedix Corporation, Tustin, CA) uses high-frequency electrocautery to remove up to 180 degrees of trabecular meshwork through a single corneal incision and reduces IOP and glaucoma medical therapy with minimal intraoperative and postoperative complications.[564-570] Case series have described the efficacy of Trabectome combined with phacoemulsification, but no randomized prospective studies have included a comparison group of phacoemulsification alone.[567, 569-574] 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.[575, 576] A failed Trabectome did not affect the success rate of subsequent trabeculectomy in one cohort study.[577] Ab interno trabeculectomy may also be achieved using the Kahook Dual Blade ([KDB]; New World Medical, Rancho Cucamonga, CA) or Goniotome (NeoMedix Corporation, Tustin, CA), and both single-use goniotomy blades may be used with cataract surgery or as a stand-alone procedure. Retrospective studies with short-term follow-up demonstrate modest IOP-lowering when KDB goniotomy is performed with or without phacoemulsification, with minimal associated complications.[578-580] One prospective case series of patients undergoing combined phacoemulsification and KDB goniotomy demonstrated reduction in IOP to the low teens at one year, but it had no control group of patients undergoing phacoemulsification alone.[581] One retrospective study found that KDB goniotomy may offer improved IOP lowering when compared with iStent use (Glaukos Corporation, Laguna Hills, CA); however, prospective, randomized trials are needed to confirm this observation.[582]

Gonioscopy-assisted transluminal trabeculotomy (GATT) involves ab interno 360-degree cannulation of Schlemm's canal with an illuminated microcatheter (iTrack, Ellex, Mawson Lakes, Australia) or suture, followed by trabeculotomy. The procedure appears to have reasonable efficacy, but data are limited to small retrospective series. One such series suggests a potential role for GATT in eyes with previous incisional glaucoma surgery, but additional studies are needed to understand its long-term safety and efficacy.[583-585] The OMNI Surgical

System (Sight Sciences, Menlo Park, CA) is an alternative means of performing 180- to 360-degree ab interno trabeculotomy using a retractable microcatheter.

In ab interno canaloplasty (ABiC), an illuminated microcatheter is used to circumferentially dilate Schlemm's canal with cohesive viscoelastic. Small retrospective studies have demonstrated IOP lowering to the midteens 1 year after ABiC, with or without concomitant cataract surgery. The success of ABiC in reducing postoperative glaucoma medication burden is less clear.[586, 587] Efficacy of ABiC appears to be comparable to that of ab externo canaloplasty.[588]

The first-generation trabecular microbypass stent, or iStent, is a single snorkel-shaped device manufactured from heparin-coated titanium that is implanted into Schlemm's canal using a preloaded inserter. The iStent is FDA approved for implantation in combination with cataract surgery in patients with mild to moderate OAG. Studies suggest that implantation of multiple stents may provide better IOP lowering than a single stent; however, placement of more than one first-generation iStent is considered off-label use in the United States.[589-592]

The second-generation iStent *inject*® system (Glaukos Corporation, Laguna Hills, CA) includes two conical implantable stents in its preloaded injector and has the same indications as its predecessor. A randomized trial comparing implantation of two iStent *inject* devices to fixed-combination latanoprost/timolol found comparable efficacy between the two groups.[593] Modest reductions in IOP and glaucoma medical therapy have been observed in patients undergoing concomitant iStent or iStent *inject* and cataract surgery compared with those receiving cataract surgery alone.[589, 594-597] Low rates of surgical complications have been reported with both the iStent and iStent *inject,* most commonly, hyphema, stent malposition, and stent obstruction.[589, 590, 594-599] A 2019 Cochrane Systematic Review found very low quality evidence that iStent may achieve better IOP control or reduction in medications, and that future research should include more quality of life outcomes. Thus, the selection of iStent or medications should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient.[600] *(I-, Insufficient Quality, Strong Recommendation)*

The intracanalicular scaffold, or Hydrus microstent (Ivantis Inc., Irvine, CA), is an 8-mm nitinol implant that is inserted into Schlemm's canal via an ab interno approach using a preloaded injector. Like the iStent, the Hydrus microstent is approved for use in patients with mild to moderate POAG who are undergoing concurrent phacoemulsification. Studies have demonstrated IOP reductions to the midteens, with a decreased need for glaucoma medications after Hydrus microstent implantation combined with cataract surgery compared with cataract surgery alone.[601, 602] At 1 year, stand-alone Hydrus microstent implantation resulted in higher success rates and use of fewer glaucoma medications compared with placement of two iStents in a randomized clinical trial.[603] The Hydrus microstent appears to have excellent safety, with complications largely limited to focal peripheral anterior synechiae. A 2020 Cochrane Systematic Review found moderate evidence that the Hydrus microstent in the short term is more effective when compared to iStent for lowering IOP in patients with OAG.[604] *(I, Moderate Quality, Strong Recommendation)*

Subconjunctival MIGS: The Xen gel stent (Allergan plc, Irvine, CA) is a 6-mm gelatinous tube that is designed for placement into the subconjunctival space via an ab interno approach using a preloaded 27-gauge needle inserter. Some surgeons prefer to insert the device via an ab externo approach, either through the intact conjunctiva or following a limited peritomy. Although several models have been studied, only the 45-micron lumen stent is FDA approved for use in refractory glaucoma. As in trabeculectomy, the use of intraoperative antifibrotic agents enhances surgical success.[605] The pivotal single-arm prospective trial demonstrated IOP in the midteens 1 year after Xen gel stent implantation with MMC. Transient postoperative hypotony was common, as was the requirement for needling.[605] No randomized clinical trials assessing the safety and efficacy of the Xen gel stent exist. A 2018 Cochrane Systematic Review did not identify any randomized controlled clinical trials assessing the safety and efficacy of the Xen gel stent. Thus, the selection of the Xen gel stent should be left to the discretion of the treating

ophthalmologist, in consultation with the individual patient.[606] *(I-, Insufficient Quality, Discretionary Recommendation)*

Suprachoroidal MIGS: The Cypass Micro-Stent (Alcon Laboratories, Fort Worth, TX) is an ab interno suprachoroidal shunt that was FDA approved for implantation at the time of cataract surgery in patients with mild to moderate POAG.[607] The Cypass underwent market withdrawal and an FDA Class I recall in 2018 after a post-approval study demonstrated significantly greater endothelial cell loss at 5 years in patients who received combined Cypass and cataract surgery versus cataract surgery alone.[608] The American Society of Cataract and Refractive Surgery Cypass Withdrawal Task Force suggests monitoring all patients with Cypass for the development of clinically significant corneal edema.[609] In cases where corneal edema is caused by a greater length of the device extending into the anterior chamber (indicated by multiple retention rings being visible), trimming the proximal end of the device is recommended rather than repositioning and/or removal.[609-611]

TABLE 6 FDA-APPROVED AB INTERNO MINIMALLY INVASIVE GLAUCOMA SURGERY (MIGS)

Procedure	Manufacturer	Anatomical Target	Description	Concomitant Cataract Surgery Required
Trabectome	NeoMedix Corporation, Tustin, CA	TM/SC	Ablation of TM/inner wall of SC using handheld electrode with irrigation/aspiration ports	No
Goniotome	NeoMedix Corporation, Tustin, CA	TM/SC	Excision of TM using serrated dual blade with optional irrigation/aspiration	No
Kahook Dual Blade (KDB)	New World Medical, Rancho Cucamonga, CA	TM/SC	Excision of TM using dual blade	No
Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)	iTrack microcatheter; Ellex, Mawson Lakes, Australia*	TM/SC	360-degree trabeculotomy using illuminated microcatheter or suture	No
OMNI Surgical System	Sight Sciences, Menlo Park, CA	TM/SC	180- or 360-degree trabeculotomy using microcatheter	No
Ab interno canaloplasty (ABiC)	iTrack microcatheter; Ellex, Mawson Lakes, Australia	TM/SC	360-degree viscodilation of SC	No
iStent (1st Generation)	Glaukos Corporation, Laguna Hills, CA	TM/SC	Single snorkel-shaped, heparin-coated titanium stent inserted into SC	Yes
iStent Inject (2nd Generation)	Glaukos Corporation, Laguna Hills, CA	TM/SC	Two conical, heparin-coated titanium stents inserted into SC	Yes
Hydrus Microstent	Ivantis Inc., Irvine, CA	TM/SC	8-mm nitinol scaffold inserted into SC	Yes
Xen Gel Stent	Allergan PLC, Irvine, CA	Subconjunctival	6-mm gelatin tube with 45-micron lumen inserted into subconjunctival space	No

FDA = Food and Drug Administration; SC = Schlemm's canal; TM = trabecular meshwork

* Manufacturer is provided for the illuminated microcatheter. Gonioscopy-assisted transluminal trabeculotomy may also be performed using a polypropylene or nylon suture as indicated above.

Perioperative care in incisional glaucoma surgery

The ophthalmologist who performs incisional glaucoma surgery has the following responsibilities:[420, 421]

- Perform gonioscopy preoperatively, especially when considering trabecular meshwork/Schlemm's canal-based MIGS
- Obtain informed consent from the patient or the patient's surrogate decision maker after discussing the risks, benefits, alternatives, and expected outcomes of surgery[612]
- Ensure that the preoperative evaluation accurately documents the findings and indications for surgery
- Prescribe topical corticosteroids in the postoperative period[613, 614]
- Perform a follow-up evaluation on the first postoperative day and at least once during the first 1 to 2 weeks to evaluate visual acuity, IOP, and status of the anterior segment[615-620]
- In the absence of complications, perform additional postoperative visits during a 3-month period to evaluate visual acuity, IOP, and status of the anterior segment[615-620]
- 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)[615-620]
- 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[466, 468, 621]
- 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 immediately[622]

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.[623, 624] Micropulse transscleral cyclophotocoagulation is an alternative approach to traditional laser cyclophotocoagulation that delivers repetitive short bursts of diode laser energy with intervening rest periods.[625] Cyclodestructive procedures have traditionally been used for refractory glaucomas, and success rates have been reported in the range of 34% to 94%.[624] They have been associated with a subsequent decrease in visual acuity[626, 627] and, rarely, cases of sympathetic ophthalmia.[628, 629] 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.[630] 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 that are otherwise poor candidates for incisional ocular surgery.

In 2005, 47% of all Medicare cyclophotocoagulation procedures were performed endoscopically, and 77% were performed in 2012.[507] 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 cable[624] that can be introduced inside the eye for direct visualization and treatment of the ciliary processes. This allows better titration of laser treatment.[631, 632] The efficacy of ECP appears to be good, with IOP reduction reported in the range of 34% to 57%.[633-635] Most studies treat 270 to 360 degrees of the ciliary body.[633, 635] Fibrin exudates, hyphema, cystoid macular edema, vision loss, hypotony, choroidal detachment,[633] and phthisis[636] 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.[634]

Endoscopic cyclophotocoagulation[633, 634, 637] 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,[638] and another study comparing ECP with the Ahmed drainage implant also showed comparable efficacy in lowering IOP, although the rate of complication with the latter surgery was higher.[639] A 2019 Cochrane Systematic Review found inconclusive evidence whether cyclodestructive procedures for refractory glaucoma result in better outcomes and fewer complications than other glaucoma treatments, or whether one cyclodestructive procedure is better than another.[640] Another 2019 Cochrane Systematic Review identified no studies on the effects of endocyclophotocoagulation for open-angle glaucoma.[641] Additional randomized clinical trials are needed to further elucidate the merits of each type of cyclophotocoagulation relative to one another as well as to other types of glaucoma surgery.[640, 641] Therefore, the selection of cyclophotocoagulation over other procedures should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient. *(I-, Insufficient Quality, Discretionary Recommendation)*

Other therapeutic considerations

There is a growing interest in complementary and alternative medicinal approaches to the treatment of glaucoma. There is a lack of conclusive scientific evidence that herbal medicines or nutritional supplements are beneficial in treating glaucoma.[642-645] 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.[646, 647] Results from the National Health and Nutrition Examination Survey (NHANES) suggest that higher intensity exercise may reduce the risk of developing glaucoma.[648]

Follow-up Evaluation

Guidelines for follow-up of patients with POAG are summarized in Table 7. These recommendations apply to ongoing glaucoma management and not to visits for other purposes. The purpose of follow-up examination is to evaluate IOP level, visual field status, and optic disc appearance as well as ONH, RNFL, and macular imaging to determine if progressive damage has occurred.

TABLE 7 CONSENSUS-BASED GUIDELINES FOR FOLLOW-UP GLAUCOMA STATUS

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

IOP = intraocular pressure; NA = not applicable

* 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
- Review of pertinent medication use, including time of last administration

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, 25, 649] measurement of CCT should be repeated after any event (e.g., refractive surgery[650]) that may alter CCT.

Home tonometry is a promising development to aid in glaucoma management. In a prospective study of the iCare Home device, the agreement between iCare Home readings and GAT was good, with 91% of readings within 5 mmHg. However, one in six participants was unable to use the device appropriately, indicating the importance of patient selection and education.[651] A contact lens sensor is commercially available (Triggerfish CLS, Sensimed AG, Lausanne, Switzerland) to measure 24-hour IOP-related patterns in an ambulatory setting.[652-654] This technology is based on the assumption that variation in IOP leads to changes in ocular volume and dimension, which the device captures through embedded strain gauges.[655]

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 should be performed periodically.

Optic nerve head and visual field evaluation

Optic nerve head evaluation should be performed regularly. Documentation by imaging, photography, or drawing[287, 656-658] and visual field evaluation[659-662] should be performed at least yearly. Periodic photography may also reveal disc hemorrhages not seen on examination[54] 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. Rapid visual field progression may be detected earlier by performing three visual fields per year during the first 2 years.

Factors that influence the frequency of evaluations include the severity of damage (mild, moderate, severe, with more frequent evaluations for more severe disease), the rate of progression,[322] 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 and imaging may be required more frequently (e.g., a second test to establish a baseline for future comparisons, to clarify a suspicious test result or apparent testing artifact, or to include an alternate visual field testing strategy).

Risk Factors for Progression

Risk factors for progression of glaucoma include the following:

- IOP: Several multicenter, randomized clinical trials have investigated the relationship between IOP and risk of glaucomatous progression (see Table 2). Higher baseline IOP,[72] higher mean IOP during follow-up,[74, 663] and higher yearly average IOP[664] were associated with greater progression of glaucoma as measured by visual field or optic nerve changes. Greater diurnal

IOP fluctuation has inconsistently been shown to be related to visual field progression and requires further study.[80, 86, 228-235]

- Older age[72, 80, 233, 663, 665, 666]
- Disc hemorrhage: The presence of a disc hemorrhage[54, 665, 667-673] and the percentage of visits with disc hemorrhage[72, 80] 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[674, 675]
- Beta-zone parapapillary atrophy: The baseline presence[667, 674] and the size[665, 676] 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 CCT: 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.[117, 126, 129, 263, 264, 266, 267, 649, 677, 678]
- 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.[128-131]
- Lower ocular perfusion pressure[80, 137]
- Poor adherence with medications[679-682]
- Progression in fellow eye: Glaucomatous progression in one eye is associated with an increased risk of progression in the fellow eye, and unilateral disease commonly becomes bilateral.[80, 683-686]

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 occur for a prolonged period in a patient taking 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, imaging, or visual field change.[680, 687-690]

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, ONH, RNFL, and macular imaging) 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. 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 in-person, 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. Patients should be encouraged to alert their ophthalmologists to physical or emotional changes that occur when taking glaucoma medications and to barriers to self-management. Ophthalmologists should remain mindful that the diagnosis of glaucoma can itself lead to negative psychological effects and to fear of blindness.[691-695]

Ophthalmologists should strive to provide education that is clear, relevant, and accessible to the patient and their caregiver(s). Patients with poor health literacy skills may be especially vulnerable to worse visual outcomes.[696] Limiting dense text and using "teach-back" techniques such as asking patients to explain what they understand about glaucoma may be helpful for patients with limited literacy skills. Patients with higher levels of literacy may ask questions that lead to a more complex discussion, but patients who do not understand the information provided to them initially may miss the opportunity to engage in their disease management.

Even patients with experience using glaucoma drops may struggle to administer drops successfully.[355] Many patients depend on companions to assist with their drops.[697] Ophthalmologists should consider instructing patients, and companions if applicable, on drop administration techniques. For some patients, drop administration may be exceedingly difficult and, if so, laser trabeculoplasty or surgery may be better options.

Glaucoma affects the patient's visual and health-related quality of life in many ways,[176, 698] including employment issues (e.g., fear of loss of job and insurance from diminished ability to read and drive), social issues (e.g., isolation, 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.[132] During LASIK, SMILE, and femtosecond laser-assisted cataract surgery, IOP briefly increases upon application of the suction ring and vacuum. This effect may cause additional damage in patients whose optic nerves already have advanced damage.[699] Therefore, these procedures 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.[700] 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.[701, 702] 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.[540] 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.[703] More information on vision rehabilitation, including materials for patients, is available at www.aao.org/smart-sight-low-vision.

SOCIOECONOMIC CONSIDERATIONS

The number of adults 40 to 80 years old worldwide with glaucoma is estimated to be more than 76 million. As the prevalence of glaucoma increases with age, this number is projected to increase to

more than 111 million in 2040.[10] Thus, the burden of disease both to the individual patient and the economic burden to society are substantial.[704]

Glaucoma can have a dramatic impact on quality of life. Patients with glaucoma may struggle with daily activities such as reading, walking, and driving.[705] Performance on these activities deteriorates with worsening of glaucoma severity or when both eyes are affected. People with glaucoma are more likely to experience falls and more likely to be involved in motor vehicle collisions compared with people without glaucoma.[706] Quality of life is affected for patients with all stages of glaucoma, even those with early disease.[707]

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 a year is spent in the United States on direct medical costs.[708] 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 modeling, one study estimated that the average direct and indirect medical costs for patients with glaucoma are $1688 higher than other patients without this condition over a lifetime.[709]

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.[710] Among patients with early glaucoma, most of the costs of care are for medications.[711] For those with advanced disease, indirect costs such as costs for home health care and rehabilitation predominate.[712, 713] Secondary forms of glaucoma may confer an even greater economic burden. In particular, the cost of care for patients with pseudoexfoliation glaucoma is significantly more than the cost of care for patients with POAG due to the increased number of office visits, surgeries, and medications.[714]

Using computer modeling, 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.[715] Other studies have compared the cost-effectiveness of using different treatment modalities. One study found use of generic prostaglandin analogs and laser trabeculoplasty to both be cost-effective treatment strategies for patients with early glaucoma.[716] The use of generic prostaglandin analogs was found to be the more cost-effective treatment option compared with laser trabeculoplasty when assuming optimal medication adherence. However, when assuming more realistic estimates of medication adherence, laser trabeculoplasty was found to confer greater value compared with prostaglandin analogs. The results of the more recent LiGHT Study support this finding.[379] Indeed, poor medication adherence has been identified as contributing to the high cost of glaucoma care across multiple studies and in different health care systems.[717]

Markov modeling based on estimates from the TVT Study suggest that both trabeculectomy and glaucoma drainage device surgery are cost-effective over a 5-year period compared with medical management, with trabeculectomy incurring a lower cost per quality-adjusted life year.[718] A separate study comparing standard trabeculectomy versus trabeculectomy with Ex-PRESS shunt found that Ex-PRESS shunt surgery incurs significantly greater cost than trabeculectomy without Ex-PRESS.[506] Ongoing studies are exploring the cost-effectiveness of MIGS procedures.[719]

When considering the economic burden of glaucoma, it is important to appreciate that glaucoma affects a disproportionately large number of racial and ethnic minorities. In fact, glaucoma is the leading cause of blindness among African Americans, 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 African Americans are less likely to undergo examinations for glaucoma relative to whites,[720, 721] have lower rates of undergoing visual field testing relative to whites in the year before glaucoma surgery,[722] and have lower rates of utilization of medical and surgical interventions for glaucoma.[723] A more recent study found that despite possessing health insurance, Latinos were significantly less likely to undergo monitoring for glaucoma relative to whites.[724] 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 race and age 50 or older, or Latino ethnicity and age 65 or older.[198] In the ever-evolving health care environment, 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.

- 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

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

	ICD-10 CM
Open-angle glaucoma	H40.10X-
Primary open-angle glaucoma	H40.111-
	H40.112-
	H40.113-
Low-tension glaucoma	H40.121-
	H40.122-
	H40.123-
Residual stage of open-angle glaucoma	H40.151
	H40.152
	H40.153
Glaucomatous atrophy of the optic disc	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 March 2019; the search strategies were as follows. Specific limited update searches were conducted after June 2020.

("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*)

("Quality of Life"[Mesh] OR "quality of life" OR qol OR hrqol 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)

(("Photography"[Mesh] AND 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 OR poag)

("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 OR poag)

("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 OR poag)

("Intraocular Pressure"[Mesh] OR IOP) AND ("Glaucoma"[Mesh] OR glaucoma) AND "optic nerve damage" AND (“disease progression”[mh] OR past OR future OR predict* OR progressive)

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND "selective laser trabeculoplasty"

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((diode AND cyclophotocoagulation) OR “diode photocoagulation”))

("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma) AND ((endoscopic AND cyclophotocoagulation) OR “endoscopic photocoagulation”))

("Refractive Surgical Procedures"[Mesh] OR “refractive surgery”) AND ("Glaucoma"[Mesh] OR "Glaucoma, Open-Angle"[Mesh] OR glaucoma OR poag)

("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]

("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] OR poag)

("Glaucoma, Open-Angle"[Mesh] OR poag)

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course Glaucoma (Section 10, 2019–2020)

Ophthalmic Technology Assessment – Free downloads available at www.aaojournal.org/content/OphthalmicTechnologyAssessment.
Swept-Source OCT for Evaluating the Lamina Cribrosa OTA (2019)
The Effect of Anti-Vascular Endothelial Growth Factor Agents on Intraocular Pressure and Glaucoma OTA (2019)
Spectral-Domain OCT: Helping the Clinician Diagnose Glaucoma OTA (2018)
Laser Peripheral Iridotomy in Primary Angle Closure OTA (2018)
Disinfection of Tonometers OTA (2017)
The Effect of Phacoemulsification on Intraocular Pressure in Glaucoma Patients OTA (2015)

Patient Education
Glaucoma Brochure (2020) (also available in Spanish)
Glaucoma Patient Education Video Collection (2015)
Laser Iridotomy Brochure (2019)
Eye Drops Brochure (2019)
Glaucoma Drainage Implant Brochure (2019)
Laser Iridotomy Brochure (2019)
Laser Trabeculoplasty Brochure (2019)
Trabeculectomy Brochure (2020)

Preferred Practice Pattern® Guidelines – Free downloads available at www.aao.org/ppp.
Comprehensive Adult Medical Eye Evaluation (2020)
Primary Open-Angle Glaucoma Suspect (2020)
Vision Rehabilitation for Adults (2017)

Focal Points
Optical Coherence Tomography in Glaucoma Diagnosis (2017)
Update on Pseudoexfoliative Glaucoma (2019)
Surgical Management of Angle Closure Glaucoma (2018)
Clinical Applications of Major Glaucoma Trials (2018)
Microinvasive Glaucoma Surgery and Cataract Surgery Synergy (2018)

To order any of these products, except for the free materials, please contact the Academy's Customer Service at 866.561.8558 (U.S. only) or 415.561.8540 or www.aao.org/store.

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