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Primary Open-Angle Glaucoma Suspect Preferred Practice Pattern®

P151

GLAUCOMA PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Glaucoma Preferred Practice Pattern® Panel** members wrote the Primary Open-Angle Glaucoma Suspect 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 partner, the Cochrane Eyes and Vision US Group, 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 Suspect 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 (85%) of the members of the Glaucoma Preferred Practice Pattern Panel 2019-2020 had no related financial relationship to disclose.

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Primary Open-Angle Glaucoma Suspect Preferred Practice Pattern®

Background:
A diagnosis of primary open-angle glaucoma (POAG) suspect is established by the presence of consistently elevated intraocular pressure (IOP), also know as ocular hypertension, or a suspicious optic nerve, retinal nerve fiber layer (RNFL), or visual field in one or both eyes. 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.

Rationale for Treatment:
The decision to treat a POAG suspect patient depends on the level of IOP and other associated risk factors, or evidence of change of the optic nerve, RNFL, or visual field indicating the development of glaucoma. In the Ocular Hypertension Treatment Study, more than 90% of patients with untreated ocular hypertension did not progress to glaucoma over 5 years, but treatment to lower IOP reduced the risk of developing POAG from 9.5% to 4.5%.

Care Process:
The goals of managing patients who are POAG suspects are to lower IOP with treatment if the eye is likely to progress to POAG and to monitor for structural or functional changes of the optic nerve. Appropriate testing to evaluate and monitor POAG suspect patients includes gonioscopy, pachymetry, tonometry, perimetry, careful examination of the optic nerve, and imaging of the optic nerve head, RNFL and macula. Patients should be followed longitudinally for the development of glaucoma. Medical therapy is most commonly used to lower IOP, but laser trabeculoplasty exists as an alternative to medications for patients with ocular hypertension.

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. Appendix 3 has an algorithm for the management of primary open-angle glaucoma (POAG) suspect. The intended users of the Primary Open-Angle Glaucoma Suspect 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 4.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

A diagnosis of primary open-angle glaucoma (POAG) suspect is established by the presence of a consistently elevated intraocular pressure (IOP), also known as ocular hypertension, or a suspicious optic nerve, retinal nerve fiber layer (RNFL), or visual field, in one or both eyes.

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

The decision to treat a POAG suspect patient depends on the level of IOP and other associated risk factors, or evidence of change of the optic nerve, RNFL, or visual field indicating the development of POAG.

In the Ocular Hypertension Treatment Study (OHTS), more than 90% of patients with untreated ocular hypertension did not progress to glaucoma over 5 years, but treatment to lower IOP reduced the risk of developing POAG from 9.5% to 4.5%.

A reasonable target for IOP reduction in a POAG suspect patient in whom the decision to treat has been made is 20%, based on the OHTS.

Appropriate testing to evaluate and monitor patients diagnosed as a glaucoma suspect includes gonioscopy, pachymetry, tonometry, perimetry, careful examination of the optic nerve, and ocular imaging. Computer-based imaging and stereoscopic photography provide different and complementary information about optic nerve status.

INTRODUCTION

DISEASE DEFINITION

A glaucoma suspect is an individual with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing primary open-angle glaucoma (POAG).

CLINICAL FINDINGS CHARACTERISTIC OF PRIMARY OPEN-ANGLE GLAUCOMA SUSPECT

An individual with an open anterior chamber angle may be diagnosed as a glaucoma suspect based on any of the following clinical findings in one or both eyes:

- Elevated intraocular pressure (IOP) associated with normal appearance of the optic disc, retinal nerve fiber layer (RNFL), and visual field
- An appearance of the optic nerve head (ONH) or RNFL suspicious for glaucomatous damage
- A visual field suspicious for glaucomatous damage in the absence of clinical signs of another optic neuropathy or retinopathy

This definition excludes the angle-closure glaucomas and known secondary causes for open-angle glaucoma, such as pseudoexfoliation syndrome, pigment dispersion syndrome, and traumatic angle recession.

PATIENT POPULATION

The patient population includes adults with open anterior chamber angles with one of the clinical findings or risk factors listed in the Clinical Findings Characteristic of Primary Open-Angle Glaucoma Suspect section.

CLINICAL OBJECTIVES

- Identify patients at high risk of developing POAG
- Document the status of the optic nerve structure at presentation by clinical evaluation and imaging, and document visual function by visual field testing
- Perform and document gonioscopy
- Consider treatment of high-risk individuals to prevent or delay the development of POAG
- Minimize the side effects of treatment and the impact of treatment 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 patient's condition
- Monitor the IOP and the structure and function of the optic nerve for evidence of glaucomatous damage

BACKGROUND

PREVALENCE

A diagnosis of POAG suspect is established by the presence of at least one of the following conditions: a consistently elevated IOP, also known as ocular hypertension, or a suspicious optic nerve or visual field.

Ocular hypertension has been defined as IOP higher than two standard deviations above the mean for the population without evidence of optic disc or visual field damage.[4] In the United States, this

definition usually includes an IOP greater than 21 mmHg. Using this definition, the prevalence of ocular hypertension in non-Hispanic whites who are 40 years and older and live in the United States is 4.5% (ranging from 2.7% in persons 43 to 49 years old to 7.7% in those 75 to 79 years old).[5] In Latinos 40 years and older, the overall prevalence is 3.5% (ranging from 1.7% in persons 40 to 49 years old to 7.4% in those 80 years and older).[6] There are no published population-based estimates for the prevalence of ocular hypertension in African Americans and Asian Americans. Overall, 3 to 6 million persons in the United States have ocular hypertension.[7, 8]

Many studies suggest that a large proportion of people who are glaucoma suspects are likely undiagnosed. For example, the Los Angeles Latino Eye Study (LALES) showed that 75% of Latinos with IOP greater than 21 mmHg were previously undiagnosed.[6] Because ocular hypertension is a major risk factor for development of glaucoma, eye care providers should measure IOP in all of their patients over the age of 40 years. However, the overall likelihood of developing glaucomatous optic neuropathy may vary among individuals and increases with the number and relative strength of their risk factors for glaucoma.[9]

The prevalence of patients diagnosed as glaucoma suspects is less understood because the definition of glaucoma suspect includes several criteria, including elevated IOP, suspicious visual fields or optic disc appearance, and RNFL abnormalities, and the criteria for "abnormal" may differ between clinicians.[10, 11] Furthermore, clinicians may consider a patient a glaucoma suspect because of a history of myopia,[12] a background including an ethnoracial group with higher risk of glaucoma,[4, 13, 14] or family history of glaucoma.[15]

RISK FACTORS

The results of epidemiological studies and clinical trials provide a framework for understanding the effects of risk factors associated with POAG. Numerous studies have identified risk factors associated with POAG (see Primary Open-Angle Glaucoma PPP for additional discussion of risk factors):

- Elevated IOP[7, 16-26]
- Older age[16, 17, 20, 21, 27-29]
- Family history of glaucoma[21, 30]
- African race or Latino/Hispanic ethnicity
- Thin central cornea[16, 17, 31]
- Low systolic and diastolic blood pressure[30]
- Low ocular perfusion pressure[30, 32, 33]
- Type 2 diabetes mellitus[34-37]
- Myopia[32, 38-40]
- Disc hemorrhage[41-45]
- Large cup-to-disc ratio[16, 17]
- High pattern standard deviation on threshold visual field testing[17, 26, 46]
- Hypothyroidism[47]
- Male sex[48, 49]

Although disc hemorrhage, increased cup-disc ratio, and higher pattern standard deviation are considered to be risk factors for the development of POAG, it can also be argued that these represent signs of early optic nerve and visual field damage from glaucoma.[17, 45, 50]

Even though conflicting data exist on the association between type 2 diabetes mellitus and POAG,[21, 34-36, 51-56] evidence from population-based studies suggests that type 2 diabetes mellitus is an important risk factor for POAG.[34-36, 52, 54] Population-based assessments of Hispanics (in Los Angeles, California),[35] non-Hispanic whites (in Beaver Dam, Wisconsin, and Blue Mountains, Australia),[34, 54] and a large cohort enrolled in the Nurses' Health Study[52] 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, longer duration of type 2 diabetes mellitus was associated with a higher risk of having POAG in the LALES.[35] 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.[53] Interestingly, authors have suggested that type 2 diabetes is directly associated with a higher IOP reading, likely related to a change in corneal biomechanics.[57] 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.[37]

Other factors that have been associated with POAG include migraine headache, sleep apnea, peripheral vasospasm (Raynaud's syndrome), cardiovascular disease, low corneal hysteresis, and systemic hypertension.[17, 58-65] However, the association between these risk factors and the development of glaucomatous optic nerve damage has not been demonstrated consistently.[17, 28, 32, 38, 66-71]

DETECTION

Patients suspected of having POAG can be identified during a comprehensive adult medical eye evaluation.[72] Although an assessment of IOP can identify individuals who are ocular hypertensive, an assessment of the optic nerve structure and function is required to identify patients who are glaucoma suspects but do not have ocular hypertension.

Medicare provides a benefit for a glaucoma screening for patients with the following risk factors: family history of glaucoma, history of diabetes, African Americans who are 50 years or older, and Hispanics who are 65 years or older.

CARE PROCESS

PATIENT OUTCOME CRITERIA

- Preservation of visual function
- Maintenance of quality of life
- Detection of progression to POAG at the earliest possible stage

DIAGNOSIS

The comprehensive initial glaucoma suspect evaluation (history and physical examination) includes all components of the comprehensive adult medical eye evaluation[72] and focuses attention on those elements 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 POAG on one visit but may return for further evaluation to confirm the diagnosis, including additional IOP measurements; gonioscopy; central corneal thickness (CCT) determination; visual field assessment; and ONH, RNFL, and macula evaluation and documentation.

History

- Ocular history (e.g., refractive error, trauma, prior ocular surgery)
- Race/ethnicity
- Family history.[22,73, 74] The severity and outcome of glaucoma in family members, including a history of visual loss from glaucoma, should be obtained during initial evaluation.[73, 74]
- Systemic history (e.g., asthma/chronic obstructive pulmonary disease, diabetes, migraine headache, vasospasm, cardiovascular disease)
- Review of pertinent records, with particular attention to IOP levels and 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 lower the IOP when compared with the presurgical baseline IOP.[75, 76] A history of laser-assisted in situ keratomileusis (LASIK), small-incision lenticular extraction (SMILE) or photorefractive keratectomy can be associated with a falsely low IOP measurement due to thinning of the cornea.[77-79]

Evaluation of Visual Function

Self-reported functional status or difficulty with vision can be assessed through patient history. Patients who are glaucoma suspects are likely to be asymptomatic.

Physical Examination

The ophthalmic evaluation focuses specifically on the following elements in the comprehensive adult medical eye evaluation:[72]

- 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 light reactivity and for a relative afferent pupillary defect.[80-82]

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 provide evidence of physical findings associated with narrow angles, such as shallow peripheral anterior chamber depth,[83, 84] corneal pathology, or a secondary mechanism for elevated IOP. 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, Scheie stripe, and/or Krukenberg spindle; iris and angle neovascularization; or inflammation.

Intraocular pressure measurement

Results from the Ocular Hypertension Treatment Study (OHTS) demonstrate that lowering elevated IOP reduces the risk of developing glaucomatous visual field and optic nerve damage.[16] It is important to evaluate the full extent of IOP fluctuation over time to determine who is at greatest risk of developing glaucoma and, therefore, who should receive treatment to prevent future glaucoma. Intraocular pressure is measured in each eye, preferably by Goldmann applanation tonometry, before gonioscopy or dilation of the pupil.[85] Recording time of day of IOP measurements may be helpful to assess diurnal variation. The significance of diurnal IOP fluctuation and the development of glaucomatous damage has yet to be fully established in the literature.[86-96] Additional IOP measurements may be indicated, either at different hours of the day on the same day or on different days. Larger inter-eye asymmetry of IOP has also been shown to be a risk for developing glaucoma.[97]

Gonioscopy

The diagnosis of POAG suspect requires careful evaluation of the anterior chamber angle to exclude angle closure or secondary causes of IOP elevation, such as angle recession,

pigment dispersion, peripheral anterior synechiae, angle neovascularization, and inflammatory precipitates.[98] 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.

(See www.gonioscopy.org for discussion of the techniques of gonioscopy.)

Optic nerve head and retinal nerve fiber layer examination

There is evidence that glaucomatous structural changes detected by optic disc and RNFL examination may precede functional defects detected by standard automated perimetry (SAP) in some patients.[99-105] In the OHTS, optic nerve damage alone without visual field loss occurred in 69 eyes and accounted for 55% of the study endpoints reached.[16]

Examination of the ONH and RNFL provides valuable structural information about glaucomatous optic nerve damage.[101, 103, 106-108] Ocular 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 large 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 rule: 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.[109-111] In approximately 80% of patients with glaucomatous cupping, the nerve contour does not follow this rule because both the inferior and superior rims are thinned.[109, 110] However, a recent study has demonstrated that normal eyes follow the ISNT rule less than 45% of the time.[111]

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.[101, 112-114] Other investigations have reported functional deficits occurring in advance of structural change.[115, 116] 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.[117-130] In the 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.[125] In the Early Manifest Glaucoma Trial, 13% of patients had disc hemorrhages at baseline examination, and hemorrhages were associated with progression.[118]

The optic nerve should be carefully examined for the above signs of glaucomatous damage, and its appearance should be documented.[103, 107, 131] The preferred technique for ONH evaluation involves magnified stereoscopic visualization (as 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.[132] Color stereophotography is an accepted method for documenting qualitative ONH appearance as well as disc hemorrhages.[45] Computer-based imaging 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 both are 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, macular degeneration, retinovascular occlusion, or other retinal disease).

Diagnostic Testing

Important ophthalmic testing includes the following:

- 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.[17, 31, 133-135] In the OHTS and European Glaucoma Prevention Study (EGPS) 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 than in eyes with a corneal thickness of 588 µm or greater. (Additional information is available in the Central Corneal Thickness section under Risk Factors in the POAG PPP.) An overestimation of the real IOP as measured by Goldmann applanation tonometry may occur in eyes with corneas that are thicker than average, whereas an underestimation of the real IOP tends to occur in eyes with corneas that are thinner than average. An exception to this is that the measurement of IOP is underestimated in eyes with corneal edema.[135] 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,[17] studies of progression have had variable findings. Some (but not all) studies found an association between glaucoma progression and thin CCT (see Table 1).[120, 136-141] Corneal hysteresis appears to provide additional, independent information associated with the risk of POAG.[63-65]

TABLE 1 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[120]	255	I	+	Thin CCT is a risk factor for progression of glaucoma (in patients with baseline IOP ≥21 mmHg)
Kim and Chen[136]	88	II	+	Thin CCT is associated with visual field progression in glaucoma
Chauhan, et al[137]	54	II	-	CCT did not predict visual field or optic disc progression
Jonas, et al[142]	454	II	-	CCT is not associated with progression of visual field damage
Jonas, et al[139]	390	II	-	CCT is not associated with optic disc hemorrhages
Congdon, et al[140]	230	II	-	CCT is not associated with glaucoma progression (although low corneal hysteresis is associated with glaucoma progression)
Stewart, et al[141]	310	III	+/-	CCT is associated with progression on univariate analysis but is not associated on multivariate analysis

CCT = central corneal thickness

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.[143] 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. Testing with a 10-2 program may 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.[144] 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. If visual field glaucomatous damage is newly detected in a glaucoma suspect patient, it is best to repeat the testing to confirm the change.[145] Repeating the same strategy that showed a new glaucomatous defect is best for confirming a visual field change.

Frequency doubling technology and short-wavelength automated perimetry (SWAP) are two alternative testing methods shown to be helpful in screening for early visual field damage, especially when SAP is normal.[143, 146, 147] Frequency doubling technology measures contrast sensitivity for a frequency doubling stimulus.[148-152] Visual field testing based on SWAP[152, 153] 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. Clinicians may use these selective functional tests to diagnose early visual loss in glaucoma suspects, but studies have not demonstrated clear advantages over standard automated achromatic visual field testing (e.g., SAP).[154-156]

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

The appearance of the optic nerve and RNFL should be documented for the glaucoma suspect patient, if possible.[103, 131] Because they are different methodologies, stereoscopic disc photographs and computerized images of the nerve are complementary with regard to the information they provide the clinician.[157] In the absence of these methodologies, a nonstereoscopic photograph or a drawing of the ONH should be recorded, but this is a less desirable alternative to stereophotography or computer-based imaging.[158-161] 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.

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.[162] A substantial number of 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. [104, 105, 163] There are three types of computer-based optic nerve imaging devices that have been used to evaluate for glaucoma: confocal scanning laser ophthalmoscopy, optical coherence tomography (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.[103, 162, 164, 165]

Abnormal results (i.e., results outside of the normative range) from these devices do not always represent disease.[166] 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 imaging represents true abnormality. As these instruments continue to improve, they may become more reliable in helping the clinician diagnose

glaucoma and to identify progressive nerve damage.[104, 105, 163] Furthermore, progression analysis programs for computer-based imaging devices are evolving to better detect optic nerve and RNFL changes that may be secondary to glaucoma.[167, 168]

Because some patients show visual field loss without corresponding optic nerve progression,[16, 99, 167-170] both structural and functional assessments remain integral to patient care. Even though digital 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.[157] 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 accepting 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, 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 suspect are as follows:

- Monitor or lower IOP through treatment if an eye is likely to progress to POAG
- Monitor for structural changes in the optic disc and retina (RNFL and/or macular analysis)
- Monitor for functional changes of the optic nerve by assessing the visual field

Intraocular pressure is the primary modifiable factor to reduce the risk of conversion to glaucoma in glaucoma suspects. The decision to begin treatment to lower IOP in the glaucoma suspect patient is complex and based on the ophthalmologist's analysis of the examination results, risk assessment, and the patient's preferences. The number and severity of risk factors present, the prognosis, the patient's life expectancy, management plan, and likelihood that

therapy, once started, can be continued long-term, should be discussed with the patient and, when feasible, with the patient's family. Risk assessment based on the OHTS and EGPS may be helpful in managing the patient who is a glaucoma suspect.[46]

In the OHTS, more than 90% of patients with ocular hypertension did not progress to glaucoma over 5 years, but treatment to lower IOP reduced the risk of developing POAG from 9.5% to 4.5%.[16] Since therapy exposes patients to the risks, side effects, and expense of long-term treatment, the decision to begin treatment for a glaucoma suspect patient is particularly important. For some patients, the risk of developing POAG is sufficiently high to justify starting treatment.[16, 17, 171] For example, untreated patients in the OHTS with a baseline IOP of 26 mmHg or above and a CCT of 555 µm or below had a 36% chance of developing optic nerve damage during long-term follow-up compared with a 2% risk for patients with a baseline IOP of less than 24 mmHg and a CCT greater than 588 µm.[17] Whether or not a patient is treated, long-term monitoring for the development of glaucoma is essential.

When treatment is appropriate, an effective medication regimen requires attention to its effect on IOP, side effects, and to the possibility of nonadherence to therapy. Laser trabeculoplasty can also be considered as primary therapy for ocular hypertension. The ophthalmologist should consider these issues in choosing a regimen that works well to lower IOP to the desired level with the fewest possible side effects. The diagnosis, number and severity of risk factors, prognosis and management plan, and likelihood of long-term therapy should be discussed with the patient.

Deciding When to Treat a Glaucoma Suspect Patient

The decision to treat a glaucoma suspect patient may arise in various settings.

- Any patient who shows evidence of optic nerve deterioration based on ONH appearance, RNFL loss, or visual field changes consistent with glaucomatous damage has developed POAG and should be offered treatment as described in the Primary Open-Angle Glaucoma PPP.[172] Clinicians can recognize subtle abnormalities in the optic disc and RNFL by using periodic fundus imaging with disc photography and computerized imaging of the ONH, RNFL, and macula.[101, 173]
- A new visual field defect that is consistent with a pattern of glaucomatous visual field defect, confirmed on retesting of visual fields, may indicate that the patient has developed POAG.[145, 174] Strategies include Goldmann visual field testing, 30-2 and 24-2 testing, and central 10-2 testing. Automated 10-2 central visual field testing has demonstrated the ability to discern central defects that can be missed with wider field perimetry.[144]
- A patient who demonstrates very high IOP in which optic nerve damage is likely to occur may require treatment.
- In some cases, initiating IOP-lowering treatment to lower the risk of glaucomatous damage may be appropriate if the patient has additional risk factors for glaucoma. Established risk factors for POAG, besides elevated IOP, include older age, family history of glaucoma, African-derived race or Latino/Hispanic ethnicity, thin central cornea, low ocular perfusion pressure, diabetes mellitus, myopia, low systolic and diastolic blood pressure, disc hemorrhage, large cup-to-disc ratio, high pattern standard deviation on threshold visual field testing, hypothyroidism, and male sex.
- Clinicians may consider using a risk calculator to determine the risk of progressing from ocular hypertension to POAG.[46, 175-177] These calculators determine the overall risk of developing glaucoma in 5 years using the risk factors of age, vertical cup-to-disc ratio, pattern standard deviation (from standard automated achromatic visual field testing), CCT, and IOP. Risk calculators are available on https://ohts.wustl.edu/risk/. They are also available as applications for smartphones.

Whatever the scenario, a discussion must occur between the physician and patient to outline the risks and benefits of treatment versus observation.

Target Intraocular Pressure

When deciding to treat a glaucoma suspect patient, it is important to remember that the goal of treatment is to maintain the IOP in a range at which visual field loss is unlikely to significantly affect a patient's health-related quality of life over his or her lifetime.[178] The estimated upper limit of this range is considered the "target pressure." Target pressure can vary among these

patients, and in the same patient it may need adjustment during the clinical course. In any patient, target pressure is an estimate and a means toward the ultimate goal of protecting the patient's vision. For a patient in whom a decision has been made to begin treatment, a reasonable target IOP based on the OHTS would be 20% lower than the mean of several baseline IOP measurements.[16] However, if the starting pressure is markedly elevated, a 20% reduction may be insufficient to prevent or adequately slow conversion to glaucoma. Current IOP and its relationship to target IOP should be evaluated at each visit and individualized for each patient.

A definite deterioration in optic nerve structure or visual field (i.e., conversion to POAG) in a patient who was a glaucoma suspect suggests that the target pressure should be lower,[118, 179] and the patient should be managed as described in the Primary Open-Angle Glaucoma PPP.[172]

Choice of Therapy

When the decision is made to treat the POAG suspect patient, the clinician can weigh the risks and benefits of each treatment modality.

Medical Treatment

Medical therapy is presently the most common initial intervention to lower IOP (see Table 2 for an overview of options available). Prostaglandin analogs are the most frequently prescribed eye drops for lowering IOP because they are the most efficacious and well-tolerated glaucoma medication, and they need to be instilled only once daily.[180, 181] Therefore, prostaglandin analogues are often considered as initial medical therapy unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude this.[182, 183]

Topical beta adrenergic antagonists are commonly prescribed to treat glaucoma and have demonstrated good efficacy and tolerability.[184] 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.[185] Topical beta-blockers may be dosed once or twice daily. However, nighttime dosing of beta-blockers is associated with limited efficacy[186] and may contribute to visual field progression via nocturnal reduction of systemic blood pressure.[187] Other glaucoma medications include, alpha$_2$ adrenergic agonists, topical and oral carbonic anhydrase inhibitors, rho kinase inhibitors and parasympathomimetics.[188, 189]

TABLE 2 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	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 2 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

CHF = congestive heart failure; 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 rapidly metabolized to latanoprost (a prostaglandin analogue) and butanediol mononitrate (a nitric oxide-donating moiety); it enhances aqueous outflow through both the uveoscleral and trabecular meshwork pathways.[190-193]

** 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 regarding the use of netarsudil in pregnant women. Animal studies did not demonstrate adverse effects on the developing fetus with clinically relevant intravenous exposures.[194]

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 the monocular trial has been recommended in the past to determine whether a glaucoma medication is effective, studies have shown that it is not a good predictor of long-term efficacy.[195, 196] A monocular trial is defined as the initiation of treatment in only one eye, followed by a comparison of the relative change of the 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 medications may have a contralateral effect.[197] 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.[198]

If a drug fails to reduce IOP sufficiently, then either switching to an alternative medication as monotherapy or adding additional medication is appropriate until the desired IOP level is attained.[131] Since some studies have shown that adding a second medication decreased adherence to glaucoma treatment,[199, 200] fixed combination therapy may improve patient adherence even though it is not recommended for initial treatment in most circumstances.

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.[131] 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 can be educated about eyelid closure or nasolacrimal occlusion to reduce systemic absorption after medication instillation (see Related Academy Materials section for patient education brochures).[201]

Adequate treatment to lower IOP requires a high level of adherence to therapy, but this is frequently not achieved. Several studies indicate relatively poor adherence to therapy.[202-205] Even with instruction, free medication, once-daily administration, use of a dosing aid, and electronic monitoring of adherence, nearly 45% of patients with glaucoma in one study took fewer than 75% of their prescribed doses.[205] 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 and comorbidities and as glaucoma progresses.[206, 207] Repeated instruction and counseling about proper techniques for using medication as well as a clearly written medication regimen, smartphone reminders, and follow-up telephone calls may improve adherence to therapy.[205, 208] 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 medication, 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.[209] *(I-, Insufficient Quality, Strong Recommendation)* At each examination, medication dosage and frequency of use should be recorded. Reviewing the time of day when medication was taken may link eye-drop administration to 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, such as laser trabeculoplasty, should be discussed. Cost may be a factor in adherence, especially when multiple medications are used.[208, 210]

Patient education and informed participation in treatment decisions may improve adherence[208] and overall effectiveness of 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.[211] 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.[212]

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,[213] rings placed in the fornix,[214] contact lenses,[215] subconjunctival injections[216]/devices,[217] intracameral delivery systems,[218] and drug-eluting intraocular devices.[219] 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.[220] In phase I/II studies, a single bimatoprost sustained-release (SR) implant showed efficacy similar to topical bimatoprost 0.03% through 4 months of follow-up, and 68% of patients had a persistent effect at 6 months.[218]

Special circumstances in pregnancy and during breastfeeding

Managing IOP in the pregnant or lactating patient involves an interdisciplinary approach to balance the risk of disease progression in the mother while minimizing risks to the fetus or nursing infant.

Pregnancy

Glaucoma medical management of the pregnant patient presents challenges with respect to balancing the risk of glaucomatous progression[221] against concerns for the safety of the fetus.[222-224] 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.[225] 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, 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 this agent while pregnant revealed no adverse effects on pregnancy and no birth defects.[226] 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.[224] Oral carbonic anhydrase inhibitors have been shown to cause teratogenicity when delivered in high doses to animals.[227]

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.[194]

Breastfeeding

Some topical glaucoma medications have been detected in breast milk, such as timolol, carbonic anhydrase inhibitors, and brimonidine. The data are controversial 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.[224, 228] Brimonidine is known to cross the blood-brain barrier and can cause apnea and somnolence in infants, toddlers, and children. For this reason, it is generally recommended that the medication not be used in mothers who are breastfeeding.[223]

Other Therapies

Laser trabeculoplasty is an alternative therapy to medications in patients with ocular hypertension.[229] In the Selective Laser Trabeculoplasty Versus Eye Drops for the First-line Treatment of Ocular Hypertension and Glaucoma (LiGHT) trial, patients randomized to laser treatment were more likely to be at or below their target pressure than those randomized to topical therapy.

Cataract surgery in patients with ocular hypertension has also been shown to produce sustained pressure-lowering effects.[76] If incisional glaucoma surgery is to be considered for

markedly elevated IOP, the patient can be managed as described in the Primary Open-Angle Glaucoma PPP.[172]

Follow-up Evaluation

The purpose of follow-up examination is to evaluate the IOP level, visual field status, optic disc appearance, and retinal imaging (RNFL and/or macula analysis) status to determine if damage has occurred. Management for each patient should be individualized. Primary open-angle glaucoma suspect patients who are being observed should be seen at least every 12 to 24 months, depending on individual risk factors. However, if a patient has multiple risk factors for conversion to POAG, then more-frequent reassessment is justified. If patients have central vision complaints or if the clinician's index of suspicion is high for central visual field defects, central visual field testing can be done to assess the central vision with greater precision. Primary open-angle glaucoma suspect patients who are being treated may need to be seen more often until IOP control has been achieved, and then they may be followed semiannually or annually.

History

The following interval history should be elicited during all follow-up visits for POAG suspect patients:

- Interval ocular history
- Interval systemic medical and medication history
- Side effects of ocular medications if the patient is being treated
- Review of pertinent medication use if the patient is being treated, including the time of the last administration

Ophthalmic examination

The following components of the ophthalmic examination should be performed during all follow-up visits for POAG suspect patients:

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

The frequency of periodic ONH evaluation and documentation,[158, 230-232] structural optic nerve and retina assessments, and visual field evaluation[233-235] is based on an assessment of each patient's individual risk. A comprehensive adult medical eye evaluation and additional eye assessments can be performed on follow-up examination,[72] with more frequent follow-up if the patient is at higher risk for developing glaucoma. Patients with a thin cornea,[16, 17, 31] elevated IOP,[7, 16-26] disc hemorrhage,[41-45, 236] large cup-to-disc ratio,[16, 17] high pattern standard deviation,[17, 26, 46] development of pseudoexfoliation or pigment dispersion syndrome, or family history of glaucoma[21, 237] may warrant closer follow-up than patients without these risk factors. Gonioscopy is indicated when there is a suspicion of development of an angle-closure component, anterior chamber shallowing, anterior chamber angle abnormalities, or if there is an unexplained change in IOP.

Adjustment of therapy

The indications for adjusting therapy in glaucoma suspect patients are as follows:

- Target IOP is not achieved and the benefits of a change in therapy outweigh the risks for the patient
- The patient is intolerant of the prescribed medical regimen

- The patient does not adhere to the prescribed medical regimen due to costs or other factors
- New systemic conditions or treatments develop that could be a contraindication to the current glaucoma therapy
- The patient under treatment has been stable for a prolonged period without progression to POAG, in which case cautious withdrawal of therapy may be considered
- The patient has converted to POAG (see Primary Open-Angle Glaucoma PPP)

PROVIDER AND SETTING

The performance of certain diagnostic procedures (e.g., tonometry, pachymetry, perimetry, fundus imaging, and photography) may be delegated to appropriately trained and supervised personnel. However, the interpretations of results and the medical management of disease require the medical training, clinical judgment, and the experience of an ophthalmologist.

COUNSELING AND REFERRAL

It is important to educate and engage patients in the management of their condition by providing in-person and written take-home and online information. This may be especially true for patients who are POAG suspects, since some authors have shown that follow-up is poor in patients with this diagnosis.[238, 239] One reason for this may relate to patients' perception that their disease is "not serious enough."[238] Patients should be educated about their condition and its potential to lead to glaucoma, the status of their condition, the rationale and goals of any intervention, 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 ophthalmologist to physical or emotional changes that occur when taking glaucoma medications. Ophthalmologists should be sensitive to these problems and provide support and encouragement. Ophthalmologists, or trained staff members, should educate patients and/or their caregivers on techniques for administering glaucoma drops.

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.[79]

SOCIOECONOMIC CONSIDERATIONS

Although there is strong evidence that medical treatment of patients with definite open-angle glaucoma is cost-effective, it is less clear whether it is cost-effective to treat glaucoma suspects. Results from the OHTS clearly demonstrate that lowering IOP reduces the risk of progressing to glaucoma, yet the majority of patients in both the treated and untreated study arms never went on to develop glaucoma. Therefore, the additional costs of treating all of these patients need to be carefully considered relative to the benefits conferred by delaying or preventing glaucoma for a small subset of patients. Based on findings from the OHTS, researchers studied the incremental cost-effectiveness of treating patients with ocular hypertension and determined that it was not considered cost-effective to treat all patients with this condition. However, they determined that treatment of patients with ocular hypertension who have an IOP of 24 mmHg or higher and a 2% or higher annual risk of developing glaucoma was indeed cost-effective.[210] These researchers also showed that patient life expectancy is an important consideration. For example, a 45-year old with ocular hypertension and a 2% or higher annual risk of glaucoma would require a life expectancy of at least 18 years for treatment to be considered cost-effective. Patients who are older at the time of first diagnosis of ocular hypertension would have to live even longer for treatment to be considered cost-effective.[240] Other authors performed a similar set of analyses and also concluded that treatment of all patients with ocular hypertension did not confer high value. However, treatment of persons with ocular hypertension who had risk factors for progressing to glaucoma (e.g., higher levels of IOP, thinner corneas, and greater cup-to-disc ratios) was indeed cost-effective.[241]

Another important question is whether it is cost-effective to screen patients for glaucoma. A systematic review of the literature on this topic concluded that screening an entire population for glaucoma is not cost-effective, but targeted screening of high-risk groups may be.[242] Medicare provides benefits for screening high-risk groups such as African Americans, Hispanics, persons with a family history of glaucoma, and those with diabetes.[243] As the sensitivity, specificity, efficiency, and safety of equipment used to properly diagnose patients with glaucoma continue to improve, it is hoped that there will soon be ways to perform screenings of large numbers of patients for glaucoma in a manner that is cost-effective.

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 suspect includes the entity of primary open-angle suspect or borderline glaucoma and related entities with the following ICD-10 classifications:

	ICD-10 CM
Primary open-angle glaucoma suspect	H40.001
	H40.002
	H40.003
Preglaucoma, unspecified	H40.001
	H40.002
	H40.003
Open angle with borderline findings, low risk (e.g., borderline IOP or optic disc appearance suspicious of glaucoma)	H40.011
	H40.012
	H40.013
1–2 risk factors*	
Steroid responders	H40.041
	H40.042
	H40.043
Ocular hypertension	H40.051
	H40.052
	H40.053
Open angle with borderline findings, high risk	H40.021
3 or more risk factors*	H40.022
	H40.023

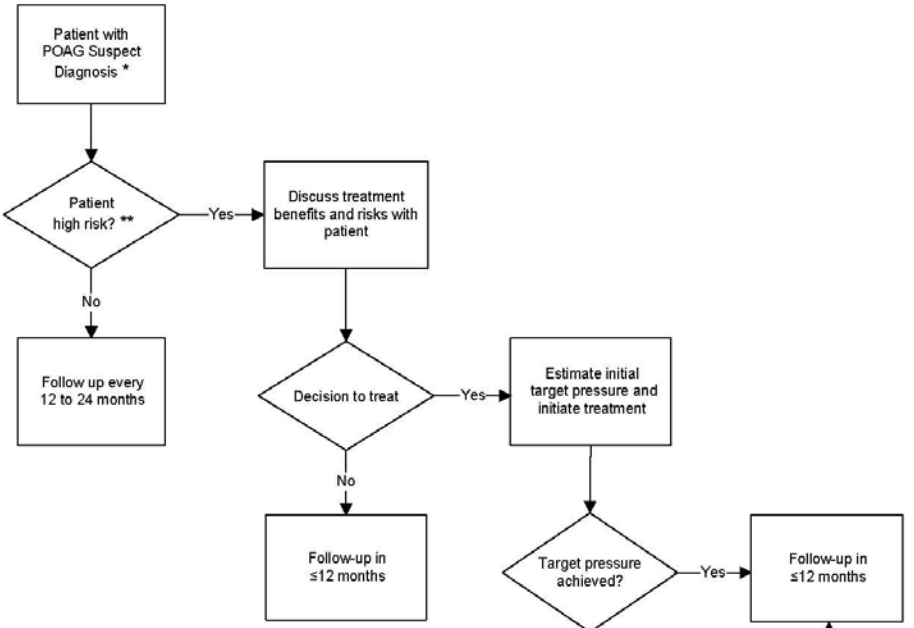
CM = Clinical Modification used in the United States; IOP = intraocular pressure

* Risk factors include family history of glaucoma, higher IOP, thinner central cornea, disc hemorrhage, larger cup-to-disc ratio, pigment dispersion syndrome, and pseudoexfoliation.

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. MANAGEMENT ALGORITHM FOR PATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA SUSPECT



* The clinical findings that define a glaucoma suspect are characterized by one of the following in at least one eye in an individual with open anterior chamber angles by gonioscopy.

- Appearance of the optic disc or retinal nerve fiber layer that is suspicious for glaucomatous damage.
- A visual field suspicious for glaucomatous damage.
- Consistently elevated IOP associated with appearance of the optic disc and retinal nerve fiber layer and with normal visual field test results.

** The overall likelihood of developing glaucomatous optic neuropathy increases with the number and relative strength of risk factors, which include the following:

- Elevated IOP
- Older age
- Family history of glaucoma
- Increased cup-to-disc ratio
- Thin central cornea
- Disc hemorrhage
- High pattern standard deviation on threshold visual field testing
- Low ocular perfusion pressure
- Low systolic and diastolic blood pressure
- Pigment dispersion syndrome
- Pseudoexfoliation

APPENDIX 4. 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 "Ocular Hypertension"[Mesh] OR “poag suspect”) AND ("Optic Atrophy"[Mesh] OR "Optic Nerve"[Mesh] OR "Optic Nerve Diseases"[Mesh] OR "Optic Disk"[Mesh] OR "Nerve Fibers"[Mesh] OR "retinal nerve fiber layer")

("Glaucoma"[Mesh] OR glaucoma OR "Ocular Hypertension"[Mesh] OR "Intraocular Pressure"[Mesh] OR “poag suspect”) AND ("corneal thickness" OR CCT OR "Cornea/pathology"[Mesh])

("Glaucoma"[Mesh] OR glaucoma OR "Ocular Hypertension"[Mesh] OR "Intraocular Pressure"[Mesh] OR “poag suspect”) AND pachymetry

("Circadian Rhythm"[Mesh] OR "circadian rhythm" OR diurnal OR nocturnal) AND ("Intraocular Pressure"[Mesh] OR "intraocular pressure" OR IOP)

(("Glaucoma, Open-Angle"[Mesh] AND suspect*) OR (POAG AND Suspect*) OR “poag suspect” OR (glaucoma AND suspect*))

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 (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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