EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE

Care of the Patient with Primary Open-Angle Glaucoma

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AMERICAN OPTOMETRIC ASSOCIATION

About the American Optometric Association

The American Optometric Association (AOA) is the leading authority on and advocate for quality eye health care, representing more than 49,000 doctors of optometry, optometry students and optometric professionals. As the sole provider in many communities across America, doctors of optometry are often a patient's first entry point into the health care system, and have extensive, ongoing training to examine, diagnose, treat and manage disorders, diseases and injuries that affect the eye and visual system. Through a nationwide public health initiative, AOA's *Eye Deserve More* campaign is fostering awareness of the importance of eye health and vision care and the overall health benefits of in-person, comprehensive eye examinations with AOA doctors of optometry for all Americans.

Disclosure Statement

This evidence-based clinical practice guideline was funded by the AOA without financial support from any commercial sources. The Evidence-based Optometry Guideline Development Group and other guideline participants provided full written disclosure of conflicts of interest prior to each meeting and prior to voting on the quality of evidence or strength of clinical recommendations contained within this guideline.

Disclaimer

Recommendations made in this guideline do not represent a standard of care. Instead, the recommendations are intended to assist the clinician in the decision-making process. Patient care and treatment should always be based on a clinician's independent professional judgment, given the patient's circumstances, and in compliance with state and federal laws and regulations.

The information in this guideline is current to the extent possible at the time of publication.

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Care of the Patient with Primary Open-Angle Glaucoma

Developed by the AOA Evidence-based Optometry Guideline Development Group

Approved by the AOA Board of Trustees Insert date

243 N. Lindbergh Blvd., St. Louis, MO 63141-7881

TABLE OF CONTENTS

EVIDENCE-BASED CLINICAL GUIDELINES

A. What is the Evidence-based Process?

Evidence-based clinical practice guidelines provide for the use of current best evidence in conjunction with clinical expertise and patient values to guide health care decisions. Scientific support for diagnosis and treatment strategies is essential to ensuring that services are safe and effective. The clinical recommendations in this guideline are evidence-based statements regarding patient care that are supported by the scientific literature or consensus of professional opinion when no quality evidence was discovered.

As a result of the Medicare Improvements for Patients and Providers Act of 2008, Congress commissioned the Secretary of Health and Human Services to create a public-private program to develop and promote a common set of standards for the development of clinical practice guidelines (CPGs). These standards address the structure, process, reporting, and final products of systematic reviews of comparative effectiveness research and evidence-based CPGs.

The Institute of Medicine (IOM), now the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (NASEM), in response to a request from the Agency for Healthcare Research and Quality (AHRQ), issued two reports in March 2011: *Clinical Practice Guidelines We Can Trust* and *Finding What Works in Health Care: Standards for Systematic Reviews.*

In *Clinical Practice Guidelines We Can Trust*[1]*,* the IOM redefined CPGs as follows:

> *"Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options."*

The report states that to be trustworthy, guidelines should:

- Be based on a systematic review of existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and key stakeholders
- Consider important patient subgroups and preferences, as appropriate
- Be based on a transparent process that minimizes conflicts of interest and biases
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes
- Provide a grading of both the quality of evidence and the strength of the clinical recommendation
- Be revised as appropriate when new evidence warrants modifications of recommendations.

Based on the IOM/NASEM reports, the AOA Evidence-based Optometry (EBO) Committee developed a 14-step process to meet the new evidence-based recommendations for trustworthy guidelines.

AOA's 14 Steps to Evidence-based Clinical Practice Guideline Development	
1.	**Guideline Development Group (GDG**: The Evidence-based Optometry (EBO) Committee selects a multidisciplinary panel of experts, including patient and public representatives, to act as the Guideline Development Group (GDG).
2.	**Transparency and COI**: The GDG manages all conflict of interest (COI), which is documented by AOA staff and reviewed during face-to-face meetings.
3.	**Clinical Questions:** The GDG defines the literature search criteria and identifies all clinical questions through a question formulation meeting.
4.	**Search for Evidence:** AOA staff send the search criteria and clinical questions for a systematic review of the literature (outside researchers) and provide all obtained papers to the Guideline Development Reading Group (GDRG). Systematic reviews, when available, are included in the guideline. No systematic review authors are participants in the GDG or GDRG. **Inclusion Criteria (must meet all):** Scientific studies written in English that address the clinical question and that meet the patient population or age range being addressed. **Exclusion Criteria (meets any of the following):** Scientific studies that are not in English, animal studies, studies outside the patient population or age range (if relevant), studies not addressing any topic of the clinical questions searched.
5.	**Grade Evidence/Quality:** Two scientific readers and one member from the GDRG are randomly selected to read and grade each paper. They separately grade the paper for quality of evidence based on predetermined grading criteria and state the clinical recommendation(s).
6.	**Articulate Clinical Recommendations/Strength*:** The GDRG and GDG clinical experts review all clinical recommendations and articulate each for inclusion in the guideline during an "articulation of recommendations" meeting(s). There are single and/or aggregate recommendations made and a strength level is assigned. Potential benefits and harms, costs, and patient preferences are identified, as well as any gaps in research, and each is documented.
7.	**Write the Draft:** AOA staff send the articulation results to the writer to develop draft 1.
8.	**Draft Review and Edits*:** The GDG reads draft 1, discusses and edits.
9.	**Rewrite/Final Drafts:** AOA staff send the draft results to the writer for writing/revisions for draft 2 (peer review draft) and send to medical editor for copy editing. Additional reviews are completed as necessary.
10.	**Approval and Posting for Peer Review:** AOA staff and/or EBO Committee chair send the peer review draft to AOA Board of Trustees for approval to post for peer and public review. The draft is posted on the AOA website, along with a comment form, and the review period is announced. Comments are solicited/collected electronically and comment authors are not made public.
11.	**Final Document Produced*:** The GDRG and GDG clinical experts review all peer comments and revise the final document. They may choose to include the peer review comment, not include the comment, and/or identify further gaps to review when preparing the next edition. All comments are documented regarding actions taken/not taken and the final draft is produced.

12.	**Final Draft Approval and Legal Review:** The final draft is reviewed by the AOA Board of Trustees and AOA Legal Counsel for approval and verification that the GDG followed the evidence-based process as outlined by the National Academies of Sciences, Engineering, and Medicine (NASEM) – Health and Medicine Division, previously the Institute of Medicine.
13.	**Post Guidelines:** AOA staff post the evidence-based guideline to the AOA website for public use.
14.	**Schedule Reviews:** The GDG schedules a review to meet the NASEM guideline development standards and reviews all previously identified gaps in medical research and any new evidence and revises the evidence-based guideline every 2 to 5 years.

**Denotes virtual meetings in 2020/2021/2022 due to the COVID-19 pandemic*

B. How to Use This Guideline

The following table provides the grading system used in this guideline for rating evidence-based clinical statements. Grades are provided for both quality of the evidence and strength of clinical recommendations.

Key to Evidence Quality and Strength of Clinical Recommendation Levels

Grade	Study Type

A	• **Meta-Analysis**
	• **Systematic Review**
	• **Randomized Clinical Trial**
	• **Diagnostic Studies** (Grade A)
	  ○ Do not have a narrow population
	  ○ Do not use a poor reference standard
	  ○ No case control studies of diseases or conditions

B	• **Randomized Clinical Trial** (weaker design)
	• **Cohort Studies**
	  ○ Retrospective
	  ○ Prospective
	• **Diagnostic Studies** (Grade B - only *one* of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	  ○ Case control studies of diseases or conditions

C	• **Case Control Studies**
	  ○ Study of sensitivity and specificity of a diagnostic test, population-based descriptive study of diseases or conditions
	  ○ Retrospective
	  ○ Prospective
	• **Diagnostic Studies** (Grade C - at least *two or more* of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	• **Studies of Strong Design**

	◦ With substantial uncertainty about conclusions or serious doubts about generalizations, bias, research design, or sample size • **Nonrandomized Trials**
D	• **Cross-sectional Studies** • **Case Reports/Series** • **Reviews** • **Position Papers** • **Expert Opinion** • **Reasoning from Principle**

Strength of Clinical Recommendation Levels
Strong Recommendation: The benefits of the recommendation clearly exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation) and the quality of evidence is excellent (Grade A or B). In some clearly identified circumstances, a strong recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should be followed unless a clear and compelling rationale for an alternative approach is present.*
Recommendation: The benefits of the recommendation exceed the harms (or the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, a recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should generally be followed but remain alert for new information.*
Discretional: The current evidence is insufficient to assess the balance of benefits and harms of the recommendation. Evidence may be lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. *There should be an awareness of this recommendation but a flexibility in clinical decision-making, as well as remaining alert for new information.*

Clinical Notes and Statements shown throughout the guideline may have quality of evidence grades (A, B, C, or D). For example, a clinical note or statement with a quality of evidence grade of “B” is shown as “(Evidence Grade: B).”

Evidence-based Action Statements will be highlighted in an “Action” box, with the quality of evidence, level of confidence, and clinical recommendation grading information listed. For example:

EVIDENCE-BASED ACTION STATEMENT: Early medical treatment should be considered for individuals with ocular hypertension (OH) who are at moderate or high risk of developing primary open-angle glaucoma (POAG). [8,9,67]

Evidence Quality: Grade A. Study type(s): Randomized Clinical Trials, Case Control
Level of Confidence: High
Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements:

Clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG.[67] (Evidence Grade: A)

There is little absolute benefit of early treatment in low-risk OH patients.[9] (Evidence Grade: A)

Patients with OH at low risk of conversion to POAG can generally be followed without treatment, as long as they are monitored regularly for signs of early disease. The use of a five-factor baseline risk model (age, IOP, CCT, larger C/D ratio and higher VF PSD) has reasonable accuracy in distinguishing high from low-risk OH patients. The benefit of early treatment is greatest in high-risk OH patients.[8] (Evidence Grade: B)

Potential Benefits: Early treatment may reduce or delay onset of POAG.	**Potential Risks/Harms**: Side effects of medication.

Benefit and Harm Assessment: Benefits significantly outweigh harms.

Potential Costs: Cost of medication.

Value Judgments: None.

Role of Patient Preferences: Moderate.

Intentional Vagueness: None.

Gaps in Evidence: None identified.

The Action Statement profile provides additional information related to the development and implementation of the clinical recommendation. The following is an explanation of the categories listed in the profile:

Evidence Quality – The quality of evidence grade (A, B, C, or D) or the aggregate quality of evidence grade (if multiple studies were available for review) and the type of research study or studies reviewed.

Level of Confidence – The consistency of the evidence and the extent to which it can be trusted specified as high, medium, or low.

Clinical Recommendation Level – The level (Strong Recommendation, Recommendation, or Discretional) assigned to the implementation of the clinical recommendation made in the Action Statement.

Evidence Statements – The clinical statements derived from research studies reviewed that support the Action Statement.

Potential Benefits – Favorable changes which would likely occur if the Action Statement was followed.

Potential Risks/Harms – Adverse effects or unfavorable outcomes that may occur if the Action Statement was followed.

Benefit and Harms Assessment – A comparison of the relationship of benefits to harms specified as "benefits significantly outweigh harms" (or vice versa) or a "balance of benefits and harms."

Potential Costs – Direct and indirect costs may include the costs of the procedure, test or medication; time spent by the eye doctor counseling the patient; administrative time; patient/parent/caregiver time off from work, etc.

Value Judgments – Determinations made by the Guideline Development Group (GDG) in the development of the Action Statement relating to guiding principles, ethical considerations, or other priorities.

Role of Patient Preference – The role the patient has in shared decision-making regarding implementation of the Action Statement specified as large, moderate, small or none.

Intentional Vagueness – Specific aspects of the Action Statement that are left vague due to factors such as the role of clinical judgment, patient variability, concerns over setting legal precedent, etc.

Gaps in Evidence – Areas identified during searches and evaluations of the research that show gaps in available evidence.

Consensus-based Action Statements, based on consensus by the Guideline Development Reading Group (GDRG), are also highlighted in an "Action" box, but without any quality of evidence or strength of clinical recommendation grading information listed. For example:

CONSENSUS-BASED ACTION STATEMENT: The frequency and scope of follow-up examinations of persons diagnosed with primary open-angle glaucoma (POAG) should be individualized based on the severity and stability of their disease and should occur at regular intervals to monitor progression and treatment efficacy.

Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.

Benefits and Harms Assessment: Implementation of this recommendation is likely to result in the earlier diagnosis and treatment of any disease progression. The benefits of this recommendation were established by expert consensus opinion.

C. Summary Listing of Action Statements

The examination of a person suspected of having primary open-angle glaucoma (POAG) should include all aspects of a comprehensive eye and vision examination, with emphasis on the evaluation of the anterior chamber angle, optic nerve head (ONH), retinal nerve fiber layer (RNFL), macular ganglion cells and visual fields (VF), and measurement of intraocular pressure (IOP) and central corneal thickness (CCT).[65,72,173,179,182,217,245] (Evidence Grade: B, Recommendation)

The use of prostaglandin analogs (PGAs) should be considered as an initial therapy in patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG), unless contraindicated.[266,275] (Evidence Grade: A, Strong Recommendation)

Patients prescribed topical intraocular pressure (IOP) lowering therapy may experience decreased tear film stability and elevated tear osmolarity and should be evaluated for ocular surface disease (OSD).[301,302,304,305,307-309,313,316] (Evidence Grade: C, Recommendation)

Pharmacological treatment of primary open-angle glaucoma (POAG) should be used with caution during pregnancy and lactation. (Consensus Statement)

Selective laser trabeculoplasty (SLT) should be considered as an initial/alternative or additive therapy to medication for achieving intraocular pressure (IOP) control in patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG).[154,324,334-338] (Evidence Grade: A, Strong Recommendation)

The frequency and scope of follow-up examinations of persons diagnosed with primary open-angle glaucoma (POAG) should be individualized based on the severity and stability of their disease and should occur at regular intervals to monitor progression and treatment efficacy. (Consensus Statement)

Progress examinations of patients with primary open-angle glaucoma (POAG) should include, but are not limited to, an interval history and measurement of visual acuity and intraocular pressure (IOP), with periodic gonioscopy, optic nerve head (ONH) and retinal nerve fiber layer (RNFL) evaluations, and visual field (VF) testing. (Consensus Statement)

Patient self-monitoring of intraocular pressures (IOP) should be considered to help support the diagnosis and/or management of patients at risk for or diagnosed with primary open-angle glaucoma (POAG).[364,372,373] (Evidence Grade: C, Recommendation)

Early medical treatment should be considered for individuals with ocular hypertension (OH) who are at moderate or high risk of developing primary open-angle glaucoma (POAG). [8,9,67] (Evidence Grade: A, Strong Recommendation)

Eye doctors should be persistent in providing education and training to patients with primary open-angle glaucoma (POAG) to improve adherence/compliance with recommended therapy.[408-410,416,417,423,424,443-445] (Evidence Grade: B, Recommendation)

Patients with primary open-angle glaucoma (POAG) who are prescribed pharmacological treatment should receive instructions on eyedrop instillation.[423,447,452,453] (Evidence Grade: B, Recommendation)

Ocular telehealth programs can provide increased access to care but should not be used alone or for the assessment or management of moderate or advanced disease in patients with primary open-angle glaucoma (POAG).[493-495] (Evidence Grade: B, Strong Recommendation)

I. INTRODUCTION AND GUIDELINE OBJECTIVES

Glaucoma is a chronic, generally bilateral but often asymmetric optic neuropathy characterized by progressive damage to the optic nerve and retinal nerve fiber layer (RNFL) that can lead to permanent loss of vision. It is a worldwide leading cause of visual dysfunction and irreversible blindness. Primary open-angle glaucoma (POAG) is the common form of the disease.

Although generally asymptomatic in early stages, if untreated or inadequately treated, patients who have POAG can suffer vision loss.[2] Although the 20-year probability of blindness due to POAG in at least one eye decreased over a 45-year period from 1965 to 2009, a significant proportion of patients still progress to blindness despite diagnostic and therapeutic advancements.[3] Therefore, it is important to address modifiable risk factors for vision loss such as advanced disease at diagnosis, high and fluctuating intraocular pressure (IOP), and poor patient compliance with treatment in order to decrease risk of vision loss in glaucoma patients.[4] (Evidence Grade: A)

This Evidence-based Clinical Practice Guideline on Care of the Patient with Primary Open-Angle Glaucoma provides examination, treatment and management recommendations designed to help preserve vision and reduce the risk of vision loss in persons with POAG. The objectives of this guideline are to assist doctors of optometry in achieving the following:

- Identification of individuals who are undiagnosed or at risk for POAG.
- Preservation of vision by reducing the risk of vision loss in persons with POAG through timely diagnosis, treatment, determination of need for additional or ongoing evaluations, and appropriate management/co-management and/or referral.
- Education of individuals and health care practitioners regarding the risks and complications of POAG.
- Education and counseling of individuals with POAG on the importance of compliance/adherence with prescribed treatment.
- Provision of, or referral for, vision rehabilitation services for persons with vision loss from POAG.
- Improvement in the quality of care rendered to people with POAG.

II. BACKGROUND

A. Disease Description

Glaucoma is a group of ocular disorders characterized by progressive optic neuropathy involving multiple risk factors and featuring recognizable patterns of structural change (neuroretinal rim of the optic disc/retinal nerve fiber layer) and functional (visual field) loss. IOP and age have been identified as important risk factors in all clinical forms of open-angle glaucoma.[5-7]

The main classifications of open-angle glaucoma (OAG) discussed in this guideline are:

- Ocular hypertension
- Primary open-angle glaucoma
- Normal tension glaucoma.

Ocular hypertension (OH) is a condition where IOP is elevated, but glaucomatous optic neuropathy is not detectable.[2] Persons with OH have an estimated 10% risk of developing glaucoma over five years.[8] (Evidence Grade: B) Those at low risk of conversion to POAG can generally be followed without treatment, as long as they are monitored regularly for signs of early disease.[9]

Primary open-angle glaucoma (POAG) is a subtype of glaucoma where the angle formed at the junction of the iris and cornea is open and there is no other underlying disease. It is a chronic, potentially progressive optic neuropathy in which there is a characteristic acquired atrophy of the optic nerve head (ONH) and loss of retinal ganglion cells (RGCs) and their axons, without other causes.

The susceptibility of the ONH and surrounding tissues to IOP is multifactorial. It varies with age, region of the ONH and from person to person.[5,10-12] Large-scale population studies have established that mean human IOP is about 16 mmHg. POAG risk increases in the presence of IOP in excess of two standard deviations above this mean or 21 mmHg.[13] Although elevated IOP is often associated with POAG and risk increases with increasing IOP, elevated IOP by itself is not necessary and sufficient to make the diagnosis.[13-15]

Normal tension glaucoma (NTG) is a subtype of POAG in which elevated IOPs outside of the “normal range” are never clinically observed.[13,16] Although certain distinguishing phenotypic features of NTG have been noted, such as increased disc hemorrhage (DH) frequency, acquired ONH pits, and both characteristic ONH cupping patterns and visual field (VF) loss, there is considerable overlap of the clinical findings of NTG and POAG suggesting that NTG is likely part of the POAG continuum.[17] They differ primarily in that the level of IOP is the predominant causative risk factor in POAG while additional IOP-independent factors take increasing importance in NTG.

B. Scope of the Problem

Most persons with POAG are initially asymptomatic,[18] therefore, there may be delays in detection, diagnosis and treatment. Patients with moderate-stage glaucoma, however, may have measurable vision-related performance and quality of life issues associated with both reduced contrast sensitivity and VF loss.[19]

Untreated POAG usually progresses slowly. The rate of untreated POAG progression is quite variable, however, and treatment may not completely halt vision loss. POAG also progresses in some eyes despite aggressive treatment.[20]

Persons with POAG may face challenges including compromise to peripheral vision, decreased contrast sensitivity, and eventually compromised central vision.[21-23] These can lead to difficulties in walking[24,25] and issues with falling,[26] reading,[27-30] driving,[31] and subsequent poor quality of life.[2,18]

- **Quality of life**

Once diagnosed, even if good subjective vision is maintained by treatment, the use of medications and/or surgery often leads to dry eye symptoms,[32,33] increased cost burden,[34-37] and subsequent decrease in quality of life.[32,38] A high proportion of patients with glaucoma report either visual complaints or ocular surface disease symptoms.[39]

Glaucoma treatment creates an additional burden for patients that is distinct from the disease burden that negatively affects quality of life and can potentially cause vision-threatening issues with both medication and appointment adherence.[40] Knowledge of the presence of the disease, even in the absence of symptoms, can lead to anxiety, often depression and fears of loss of independence, the ability to work and blindness.[41-44] In addition, losses in psychosocial function (e.g., self-image, psychological well-being, and reduced confidence in health care) may occur.[45]

- **Risk of falling**

Persons with mild glaucoma have a higher risk of falls than individuals without glaucoma and those with moderate and advanced glaucoma have a higher fear of falling and avoid at-risk activities. Interventions to decrease falls and improve emotional and social well-being should be considered in patients with glaucoma starting early in the disease course.[46] (Evidence Grade: D) Visual acuity in the worse eye, history of previous falls, hypertension and diabetes mellitus (DM),[47] as well as rate of VF loss,[48] appear to be particular risk factors for falls in POAG patients.

- **Visual impairment and blindness**

A study of treated patients with POAG in the United States found a 9% probability of bilateral blindness and 26% probability of blindness in at least one eye at 20 years after diagnosis of glaucoma.[49] In another study, 15% of patients were found to be blind from glaucoma over a 14-year period. Higher IOP, a worse VF status at time of diagnosis, and older age at death are important risk factors for blindness associated with glaucoma.[50]

C. Epidemiology of Primary Open-Angle Glaucoma

1. Prevalence of Primary Open-Angle Glaucoma

Glaucoma is a leading cause of irreversible blindness in the world.[51] It is estimated that over 64 million people world-wide had glaucoma in 2013 and this number is projected to increase to almost 112 million by 2040, disproportionally affecting people residing in both Asia and Africa.[52] In 2021, the worldwide prevalence of POAG in persons 40 years of age or older was estimated to be 2.4% with the highest prevalence in Africa (4.0%).[53] A systematic review of population surveys estimated POAG prevalence in African ancestry populations of 5.2% at 60 years of age, increasing to 12.2% at 80 years of age. Both whites and Hispanics have shown high increases in prevalence per decade of life, and men were more likely to have POAG than women.[54]

A meta-analysis[55] estimated 2.71 million POAG cases in the United States in 2011, with the highest prevalence among populations 70-79 years of age (31%), women (53%), and non-Hispanic whites (44%). More recently, overall prevalence of glaucoma in the United States was estimated by ONH photography at slightly more than 2%, or 2.9 million individuals. This study found the prevalence was greatest among non-Hispanic African Americans, and included 1.4 million women, 1.5 million men, and 2.3 million people more than 60 years old.[56]

The prevalence of POAG increases with higher IOP, extremes of eye size, family history, some racial groups, myopia, systemic diseases (e.g., DM, hypothyroidism) and is directly related to age.[14,57,58] In the Baltimore Eye Survey, POAG age-adjusted associations with a family history of the same disease were 3.7 times higher in siblings and 2.2 times higher in parents relative to individuals with no family history.[59] Persons of African heritage are at greater risk for developing POAG.[60] The Baltimore Eye Survey also found that the overall prevalence of POAG among African Americans was 4.3 times that found in whites.[61]

2. Vision Loss in Primary Open-Angle Glaucoma

The majority of treated POAG patients retain useful vision for life, but a significant proportion will become visually impaired or blind.[2] One large worldwide meta-analysis calculated that 2.1 million people were blind and 4.2 million people visually impaired due to glaucoma in 2010. Glaucoma caused 6.6% of all blindness and 2.2% of all moderate and severe vision impairment.[62]

D. Risk Factors for Primary Open-Angle Glaucoma

1. Ocular and Systemic Risk Factors for Primary Open-Angle Glaucoma

Several ocular and systemic conditions have been found to be risk factors for POAG.

Table 1: Modifiable and Non-modifiable Risk Factors for Primary Open-Angle Glaucoma

Modifiable Risk Factors	
Elevated IOP	Several studies have confirmed that IOP is a significant risk factor for the development of POAG.[5,63,64] The Early Manifest Glaucoma Trial (EMGT) suggested that any elevated IOP is a strong factor for glaucoma progression.[65] (Evidence Grade: B)

	IOP is a particularly important risk factor in that it is the only factor that is currently modifiable with topical medical treatment, laser therapy and/or surgery.[66] Several randomized clinical trials have demonstrated the efficacy of lowering IOP, either by a percentage of baseline, or to a specified level.[67-69] Although increased IOP is generally associated with increased risk of glaucomatous ocular damage, there is no clear IOP below which there is no risk. However, most patients who sustain IOP>30 mmHg will eventually experience optic nerve damage.[70]
Non-modifiable Risk Factors	
Increasing age	The Rotterdam Study[71] (Evidence Grade: B), Ocular Hypertension Treatment Study (OHTS)[5] (Evidence Grade: B) and the Barbados Eye Study[63] confirm that baseline age is a predictive risk factor for POAG, with the incidence of POAG increasing significantly with age.
Genetics and positive family history	There is a high genetic disposition in all types of glaucoma,[72] especially in mothers and siblings of individuals with glaucoma.[73] (Evidence Grade: C)
Race/ethnicity	The Baltimore Eye Survey reported African-Americans are at higher risk of POAG than whites.[74] The Los Angeles Latino Eye Study (LALES) found prevalence of open-angle glaucoma is high among Latinos of Mexican ancestry.[75]
Myopia	Individuals with myopia have an increased risk of developing POAG.[76 77,78] (Evidence Grade: A) The prevalence of glaucoma-like optic neuropathy (GON) increases with longer axial lengths in highly myopic eyes.[79] (Evidence Grade: D) POAG patients with myopia >6 diopters (D) had a greater progression of VF loss.[80,81] (Evidence Grade: C)[82] Myopia <1D, however, may be a risk factor for increased VF loss in NTG.[83]
Corneal thickness	Central corneal thickness (CCT) is an important independent risk factor for OAG.[5,84,85] Persons with thin CCTs have a significantly higher prevalence of OAG than those with normal or thick CCTs at all levels of IOP.
Type 2 diabetes mellitus (DM)	Individuals with DM have an increased risk of developing POAG.[86]
Hypertension/hypotension	Systemic hypertension increases the risk for developing POAG.[87] Low nocturnal blood pressure (BP), especially more than 10 mmHg below daytime mean arterial pressure, is predictive of progression of VF defects in NTG.[88] (Evidence Grade: B)
Corneal rigidity or hysteresis	Corneal hysteresis (an assessment of the cornea's ability to absorb and dissipate energy) was significantly associated with the rate of VF loss in a cohort of glaucoma patients over time. Eyes with lower baseline hysteresis tended to progress significantly faster than those with higher hysteresis values.[89] (Evidence Grade: B) Assessment of corneal biomechanical properties supports corneal hysteresis as a glaucoma progression risk factor.[90] (Evidence Grade: B) [91] (Evidence Grade: B)

POAG Draft Two

2. Drugs That Influence Primary Open-Angle Glaucoma Risk

Various systemic medications can affect optic nerve perfusion, RGC survival, and aqueous humor outflow facility suggesting these medications modulate both POAG risk and disease progression.[92] They include:

- Corticosteroids are known to elevate IOP leading to POAG like disease.[93,94] Risk increases with frequency, duration, and relative drug potency. All modes of corticosteroid administration have the potential to elevate IOP,[95] but risk is somewhat lower with systemic use than when locally applied.[94,96]

Additional drugs that can elevate IOP (and cause POAG) include, but are not limited to:

- Anti-neoplastic agents (docetaxel and paclitaxel)[94]
- Selective serotonin reuptake inhibitor antidepressants[97]
- Anticholinergics[98]
- Systemic calcium channel antagonists[99]
- Intravitreal anti-vascular endothelial growth factor (anti-VEGF)[100]

Other drugs may increase IOP through pupillary dilation, swelling of the crystalline lens, or forward movement of the lens-iris diaphragm (e.g., topiramate). Through mechanical mechanisms (acute increased ocular volume and/or clogging the trabecular meshwork), visco-elastic agents, silicone oil, or anti-VEGF agents surgically introduced into the globe (seven or more injections annually) can elevate IOPs.[101,102,103]

E. Co-morbidities Associated with Primary Open-Angle Glaucoma

Patients with POAG are believed to be at increased risk for several chronic conditions and comorbidities. These conditions negatively affect POAG patients' health and quality of life.

Table 2: Comorbidities Associated with Primary Open-Angle Glaucoma

Dementia/cognitive decline	Both research and clinical findings point to a possible common causal relationship between Alzheimer's disease and POAG.[104] Both diseases share a strong age-related incidence, RGC degeneration, and extracellular fibular deposition.[105] Although one study showed a strong association between POAG and subsequent Alzheimer's dementia,[106] the relationship between POAG and Alzheimer's disease (and other dementia) remains controversial.[107]
High/low blood pressure	The relationship between BP and POAG is both controversial and complex.[108] Both high and low BP (and especially low nighttime diastolic pressure) have been associated with glaucoma. Low BP is particularly associated with progression in NTG.[88] Ocular perfusion pressure (OPP) reflects the vascular status of the ONH and is a biologically plausible etiology of RGC damage at the ONH. It may be more relevant in POAG than BP alone.[109] Low OPP, high systolic and low diastolic BPs, and high mean BP were all associated with POAG in LALES.[110] South Korean patients diagnosed with high BP (both high systolic and diastolic BP) were also more likely (1.16 times) to develop POAG.[111]
Type 2 diabetes mellitus	The relationship between type 2 DM and POAG is unclear, however, both the presence and duration of type 2 DM were associated with POAG in

	LALES.[112] Of the metabolic syndrome components, both hypertension and impaired glucose tolerance contributed to an increased risk of NTG in other research.[113]
Cardiovascular disorders	Both migraine and vasospasm (e.g., Raynaud's phenomenon) have been associated with risk of ONH damage and glaucoma progression. Also, atrial fibrillation, independent of other known cardiovascular risk factors, increases the risk of NTG.[114]
Sleep disorders	Sleep disorders are more prevalent in patients with glaucoma, especially NTG.[115] Obstructive sleep apnea (OSA) has been reported to be a potential risk factor in the development of glaucoma,[116,117] though there is evidence to the contrary, especially if patients are matched for known OSA risk factors.[118-120]
Depression/anxiety	POAG has been associated with both depression and anxiety.[121-123] Reduced health-related quality of life (HRQOL) scores are common in both surgically and medically treated glaucoma patients.[124]

F. Natural History of Primary Open-Angle Glaucoma

Although there is a clear, direct and dose-dependent relationship between IOP elevation and POAG in many patients, it is also clear that many POAG patients continue to lose VF sensitivity with IOPs never elevated above, or consistently maintained at "normal" levels. Many patients with elevated IOPs also never develop glaucomatous ocular damage. This pair of observations have led to the exploration of other pathogenic mechanisms.

The identification of IOP and age as important and independent factors in all clinical forms of OAG has prompted ongoing research on how the optic disc and surrounding tissues respond to IOP and aging to better understand the pathophysiology of glaucoma. Early experiments involving both acute and sustained elevation of IOP in a primate model identified the OHN as the primary site for disturbances in ganglion cell exonal transport [125-127] and that displacement of the lamina cribrosa was related to increases in IOP.[128,129]

With the availability of more advanced imaging technologies, these findings have been further quantified and the effects of acute changes in IOP on load-bearing structures of the posterior segment have been studied in healthy and diseased eyes.[130-138] These studies, along with histological evidence, have identified the peripapillary connective tissue, lamina cribrosa, neural tissue and optic nerve vasculature as structures susceptible to IOP-related stress.[139-141]

Over a lifetime, the ONH connective tissues are exposed to substantial levels of IOP-related stress and strain at normal levels of IOP, which increases further when IOP is elevated. These biomechanical forces at a given level of IOP are physiologic or pathophysiologic depending on the response of the tissues.[142] IOP therefore is not so much "normal" as "physiologic" or "pathophysiologic" and what distinguishes these will vary depending upon the susceptibility of the tissue. Therefore, in the setting of more susceptible tissue, even a "normal" range of IOP could produce a pathologic response (e.g., NTG) while less susceptible tissues may withstand higher levels of IOP (e.g., OH).

Principal causes of ONH susceptibility likely include the level of IOP, the geometry and material properties of the ONH and surrounding tissues, age-related alterations in the ONH biomechanics, the volume flow and perfusion pressure of blood within the capillaries of the lamina cribrosa, nutrient diffusion to the astrocyte, the molecular response of astrocytes and glia to physical strain, and the presence of physiologic stress within their microenvironment. Additionally, RGC factors that make axons more susceptible to damage within the ONH, or its stroma more susceptible to apoptosis in response to axonal distress may also play a role.[142]

Increased susceptibility of the ONH to the effects of IOP may reflect a structural predisposition for pathophysiologic change, the consequence of the tissue response to increased IOP, or some combination of variables.[143] Given the multifactorial nature of glaucoma, the individualized susceptibility of the optic nerve and surrounding tissues, and variables associated with the delivery of care, the clinical management of the condition should be individualized.

The well-established roles of family history,[144] ocular anatomy, and race (or ethic group) also suggest genetic influence if not etiology for many if not all types of glaucoma. While the functions of genes and genomic loci remain incompletely understood, about 20 genetic loci (perhaps up to 100) on many chromosomes have been associated with glaucoma, and >15 loci in particular have been suggested to play a role in POAG.[145,146,147] It is most likely that multiple genes and/or environmental factors contribute to the complex inheritance of POAG.[148]

G. Landmark Glaucoma Studies

Evidence-based clinical trials such as the Ocular Hypertension Treatment Study (OHTS), the Collaborative Normal Tension Glaucoma Study (CNTGS) and the Laser in Glaucoma and Ocular Hypertension Study (LiGHT) provide important data on POAG disease progression and treatment. Table 3 provides summaries of the results of landmark glaucoma clinical trials of current clinical relevance.

Table 3: Major Glaucoma Clinical Trials

Clinical Trial	Study Results
Early Manifest Glaucoma Trial (EMGT) (Study began in 1992)	The EMGT evaluated the effect of immediate treatment to reduce IOP in early, previously untreated open-angle glaucoma patients as compared with no initial treatment or later treatment. Treated patients had argon laser trabeculoplasty and received topical betaxolol hydrochloride twice daily.[149] Analysis showed considerable beneficial effects of treatment that significantly delayed progression. Patients treated had half of the progression risk of those not receiving treatment. Although progression varied across patient categories, treatment effects were present in both older and younger patients, high- and normal-tension glaucoma, and eyes with less and greater visual field loss.[68] (Evidence Grade: A) After a median of eight years of treatment and follow-up, IOP continued to have a marked influence on progression, regardless of baseline IOP. Other significant factors were age, bilaterality, exfoliation and DH. Lower systolic perfusion pressure, lower systolic BP, and cardiovascular disease history emerged as predictors, suggesting a vascular role in glaucoma progression.[20] (Evidence Grade: B)
Collaborative Normal-Tension Glaucoma Study (CNTGS) (Study began in 1998)	The CNTGS analyzed the effect of a 30% IOP reduction on the subsequent course of glaucoma. In the study, one eligible eye of 145 individuals with NTG was randomized either to no treatment (control) or to a 30% IOP reduction from baseline.[150] Progression of VF defects (5-7 years follow-up) was noted in 60% of untreated NTG individuals, while treatment targeting IOP-lowering of >30% decreased progression to 20%.[150] After more than eight years, 20% of the patients progressed despite treatment, 30% had a slowed loss of VF in response to reduction of IOP of at least 30%, and 65% remained stable in the absence of

	treatment. High peak IOP was a significant factor for progression.[151] (Evidence Grade: B) The CNTGS concluded that patients with NTG benefit from lowering of IOP. Treatment should be individualized according to the stage of disease and rate of progression.
Ocular Hypertension Treatment Study (OHTS) (Study began in 1994)	The goals of the OHTS were to determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG in patients with OH and to identify baseline clinical and demographic factors that predict which patients would or would not develop POAG. Participants with no evidence of glaucomatous damage and with an IOP between 24 mmHg and 32 mmHg were randomized to either observation or treatment with commercially available topical ocular hypotensive medication. The goal in the medication group was to reduce the IOP by 20% or more and to reach an IOP of 24 mmHg or less.[67] (Evidence Grade: A) The OHTS[5] (Evidence Grade: B) found that the conversion rate from OH to POAG over five years was 4.4% in treated patients (IOP decreased 20%) compared with 9.5% in untreated patients. Of OHTS participants evaluated in a 20-year follow-up cohort, about 45% converted to POAG (49% in the observation and 42% in the treatment groups) and 25% developed VF loss in one or both eyes.[152] (Evidence Grade: B) The study found that topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP,[67] (Evidence Grade: A) and the greatest benefit was seen in high-risk individuals.[9] (Evidence Grade: A) OHTS findings suggest that 19 people would need to be treated unnecessarily to prevent one person with OH converting to POAG, not considering other risk factors. Baseline risk factors associated with the conversion to POAG included advanced age, CCT lower than the study mean, increased ONH cup-to-disc ratio, and increased VF pattern standard deviation.
Laser in Glaucoma and Ocular Hypertension Study (LiGHT) (Study began in 2012)	The LiGHT Study evaluated whether initial treatment with selective laser trabeculoplasty (SLT) is superior to initial treatment with topical medication for POAG or OH. Patients in the study were randomized to initial SLT followed by medical therapy or medical therapy without laser treatment. Primary SLT achieved comparable early absolute IOP-lowering in OH versus OAG eyes. Drop-free disease-control was achieved at 36 months after one or two SLTs, with 58.2% of these after a single SLT and 74.6% after two SLTs.[153] (Evidence Grade: A) This clinical trial showed that SLT is safe and effective as a first-line treatment for POAG and OH. SLT provided superior IOP stability to drops, at a lower cost and it allowed almost three quarters of patients to be successfully controlled without drops for at least three years after starting treatment.[154] (Evidence Grade: A) After six years of treatment and monitoring, SLT safely provided IOP control without the need for medical or surgical treatment in approximately 70% of eyes with OH or POAG, while demonstrating a reduction in progression rates and the need for glaucoma surgery.[155] (Evidence Grade: A)

Advanced Glaucoma Intervention Study (AGIS) (Study began in 1988)	AGIS was designed to study the long-term clinical course and comparative outcomes of two sequences of surgical treatments in patients with medically uncontrolled glaucoma. One sequence began with argon laser trabeculoplasty (ALT), followed by trabeculectomy, should ALT fail to control the disease, and by a second trabeculectomy should the first trabeculectomy fail (ATT). The other sequence began with trabeculectomy, followed by ALT should the trabeculectomy fail, and by a second trabeculectomy should ALT fail (TAT).[156] Although IOP was lowered in both sequences in African American and white patients, long-term visual function outcomes were better for the ATT sequence in African American patients and better for the TAT sequence in white patients.[157,158] Both intervention sequences were shown to be effective in slowing the progression of VF deterioration in POAG patients who were uncontrolled medically. Specifically, maintaining IOP below 12 mmHg was shown to be effective in reducing VF deterioration.[7] (Evidence Grade: A)
Collaborative Initial Glaucoma Treatment Study (CIGTS) (Study began in 1993)	CIGTS evaluated whether medical therapy or trabeculectomy is the better initial treatment for patients with OAG. While both surgical and medication treatments were effective at lowering IOP during initial POAG treatment, surgery reduced IOP more than topical medications (2.2 mmHg). Age, gender and race were not predictive factors over time in treatment outcomes; however, smoking negatively impacted IOP reduction in surgically treated patients.[159] (Evidence Grade: B) The CIGTS intervention protocol led to a lowering of IOP that persisted over time in both treatment groups. The study concluded that initial surgery may be beneficial for subjects who present with more advanced VF loss, but detrimental for patients with diabetes.[160] The results also support considering more aggressive treatment when undue elevation or variation in IOP is observed.[161] (Evidence Grade: A)
Tube vs Trabeculectomy Study (TVT) (Study began in 2010)	The Tube Versus Trabeculectomy (TVT) Study was a multicenter randomized clinical trial comparing the safety and efficacy of Baerveldt tube shunt surgery to trabeculectomy with mitomycin-C (MMC) in eyes with previous cataract and/or unsuccessful glaucoma surgery.[162] The incidence of postoperative complications was higher after trabeculectomy with MMC than tube shunt surgery. Serious complications resulting in reoperation and/or vision loss occurred with similar frequency with both surgical procedures.[163] (Evidence Grade: A) No statistical difference in Vision Specific Quality of Life (QoL), nor QoL changes over five years of follow-up were found with either surgical intervention.[164] (Evidence Grade: A) Tube shunt surgery had a higher success rate compared to trabeculectomy with MMC during five years of follow-up. Both procedures were associated with similar IOP reduction and use of supplemental medical therapy. Additional glaucoma surgery was needed more frequently after trabeculectomy with MMC than tube shunt placement. Study results show that both are surgical options for treating

	medically uncontrolled glaucoma in patients with previous cataract extraction or failed filtering surgery.[165] (Evidence Grade: A)
United Kingdom Glaucoma Treatment Study (UKGTS) (Study began in 2007)	The UKGTS tested the hypothesis that treatment with a topical prostaglandin analog (latanoprost 0.005%), compared with a placebo, reduces the frequency of VF deterioration events in patients with open-angle glaucoma by 50% over a two-year period.[166] At 24 months, mean reduction in IOP was 3.8 mmHg in 231 patients in the latanoprost group and 0.9 mmHg in 230 patients in the placebo group. The study demonstrated preservation of visual function, notably VF, in patients treated with latanoprost.[69] (Evidence Grade: A) In addition, bilateral disease, higher IOP and DH were confirmed as risk factors for VF deterioration.[167] (Evidence Grade: A)

III. THE CARE PROCESS

A. Screening for Primary Open-Angle Glaucoma

The role of community screening for glaucoma is controversial. The United States Preventive Services Task Force (USPSTF) reviewed published literature to evaluate benefits and harms of glaucoma screening. It found that the evidence was insufficient to assess the benefits and harms of glaucoma screening in asymptomatic adults. Screening tests can identify persons with glaucoma and treatment was associated with a lower risk of glaucoma progression, but evidence of improvement in visual outcomes, quality of life, and function remains lacking.[168] (Evidence Grade: A)

In addition, screening for glaucoma in the general population has not been found to be cost-effective.[169] Many individuals who are identified as possibly having POAG at a screening fail to attend a subsequent professional examination. Even providing counseling and prescheduled appointments is only modestly successful when other social barriers exist (e.g., poor access to transportation, low income).[170] A lack of adequate knowledge about glaucoma may be more significantly associated with poor follow-up rates than true lack of access to care (e.g., medical insurance, availability of local eye doctors).[171]

B. Primary Open-Angle Glaucoma Examination

The goals of a POAG examination should be to:

- Make a differential diagnosis
- Establish a disease baseline
- Estimate the risk of future glaucomatous damage
- Decide whether, by what method, and/or how aggressively to initially treat
- Determine the timing of future monitoring examinations.

In addition to the testing included in a comprehensive eye and vision examination [Comprehensive Adult Eye and Vision Exam.pdf (aoa.org)], a POAG confirmatory examination should include expanded investigations in the following areas:

1. Patient History

Clinicians should obtain an in-depth family history, which should be continually updated during follow-up visits based on the importance of genetics in glaucoma.[72] (Evidence Grade: D) The patient's personal and family history should include questioning about:

- Systemic or ophthalmic surgeries (including refractive surgeries which can affect refractive error, central corneal thickness and IOP readings) and traumas.

- Personal and/or familial history of glaucoma and eye drop use, including which relatives, (especially mothers and siblings)[73] and level of severity.

- Systemic history of hypertension, cardiovascular disease, asthma, migraine, vasospasm and DM.

- All medications both prescribed and over the counter.

- Allergies and previous reactions to medication.

2. Tonometry

Tonometry, by itself, is not a valid nor effective screening or diagnostic tool to identify glaucoma. However, any elevated IOP is a risk factor for glaucoma development or progression.[65] (Evidence Grade: B) Therefore, it is an important test for use in diagnosis and monitoring of OH or POAG.

The current standard for tonometry is the Goldmann applanation tonometer, which is available in several forms, but there are also alternative methods, including both contact and non-contact devices. One newer technology, rebound tonometry, correlates well with Goldmann results and is similarly affected by central corneal thickness.[172] (Evidence Grade: C) IOP measurement by both rebound tonometry and Tonopen are comparable to Goldmann applanation tonometry but not interchangeable.[173] (Evidence Grade: C) The device used as well as time of day of the measurement should be noted.

> ***Clinical note:*** *High baseline IOP is a significant risk factor for glaucoma progression.*[174] *(Evidence Grade: B)*

IOP is not a constant. It is known to peak in early morning, decline progressively throughout the day, to peak again during nocturnal periods. POAG patients are known to have greater IOP fluctuations throughout the 24-hr cycle than do non-glaucomatous patients,[175] (Evidence Grade: D) and long-term IOP variation is a significant factor in NTG progression.[176] (Evidence Grade: B)

Monitoring the circadian IOP pattern may help the clinician to better manage glaucoma, mainly when progression occurs despite apparently adequate IOP control.[177] (Evidence Grade: D) Clinicians should also consider the significantly higher supine IOP typically peaking in early morning, which may be missed with normal in-office IOP measurements. This may be useful in unexplained progressive glaucoma.[178] (Evidence Grade: D)

> ***Clinical note:*** *It may be helpful to obtain several IOP measurements at different times of day prior to initiating treatment to help establish a baseline IOP from which to judge treatment effectiveness. Tonometry should be performed before gonioscopy and pupil dilation.*

3. Gonioscopy

The diagnosis of POAG requires the exclusion of angle closure glaucoma (ACG) and other forms of secondary glaucoma. Careful gonioscopic evaluation of each anterior chamber angle will help determine the presence of ACG, pigment dispersion, peripheral anterior synechiae, angle recession or neovascularization.

> ***Clinical note:*** *Gonioscopy is superior to the Van Herick technique to evaluate the anterior chamber angle in both differentiation of POAG from ACG, as well as determining whether it is safe to pharmacologically dilate the pupil.*[179] *(Evidence Grade: B)*

Anterior segment-optical coherence tomography (AS-OCT) demonstrates good sensitivity for differentiating between an open angle and a closed angle. However, it should not serve as a replacement for gonioscopy.[180] (Evidence Grade: A) Clinicians should consider whether the diagnostic accuracy of AS-OCT is acceptable for their specific clinical use before adopting it.

4. Pachymetry

Measurement of central corneal thickness (CCT) is indicated as part of the evaluation of the patient with suspected glaucoma or OH.[181] CCT is not only a critical measure at initial presentation to help the clinician evaluate POAG risk, but also the risk of both progression and severity.[182] (Evidence Grade: C) This procedure is generally performed once for purposes of assessing POAG risk.

Reduced CCT of 555um or less was found to be a powerful predictive factor for conversion from OH to POAG in the OHTS.[5] (Evidence Grade: B) POAG predictive models, however, do not improve by adjusting IOP for CCT even while IOP and CCT remain individually significant.[183] (Evidence Grade: B)

> ***Clinical note:*** *Some refractive surgeries thin the cornea and may make the correlation of CCT in POAG assessment more difficult.*

5. Structural Assessment

The following tests can provide evidence of structural changes:

a. Ophthalmoscopy

Careful binocular ophthalmoscopy of the ONH through a dilated pupil with sufficient magnification to evaluate glaucomatous damage is essential. The optic nerve size, both horizontal and vertical meridians, and cup-to-disc (C/D) ratio should be evaluated and recorded**.**

> ***Clinical note:*** *If the vertical or horizontal C/D ratio is not the largest, the clinician should note the meridian with the largest C/D ratio.*

This assessment may be documented with (stereo) photography or a detailed drawing. Clinical biomicroscopic examination of the optic nerve and nerve fiber layer yields a true stereoscopic view of the structures that may reveal glaucomatous features that are not visible from imaging technology (e.g., optical coherence tomography), such as optic DH and cases of severe glaucoma.[184] Direct monocular ophthalmoscopy views of the ONH may be of additional value in some instances where greater magnification is more helpful than stereoscopic impressions.

Unfortunately, there are no pathognomonic glaucoma-specific ONH characteristics. But the following are all suggestive of possible glaucomatous ONH damage:

- **Vertical elongation of the cup** - especially cupping 0.7-disc diameters or greater.

- **Asymmetry between the two cups** - 0.2-disc diameters or greater difference in either axis in the absence of other known etiologies (such as anisometropia, asymmetric disc size). While observation of vertical C/D ratio asymmetry should initiate a more comprehensive glaucoma workup, it is not an appropriate standalone screening tool for glaucoma.[185] (Evidence Grade: D)

- **ONH size** - Accurate identification of glaucomatous optic neuropathy is significantly influenced by optic disc size**.** Optic discs meeting structural criteria for glaucoma are larger than normal nerves.[186] Typically, large diameter optic nerves have corresponding larger cups, which can be clinically deceiving. Misdiagnosis is more likely when observing glaucomatous smaller ONHs and normal larger ONHs.[187] (Evidence Grade: B)

- **Narrowing or notching of the optic disc rim** - The normal ONH neuro-retinal rim is widest *inferiorly*, followed in width by the *superior rim*, then the *nasal rim*, and least at the *temporal rim*. The mnemonic for this clinical observation has been termed the "***ISNT rule***,"[188] violations of which should lead the clinician to consider glaucoma as a diagnosis. Myopic tilted discs are particularly challenging, however, so the clinician may have to consider other signs for diagnosis and monitoring.[189,190]

- **Acquired pits of the optic nerve (APON)** - Patients with APON show a significantly faster rate of VF deterioration, specifically faster decay rate in mean deviation (MD), Visual Field Index (VFI), and Glaucoma Rate Index (GRI), than do non-APON POAG patients.[191] (Evidence Grade: B)

- **Retinal arteriolar narrowing** - Early vascular changes involved in the pathogenesis of glaucoma suggest that quantitative measurements of retinal vessel caliber from retinal photographs may be useful to identify people with an increased risk of developing POAG.[192]

- **Vascular signs** - ONH signs of blood vessel baring, bayoneting or nasalization may be noted clinically.[193,194]

- **Optic DH** - Patients with DH have a greater risk of developing POAG across many populations.[195,196] DH has a 20% positive predictive value of glaucomatous optic nerve damage and there is a higher frequency of DH in NTG than in POAG.[197] (Evidence Grade: D) Predictive factors for DH in POAG are a smaller neuro-retinal rim and perhaps larger β-zone parapapillary atrophy.[198] (Evidence Grade: B) DH in NTG was associated with systemic hypertension, (Evidence Grade: D), migraine, baseline narrower neuro-retinal rim width, low systolic BP, mean arterial ocular perfusion pressure, and use of systemic beta-blockers.[199] (Evidence Grade: A)

- **β-zone parapapillary atrophy** - Glaucomatous eyes with β-zone parapapillary atrophy are at increased risk for progressive RNFL thinning.[200] The volume of choroid adjacent to the ON was significantly reduced in POAG eyes when β–zone parapapillary atrophy was present. This suggests that β-zone parapapillary atrophy may be a measurable factor for juxtapapillary choroidal atrophy and associated POAG vascular compromise.[201] (Evidence Grade: B)

Clinical note: *Clinicians should consider any loss of RNFL in the parapapillary β-zone, any thinning of the RNFL and/or any defects or arcuate gaps suggestive of RGC damage.*

b. Fundus Photography

Results from the OHTS revealed that stereophotographic assessment is more sensitive at detecting optic DH than clinical examination.[202] Serial color ONH stereophotography has been considered a complimentary method for documenting qualitative ONH appearance and then following any changes to assist in monitoring various types of glaucoma.[203] Although stereoscopic slide film has traditionally been the gold standard technology, film has now been displaced by digital imaging in photography. Compressed two and three-dimensional digital imaging is comparable to previous film for this application.[204] (Evidence Grade: C)

The classification of glaucomatous ONH features on stereophotographs such as vertical C/D ratio and neural retinal rim width (especially the inferior-temporal rim) can differentiate healthy eyes from those with or suspected of glaucoma by standard automated perimetry (SAP) and spectral domain-optical coherence tomography (SD-OCT).[205] (Evidence Grade: D). However, stereophotographic signs of focal damage (e.g., neuro-retinal rim thinning and RNFL loss) could also be due to intrasubject variability and limitations in stereophotography to define the optic disc margin.[206] (Evidence Grade: C).

Although a useful source of cross-sectional data, clinical and photographic review is less sensitive to changes over time associated with glaucoma progression. In fact, consensus using stereophotographs to detect progression is difficult to achieve, even among glaucoma experts.[207,208] OCT overcomes some of the limitations of the clinical evaluation and can be used to provide objective and quantifiable measurements of the RNFL, ONH and macula, which are useful for glaucoma diagnosis and progression analysis.[209]

c. Optical Coherence Tomography

Computer-based digital imaging provides quantitative information to supplement the clinical examination. OCT is useful for documenting the status and progression of the ONH, RNFL and other aspects of the posterior segment. Objective structural analysis with OCT is complimentary to subjective functional analysis such as VF testing for monitoring glaucoma progression. Generally, structural glaucomatous characteristics can be observed clinically before functional loss is evident.

Because no clinical test can be expected to demonstrate 100% sensitivity and specificity, relying solely on automated imaging classification to diagnose glaucoma or using this as a replacement for VF testing is not recommended.[184] Clinicians should incorporate OCT results into the broader clinical assessment of their patients, including other related factors (e.g., age, IOP, clinical ONH/RNFL examination, CCT, family history, and VF status).

Use of OCT enables objective quantitative assessment of glaucomatous structural loss. SD-OCT provides objective and reliable data on peripapillary nerve fiber layer, macular ganglion cell (MGC) thicknesses and ONH parameters.

<u>OCT Assessment of the ONH</u>

OCT can image and measure clinically/photographically invisible extensions of Bruch's membrane (BM) inside the disc margin and accounts for the rim tissue orientation.[210] The two-dimensional parameter Bruch's Membrane Opening-Minimum Rim Area (BMO-MR) shows comparable levels of diagnostic power to detect glaucoma compared to established parameters such as RNFL thickness.[211] In the setting of tilted discs, OCT-derived Bruch's Membrane Opening-Minimum Rim Width (BMO-MRW) analysis provides significantly greater specificity than RNFL irrespective of the refractive error, and it is more specific than Ganglion Cell Analysis (GCA) in tilted discs with moderate myopia.[212] In addition, rim area measurement accuracy was not affected by disc size in one study using a high-definition OCT.[213] (Evidence Grade: B).

<u>OCT Assessment of the Retinal Nerve Fiber Layer</u>

SD-OCT measured RNFL thickness parameters (global, inferior and superior) performed well in detecting (but not necessarily following progression in) glaucoma across the disease spectrum, but both increased myopia and age might be challenging confounding factors.[214] (Evidence Grade: D) Asymmetry of OCT derived RNFL thickness profiles between an individual's two eyes may be as helpful in diagnosing glaucoma as comparisons with normative data.[215] (Evidence Grade: B) SD-OCT demonstrates RNFL loss in the contralateral eyes of patients with previously diagnosed unilateral glaucoma progression (by VF and stereophotographic changes).[216] (Evidence Grade: C) OCT also provides quantitative information about the ONH, RNFL and ganglion cell layers (peripapillary and macular) with high reproducibility and is useful in detecting onset of glaucoma stages.[217] (Evidence Grade: B)

> ***Clinical note**: OCT RNFL thickness measurement may be more effective at detecting glaucoma progression than VF evaluation in patients with mild VF defects.[218] (Evidence Grade: C)*

Characteristic patterns of the OCT deviation map can provide useful clues to distinguish glaucomatous changes from false-positive findings.[219] (Evidence Grade: D) Research has demonstrated the overall rate of false-positive diagnostic classification of SD-OCT GCA and RNFL maps as 40.4% and 30.8%, respectively. Abnormal GCA diagnostic classification was associated with longer axial length and larger fovea-disc angle, whereas longer axial length and smaller disc area were associated with abnormal RNFL diagnostic classification.

Within RNFL scans, the nasal and temporal parameters are more poorly diagnostic than the average superior and inferior parameters. The diagnostic capacity of OCT measured RNFL is similar to segmented macular regions and better than total macular thickness.[220] (Evidence Grade: A).

SD-OCT localized RNFL thinning and rates of change are modestly statistically associated with pointwise 24-2 VF sensitivity loss at all locations.[221] (Evidence Grade: B) OCT RNFL thickness assessment was able to detect glaucomatous change before the appearance of Humphrey visual field (HVF) 24-2 [Swedish Interactive Threshold Algorithm (SITA)] changes,[222] (Evidence Grade: C) especially during early stages of disease. Some patients, however, have a glaucomatous VF without detectable structural abnormalities.[223] Additionally, an increase in disease severity at baseline increased the chance that the eye would be detected as progressing by SAP but not SD-OCT.[224] The extent to which structural and functional glaucomatous damage agree likely depends upon various factors, such as the particular test and test measures used, and the baseline conditions for a particular patient.[225,226]

OCT Assessment of Macular Ganglion Cells

Decreases in macular thickness that are believed to be due to loss of RGCs and that correlate significantly with glaucoma status of both RNFL thickness and VF defects have been reported in glaucomatous eyes. Macular thickness changes are well correlated with changes in visual function and RNFL structure in glaucoma[227] and may be a surrogate indicator of RGC loss.[228]

Macular measurements are particularly helpful in glaucoma progression analysis by SD-OCT due to the high density of ganglion cells in this area and the frequent early involvement of the macula in the glaucomatous process.[229] (Evidence Grade: D) SD-OCT data also suggests that segmented inner plexiform layer (IPL) thicknesses [RNFL, ganglion cell layer, ganglion cell-inner plexiform layer (GCIPL), macular GCC] are all reduced in association with POAG degree.[230] However, measuring the whole macular thickness as a surrogate for glaucoma has the disadvantage of taking into account cell layers (e.g., outer retinal layers) that are not affected in glaucoma, thus obscuring the actual contribution of the RGC layer to the process.[231]

Focusing macular scans on the retinal nerve fiber and ganglion cell layers may increase the predictive value of these scans. Whether or not to combine or separately analyze the IPL in macular OCT scans is unclear. Preliminary work isolating the IPL has suggested a glaucoma-related increase in IPL density, along with the altered reflectance pattern. This may be a consequence of dendritic remodeling (and accompanying mitochondrial redistribution for synapse maintenance and/or glial response for tissue cleaning), rather than dendrite atrophy, even in the absence of detectable alterations in the RGC layer and RNFL.[232] Combined or not, the influence of glaucoma on macular layers may be particularly useful in assessment of glaucomatous eyes with tilted discs or significant peripapillary atrophy.[233] (Evidence Grade: C)

Combining RNFL and Macular Ganglion Cell Assessments

Combining optic nerve parameters, RNFL and macular ganglion cell SD-OCT structural measurements improves the diagnostic sensitivity for glaucoma compared with any one of these variables while maintaining high specificity.[234] (Evidence Grade: D) Careful observation of both the average 6 and 11 o'clock RNFL sectors and inferotemporal and minimum GCIPL thicknesses can be particularly helpful for evaluating glaucoma progression by SD-OCT.[235]

- **OCT-angiography**

Because there is evidence of vascular dysfunction in glaucoma pathogenesis, highly repeatable and reproduceable OCT-A measurement of both peripapillary retina and macula vascular density may be useful.[236-238] OCT-A can image glaucomatous peripapillary capillary density changes[239] (Evidence Grade: B), which significantly corelates with VF damage severity independent of structural loss.[240] (Evidence Grade: D) Although OCT-A has shown promise in monitoring glaucoma, evidence to date of reliability has been conflicting.

6. Functional Assessment

a. Visual Fields

Evaluating visual function with standard automated perimetry (SAP) is a fundamental test for detecting VF loss and for monitoring the rate of VF change over time. SAP is used to evaluate the threshold sensitivity within the central 10 degrees, 24 degrees and 30 degrees from fixation using varying stimulus size to detect a VF defect. If SAP cannot be performed, then an alternative form of testing for diagnosing and monitoring glaucoma, such as threshold frequency doubling technology (FDT), can be considered.[241] (Evidence Grade: B)

Although classically POAG damages the peripheral VF (in patterns such as arcuate scotomata, nasal steps, generalized depression, and temporal wedge defects), glaucomatous patients also suffer paracentral vision loss.[5,242,243] Macular damage (within 8 degrees of the central field) to retinal ganglion cells and associated central VF defects may occur in glaucoma, even in early stages. A 10-2 VF testing model showed a stronger association with the National Eye Institute Visual Function Questionnaire (NEI-VFQ)-25 score than did a 24-2 VF model. Patients with disproportionately low quality of vision relative to patients with 24-2 VF damage may have damage on the central field missed by the 24-2 grid.[244] (Evidence Grade: C)

> ***Clinical note****: Central VF damage is often missed with the 24-2 testing strategy. Therefore, clinicians should consider performing 10-2 central VF tests.[245] (Evidence Grade: B) or an alternative test pattern that includes more central points.*

Perimetry is subjective and highly variable. Therefore, it is important to confirm VF defects in patients who have glaucoma and glaucoma suspects.[5,246] When a VF defect is detected by SAP, it is preferred to confirm the defect with the same VF testing modality. Confirming VF abnormalities increases confidence in the functional status of patients.[247] (Evidence Grade: D)

SAP VFs also have special value in helping the clinician to distinguish between rapid and slow POAG progressors, which assists in determining the aggressiveness of therapeutic intervention. Three examinations per year are required to identify an overall change in MD of 4 dB over two years in a patient with average visual field variability.[248]

EVIDENCE-BASED ACTION STATEMENT: The examination of a person suspected of having primary open-angle glaucoma (POAG) should include all aspects of a comprehensive eye and vision examination, with emphasis on the evaluation of the anterior chamber angle, optic nerve head (ONH), retinal nerve fiber layer (RNFL), macular ganglion cells and visual fields (VF), and measurement of intraocular pressure (IOP) and central corneal thickness (CCT).[65,72,173,179,182,217,245]

Evidence Quality: Grade B, Study type(s): Diagnostic, Case Control, Cohort-prospective, Cohort-retrospective, Cross-sectional
Level of Confidence: Medium
Clinical Recommendation Strength: Recommendation. This recommendation should generally be followed but remain alert for new information.

Evidence Statements:

Any elevated IOP is a strong factor for glaucoma development or progression.[65] (Evidence Grade: B) Therefore, it is an important test for use in the diagnosis and monitoring of OH or POAG.

Gonioscopy is superior to the Van Herick technique to evaluate the anterior chamber angle in differentiation of POAG from ACG.[179] (Evidence Grade: B)

OCT provides quantitative information about the ONH, RNFL and ganglion cell layers (peripapillary and macular) with high reproducibility and is useful in detecting onset of glaucoma stages.[217] (Evidence Grade: B)

Central visual field damage is often missed with the 24-2 testing strategy. Therefore, clinicians should consider performing 10-2 central visual field tests.[245] (Evidence Grade: B)

Central corneal thickness (CCT) is not only a critical measure at initial presentation to help the clinician evaluate POAG risk, but also the risk of both progression and severity.[182] (Evidence Grade: C)

IOP measurement by both rebound tonometry and Tonopen are comparable to Goldmann applanation tonometry but not interchangeable.[173] (Evidence Grade: C)

Clinicians should obtain an in-depth family history of glaucoma, which should be continually updated during follow-up visits based on the importance of genetics in glaucoma.[72] (Evidence Grade: D)

Potential Benefits: Enhanced ability to effectively diagnose and manage patients with POAG and OH.	**Potential Risks/Harms**: None.
Benefit and Harm Assessment: Benefits significantly outweigh harms.	
Potential Costs: Direct and indirect cost of testing.	
Value Judgments: None.	
Role of Patient Preferences: Moderate.	
Intentional Vagueness: None.	
Gaps in Evidence: Research is needed to determine the utility of anterior segment-optical coherence tomography (AS-OCT), including longitudinal studies to determine the significance of eyes classified to have closed angles by AS-OCT but open by gonioscopy.	

7. Primary Open-Angle Glaucoma Staging Systems

Staging systems allow classifying patients according to the severity of their disease. Staging also gives clinicians an opportunity to explain to their patients the relative severity of their condition and to monitor the course of patients' disease, whether stable, worsening or improving.[249]

Several POAG and VF staging systems (e.g., Hodapp-Parish-Anderson, Bascom Palmer Glaucoma Staging System, Enhanced Glaucoma Staging System, Visual Field Index) have been proposed to facilitate both proper diagnosis, care, and medical coding.[250,251] Some use criteria from the AGIS or the CIGTS.[223,252,253] Glaucoma staging systems (GSSs)[254] typically score VF defects and no other clinical factors such as ONH and nerve fiber layer evaluations. Each GSS has its own distinct advantages and disadvantages and stage severity differently.[255] Also, as these staging paradigms do not utilize macular measures, disease severity could be underestimated in at least some patients.[256]

The Mean Deviation (MD) Index can also be used to clinically stage the severity of glaucoma. It measures the average difference between a patient's overall visual field sensitivity compared to an age-matched reference database. AGIS and CIGTS scores and MD VF indices are more or less equivalent and relate to structural measurements equally.[257] (Evidence Grade: D)

The International Classification of Diseases -10th revision (ICD-10)[258] has staged glaucoma into mild, moderate or advanced disease. The following staging applies to all forms of glaucoma, including POAG:

- **Mild or Early**: Definite optic disc, RNFL, or macular imaging abnormalities consistent with glaucoma and no visual field abnormalities.

- **Moderate:** Definite optic disc, RNFL, or macular imaging abnormalities consistent with glaucoma and visual field abnormalities in one hemifield that are not within five degrees of fixation.

- **Advanced, Late, Severe:** Definite optic disc, RNFL, or macular imaging abnormalities consistent with glaucoma, and visual field abnormalities in both hemifields and/or loss within five degrees of fixation in at least one hemifield.

- **Indeterminate:** Inability of patient to perform visual field testing, unreliable/uninterpretable visual field test results, or visual fields not yet performed.

IV. TREATMENT AND MANAGEMENT OF PRIMARY OPEN-ANGLE GLAUCOMA

Medical, laser and surgical treatments for open-angle glaucoma lower intraocular pressure and reduce the risk for optic nerve damage over the short- to medium-term. However, the direct effect of treatments on visual impairment and the comparative efficacy of different treatments are not clear.[259] (Evidence Grade: A)

The goal of treatment is to minimize the risk of visual impairment over the lifetime of the patient while also minimizing the expense and side effects of treatments. An individualized treatment plan should be developed and modified based on the aggressiveness of the disease and may utilize medical, laser and/or surgical interventions alone or in combination. *(See Appendix 1: Optometric Management of the Patient with Open-Angle Glaucoma: A Flowchart)*

A. Determining a Target Pressure

As reducing IOP continues to be the primary treatment of all types of OAG, often a “target IOP” or “target range of IOP,” specific or approximate, is determined as well as the time course of additional monitoring examinations. The goal of establishing a “target pressure” for treating patients with POAG is to maintain their IOP within a range at which visually significant VF loss is unlikely to occur. The specific target pressure is initially an estimate and may be determined as a percentage reduction from the patient’s baseline IOP or as an absolute IOP level.[260]

Factors clinicians should consider when choosing a target pressure range include baseline IOP, the degree of optic nerve damage and/or VF loss, age of patient, and prior rate of progression.[6] In mild glaucoma, the initial target IOP range could be set at 15-17 mmHg, for moderate glaucoma 12-15 mmHg and in the severe stage of glaucomatous damage 10-12 mmHg.[261] The IOP target range may also be based on a percentage reduction from baseline. (See Table 4)

The effectiveness of the target pressure chosen should be periodically reevaluated by comparing optic nerve status and VF testing with results from previous examinations. The target IOP may change depending on the results of long-term monitoring.

Table 4: Baseline IOP, IOP Reduction Goal, Progression and Clinical Endpoint in Studies of Open-Angle Glaucoma

Study	Baseline IOP	IOP Reduction Goal	Progression	Clinical Endpoint
Ocular Hypertension Treatment Study[262]	24.9 mmHg	20%	4.4% in treated patients/9.5% in untreated	19.3 mmHg
Early Manifest Glaucoma Trial[263]	20.6 mmHg	25%	45% in treated patients/62% in untreated	Mean reduction 5.2 mmHg
Collaborative Normal Tension Glaucoma Study[10]		30%	12% in treated patients/35% in untreated	
Collaborative Initial Glaucoma Treatment Study[161] (Medical treatment) (Surgical treatment)	27 mmHg 27 mmHg	38% 46%	15% progressed and 15% improved	17-18 mmHg 14-15 mmHg
Advanced Glaucoma Intervention Study[7]	23.7 -24.8 mmHg	IOP mean 12.3 mmHg	Did not progress	

Stewart, et al. Factors associated with long-term progression or stability in POAG.[264]	19.5 ± 3.8 mmHg		0% 6% 26%	<12 mmHg <17 mmHg ≥18 mmHg

Adapted from: Sihota R, Angmo D, Ramaswamy D, Dada T. Simplifying "target" intraocular pressure for different stages of primary open-angle glaucoma and primary angle closure glaucoma. Indian J Ophthalmol 2018:495-505.

B. Medical Treatment

Medical treatment is generally used initially for most forms of POAG. Topical treatment is minimally invasive, avoids first pass metabolism of drugs in the liver, as well as permitting selective targeting of the ocular anterior chamber. Only 1-7% of the instilled drug reaches the ocular anterior chamber, however, due to the combined effects of pre-corneal tear drainage, the corneal epithelial layer barrier, and patient compliance.[265]

There are several principles of topical treatment:

- Start with the drug that provides the least patient risk and most efficacious treatment, considering ocular and systemic side effects, costs, patient preferences, and dosage inconvenience.

- Prostaglandin analogs (PGAs) have been found to provide the best IOP-lowering among all the monotherapy topical drugs. Combining a PGA and another category of topical drug further enhances IOP decrease. Incidents of adverse effects of medication should be considered, not just its IOP-lowering efficacy.[266] (Evidence Grade: A)

- Drugs within a glaucoma medication class share similar mechanisms of action and efficacy, and therefore generally can be expected to result in similar IOP reduction. It is usually best to change class or add a medication of a different class to improve therapy. Switching within a class, however, may minimize systemic or local adverse reactions.[267] (Evidence Grade: D)

- Combining glaucoma medications (e.g., adding a second and perhaps third drop) to the treatment regimen, usually from different classes, may be beneficial to patients who require a lower IOP,[268] (Evidence Grade: A) but use as few medications as reasonable to decrease toxicity and compliance complexity.

- If more than one drug is to be topically applied, educate patients to allow time in between drops of at least three to five minutes to allow for proper absorption.

- Proper eye drop technique helps in achieving good IOP control, decreasing risk of contamination and reducing systemic absorption. Educate patients to avoid touching the bottle tip to the eyes or face, to place just one drop into the cul de sac, and to employ lid and/or nasolacrimal duct closure to enhance drug effectivity while minimizing systemic absorption.[183,269,270]

Multiple pharmaceutical agents are currently available for the treatment of POAG. To access to the most current information on specific medications to treat glaucoma, see the following Glaucoma Research Foundation's online Medication Guide:

Medication Guide | glaucoma.org

1. Prostaglandin Analogs

Prostaglandin analogs (PGAs) increase uveo-scleral outflow and decrease IOP about 25% to 30%. Because of generally good IOP-lowering effectivity,[271] limited systemic and ocular side effects, and once-daily dosing at bedtime (HS), PGAs have become "first-line" treatment for many of the glaucomas.[272] (Evidence Grade: D) Currently available PGAs include bimatoprost, latanoprost, travoprost and tafluprost.

Monotherapy with topical travoprost, for example, was shown to consistently control IOP over 24 hours in a significant proportion of POAG patients.[273] (Evidence Grade: B) Side effects of PGAs can include, but are not limited to, eye color change, darkening of eyelid skin, eyelash growth, ptosis, orbital soft tissue changes, stinging, eye redness, and itching. Chronic monotherapy with PGAs decreases corneal hysteresis, corneal resistance factor, and CCT (which all reverse when PGAs are discontinued), which can contribute to underestimation of IOP measurement.[274] (Evidence Grade: C)

***Clinical note**: A large meta-analysis concluded that overall, PGAs are more efficacious in lowering IOP at three months than beta-blockers, alpha-agonists, or carbonic anhydrase inhibitors. Bimatoprost, latanoprost, and travoprost are among the most efficacious drugs at lowering IOP, and the within class differences are small and may not be clinically meaningful.[275] (Evidence Grade: A)*

EVIDENCE-BASED ACTION STATEMENT: The use of prostaglandin analogs (PGAs) should be considered as an initial therapy in patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG), unless contraindicated.[266,275]

Evidence Quality: Grade A. Study type(s): Systematic Reviews
Level of Confidence: High
Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements:

PGAs have been found to provide the best IOP-lowering among all the monotherapy topical drugs. Combining a PGA and another category of topical drug further enhances IOP decrease. Incidents of adverse effects of medication should be considered, not just its IOP-lowering efficacy.[266] (Evidence Grade: A)

Overall, PGAs are more efficacious in lowering IOP at three months than beta-blockers, alpha-agonists, or carbonic anhydrase inhibitors. Bimatoprost, latanoprost, and travoprost are among the most efficacious drugs at lowering IOP, and the within-class differences are small and may not be clinically meaningful.[275] (Evidence Grade: A)

Potential Benefits: Preventing and/or minimizing vision loss.	**Potential Risks/Harms**: Side effects of medication.

Benefit and Harm Assessment: Benefits significantly outweigh harms.

Potential Costs: Cost of medication.

Value Judgments: None.

Role of Patient Preferences: Moderate.

Intentional Vagueness: None.

Gaps in Evidence: Research on current medical treatments compared with surgery is needed, particularly for people with severe glaucoma and in ethnic groups.

2. Adrenergic Antagonists (Beta Blockers)

Beta blockers (β-blockers) act by inhibiting ultrafiltration in the ciliary body, thereby limiting aqueous humor secretion. Ophthalmic β-blockers can be either non-selective (inhibiting both β1 and β2 receptors) or cardio-selective (inhibiting β1>β2). Non-selective β-blockers have greater IOP-lowering effects but also more systemic side effects. β–blockers include timolol maleate, levobunolol, metipranolol and betaxolol HCL.

Ocular side effects are usually mild but include dry eye, lid ptosis, conjunctival hyperemia, corneal anesthesia, and blurred vision. Non-selective β-blockers should be avoided in patients with asthma, chronic obstructive pulmonary disease, atrioventricular block, bradyarrhythmia, unstable congestive heart failure, depression, myasthenia gravis, and persons with DM who are prone to hypoglycemic events or patients using calcium channel blockers. β-blockers also reduce the effectiveness of epinephrine used in anaphylactic crisis and should be avoided in patients who might experience such events.

> ***Clinical note:*** *Non-selective β-blockers significantly affect lung function and increase asthma morbidity and should be avoided if better, safer agents are available for these patients.*[276] (*Evidence Grade: A)*

The safety of ophthalmic β-blockers can be increased by minimizing systemic absorption (such as by having the patient practice self-punctal occlusion during drop application).[277] (Evidence Grade: D)

3. Adrenergic Agonists

Adrenergic agonists affect both alpha- and beta-adrenergic receptors, if non-selective, and reduce IOP by both decreasing aqueous formation and resistance at the trabecular meshwork (TM). Brimonidine tartrate and apraclonidine HCL are currently available adrenergic agonists.

- **Non-selective** -The side effects of rare cardiac arrhythmias, conjunctival injection, and cystoid macular edema, as well as the development of pigment spots on the tarsal conjunctiva, limit current usage.

- **Selective alpha2 receptor agonists** - These drugs are contraindicated in patients taking monoamine oxidase inhibitors (risk of hypertensive crisis) and in children (risk of cardiorespiratory and central nervous system depression). They may potentiate syndromes associated with vascular insufficiency and may cause, but are not limited to, lid retraction, anterior uveitis, fatigue/drowsiness, dizziness and dry nose/mouth. There are also concerns for the development of both allergic (especially follicular) conjunctivitis, dermatitis, and tachyphylaxis, especially with use of apraclonidine.[278,279] (Evidence Grade: D)

4. Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) are known to lower IOP by suppressing aqueous production through blockade of carbonic anhydrase in local tissues, increasing CO_2 and/or lowering pH to result in vascular dilation and increased blood flow. CAIs include acetazolamide, brinzolamide, dorzolamide HCL and methazolamide.

Allergies and previous reactions to sulfa drugs may limit the use of CAIs. Topical CAIs (e.g., dorzolamide and brinzolamide) have fewer systemic concerns and may be used as monotherapy, though they are most often used in combination with other glaucoma medications.

5. Rho-kinase Inhibitors

Rho-kinase inhibitors (e.g., netarsudil) decrease IOP 25 to 30% by decreasing TM resistance.[280,281] (Evidence Grade: D) These medications may serve well as adjuncts to established glaucoma medications.

Local side effects include blurred vision, tearing, conjunctival hyperemia and hemorrhage, cornea haze and verticillate. Although a greater number of patients using netarsudil than using timolol or latanoprost discontinued treatment due to adverse effects, it works well with lower IOPs and may have a role in treating NTG.[282] (Evidence Grade: D)

6. Cholinergic Agents

Cholinergic agents act by stretching the TM, which decreases IOP by increasing trabecular aqueous outflow. Available medications include pilocarpine HCL and carbachol. Cholinergics can be used alone or combined with other glaucoma medications.

Ocular and systemic side effects include miosis, ciliary muscle spasm (leading to increased myopia and brow-headaches in patients capable of accommodation), stinging and burning, posterior synechiae, narrowed anterior chamber angle, cataract, brachycardia, bronchospasm, central nervous system depression, and gastrointestinal distress. These side effects and the need for frequent dosing limit current use.

7. Combination Products

POAG patients commonly benefit from the synergy of the concomitant use of several classes of IOP-lowering topical agents. When dual therapy is indicated, offering a single bottle with multiple active drugs may enhance patient adherence[272] and compliance, while decreasing complexity, inconvenience, (preservative) toxicity, and perhaps cost.

Many such combinations are available in both commercial and compounded preparations including:

- A brinzolamide 1%/brimonidine 0.2% combination showed good 24hr IOP-lowering efficacy[283] while reducing the treatment burden in patients who require multiple IOP-lowering medications.[284] (Evidence Grade: A)

- A fixed combination of dorzolamide/timolol was found to be both safe and effective in treating NTG.[285] (Evidence Grade: B).

- A fixed combination of latanoprost and netarsudil lowered IOP more than either drug alone.[286] (Evidence Grade: D)

- Non-preserved fixed combination timolol/dorzolamide drops were effective at reducing IOP and better tolerated in benzalkonium chloride (BAK)-sensitive patients than preserved drops.[287] (Evidence Grade: B).

- Both brimonidine/timolol and dorzolamide/timolol therapies tended to increase OPP and retrobulbar blood flow, with no statistically significant differences between treatments after one month in patients with POAG and well-controlled IOP.[288] (Evidence Grade: B).

8. Generic Formulations

Ophthalmic generic drugs must have therapeutic equivalence and be identical in strength, dosage form, route of administration, have the same indications/contraindications, and abide by the same Good Manufacturing Practices as the innovator agent. A meta-analysis noted no evidence of difference between generic and original formulations of ophthalmic PGAs regarding efficacy or tolerability.[289] (Evidence Grade: A) For example, both generic latanoprost and Xalatan (brand name of latanoprost) were effective in reducing IOP about 28% in one study.[290] (Evidence Grade: A)

Generic compounds may differ from innovator agents with regards to performance under environmental stress, relative acidity, and bottle size/rigidity. Matching ingredient profiles may therefore not result in consistently comparable drug compositions and clinical effects.[291] (Evidence Grade: D)

9. Relative Effectivity Trials

Several studies have shown the effectiveness of different topical medications in lowering IOP:

- In both POAG and OH patients, latanoprost, brimatoprost and travoprost are equally effective at lowering IOP, equally well tolerated systemically, but significantly fewer patients reported ocular hyperemia with latanoprost.[292] (Evidence Grade: A)

- Topical latanoprost and bimatroprost produce a statistically significant IOP reduction compared to timolol but are associated with a higher risk of conjunctival hyperemia.[293] (Evidence Grade: A)

- Both bimatoprost .001% and timolol 0.5% lower mean 24hr IOP effectively, but timolol is not as effective in nocturnal IOP control.[294] (Evidence Grade: B)

- Tafluprost had better overall IOP-lowering effect when compared to timolol 0.5% with decreased diurnal IOP and fewer overall adverse events.[295] (Evidence Grade: B)

- Brimonidine provides greater IOP-lowering efficacy than topical CAIs as adjunctive therapy to β-blockers or PGAs. Alpha adrenergics, as adjunctive therapy, seem to be better tolerated than CAI adjunctive therapy.[296] (Evidence Grade: B)

- Unpreserved timolol gel 0.1% maintained the efficacy of preserved latanoprost drops and reduced intolerance signs and symptoms in almost all OAG or OH patients using preserved latanoprost.[297] (Evidence Grade: B)

- Latanoprostene bunod 0.024% dosed once in the evening is well tolerated and is non-inferior to timolol 0.5% used twice a day. It results in significantly reduced mean diurnal IOP over three months of treatment in both OAG and OH patients.[298] (Evidence Grade: A) Latanoprostene bunod used every evening demonstrated greater IOP-lowering effect throughout the day than timolol used twice a day over three months of treatment. The drug was found to be safe in adults with POAG and OH.[299] (Evidence Grade: A)

10. Sustained Drug Delivery

The glaucoma treatment paradigm may soon undergo changes as novel sustained drug delivery systems become available to individuals with OH or POAG. Several options (e.g., ocular inserts, medication-eluting contact lenses, intraocular implants) will likely become available soon to ease the burden of daily topical administration of chronic therapy with IOP-lowering drugs.[300] (Evidence Grade: D)

11. Ocular Surface Disease in Glaucoma Therapy

Glaucoma patients using topical IOP-lowering therapy have a significantly higher prevalence of ocular surface disease (OSD) symptoms than is found in the general population.[301] (Evidence Grade: B) [302] (Evidence Grade: C) This is probably related to the drop preservatives, long treatment durations, and patient's age.[303] (Evidence Grade: D) More attention should, therefore, be given to the ocular surface status of patients on long-term anti-glaucoma medications with consideration for alternatives that have a less toxic effect on the ocular surface.[304] (Evidence Grade: C)

Active ingredients, preservatives, the number of concomitant drugs, and the number of eye drops instilled per day are felt to all be elements able to induce different ocular surface changes, potentially with synergistic effects.[305] (Evidence Grade: B) There is insufficient evidence, however, to suggest that patients without OSD need to use preservative-free glaucoma medications, especially if they require few medications (defined as 1-2 drops/day).[306] (Evidence Grade: B)

Anti-glaucoma medications have shown toxic effects on conjunctival epithelium,[307] (Evidence Grade: B) meibomian glands,[308] (Evidence Grade: D) and the development of dry eye symptoms.[309] (Evidence Grade: C) Use of combinations of anti-glaucoma topical medications were also found to be a contributing factor for the development of lacrimal duct obstruction.[310] (Evidence Grade: D) Chronic use of preserved topical drops may affect the ocular surface indigenous bacterial flora. The long-term use of preserved PGA drops has been found to affect bacterial resistance to antibiotics.[311] (Evidence Grade: C)

Preservative free eye drops are associated with less ocular irritation symptoms than preserved eye drops.[312] (Evidence Grade: D) The use of less toxic ophthalmic preservatives or the reduction of the number of preserved eye drops used per day, can significantly reduce some clinical OSD signs.[313] (Evidence Grade: D) Although topically applied medications are usually safer than systemic counterparts, due to lessened systemic side effects, both drugs and especially preservatives in all multidose ophthalmic topical preparations are known to have side effects,[314] (Evidence Grade: C) principally on the tears and ocular surface.[315]

***Clinical note**: Recognition and treatment of OSD in glaucoma patients may improve patient quality of life, medication adherence, and both patient and physician satisfaction.[316] (Evidence Grade: D)*

Controlling OSD may lead to improvement in IOP control and management of glaucoma.[317] Co-treatment for osmo-protection with an artificial tear solute of 0.5% carboxymethylcellulose and 0.9% glycerin significantly improved the ocular surface of patients taking topical β-blockers or PGAs[318] (Evidence Grade: B) and improved IOP control.[319] (Evidence Grade: D)

Even though many POAG patients using preserved topical medications present with OSD signs and symptoms, many remain highly satisfied with their treatments. Treatment change should be considered, however, with either clinical signs or patient reported symptoms.[320] (Evidence Grade: D)

EVIDENCE-BASED ACTION STATEMENT: Patients prescribed topical intraocular pressure (IOP) lowering therapy may experience decreased tear film stability and elevated tear osmolarity and should be evaluated for ocular surface disease (OSD).[301,302,304,305,307-309,313,316]

Evidence Quality: Grade C. Study type(s): Cohort-prospective, Cohort-retrospective, Case Control, Cross-sectional, Review/Position paper, Case Series
Level of Confidence: Medium
Clinical Recommendation Strength: Recommendation. This recommendation should generally be followed but remain alert for new information.

Evidence Statements:

Glaucoma patients using topical IOP-lowering therapy have a significantly higher prevalence of ocular surface disease (OSD) symptoms than is found in the general population.[301] (Evidence Grade: B) [302] (Evidence Grade: C)

Active ingredients, preservatives, the number of concomitant drugs, and the number of eye drops instilled per day are felt to all be elements able to induce different ocular surface changes, potentially with synergistic effects.[305] (Evidence Grade: B)

Anti-glaucoma medications have shown toxic effects on conjunctival epithelium,[307] (Evidence Grade: B) meibomian glands,[308] (Evidence Grade: D) and the development of dry eye symptoms.[309] (Evidence Grade: C)

More attention should be given to the ocular surface status of patients on long-term anti-glaucoma medications with consideration for alternatives that have a less toxic effect on the ocular surface.[304] (Evidence Grade: C)

The use of less toxic ophthalmic preservatives or the reduction of the number of preserved eye drops used per day, can significantly reduce some clinical OSD signs.[313] (Evidence Grade: D)

Recognition and treatment of OSD in glaucoma patients may improve patient quality of life, medication adherence, and both patient and physician satisfaction.[316] (Evidence Grade: D)

Potential Benefits: Improved ocular surface health and patient adherence to medication use.	**Potential Risks/Harms**: None.

Benefit and Harm Assessment: Benefits significantly outweigh harms.
Potential Costs: Direct and indirect costs of testing.
Value Judgments: None.
Role of Patient Preferences: Moderate.
Intentional Vagueness: None.
Gaps in Evidence: Research to evaluate the complex relationship between glaucoma medication and ocular surface disease.

12. Pharmacological Treatment in Pregnancy

Medical management of the pregnant patient with POAG presents a need to balance the risk of glaucoma progression against concerns for the safety of the fetus. It is important to coordinate ophthalmic care with the patient's obstetrician and neonatologist. Pharmacological treatment of glaucoma during pregnancy and lactation should follow United States Food and Drug Administration (FDA) safety profiles and consider glaucoma severity and pregnancy stage.

Sympathomimetics (e.g., brimonidine) are a Category B IOP-lowering drug with presumed safety in pregnancy based on animal studies, but brimonidine is believed to be secreted in breast milk and should be discontinued late in the third trimester out of concern for central nervous system depression, hypotension and apnea in infants.[321] (Evidence Grade: D) Other IOP-lowering medications (β-blockers, CAIs, PGAs, and parasympathomimetics) are all Category C with known side effects in animal studies but no human data.

To minimize exposure to potentially harmful medical therapy, consider early surgical management, especially laser procedures[321] (Evidence Grade: D) in advanced or high-risk patients, and recommend punctal occlusion to minimize systemic absorption in pregnant patients utilizing medical therapies.[322] (Evidence Grade: D) Laser and other surgical glaucoma treatment options are all alternatives to medication except in the first trimester.[323] (Evidence Grade: D)

CONSENSUS-BASED ACTION STATEMENT: Pharmacological treatment of primary open-angle glaucoma (POAG) should be used with caution during pregnancy and lactation.
Evidence Quality: A systematic evaluation of research to support or refute the use of this recommendation was not conducted for this guideline
Benefits and Harms Assessment: Implementation of this recommendation is likely to enhance safety when treating patients with OH or POAG who are also pregnant (prenatal, perinatal, postnatal). The benefits of this recommendation were established by expert consensus opinion.

C. Laser Therapy

Initially considered as adjunctive treatment for eyes not achieving IOP control with topical medications, selective laser trabeculoplasty (SLT) has become increasingly used for the initial treatment of OH and POAG. This is especially the case for patients at risk due to poor medication adherence and/or professional follow-up compliance.

SLT treatments consist of an application of a series of laser burns to the TM leading to increased outflow facility. Both 180 and 360 degree treatments have been well studied in SLT and are reasonable as initial therapy for POAG and OH.[324] (Evidence Grade: A) The application of 360 degree SLT appears to be an effective treatment with approximately 60% of eyes achieving an IOP reduction of 30% or more.[325] (Evidence Grade: B) Laser trabeculoplasties appear successful in lowering intraocular pressure for patients with OAG.[326]

> ***Clinical note:*** *Laser treatments commonly lose efficacy over time. Therefore, it is important to continue regular monitoring of treated patients.[327] (Evidence Grade: D)*

Acute IOP elevation after laser therapy is a common adverse effect. Most of these IOP elevations are transient, but even temporarily elevated IOP may cause further optic nerve damage, worsening of glaucoma, or loss of vision. IOP increase (“spikes”) is a concern with heavily pigmented TMs, as is corneal endothelial cell loss. Perioperative medications (apraclonidine or brimonidine) are superior to no medication or placebo to suppress IOP spikes and enhance IOP reduction during the first two hours and up to 24 hours following laser trabeculoplasty.[328] (Evidence Grade: A)

1. Argon Laser Trabeculoplasty

Argon laser trabeculoplasty (ALT) has been shown to be a relatively safe and effective procedure.[329] However, clinically, it has been replaced by SLT.

2. Selective Laser Trabeculoplasty

A systematic review of published studies found that SLT therapy was not inferior to medication-only treatment in IOP reduction and success rate of IOP control. It significantly decreased the mean number of medications needed. SLT was found to be a safe procedure during long-term follow-up and may be a choice of first-line therapy in OAG.[324] (Evidence Grade: A)

SLT uses lower energy than ALT, so it causes less tissue damage and therefore is repeatable. Patients who demonstrate an initial IOP decrease from SLT with subsequent loss of effect over time should expect a similar result from a repeat SLT.[330] (Evidence Grade: C) In those glaucoma patients who may benefit from repeat SLT, either SLT or ALT were found to be about equal in IOP-lowering effect one year post operative (about 3 mm Hg).[331] (Evidence Grade: A)

Repeat SLT is effective at achieving IOP control in OAG and OH eyes requiring retreatment within 18 months of initial SLT. It may provide an equivalent and possibly longer duration of clinical benefit than after initial SLT alone. Repeat SLT is reported to be safe, with minimal laser-related side effects.[332] (Evidence Grade: B) SLT induces little and only short-lived anterior segment inflammation and the IOP-lowering effect of the SLT is not influenced by the use of anti-inflammatory medication after laser treatment.[333] (Evidence Grade: A)

SLT is considered an established and effective glaucoma treatment in early to moderate stages of OAG. It may also be effective in patients with advanced glaucoma, those with moderate IOP elevation on maximum topical medications, and those with co-existing systemic diseases or medication (e.g., warfarin, phenprocoumon), which makes filtering surgery difficult or potentially dangerous.[334] (Evidence Grade: B)

In the LiGHT study, SLT was shown to be a safe and effective drop-free alternative to achieve good IOP control in glaucoma patients for a period of at least three years; 58% of patients were successfully controlled with one treatment while an additional 17% were successful after two treatments. At six-year follow-up, no significant differences were found. SLT is a safe treatment for OAG and OH, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma and cataract surgery.[155] (Evidence Grade: A)

SLT offers a promising primary treatment strategy for POAG patients in lieu of topical drop glaucoma regimen, with notable improved quality of life.[154] (Evidence Grade: A) A slightly greater proportion of OH and OAG patients initially treated with topical medical therapy underwent rapid VF progression compared to those treated initially with SLT. Treating patients first with SLT may delay VF progression in comparison with initial medical therapy.[335] (Evidence Grade: A)

In a randomized clinical trial of POAG and OH patients who were well-controlled with medical therapy, SLT maintained good IOP control with reduction in number of medications. SLT as replacement therapy may reduce problems of non-compliance and medication side-effects.[336] (Evidence Grade: A)

Two other clinical trials found that SLT seems to have equivalent efficacy to topical latanoprost monotherapy over 12 months independent of angle pigmentation[337] (Evidence Grade: B) and IOP reduction was similar for SLT and PGA medication upon initial therapy for POAG.[338] (Evidence Grade: B) One study, however, found SLT was not superior to medication as a first line therapy in improving glaucoma-specific quality of life scores. IOP reduction was superior in the medication arm of the study.[339] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Selective laser trabeculoplasty (SLT) should be considered as an initial/alternative or additive therapy to medication for achieving intraocular pressure (IOP) control in patients with ocular hypertension (OH) or primary open-angle glaucoma (POAG).[154,324,334-338]

Evidence Quality: Grade A. Study type(s): Randomized Clinical Trials, Systematic Review, Cohort-prospective, Cohort-retrospective, Case Series
Level of Confidence: High
Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements:

SLT offers a promising primary treatment strategy for POAG patients in lieu of topical drop glaucoma regimen, with notable improved quality of life.[154] (Evidence Grade: A)

SLT therapy was not inferior to medication-only treatment in IOP reduction and success rate of IOP control. SLT significantly decreased the mean number of medications needed and was observed to be a safe procedure during the long-term follow-up.[324] (Evidence Grade: A)

Treating patients first with SLT may delay visual field progression in comparison with initial medical therapy.[335] (Evidence Grade: A)

In POAG or OH patients who were well-controlled with medical therapy, SLT maintained good IOP control with reduction in number of medications. SLT as replacement therapy may reduce problems of non-compliance and medication side-effects.[336] (Evidence Grade: A)

SLT seems to have equivalent efficacy to topical latanoprost monotherapy over 12 months independent of angle pigmentation.[337] (Evidence Grade: B)

IOP reduction was similar for SLT and PGA medication upon initial therapy for POAG.[338] (Evidence Grade: B)

SLT is considered an established and effective glaucoma treatment in early to moderate stages of open angle glaucoma. SLT may also be effective in patients with advanced glaucoma and moderate IOP elevation, on maximum topical medications, and with co-existing systemic diseases or medication.[334] (Evidence Grade: B)

Potential Benefits: Preservation of vision through effective lowering of IOP, increased adherence and decreased need for medications.	**Potential Risks/Harms**: Complications from laser treatment.

Benefit and Harm Assessment: Benefits significantly outweigh harms.
Potential Costs: Direct and indirect costs of laser treatment.
Value Judgments: None.
Role of Patient Preferences: High.
Intentional Vagueness: None.
Gaps in Evidence: None identified.

D. Surgical Treatment

Surgical treatment becomes an option when IOP cannot be sufficiently reduced with medical or laser therapy. Surgery may also be an appropriate initial treatment for eyes with very advanced damage, uncontrolled IOP, or known rapid POAG progression. Surgical IOP treatment can significantly reduce the incidence and rate of VF progression in patients with glaucoma who demonstrate preoperative progression and it may prevent subsequent VF progression in eyes with unsatisfactory IOP control prior to surgery.[340]

1. Cataract Surgery

Cataract surgery can decrease IOP, at least initially, by up to a few mmHg.[341] A more anteriorly positioned crystalline lens prior to phacoemulsification was significantly predictive for a greater post-operative IOP reduction in non-glaucomatous eyes. Such a relationship also existed for glaucomatous eyes but with less significance.[342] (Evidence Grade: C)

For patients with POAG (including NTG) that is controlled with one or two topical medications, phacoemulsification results in a modest IOP decrease (13%) and reduced medication requirement (12%) and seems to be relatively safe. Some patients (up to 26%), however, experience worse IOP control and may require additional medications, laser surgery or both.[343] (Evidence Grade: B). Combined cataract extraction and endoscopic cyclophotocoagulation (CPC) resulted in a greater postoperative IOP reduction and number of medications than phacoemulsification alone in POAG.[344] (Evidence Grade: C)

2. Minimally Invasive Glaucoma Surgery

Several “minimally invasive” glaucoma surgery (MIGS) devices are available as alternatives to laser trabeculoplasty, invasive trabeculectomies[345] and glaucoma drainage devices (GDDs). MIGS produce direct channels from the anterior chamber to Schlemm’s canal, the subconjunctival space, or the suprachoroidal space, thus bypassing the juxtacanicular TM and inner wall of Schlemm’s canal (believed to be the site of greatest aqueous flow resistance in POAG). MIGS are characterized by minimal external dissection, short operating times, relatively good safety profiles, and rapid recoveries.[346] MIGS devices have been shown to provide a safe surgical approach and may provide good long-lasting intraocular pressure–lowering effectiveness and the opportunity to reduce or eliminate ocular hypotensive medications.[347] (Evidence Grade: D)

To minimize the risk of additional surgeries, many MIGS are utilized at the time of cataract surgery, where both the removal of the crystalline lens and implantation of one or more MIGS devices have shown a good combined effect.[348] (Evidence Grade: B) Trabectome surgery may be used in combination with cataract surgery to ablate and remove a portion of the TM and inner layer of Schlemm’s canal. It may also be considered a viable procedure for patients with failed filtering blebs and uncontrolled IOP.[349] (Evidence Grade: D)

MIGS may also be a stand-alone procedure for the right patient with certain types and severity of glaucoma. Overall, while MIGS as a class have some advantages, there are also some individual device and class disadvantages such as insufficient IOP reduction and complications (e.g., device failure and adverse events). Larger randomized trials and real-world observational studies are needed for MIGS devices to better assess clinical and economic effectiveness.[350] (Evidence Grade: A)

3. Canaloplasty

Canaloplasty is a non-penetrating surgery for the reduction of IOP. It is a non-filtering, bleb-free, visco-canalostomy using a 360-degree tension suture within Schlemm's canal to restore the physiological outflow pathways of the aqueous humor. Canaloplasty is indicated in patients with mild to moderate POAG, and the combination with cataract phacoemulsification may provide further intraocular pressure reduction. Compared to trabeculectomy, however, canaloplasty is not as effective in lowering IOP but has less risk of complications.[351, 352]

4. Trabeculectomy

Trabeculectomy is commonly used to treat medically uncontrolled POAG. An alternative aqueous humor outflow path is surgically created from the anterior chamber through the sclera (guarded sclerectomy) to the sub-conjunctival space to create a filtering bleb from which fluid passes through the conjunctiva to the tear layer.

Long-term (up to seven years) complications of patients randomized to trabeculectomy in the CIGTS were mainly cataract. Extraction was noted to occur earlier and more frequently than for patients initially treated with medications. Rates of endophthalmitis and bleb-related complications such as bleb leak, hypotony and blebitis were all low.[353] (Evidence Grade: B) However, the potential efficacy of trabeculectomy must be weighed against the long-term risk of complications, especially endophthalmitis, when selecting treatments for patients. Although risks are low, they can lead to significant loss of vision if they occur. These are lifelong risks not just in the postoperative period.

A study in the United Kingdom found that after 20 years, 57% of patients who had trabeculectomy were classified as a complete success, 88% were classified as qualified success, and 15% had become blind. Patient age, preoperative topical medication use, glaucoma type and glaucoma severity independently influenced this outcome. Trabeculectomy surgery is therefore a long-term management option for IOP control.[354] (Evidence Grade: B)

5. Glaucoma Drainage Devices

Glaucoma Drainage Devices (GDD) compete with trabeculectomy in the treatment of advanced glaucoma or glaucoma resistant to medical and laser management. Also called "tube shunts," with many different names (e.g., Moltino, Krupin, Optimed, Baerveldt, Ahmed), these devices directly connect an eye's anterior chamber with the conjunctiva to bypass the TM and reduce IOP.

Both Ahmed and Baerveldt GDDs had similar surgical success measured at five years post-operative. Baerveldt GDDs resulted in greater IOP reduction but more early and serious complications than was encountered with patients receiving Ahmed valves.[355] (Evidence Grade: A) Known complications of GDDs include diplopia, endophthalmitis, superchoroidal hemorrhage, retinal detachment, hypotony, cataract, corneal edema, tube or plate erosion, hyphema, choroidal effusion, and superior orbital vein occlusion.

6. Ciliary Body Ablation

Ciliary body ablation or destructive procedures use diathermy, cryotherapy or ultrasound to directly damage the ciliary body of eyes with refractory severe glaucoma, impairing the ability to produce aqueous humor. Laser cyclophotocoagulation (CPC) has become the common method. However, such procedures are often a last resort after all other treatments have failed.

CPC procedures include transpupillary, transvitreal, endoscopic (performed from inside the eye and thus having less collateral ocular damage but more attendant risk from surgery), and transscleral, based on the different paths used to approach the ciliary body. Common complications include hypotony, intraocular inflammation, hemorrhage, and pain.

Patients treated with endocyclophotocoagulation (ECP) via the pars plana had lower IOPs, needed fewer glaucoma medications, and had a higher success (with up to two years of follow-up) than patients similarly treated via the limbus (anterior ECP), even after adjusting for other confounding factors such as degree of treatment, preoperative metrics, and whether or not the surgery was combined with phacoemusification.[356] (Evidence Grade: B)

E. Primary Open-Angle Glaucoma Progress Examination

Progress evaluations for POAG should be specific to each patient. Use of dynamic and personalized testing schedules can enhance the efficiency of POAG progression detection and reduce diagnostic delay, compared to fixed yearly monitoring intervals.[357] Patients who are early in their care process or who appear less stable might be followed every few weeks or months, while those who have "well-controlled" IOPs and seemingly stable ONHs and VFs should require less frequent visits. Treatment should be adjusted at each visit as needed. Delays in appropriate care for any reason can result in deterioration of vision.[358]

> ***Clinical note:*** *Patients with advanced glaucoma should be seen more often and treated more aggressively than patients with OH, or early or moderate glaucoma.[359]* (*Evidence Grade: B)*

Because glaucomatous progression is so highly variable, identifying factors that predict progression should guide both clinical practice and patient treatment and monitoring. Bilateral disease, higher baseline IOP and DH at baseline were risk factors for VF deterioration while older age, systolic OPP and CCT were not confirmed as progression risk factors in the UKGTS.[167] (Evidence Grade: A) Macular GCC focal loss as determined by SD-OCT and VF studies, along with thinner CCT values, are strong baseline predictors for determining rate of glaucoma progression.[360] (Evidence Grade: C)

CONSENSUS-BASED ACTION STATEMENT: The frequency and scope of follow-up examinations of persons diagnosed with primary open-angle glaucoma (POAG) should be individualized based on the severity and stability of their disease and should occur at regular intervals to monitor progression and treatment efficacy.

Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.

Benefits and Harms Assessment: Implementation of this recommendation is likely to result in the earlier diagnosis and treatment of any disease progression. The benefits of this recommendation were established by expert consensus opinion.

A progress evaluation (not a comprehensive eye and vision examination) should include:

- **Interval history** noting any changes in vision or general health, evaluation of medication utilization to assess patient adherence, and consideration of any symptoms or side effects.
- **Measurement of best corrected visual acuities**
- **Tonometry**

With periodic:

- **ONH evaluation** should be especially watchful for changes in the neuro-rim, disc vessels, and/or DH as signs of POAG progression.
- **RNFL and ONH imaging** should be repeated at least yearly for the first several years of follow-up.

- **Gonioscopy** should be assessed periodically and when there is a suspicion of anterior chamber angle abnormalities or if there is an unexplained change in IOP.

- **VF testing** should be conducted as needed to obtain sufficient information to identify patients who are rapidly progressing, gain a sense of each patient's variability, and establish a baseline. Semi-annual testing in the initial years following diagnosis may be a reasonable compromise for obtaining sufficient statistical power to rule out rapid VF progression while minimizing the testing burden.[361]

  Clinical note: *Patients with more advanced VF loss or presenting with mild damage at a younger age may require more frequent VF testing when considering risk factors for progression and factors such as age and life expectancy.[362] (Evidence Grade: C)*

CONSENSUS-BASED ACTION STATEMENT: Progress examinations of patients with primary open-angle glaucoma (POAG) should include, but are not limited to, an interval history and measurement of visual acuity and intraocular pressure (IOP), with periodic gonioscopy, optic nerve head (ONH) and retinal nerve fiber layer (RNFL) evaluations, and visual field (VF) testing.

Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.

Benefits and Harms Assessment: Implementation of this recommendation is likely to result in the earlier diagnosis and treatment of any disease progression. The benefits of this recommendation were established by expert consensus opinion.

F. Patient Self- or Home-based Monitoring

To assist in care, several devices are being developed for home use by patients with glaucoma. Both IOP and VF monitoring devices are being considered and may eventually prove useful in the care process.[363-366] Several studies suggest the use of tablet computers, smart phones and head-mounted functional testing devices as alternative, inexpensive, highly portable, and compact platforms for VF testing.[367-370]

IOP home monitoring may be feasible for some patients. Self-tonometry (e.g., rebound) has the potential to address an unmet need by more effectively engaging patients in their own care,[371] as well as providing IOP measurements over the entire diurnal cycle.[372] (Evidence Grade: C) Self-tonometry also has the potential to assist clinicians in both supporting the diagnosis and assessing the effectiveness of treatment earlier than the standard clinical review period of two-to-four weeks, hence reducing delays to effective reduction of IOP for patients initiating treatment.[364] (Evidence Grade: C)

Patient-measured rebound tonometry demonstrates good agreement with Goldmann applanation tonometry performed by clinicians and may be suitable for measurement of IOP outside of the clinical setting.[373] (Evidence Grade: C) However, one study suggests that it over-estimates IOP relative to Goldmann applanation tonometry measurments.[374] (Evidence Grade: C)

EVIDENCE-BASED ACTION STATEMENT: Patient self-monitoring of intraocular pressures (IOP) should be considered to help support the diagnosis and/or management of patients at risk for or diagnosed with primary open-angle glaucoma (POAG).[364,372,373]

Evidence Quality: Grade C. Study type(s): Case Control, Cohort-prospective, Diagnostic
Level of Confidence: Medium
Clinical Recommendation Strength: Recommendation. This recommendation should generally be followed but remain alert for new information.

<table>
<tr><td colspan="2"><u>Evidence Statements</u>:

Self-tonometry has the potential to assist clinicians in both supporting the diagnosis and assessing effectiveness of treatment earlier than the standard clinical review period of two to four weeks, hence reducing delays to effective reduction of intraocular pressure for patients initiating treatment.[364] (Evidence Grade: C)

IOP home monitoring may be feasible for some patients. The use of a rebound tonometry self-monitoring device has the potential to address an unmet need by providing more frequent IOP measurements over the entire diurnal cycle.[372] (Evidence Grade: C)

Patient-measured rebound tonometry demonstrates good agreement with Goldmann applanation tonometry performed by clinicians and may be suitable for measurement of IOP outside of the clinical setting.[373] (Evidence Grade: C)</td></tr>
<tr><td><u>Potential Benefits</u>: Provides more frequent monitoring of IOP and may reduce delays in initiating treatment.</td><td><u>Potential Risks/Harms</u>: None.</td></tr>
<tr><td colspan="2"><u>Benefit and Harm Assessment</u>: Benefits significantly outweigh harms.</td></tr>
<tr><td colspan="2"><u>Potential Costs</u>: Cost of IOP monitoring device.</td></tr>
<tr><td colspan="2"><u>Value Judgments</u>: None.</td></tr>
<tr><td colspan="2"><u>Role of Patient Preferences</u>: Large.</td></tr>
<tr><td colspan="2"><u>Intentional Vagueness</u>: None.</td></tr>
<tr><td colspan="2"><u>Gaps in Evidence</u>: Research to investigate the use of self-tonometry for the measurement of diurnal intraocular pressure fluctuation.</td></tr>
</table>

G. Initiation of Treatment and Patient Monitoring

1. Ocular Hypertension

The OHTS established that medically treating OH is efficacious in delaying or preventing the onset of glaucoma. However, not all patients with borderline or elevated IOP should receive medication.[67] (Evidence Grade: A) There is little absolute benefit of early treatment in low-risk OH patients.[9] (Evidence Grade: A) In addition, clear evidence does not exist that "intensive monitoring" is of benefit in persons with OH from a scientific or financial standpoint.[375] (Evidence Grade: A)

While early medical treatment of OH patients reduced the five-year incidence of POAG by 60% in the OHTS, the benefit of early treatment is greatest in high-risk OH patients. Clinicians should consider initiating treatment for individuals with OH who are at moderate or high risk for developing POAG.[67] (Evidence Grade: A). The use of a five-factor baseline risk model (age, IOP, CCT, larger C/D ratio and higher VF pattern standard deviation [PSD]) has reasonable accuracy in distinguishing high from low-risk OH patients. Clinicians and patients can decide on the potential benefit of early treatment based on risk level and patient age, health status, life expectancy and personal preference.[8] (Evidence Grade: B)

A risk calculator can assist in making treatment recommendations and thereby improve the consistency and confidence of clinician decision-making.[376] (Evidence Grade: C) The following link provides two methods that can be used to estimate the five-year risk of developing POAG. The predictions derived using these methods are designed to aid but not to replace clinical judgment.

Risk Calculators for Primary Open-Angle Glaucoma - American Academy of Ophthalmology (aao.org)

Patients with OH at low risk of conversion to POAG can generally be followed without treatment, as long as they are monitored regularly for signs of early disease.[8] (Evidence Grade: B) It is necessary to continually assess structural and functional parameters in OH patients to determine if POAG has developed and/or is progressing. Measuring the rate of structural change (e.g., rim area loss is faster in eyes that develop POAG) can provide important information for the clinical management of OH patients.[377] (Evidence Grade: A)

> ***Clinical note:*** *Observation of DH is a strong predictor of the subsequent conversion to POAG.[195] (Evidence Grade: B)*

In addition, OH eyes that develop POAG and display both optic disc and VF change, not necessarily concurrently, had significantly more rapid VF deterioration than eyes developing POAG but only displaying change in their VF or in their optic disc. In persons with OH, VF changes occur at only a small number of locations. Local change is more likely to cause Corrected Pattern Standard Deviation (CPSD) or Glaucoma Hemifield Test (GHT) change.[378] (Evidence Grade: B)

EVIDENCE-BASED ACTION STATEMENT: Early medical treatment should be considered for individuals with ocular hypertension (OH) who are at moderate or high risk of developing primary open-angle glaucoma (POAG).[8,9,67]	
Evidence Quality: Grade A. Study type(s): Randomized Clinical Trials, Case Control **Level of Confidence**: High **Clinical Recommendation Strength**: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: Clinicians should consider initiating treatment for individuals with OH who are at moderate or high risk for developing POAG.[67] (Evidence Grade: A) There is little absolute benefit of early treatment in low-risk OH patients.[9] (Evidence Grade: A) Patients with OH at low risk of conversion to POAG can generally be followed without treatment, as long as they are monitored regularly for signs of early disease. The use of a five-factor baseline risk model (age, IOP, CCT, larger C/D ratio and higher VF PSD) has reasonable accuracy in distinguishing high from low-risk OH patients. The benefit of early treatment is greatest in high-risk OH patients.[8] (Evidence Grade: B)	
Potential Benefits: Early treatment may reduce or delay onset of POAG.	**Potential Risks/Harms**: Side effects of medication.
Benefit and Harm Assessment: Benefits significantly outweigh harms.	
Potential Costs: Cost of medication.	
Value Judgments: None.	

Role of Patient Preferences: Moderate.
Intentional Vagueness: None.
Gaps in Evidence: None identified.

2. Primary Open-Angle Glaucoma

Monitoring POAG progression involves evaluation of both structural and functional changes. Differentiating clinically relevant disease progression from inherent variability and fluctuation is a major challenge in managing POAG. Worsening optic disc excavation, RNFL atrophy and deterioration in visual function are all evidence of the progression of glaucoma. If progression is confirmed, management needs to be modified or enhanced to prevent further irreversible loss of the patient's visual function.

a. Monitoring Structural Changes

There may be good agreement between structural (OCT) and functional (VF) tests used to evaluate glaucoma progression in early disease.[379] (Evidence Grade: C) Decreases in the RNFL may be helpful in monitoring early and moderate POAG, but OCT may not be as useful as SAP in advanced glaucoma.

Progressive structural OCT changes often proceed functional VF loss, and patients who show faster changes in OCT are at increased risk of worsening VF loss.[380] Characteristic patterns of the OCT deviation map can provide useful clues to distinguish glaucomatous changes from false-positive findings.

> ***Clinical note:*** *OCT is more likely to detect progression in early glaucoma; VF and stereo-disc photos may be better at detecting progression in advanced glaucoma.[381] (Evidence Grade: C)*

Progressive RNFL thinning is predictive of detectable functional VF decline in glaucoma,[382] (Evidence Grade: B) which suggests that RNFL thinning may indicate the need for more aggressive IOP-lowering. For detecting glaucomatous local RNFL progression, the OCT "region of interest" (a specific region around the ONH that was abnormal at an earlier visit) approach appears superior to global[383] (Evidence Grade: C) or circumpapillary[384] (Evidence Grade: C) RNFL thickness change.

> ***Clinical note:*** *OCT measured rate of structural ONH rim loss is five times faster in eyes that convert to POAG than in those that remain OH.[377] (Evidence Grade: A)*

OCT allows detection of localized and diffuse RNFL loss and measurement of RNFL thickness rate of change, which is beneficial in discerning glaucoma progression course, disease progression prediction, and evaluation of treatment response. The inferior temporal sector was the most frequent location showing progression.[385] (Evidence Grade: C) VF progression was related to OCT GPA RNFL topographic progression characteristics (widening or deepening pattern). Other topographic characteristics (e.g., location, size and shape) may also have utility in determining the risk of VF progression.[386] (Evidence Grade: B)

b. Monitoring Functional Changes

Numerous factors impact VF progression interpretation, such as reliability indices, fixation tracking and cognitive decline.[361] Cognitive decline was associated with increased VF variability in fixation losses, false positive and negative errors. Screening and monitoring cognitive dysfunction may be important in the assessment of glaucomatous VF progression as patient concentration and cooperation is increasingly affected. Clinicians may need to become more reliant on structural alterations to monitor for progression.[387] (Evidence Grade: B)

SAP remains the reference standard to detect glaucomatous VF progression. There is no evidence that short wavelength automated perimetry (SWAP) and frequency-doubling perimetry have any significant benefits over SAP in monitoring glaucoma progression.[388] (Evidence Grade: B)

It is important to retest unreliable or suspected progression of VFs to ensure repeatability. Interpretation of test results can be improved using statistical packages that analyze the data relative to age-matched norms (total deviation) or scan for focal defects by eliminating the influence of diffuse loss (pattern deviation). Due to the diffuse nature of early functional damage in glaucoma, relying on pattern deviation may underestimate the degree of damage which has occurred.[262] (Evidence Grade: B)

> ***Clinical note:** In eyes with manifest glaucoma, progression in the VF was detected first more than four times as often as progression in the optic disc in the EMGT. Among fellow eyes without VF loss at baseline, progression was detected first as frequently in the optic disc as in the VF.[263] (Evidence Grade: A)*

In a study of patients with treated POAG, DH was the single most significant predictor for VF deterioration.[389] (Evidence Grade: B) Rates of progressive VF loss in eyes with DH were significantly faster that in eyes without hemorrhages, confirming the role of DH as an important risk factor for glaucoma progression. Rates of functional loss after an episode of DH were significantly related to IOP reduction, suggesting a treatment benefit in decreasing progression rates in these eyes.[390] (Evidence Grade: B)

Both trend and event analyses can be used for establishing change within a series of VF evaluations. Event-based analyses take into account expected localized test-retest variabilities in sensitivity, and trend-based analyses are helpful for determining and predicting overall visual function.[391] Clinicians may benefit from reviewing the results of cluster trend analysis in addition to whole VF trend analyses and pointwise VF sensitivity for determining the rate of VF progression.[392] (Evidence Grade: C)

> ***Clinical note:** VF threshold values below 15-19 dB should be interpreted with caution as they may not be reliable for assessing the true level of damage or of glaucomatous progression.[393] (Evidence Grade: C)*

Both IOP-dependent and -independent factors affect POAG VF progression in treated glaucoma. Peak IOP is a better predictor of progression than is mean IOP or fluctuation, but other clinical information (e.g., ophthalmoscopy observed peripapillary atrophy) influences risk assessment for future progression.[394] (Evidence Grade: B) Treated glaucomatous eyes with documented optic nerve progression are at increased risk of visual field loss over time, with moderate agreement between the location of optic nerve change and the hemifield with the most rapid sensitivity decline. For a given similar rate of MD progression (conventionally measured in dB/year), eyes with different levels of baseline damage can have very different progression rates reflecting the rate of RGC and RNFL thickness loss leading to the need for customized individual progression concepts.[395] (Evidence Grade: B)

3. Normal Tension Glaucoma

The general principles of treatment for NTG patients do not differ from that of managing chronic POAG. Treatment should be directed at lowering the IOP substantially from what is thought to be a damaging level in that individual. NTG patients tend to progress more slowly and have a lower risk of rapid evolution to blindness than patients with POAG. High intragroup variability exists however, and specific treatment for all NGT patients should be guided by individual presentation and course.

Clinicians may initiate treatment of patients with mild to moderate NTG with PGAs without waiting for further progression.[396] (Evidence Grade: D) However, an initially non-glaucomatous fellow eye of a unilaterally NTG patient may be observed without treatment until or unless glaucoma can be diagnosed.[397] (Evidence Grade: B)

Distinguishing NTG from non-glaucomatous optic neuropathies is often challenging. Assessment of ONH cupping by OCT evaluation of the minimum rim width at Bruch's membrane opening suggests a way to discriminate between NTG from other ONH disease.[398] (Evidence Grade: C) The key to the assessment remains identifying the presence of optic nerve head cupping.

In one study of patients with NTG followed for an average of twelve years, the amount of IOP reduction using topical medications was related to NTG progression and lower percentage reduction in IOP was a consistent risk factor for progression. Disc hemorrhage was another important risk factor for NTG progression, implying the presence of a non-IOP-dependent mechanism.[399]

Some cases of NTG progress more rapidly than others. Although approximately half of cases in one study showed a confirmed localized VF deterioration by seven years, the change was typically small and slow, often insufficient to measurably affect the MD index.[400] In another study, over half of the patients with NTG showed glaucoma progression despite treatment after more than eight years. High peak IOP was a significant risk factor for progression. Identifying patients at risk may warrant closer follow up and more aggressive treatment in order to preserve visual function in patients with NTG.[151] (Evidence Grade: B)

H. Patient Education and Counseling

Educating patients about glaucoma and the use of medical, laser and/or surgical treatment in preventing blindness is vitally important.[401] Although there is a need for improved glaucoma education across all patients, those of a lower socioeconomic status may have a greater need for information about the disease.[402,403]

Patients with decreased health literacy skills also may benefit from educational efforts tailored to address their health literacy level and learning style.[404] (Evidence Grade: A) They may have poorer compliance, worse disease understanding, and greater disease progression compared to individuals with adequate health literacy.[405] (Evidence Grade: D) One study, however, found that individuals with lower health literacy did not appear to have worse overall vision-related quality of life compared to those with higher literacy.[406] (Evidence Grade: D)

> ***Clinical note****: Education programs for increasing glaucoma awareness and knowledge may be a key to improving quality of life in patients with glaucoma.[407] (Evidence Grade: D)*

Targeted educational interventions and counseling should focus on the patient's understanding of the risk of irreversible blindness from glaucoma, the long-term nature of treatment, and the importance of attending follow-up visits despite the lack of visual symptoms.[408] (Evidence Grade: C) Brief instructional sessions offered to newly diagnosed glaucoma patients can result in better one-year persistence.[409] (Evidence Grade: B)

Providing educational materials at a readable level (6-8th grade) may enhance patient understanding of treatment and management strategies and aid in self-care and adherence in POAG.[410] (Evidence Grade: A) In a study in both academic and community practice settings, about 30% of glaucoma patients had marginal or inadequate literacy skills. It found that patients better comprehend and were more receptive to educational materials written at 5th grade reading level with illustrations, regardless of initial literacy level.[411] (Evidence Grade: A)

Current doctor-patient communication is often physician-centered rather than patient-centered.[412] (Evidence Grade: B) Patient-centered physician-provided education and communication improves medical glaucoma therapy outcomes[413] (Evidence Grade: D) [414] (Evidence Grade: D) and patient satisfaction.[415] (Evidence Grade: D) Patient discussions should include open-ended questioning regarding medication use and recommendations for how to best fit the medication into the patient's life and address any identified barriers.[416] (Evidence Grade: D)

Patient communication, including question/answer discussions, are important with patients who have POAG to remove any barriers regarding medication use, improve their understanding of treatment strategies, and create an open, approachable relationship with their eye care provider.[417] (Evidence Grade: D) A simple validated questionnaire administered on arrival of a patient at glaucoma follow-up visits could allow issues impacting adherence to be immediately addressed.[418] (Evidence Grade: D)

Telephone-based counseling about glaucoma followed by mailed information, in addition to the usual physician delivered care and information, improved knowledge and reduced anxiety in newly diagnosed glaucoma patients.[419] (Evidence Grade: A) Intensive educational mailings to patients and their physicians alone, however, did not improve medication adherence in a large cohort of elderly glaucoma patients.[420] (Evidence Grade: A)

Patients' desires for personalized one-on-one discussions with clinicians, as well as printed and online materials, create an opportunity for doctors to provide and/or direct patients to high quality educational resources and thereby enhance patient self-management.[421] While it is important to discuss visual quality of life with all glaucoma patients, African American and younger patients were less likely to discuss this with their doctors.[422] (Evidence Grade: C)

> ***Clinical note***: *Clinicians should always educate, simplify medication regimens, and personally provide positive verbal reinforcement regarding medication use.[423] (Evidence Grade: B) [424] (Evidence Grade: A)*

1. Patient Adherence/Compliance

Poor adherence to prescribed glaucoma treatment protocols is quite common.[425] (Evidence Grade: B) It poses an ongoing[426] (Evidence Grade: A) and refractory challenge to treating clinicians,[427] especially when motivation is weak (e.g., when disease is mostly asymptomatic). Patients diagnosed with POAG are reported to be more compliant with pharmacotherapy than those diagnosed with OH.[428] (Evidence Grade: B) Although doctors recognize that nonadherence with glaucoma medication is a problem, most lack the skill set to identify non-adherent patients and the causes of nonadherence.

Poor adherence in POAG treatment often results in both VF and sensitivity loss as well as unnecessary additional medications and surgeries.[429] In the CIGTS, an increase in the number of visits at which a patient reported a missed medication dose was significantly associated with a decrease (worsening) in MD (estimated at 0.14 dB per missed dose visit).[430] (Evidence Grade: B)

> ***Clinical note:*** *Patient adherence to glaucoma medications over the first year of treatment tends to be indicative and reflective of adherence over subsequent years. Therefore, effective means of maximizing adherence during the first year of treatment will likely lead to better adherence thereafter.[431] (Evidence Grade: B)*

Multiple barriers to medication adherence exist, with low self-efficacy (lack of confidence) and forgetfulness being commonly reported factors.[432] (Evidence Grade: D) Additional factors that have been shown to contribute to medication nonadherence are listed in Table 4.

Table 4. Factors That Affect Medication Nonadherence

Cost of medication[433] (Evidence Grade: B)	Inability to correctly instill drops [434] (Evidence Grade: C)
Patient's age, sex and baseline IOP[435] (Evidence Grade: B)	Choice of therapy[436] (Evidence Grade: B)
Regimen complexity[437] (Evidence Grade: C)	Race/ethnicity[408] (Evidence Grade: C)
Socioeconomic status[438] (Evidence Grade: C) [402] (Evidence Grade: C)	Lack of social support, educational level[439] (Evidence Grade: C)
Higher level of glaucoma-related distress[439] (Evidence Grade: C) and psychosocial issues (such as depression and hypochondriasis)[440] (Evidence Grade: B)	Poor physician-patient communication[441]

> ***Clinical note***: *The bureaucratic and administrative hurdles insurers and pharmacy benefit managers use to motivate patients to switch from brand-name products to generics are often effective at persuading many patients to switch to the cheaper generic products; however, there is a subset of patients who are unable to*

effectively make the switch to the generic product. These patients, who end up going untreated, are at increased risk for worsening of their OAG and later ultimately may require costly surgical interventions.[433] (Evidence Grade: B)

Patients with lower health literacy are less likely to express medication related problems, side effects or poor adherence.[442] (Evidence Grade: D) Medication adherence likely improves with a comprehensive strategy consisting of both education and reminder systems.[443] (Evidence Grade: A) A multipronged approach using audio-visual aids to improve physician-patient communication along with an automated reminder system helps to improve glaucoma medication administration adherence.[444] (Evidence Grade: A)

When clinicians educate patients and assess their views about glaucoma and its treatment, patients report higher medication self-efficacy. Patients who ask more medication questions may have less confidence in their ability to overcome adherence barriers.[445] (Evidence Grade: B)

***Clinical note:** Numerous potential barriers can affect a patient's proper adherence to glaucoma medication. It is incumbent on the clinician to promote proper adherence, as well as utilize the patients' primary care physician in the promotion of adherence.*[446] (*Evidence Grade: B)*

EVIDENCE-BASED ACTION STATEMENT: Eye doctors should be persistent in providing education and training to patients with primary open-angle glaucoma (POAG) to improve adherence/compliance with recommended therapy.[408-410,416,417.423,424,443-445]

Evidence Quality: Grade B. Study type(s): Randomized Clinical Trials, Systematic Reviews, Cohort-prospective, Case Series, Cross-sectional
Level of Confidence: Medium
Clinical Recommendation Strength: Strong Recommendation.
This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements:
Medication adherence likely improves with a comprehensive strategy consisting of both education and reminder systems.[443] (Evidence Grade: A)

Providing education materials at a readable level (6-8th grade) may enhance patient understanding of treatment and management strategies and aid in self-care and adherence in POAG.[410] (Evidence Grade: A)

A multipronged approach using an audiovisual aid to improve physician-patient communication along with an automated reminder system helped to improve glaucoma medication administration adherence.[444] (Evidence Grade: A)

Clinicians should always educate, simplify medication regimens, and personally provide positive verbal reinforcement regarding medication use.[423] (Evidence Grade: B) [424] (Evidence Grade: A)

Brief instructional sessions offered to newly diagnosed glaucoma patients can result in better persistence rates over one year follow-up.[409] (Evidence Grade: B)

When clinicians educate patients and assess their views about glaucoma and its treatment, patients report higher medication self-efficacy. Patients who ask more medication questions may have less confidence in their ability to overcome barriers to adherence.[445] (Evidence Grade: B)

Targeted educational interventions and counseling should focus on the patient’s understanding of the risk of irreversible blindness from glaucoma, the long-term nature of treatment, and the importance of attending follow-up visits despite the lack of visual symptoms.[408] (Evidence Grade: C) Patient discussions should include open-ended questioning regarding medication use and recommendations by the physician for how to best fit the medication into the patient's life and address any identified barriers.[416] (Evidence Grade: D) Patient communication, including question/answer discussions, are important with patients who have POAG to remove any barriers regarding medication use, improve their understanding of treatment strategies, and foster an open, approachable relationship with their eye care provider.[417] (Evidence Grade: D)	
<u>Potential Benefits</u>: Counseling and educating patients may improve adherence to help maintain ocular health and visual function.	**<u>Potential Risks/Harms</u>**: None.
<u>Benefit and Harm Assessment</u>: Benefits significantly outweigh harms.	
<u>Potential Costs</u>: Direct and indirect costs of counseling and educational services.	
<u>Value Judgments</u>: None.	
<u>Role of Patient Preferences</u>: Moderate.	
<u>Intentional Vagueness</u>: None.	
<u>Gaps in Evidence</u>: Research to identify medication persistence rates in patients with glaucoma at different stages of disease progression.	

2. Medication Instillation Training

Education about how to administer glaucoma drops is positively associated with adherence.[423] (Evidence Grade: B) Most glaucoma patients may not be correctly instilling eye drops. This can lead to serious consequences resulting in reduced quality of life. It also highlights the importance of patient education with regard to eye drop instillation whenever glaucoma topical medications are prescribed.[447] (Evidence Grade: D)

Variability in the force required to apply drops from different bottle design,[448,449] as well as older age and worse visual acuities,[450] can lead to patients who are challenged to properly apply medications.[451] (Evidence Grade: B) In one study, increasing age was found to be an independent risk factor for the inability to correctly instill drops resulting in considerable wasting of doses.[434] (Evidence Grade: C)

Poor eye drop technique is a significant impediment to achieving good control of intraocular pressure in glaucoma. Showing a short clinical education video when patients are prescribed eye drops is likely to improve their drops installation techniques significantly.[452] (Evidence Grade: A) Positive value was found in eye drop technique videos, especially those about performing punctal occlusion, closing the eye after instillation, correctly mixing medication, cap hygiene, not touching the eye and installing the drop accurately.[453] (Evidence Grade: B) There is often sufficient wait time during both new and return evaluations which could be utilized for key portions of glaucoma education such as eye drop instillation technique(s).[454] (Evidence Grade: B)

Additional approaches to enhancing medication compliance may include:

- Educational workshops[455] (Evidence Grade: D) and organized patient support groups which enhance all aspects of compliance/adherence (e.g., drug utilization, appointment keeping, prescription refills[456] and health literacy).[457,458]

- Use of automated, interactive, telephone-based reminder protocols.[459,460] (Evidence Grade: A)

- A glaucoma logbook may influence glaucoma knowledge, possibly due to enhanced engagement.[461] (Evidence Grade: D)

- An eye drop satisfaction questionnaire used as a tool to evaluate adherence problems that need to be addressed.[462] (Evidence Grade: D)

- A modest adherence-contingent rebate can provide a financial incentive to significantly improve medication adherence rates.[463] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Patients with primary open-angle glaucoma (POAG) who are prescribed pharmacologic treatment should receive instructions on eye drop instillation.[423,447,452,453]

Evidence Quality: Grade B. Study type(s): Randomized Clinical Trial, Cohort-prospective, Cross-sectional
Level of Confidence: Medium
Clinical Recommendation Strength: Recommendation. This recommendation should generally be followed but remain alert for new information.

Evidence Statements:

Showing a short clinical education video when patients are prescribed eye drops is likely to improve their drop instillation technique significantly.[452] (Evidence Grade: A)

Positive value was found in eye drop technique videos, especially those about performing punctal occlusion, closing the eye after instillation, correctly mixing medication, cap hygiene, not touching the eye and instilling the drop accurately.[453] (Evidence Grade: B)

Education about how to administer glaucoma drops and patient glaucoma medication adherence self-efficacy are both positively associated with adherence.[423] (Evidence Grade: B)

Most glaucoma patients may not be correctly instilling eye drops. This can lead to serious consequences resulting in reduced quality of life of patients. It also highlights the importance of patient education with regard to eye drop instillation whenever glaucoma topical medications are prescribed.[447] (Evidence Grade: D)

Potential Benefits: Better adherence to and efficacy of treatment.	**Potential Risks/Harms**: None.

Benefit and Harm Assessment: Benefits significantly outweigh harms.

Potential Costs: Direct and indirect costs of counseling and education.

Value Judgments: None.

Role of Patient Preferences: Moderate.
Intentional Vagueness: None.
Gaps in Evidence: None identified.

3. Low Vision Rehabilitation and Counseling

Low vision rehabilitation emphasizes care for people who have degraded visual function such as reduced visual acuity, VFs, or contrast sensitivity to the point that restoration of previous visual skills with standard optical corrective techniques like glasses and contact lenses or surgical procedures is no longer possible. Low vision is a deficit in one or more of the three primary visual functions leading to less-than-optimal quality of life:

- Visual acuity generally in the range of 20/60 to 20/400
- VF deficit to 20 degrees diameter or impacting potential to use VF for planning and/or execution of a task for which VF is essential
- Contrast sensitivity deficit resulting in unsatisfactory functional ability to perform daily tasks.

Individuals with glaucoma are at increased risk of chronic vision loss, subsequent functional impairment, and resultant disability. Visual impairment has physical, psychological, behavioral, and social consequences that affect patients, their family, friends, and caregivers. Health care providers and stakeholders may be unaware of the overall impact of vision loss on the health and well-being of the patient.

Providing counseling to maximize patients' independence at work, home, and in the community should be considered. Concurrent with medical interventions, vision rehabilitation services, including disease education, are of great value and can be provided by doctors of optometry as well as other professionals. Many patients with impaired vision can attain access to additional benefits and services.[464] (Evidence Grade: D)

Persons with glaucoma-related vision loss should be evaluated to determine their potential to benefit from low vision rehabilitation. This process provides the only currently available treatment option for patients with chronic vision loss. Vision rehabilitation can help individuals with vision loss attain maximum function, independence, and quality of life.

I. Socioeconomic Considerations

1. Access and Cost of Care

The socioeconomic burden from glaucoma increases significantly as the disease progresses.[465] Access to professional glaucoma care and treatment is often affected by affordability[466] as well as availability. Frequency of examinations and likelihood of laser or surgical treatment all increase with glaucoma progression, leading to increased costs of care. Early POAG assessments and treatments that decrease or prevent progression should have a social economic benefit.[467]

Medical social workers can play a pivotal role in helping glaucoma patients overcome barriers to care, which are numerous and include lack of insurance, doctor visit costs, poor transportation, and language issues.[468] (Evidence Grade: C)

2. Lifestyle

Enhanced lifestyle strategies, especially those affecting cardiovascular factors such as obesity, diabetes, and sleep apnea, may directly enhance the treatment of several eye diseases including POAG.[469] (Evidence Grade:

D) However, there is currently insufficient evidence that changing lifestyle habits (e.g., environmental factors, behaviors like exercise, and diet) has a proven effect on the progression of glaucoma.[470,471] It is possible that lifestyle plays an important role, yet the lack of robust randomized controlled trials currently precludes any definite conclusions. Awareness of the possible influences of certain habits, however, should help guide clinical advice on an individual patient basis.[470]

J. Alternative/Complementary Medicine

There is little evidence-based medicine that assesses whether alternative and complementary therapies may prevent glaucoma or slow down POAG progression.[472] POAG patients should be educated on the primary role of IOP reduction in POAG management so that alternative and complementary therapies which lack robust effectivity evidence are not used to replace conventional and evidence-based treatments.[473]

Some patients may want to use medical marijuana (cannabis) to treat glaucoma even though scientific evidence does not support more than a possible modest and transient effect on IOP with numerous reported adverse systemic and ophthalmic effects.[474-477] (Evidence Grade: D) Even when patients have been counseled and educated, many may still believe in the treatment, especially when they are dissatisfied with their other treatment options.[478,479]

It is impossible to draw reliable conclusions from available data to support the use of acupuncture for the treatment of glaucoma.[480] There is some evidence that sleeping in a 30 degree head-up position lowers nocturnal IOP.[481] (Evidence Grade: C). Also, meditation, although not an FDA-approved intervention for glaucoma, may be a useful adjunctive therapy for POAG patients through stress reduction.[482]

Nutritional supplementation, especially with flavonoids or forskolin, holds considerable theoretical promise in glaucoma treatment, especially as an adjunct to IOP-lowering therapy.[483] (Evidence Grade: A) Oral nutritional supplements such as vitamins (e.g., B_1, B_2), ginkgo biloba and resveratrol also have theoretical promise for glaucoma (or concomitant secondary OSD[484]) treatment but to date have shown no real superiority to conventional treatments.

Oral antioxidant supplementation with or without omega-3 fatty acids does not appear useful as an adjuvant treatment for mild/moderate POAG in the short term[485] (Evidence Grade: B). However, forskolin and rutin given as oral treatment appear to contribute to a better control and a small reduction of IOP in patients who were poorly responsive to maximum tolerated medical treatment.[486] Anthocyanins and ginkgo biloba extract may be helpful in improving NTG patients' visual function.[487] (Evidence Grade: C) While promising, these effects have yet to be validated or generally accepted.

K. Telehealth

Eye care delivery systems strive to improve quality while reducing costs and removing barriers to care such as travel time.[488] (Evidence Grade: B) Telehealth/telemedicine programs (including tele-glaucoma initiatives) may contribute toward reaching this goal, particularly among underserved populations at-risk for chronic blinding diseases.[489] (Evidence Grade: D)

Telehealth ranges from patient self-administered screening [e.g., computer-tablet VF[490] (Evidence Grade: D) or self-tonometry in selected cases[491]] to clinical batteries of tests administered by technical personnel with remote professional decision-making, to digital sensors used to confirm eyedrop medication utilization, provide reminders and notifications, and aid in medication administration.[492] While diagnostic results in tele-glaucoma are in fair to good agreement compared to in-person care, sensitivity is very variable. As there is only fair agreement between remote and in-person glaucoma assessments, remote assessment alone may be inappropriate for the management of glaucoma.[493] (Evidence Grade: D)

When compared to in-person care, tele-glaucoma is more time and cost-effective, shows high patient satisfaction and fair to good agreement with in-person care; however, there is great variation in the reported sensitivity of tele-glaucoma screening, warranting further studies to establish its efficacy. For glaucoma management, both sensitivity and specificity must be further improved before being employed extensively.[494] (Evidence Grade: A)

[AOA_Policy_Telehealth.pdf]

The following results have been reported from several studies utilizing tele-glaucoma care:

- Telehealth may be an effective screening tool for glaucoma, specifically for remote and underserved communities [495] (Evidence Grade: B) and between one third and one half of patients had favorable attitudes towards using telemedicine for glaucoma care.[496]

- A virtual glaucoma clinic was found to offer a safe, logistically viable option for professional care decisions in selective patients with glaucoma of low progressive risk for significant visual loss.[497]

- Good correlation was noted for diagnosis into “no glaucoma,” “glaucoma,” and “glaucoma suspect” between subjects evaluated through a set of tele-glaucoma stations (without either VF or anterior segment examination) and clinical exams.[498]

- Low-risk POAG suspects were followed for two years by tele-evaluation of vision, IOP and OCT assessment of the RNFL and only referred for more thorough evaluation if evidence of progression was noted. Patient satisfaction and retention were both high and the number of patients who met the criteria for additional care and treatment were similar to the results of the OHTS study.[499]

- A comprehensive tele-glaucoma protocol (remotely provided by optometrists or comprehensive ophthalmologists with decision making by glaucoma specialists) showed high reliability with respect to clinical decision making and treatments, was cost effective, and demonstrated both high patient satisfaction and improved wait times for evaluation.[500]

EVIDENCE-BASED ACTION STATEMENT: Ocular telehealth programs can provide increased access to care but should not be used alone or for the assessment or management of moderate or advanced disease in patients with primary open-angle glaucoma (POAG).[493-495]

Evidence Quality: Grade B. Study type(s): Systematic Review, Cross-sectional, Cohort-prospective
Level of Confidence: High
Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements:

There is great variation in the reported sensitivity of tele-glaucoma screening, warranting further studies to establish its efficacy. For glaucoma management, both sensitivity and specificity must be further improved before being employed extensively.[494] (Evidence Grade: A)

Telehealth may be an effective screening tool for glaucoma, specifically for remote and under-served communities.[495] (Evidence Grade: B)

As there is only fair agreement between remote and in-person glaucoma assessments, remote assessment alone may be inappropriate for the management of glaucoma.[493] (Evidence Grade: D)

Potential Benefits: Increased access to care.	**Potential Risks/Harms**: Patients may mistakenly equate telehealth screening with an in-person eye examination.

Benefit and Harm Assessment: Benefits equal harms.

Potential Costs: Direct and indirect cost of testing.
Value Judgments: None.
Role of Patient Preferences: Large.
Intentional Vagueness: None.
Gaps in Evidence: Research on the sensitivity and specificity of telehealth screening and management services for patients with primary open angle glaucoma.

L. Conclusion

Primary open-angle glaucoma (POAG), the most common type of glaucoma, is a serious and significant public health concern, and a leading cause of permanent vision loss in the United States. Most cases of vision loss from POAG occur pain-free and without warning signs. As such, the disease has historically been referred to as the "silent thief of vision." Early in the disease process, glaucoma commonly degrades peripheral vision. If the disease progresses and the patient goes untreated, or not treated aggressively enough, central vision can also be compromised with the possibility of total loss of vision or legal blindness. These changes in vision are permanent.

High quality peripheral and central vision are essential components to maintaining quality of life. Progressive vision loss due to POAG and the other forms of glaucoma are a significant economic burden to the individual and to society. Treatment is aimed at stabilizing the condition. However, no medication, laser treatment or surgical intervention is capable of restoring vision lost from glaucoma.

Certain risk factors such as family history, increasing age, certain racial populations, decreased socioeconomic status, limited access to eye care, history of eye trauma, and an extensive list of systemic health conditions increase the risk of developing glaucoma. All individuals need to be made aware of these risk factors and the benefits of early diagnosis and treatment.

Technologies to detect glaucoma in its earliest stages are continually improving. Annual in-person, comprehensive eye and vision examinations with an emphasis on patient education and access to diagnostic resources is the best way to identify the disease in its early phases. If the disease advances despite treatment, some patients may be referred to other eye care providers for additional intervention to slow progression. In cases of POAG with vision loss, patients may be referred to providers who specialize in vision rehabilitation or low vision services.

Doctors of optometry make up the frontlines of glaucoma diagnosis and treatment and as such should continually educate themselves and their patients on the most current forms of glaucoma management. With early diagnosis and treatment, doctors of optometry can lessen the burden of glaucoma related vision loss in the United States and improve patient's quality of life.

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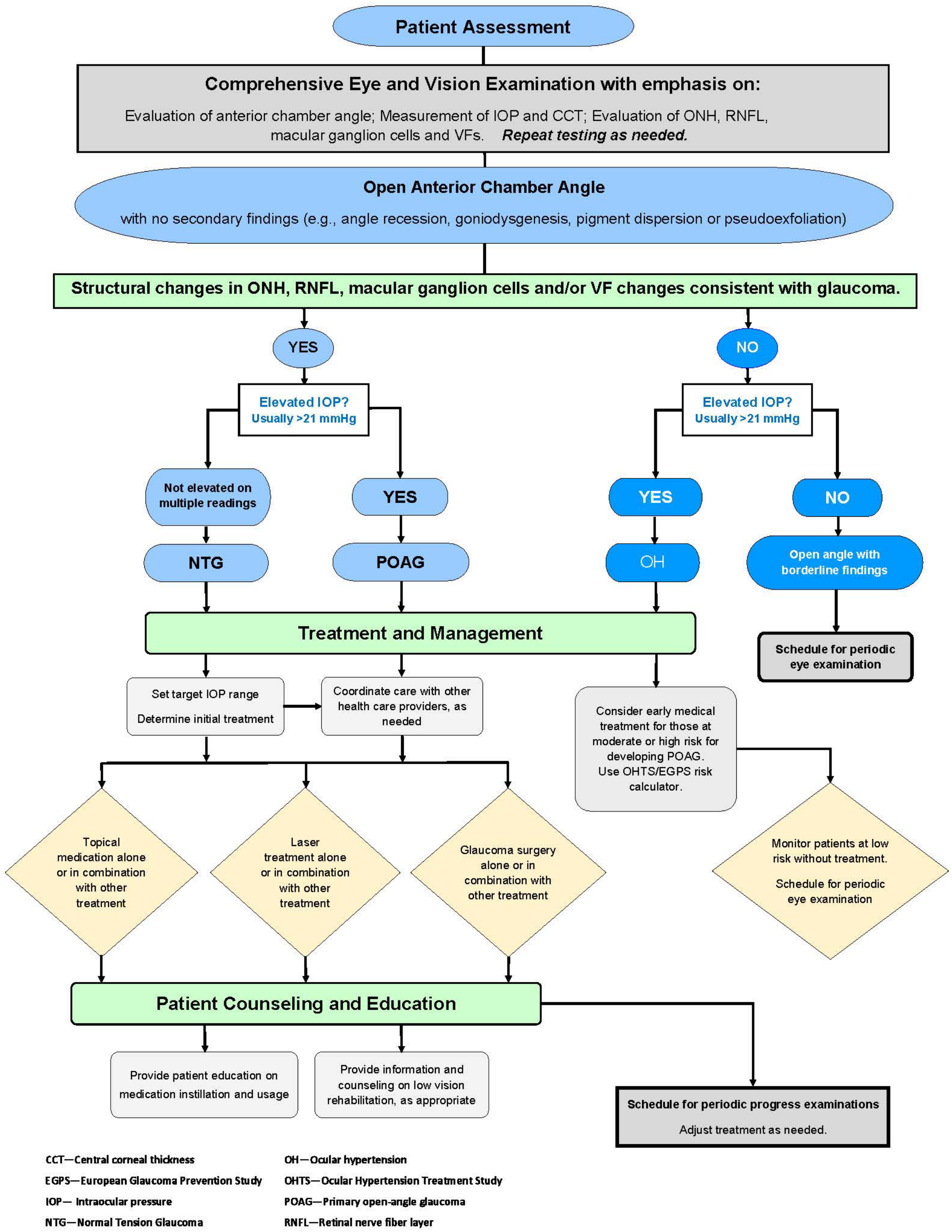
VI. APPENDICES

Appendix 1: Optometric Management of the Patient with Open-Angle Glaucoma: A Flow Chart



Appendix 2: Abbreviations/Acronyms

ACG	Angle closure glaucoma
AGIS	Advanced Glaucoma Intervention Study
ALT	Argon laser trabeculoplasty
AOA	American Optometric Association
APON	Acquired pits of the optic nerve
AS-OCT	Anterior segment-optical coherence tomography
β-BLOCKERS	Beta blockers
BMO-MR	Bruch’s membrane opening-minimum rim area
BP	Blood pressure
CAI	Carbonic anhydrase inhibitors
CCT	Central corneal thickness
C/D	Cup-to-disc
CIGTS	Collaborative Initial Glaucoma Treatment Study
CNTGS	Collaborative Normal Tension Glaucoma Study
CPC	Cyclophotocoagulation
CPG	Clinical practice guideline
D	Diopter
dB	Decibel
DH	Disc hemorrhage
DM	Diabetes mellitus
EBO	Evidence-based optometry
EMGT	Early Manifest Glaucoma Trial
FDA	GSS
GCA	Ganglion cell analysis
GCC	Ganglion cell complex
GCIPL	Ganglion cell-inner plexiform layer
GDD	Glaucoma drainage devices
GDG	Guideline Development Group
GDRG	Guideline Development Reading Group
GSS	Glaucoma staging systems
HRQOL	Health related quality of life
IOM	Institute of Medicine
IOP	Intraocular pressure
IPL	Inner plexiform layer
LALES	Los Angeles Latino Eye Study
LiGHT	Laser in Glaucoma and Ocular Hypertension Trial
MD	Mean deviation
MIGS	Minimally-invasive glaucoma surgery
MMC	Mitomycin-C
mmHg	Millimeters of mercury
NASEM	National Academies of Sciences, Engineering, and Medicine
NTG	Normal tension glaucoma

OAG	Open-angle glaucoma
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
OH	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
ONH	Optic nerve head
OPP	Ocular perfusion pressure
OSA	Obstructive sleep disorder
OSD	Ocular surface disease
PGA	Prostaglandin analogs
POAG	Primary open-angle glaucoma
PSD	Pattern Standard Deviation
QoL	Quality of life
RGC	Retinal ganglion cell
RNFL	Retinal nerve fiber layer
SAP	Standard automated perimetry
SD-OCT	Spectral domain-optical coherence tomography
SLT	Selective laser trabeculoplasty
TM	Trabecular meshwork
TVT	Tube Versus Trabeculectomy Study
UKGTS	United Kingdom Glaucoma Treatment Study
VEGF	Vascular endothelial growth factor
VF	Visual field

Appendix 3: Gaps in Research Evidence

During the development of this guideline, the Evidence-based Optometry GDG identified the following gaps in evidence as potential areas for future research:

- Research to develop more sensitive and reliable indicators for glaucoma progression.
- Research to develop clinically useful measures of ocular perfusion pressure and its influence on glaucoma progression.
- Research to determine the utility of anterior segment-optical coherence tomography (AS-OCT), including longitudinal studies to determine the significance of eyes classified to have closed angles by AS-OCT but open by gonioscopy.
- Research to investigate the use of self-tonometry for the measurement of diurnal intraocular pressure fluctuation.
- Research to evaluate the complex relationship between glaucoma medication and ocular surface disease.
- Research to identify medication persistence rates in patients with glaucoma at different stages of disease progression.
- Research to identify the optimal strategy to detect RNFL progression with the RNFL thickness map.

- Research to investigate the utility and validity of clinical testing outside the office setting (home monitoring)

- Research on new visual field parameters aimed at reducing variability and improving patient acceptance.

- Research on current medical treatments compared with surgery, particularly for people with severe glaucoma and in ethnic groups.

- Research to determine how best to apply rate of change information to the individual ocular hypertensive patient.

- Research to investigate the role of deep layer microvasculature damage in the pathophysiology of glaucoma.

- Research on the sensitivity and specificity of telehealth screening and management services for patients with POAG.

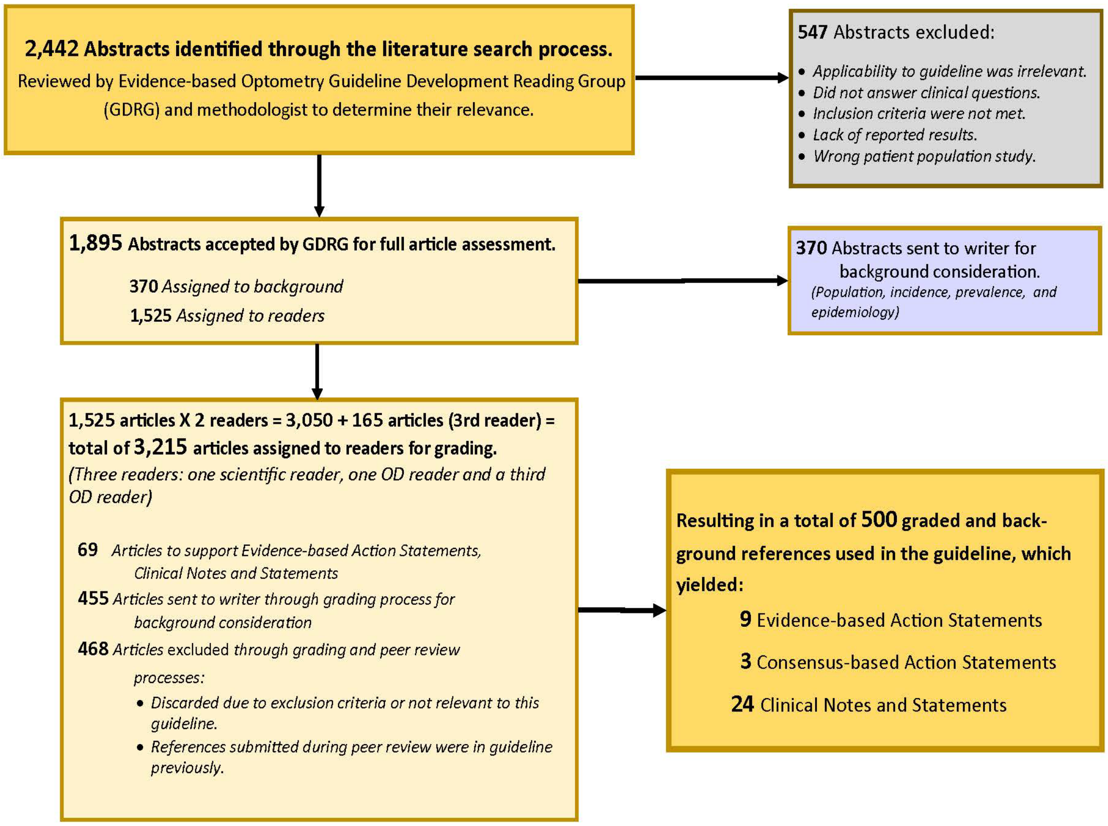
- Research on the impact of diet/lifestyle on risks for POAG.

VII. METHODOLOGY FOR GUIDELINE DEVELOPMENT

This guideline was developed by the AOA Evidence-based Optometry Guideline Development Group (GDG). Clinical questions to be addressed in the guideline were identified and refined during an initial meeting of the GDG and served as the basis for a search of the clinical and research literature.

An English language literature search for the years 2009 to 2023 was conducted by a trained researcher. If the search did not produce results, the search parameters were extended an additional 5 years, and subsequently 10 years back. In addition, a review of selected earlier research publications from 1970 to 2000 was conducted to provide background support for the “Natural History of Primary Open-Angle Glaucoma” section of the guideline. The literature search was conducted using the following electronic databases:

- Centers for Disease Control and Prevention, National Center for Health Statistics
- Cochrane Library
- Google Scholar
- Ovid MEDLINE
- PubMed
- VisionCite
- Scopus



All references meeting the criteria were reviewed to determine their relevance to the clinical questions addressed in the guideline. They were assigned to three readers who independently reviewed and graded the quality of evidence and the clinical recommendations for each article, based on a previously defined system for grading quality.

During thirty-six articulation meetings of the Evidence-based Optometry Guideline Development Reading Group (GDRG), all evidence was reviewed and clinical recommendations were developed. Grading for the recommendations was based on the quality of the research and the benefits and risks of the procedure or therapy recommended. Where direct scientific evidence to support a recommendation was weak or lacking, a consensus of the GDRG members was required to approve a recommendation.

At the draft reading meeting of the Evidence-based Optometry Guideline Development Group (GDG), the guideline document was reviewed and edited and the completed draft was approved by the GDG by conference call. The approved draft of the guideline was then made available for peer and public review for 30 days for numerous stakeholders (individuals and organizations) to make comments. All suggested revisions were reviewed, and, if accepted by the GDG, incorporated into the final guideline.

The guideline will be periodically reviewed and updated as new scientific and clinical evidence becomes available.

VIII. EVIDENCE-BASED OPTOMETRY GUIDELINE DEVELOPMENT GROUP

AOA Evidence-based Optometry Committee

- Carl Urbanski, O.D., *Chair – Private Practice, Family Vision Care of Kingston, Kingston, Pennsylvania*
- Diane Adamczyk, O.D. – *Professor, Director of Residency Education, State University of New York College of Optometry, New York, New York*
- John F. Amos, O.D., M.S. – *Emeritus Dean and Professor, UAB School of Optometry, University of Alabama at Birmingham, Birmingham, Alabama*
- Benjamin Casella, O.D. – *Private Practice, Casella Eye Center, Augusta, Georgia*
- Michael Chaglasian, O.D. – *Associate Professor, Illinois College of Optometry, Chicago, Illinois*
- Mitchell Dul, O.D., M.S. – *Professor, Department of Biologic and Vision Science, State University of New York College of Optometry, New York, New York*
- Bonnie Gauer, O.D., M.S. – *Private Practice, Roseburg, Oregon*
- Bennett McAllister, O.D. – *Associate Professor, Western University of Health Sciences College of Optometry, Pomona, California*
- Breanne McGhee, O.D. – *Ochsner Medical Center, New Orleans, Louisiana*
- Beatrice Reed, O.D. – *Retired, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas*
- Trennda Rittenbach, O.D. – *Technology-based Eye Care Services (TECS) VA Medical Center, Gig Harbor, Washington*
- Sean McKeown, O.D. – *Tri-County Vision, Willimantic, Connecticut*
- Gregory S. Wolfe, O.D., MPH – *Southern College of Optometry, The Eye Center, Memphis, Tennessee*

Multidisciplinary and Patient Stakeholders

- Christie Burdek – *Patient Advocate, O'Fallon, Missouri*
- Kellie Cannon – *Patient, Florissant, Missouri*
- Scott LaBorwit, MD – *Assistant Professor, Wilmer Eye Institute, John Hopkins University School of Medicine, Towson, Maryland*
- Danica Marrelli, O.D. – *Clinical Professor, Director, Ocular Diagnostic and Medical Eye Service University of Houston Optometry, Houston, Texas*
- Pinakin Davey, O.D., PhD. – *Professor, College of Optometry Western University of Health Services, Pomona, California*

Non-voting Members

- Barry Weissman, O.D., PhD. – *Editor/Writer, Emeritus Professor, Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, and Retired Professor of Optometry, Southern California College of Optometry at Marshall B. Ketchum University, Fullerton, California*
- Stephen C. Miller, O.D. – *Assistant Editor/Writer, Innovative Writing Works, St. Louis, Missouri*
- Beth Kneib, O.D. – *Former Director, Clinical Resources Group, American Optometric Association, Seattle, Washington*
- Andrew Morgenstern, O.D. – *Director, Clinical Resources Group, American Optometric Association, Alexandria, Virginia*
- Alisa G. Krewet – *Senior Coordinator, Quality Improvement, American Optometric Association, St. Louis, Missouri*
- Liway Arceo – *Former Coordinator, Quality Improvement, American Optometric Association, St. Louis, Missouri*

Scientific Readers, Non-voting Members

- Daniel Cho, MD, PhD – *Craniofacial Plastic Surgery Fellow, University of Pennsylvania*, *Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*
- Jasna Despot, MS – *St. Louis, Missouri*
- Julia Frantz, BA – *St. Louis, Missouri*

- Angela Minic, MS – *Thornton, Colorado*