

Unmet Needs in the Detection, Diagnosis, Monitoring, Treatment, and Understanding of Primary Open-Angle Glaucoma: A Position Statement of the American Glaucoma Society and the American Society of Cataract and Refractive Surgery

J. Crawford Downs, PhD - *Birmingham, Alabama*

David Fleischman, MD, MS - *Chapel Hill, North Carolina*

on behalf of the 2020–2022 Research Committee of the American Glaucoma Society and the 2020–2022 Glaucoma Clinical Committee of the American Society of Cataract and Refractive Surgery

Glaucoma is a common ophthalmic disorder characterized by typical optic nerve damage and vision loss. It is most commonly associated with elevated or dysregulated intraocular pressure (IOP), although there is evidence that other factors contribute to the disease. Glaucoma is a leading cause of irreversible blindness worldwide. Its prevalence in the United States is approximately 1900 per 100 000 persons aged > 40 years, and the condition is responsible for upward of 9 million clinic visits each year.^{1–3} In the United States, where the annual spending on optic nerve disorders is estimated at \$5.8 billion,⁴ glaucoma is a significant public health concern. The American Glaucoma Society (AGS) and the American Society of Cataract and Refractive Surgery (ASCRS) are committed to bringing greater attention to the current challenges that exist in the detection, diagnosis, monitoring, treatment, and understanding of open-angle glaucoma.

Background

Individually and collectively, our organizations include and represent thousands of patients and the leading clinical and scientific experts in the fields of ophthalmology and glaucoma:

1. The AGS is composed of > 1300 glaucoma specialists dedicated to sharing clinical and scientific information for the benefit of patients, colleagues, fellows, and residents. Together with other health care organizations, the AGS serves as an important patient advocacy force to promote glaucoma awareness among policymakers and the general population.
2. The ASCRS is an international educational society with nearly 8000 ophthalmic surgeons. Its mission is to empower anterior segment surgeons to improve the vision, outcomes, and quality of life (QoL) for their patients through innovative approaches to education, advocacy, and philanthropy.

Members of these societies provide clinical care and conduct research aimed at better understanding, treating,

and curing glaucoma. Despite significant recent advances, there are still substantial deficits in each of these categories, herein described as “unmet needs.”

Specific Areas of Unmet Need

The AGS and ASCRS work collaboratively with patients, providers, payors, and federal and state governments to better address the clinical burdens of glaucoma. We are also committed to advancing the state of the art in glaucoma treatment, with the support of the research community. A review of current evidence examining the diagnosis and management of glaucoma has identified key challenges to the effective treatment of glaucoma. Collectively, we urge researchers, clinicians, and other stakeholders to implement strategies that address these gaps, with the goal of increasing the effectiveness and efficiency of glaucoma treatment and clinical management.

The following **6 key areas of unmet needs** are listed in a logical but arbitrary order, whereas the specific unmet needs listed in each numbered section below are given in the priority order as determined by unanimous consent of the AGS Research Committee. This is a dynamic list that will be reviewed and updated regularly as needs are addressed and new unmet needs are identified, as specified in the [Appendix](https://doi.org/10.1016/j.ogla.2022.02.008) (available at www.ophtalmologyglaucoma.org).

1. Primary open-angle glaucoma (POAG) manifests as a group of related neurodegenerative conditions acting through varying eye-specific pathophysiologic processes that share some common elements: retinal ganglion cell axonal damage that is believed to occur primarily at the optic nerve head, which frequently results in clinical cupping of the optic nerve head and the particular pattern of permanent visual field loss typical of the disease. The course of POAG can be relatively aggressive, manifesting in just a few years, but more commonly vision loss is slow, occurring over many years and even decades. Due to the complexity and diversity of POAG etiology and its manifestation, coupled with the difficulty in the clinical assessment of risk factors and

detection of disease onset and progression, screening and management remain very challenging. In addition, there are significant numbers of patients in whom POAG goes undetected until significant permanent vision loss has occurred. Many patient populations do not have sufficient access to highly trained clinicians who can adequately manage POAG and its associated vision loss. Hence, **unmet needs in POAG screening and management** are as follows:

- i. Improve glaucoma screening techniques and methods to ensure a follow-up in those who screen positive. Attempt to minimize false positives and negatives. Develop strategies to best deploy screening in populations at high risk when appropriate.
 - ii. Improve telemedicine for glaucoma management such that it is viable for clinical practices.
 - iii. Develop improved assessment and characterization of POAG, with a focus on disease definition and staging.
2. The complexity of POAG etiology and its manifestations, coupled with the lack of methods to accurately quantify known risk factors and the insensitivity and variability of gold-standard visual function testing, combine to make it difficult to definitively diagnose POAG onset and accurately monitor its progression. Although new imaging and diagnostic modalities have greatly improved eye care in recent years, these approaches have been slow to benefit POAG diagnostics and monitoring. As a result, the relationships between risk factors and POAG susceptibility, onset, and progression require further investigation. Hence, **unmet needs in POAG diagnostics and monitoring** are as follows:
- i. Develop robust, sensitive biomarkers for POAG susceptibility, onset, and progression, with a focus on detecting disease early and identifying those patients at the greatest risk of progression.
 - ii. Develop safe, accurate 24-hour IOP telemetry/monitoring technologies.
 - iii. Develop new technologies to accurately and sensitively assess visual and retinal ganglion cell function, with a focus on early and reliable change detection using patient-friendly methods.
3. Although many POAG risk factors have been identified, the relationships between these risk factors and POAG susceptibility, onset, and progression require further elucidation. Lowering IOP is the only accepted treatment for the disease, and yet many patients with glaucoma never present with an elevated IOP. In addition, the pathways through which these factors act to damage retinal ganglion cell axons remain largely unknown. Hence, **unmet**

needs in understanding the pathophysiology of POAG are as follows:

- i. Develop an in-depth understanding of non—IOP-related factors that contribute to POAG susceptibility, onset, and progression, with a focus on the following:
 - a. Vascular perfusion/ocular perfusion pressure
 - b. Cellular and molecular pathways
 - c. Cerebrospinal fluid pressure
 - d. Ocular biomechanics
 - e. Retinal ganglion cell soma and axonal health
 - f. Genetic factors
 - ii. Develop an in-depth understanding of IOP-related factors that contribute to POAG susceptibility, onset, and progression, with a focus on nocturnal IOP effects, IOP fluctuations, IOP control mechanisms, and their manifestations at the tissue, cellular, and molecular levels.
 - iii. Further develop high-fidelity model systems for studying POAG pathogenesis and treatment approaches.
4. Therapeutics for lowering IOP, the only accepted clinical treatment for POAG, could be improved, especially in challenging patients who do not adequately respond to current therapies or those in whom IOP is already within the normal range. In addition, there are many other potential pathways that could be targeted to slow or arrest the progression of POAG that do not involve modulating IOP. Hence, **unmet needs in POAG therapeutics** are as follows:
- i. Develop methods to improve patient compliance and medication adherence, with a focus on sustained-release drug delivery systems that reduce the need for patient compliance/adherence and pharmacogenetic approaches to assess which drugs will work best in a particular patient.
 - ii. Develop additional and/or more effective IOP-lowering therapies.
 - iii. Develop non—IOP-related therapeutics focused on the following:
 - a. Neuroprotection
 - b. Ocular blood pressure/flow/perfusion maintenance and modulation
 - c. Intracranial/cerebrospinal fluid pressure modulation
 - d. Neural regeneration and synaptogenesis
 - e. Stem cell therapy/cell reprogramming
 - f. Biomechanical reinforcement
 - iv. Develop new invasive and noninvasive surgical approaches or co-therapies that improve patient outcomes and reduce long-term failure rates.
5. Maintenance and improvement of QoL of patients with POAG is the eventual goal of clinical glaucoma

management. Hence, **unmet needs in patient outcomes and QoL** are as follows:

- i. Improve vision rehabilitation among patients with advanced glaucoma-related vision loss.
- ii. Improve the definitions and characterization of clinically relevant POAG progression and its direct impact on vision-related QoL.
- iii. Develop a glaucoma-specific QoL questionnaire that can be used to assist in measuring the true impact of this disease on patients. This QoL

questionnaire could also help in standardizing further research efforts.

6. To achieve the aforementioned goals, we will also need to **improve the development of clinician-scientists**, as well as **further educate the public about glaucoma** and the importance of regular clinical wellness visits with glaucoma screening.

As research and innovation in the field advance, it is vital that public health policy and coverage standards develop in parallel. We expect that efforts to overcome the clinical challenges outlined here will be a key marker of successful treatment and management of glaucoma.

Footnotes and Disclosures

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures: J.C.D.: Grants – National Institutes of Health (R01-EY027924 and R01-EY026035); Payment or Honoraria for Lectures – University of Florida (research symposium lecture), University of Wisconsin – Madison (visiting faculty lecture), NC Specialty Eye Physicians Annual Symposium (research symposium lecture); Support for Travel – University of Wisconsin – Madison (visiting faculty travel costs reimbursement); Research Committee Member – American Glaucoma Society.

D.F.: Grants – Optopol (PI for industry-sponsored study on Optopol perimeter vs Zeiss SFA); Payment or Honoraria for Lecture – Osler Review Course (lecture on glaucoma).

This manuscript was reviewed and approved by the American Glaucoma Society Board of Directors and does not follow the standard editorial process of Ophthalmology Glaucoma.

Correspondence:

J. Crawford Downs, PhD, Department of Ophthalmology and Visual Sciences, University of Alabama at Birmingham, 1670 University Boulevard, Volker Hall 390A, Birmingham, AL 35294-0019. E-mail: cdowns@uabmc.edu.

References

1. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol*. 2004;122:532–538.
2. Schappert SM. Office Visits for Glaucoma: United States, 1991-92. *Vital and Health Statistics, No. 262*. Washington, DC: Centers for Disease Control and Prevention and National Center for Health Statistics; 1995.
3. Lee PP, Walt JG, Doyle JJ, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol*. 2006;124:12–19.
4. Wittenborn JS, Zhang X, Feagan CW, et al. The economic burden of vision loss and eye disorders among the United States population younger than 40 years. *Ophthalmology*. 2013;120:1728–1735.