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Review Article

A Comprehensive Systematic Review of Glaucoma: Diagnosis, Management, and Emerging Trends in Artificial Intelligence

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Abstract

Glaucoma is a progressive and often asymptomatic condition that leads to irreversible vision loss if left untreated, earning it the label of "the silent thief of sight." Slow disease progression often results in delayed diagnosis. Treatment approaches for glaucoma range from pharmacological interventions to laser therapies and surgical procedures with the primary goal of reducing intraocular pressure (IOP). This review examines the current landscape of glaucoma diagnosis and treatment, highlighting the role of newer drug delivery techniques, advancements in laser and surgical options, and emerging use of artificial intelligence (AI) for enhanced patient outcomes. AI has made impressive progress in the field of glaucoma in recent years, with various machine learning models applied to diagnose glaucoma based on fundus photographs and optical coherence tomography, promising earlier detection and better patient management.

The prognosis of glaucoma is highly dependent on the stage at which it is detected, and the extent of optic nerve damage at the time of diagnosis. Early detection significantly improves the outcome, with proper treatment able to slow or halt the disease progression. The prognosis is generally favorable as long as the patients strictly adhere to their prescribed treatment regimen.

By analyzing both traditional and innovative therapeutic approaches, this study highlights the importance of personalized and targeted treatment to maximize the efficacy of glaucoma management. The incorporation of emerging technologies, particularly AI, represents a promising direction for improving the accuracy of diagnosis and enhancing future treatment strategies.

Introduction

Glaucoma is a group of disorders characterized by progressive optic neuropathy that leads to irreversible vision loss if left untreated [1]. Glaucoma is the leading cause of irreversible blindness worldwide, affecting approximately 80 million people [2]. Although primarily seen in adults, glaucoma also significantly affects the pediatric population, with more than 300,000 children affected globally, contributing to 5% of childhood blindness cases [3]. The management of glaucoma includes a variety of approaches such as medication (eye drops and oral pills), laser surgery, traditional incisional surgery, or a combination of these treatments [4]. In adults, medical management typically serves as the first-line treatment with topical medications such as beta-blockers or prostaglandin analogs, which are often prescribed. Rapid advancements in medical therapies have led to exponential improvements in glaucoma care. However, several challenges still remain [5,6]. Emerging therapies are gaining attention, in addition to conventional treatments. Evidence supporting dietary supplementation as an adjunctive treatment is growing and presents a novel approach to managing this disease [7]. Furthermore, innovations in drug delivery systems, such as smart gels with various in situ formulation mechanisms, aim to improve therapeutic outcomes by addressing drug bioavailability issues, a persistent challenge in glaucoma treatment [8]. Future directions in glaucoma therapy may focus on targeting neuroprotective pathways, such as glutamate inhibition, along with continued efforts to resolve the bioavailability limitations of the current treatments. These advancements represent promising steps towards more effective long-term management and potentially reduce the global burden of blindness caused by glaucoma [9].

The advent of artificial intelligence (AI) has revolutionized glaucoma care by introducing novel tools for diagnosis, treatment, and prognosis; promising earlier detection; personalized therapy; and improved patient outcomes.

1. Etiology of Glaucoma

The etiology of glaucoma is complex and multifactorial, involving a combination of genetic predispositions and environmental influences. Despite advances in research, the exact mechanisms underlying glaucomatous neurodegeneration remain incompletely understood, although several key risk factors are well-established [10].

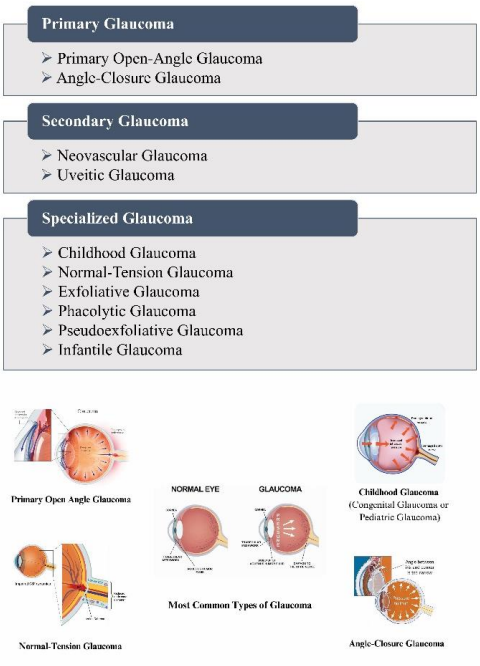

Figure 1: Overview of Glaucoma Classification.

The most common types of glaucoma include Primary Open-Angle Glaucoma (OAG), Angle-Closure Glaucoma (ACG), Childhood Glaucoma, and Normal-Tension Glaucoma (NTG). These types differ in their pathophysiology but all share the hallmark features of optic nerve damage. On the other hand, less common forms of glaucoma, such as Exfoliative Glaucoma, Neovascular Glaucoma, Phacolytic Glaucoma, Pseudoexfoliative Glaucoma, Infantile Glaucoma, and Uveitic Glaucoma, represent a smaller subset of cases, but are equally important to understand in clinical practice.

2. Glaucoma Diagnostic Approaches

2.1. Clinical Diagnostic Techniques

The diagnosis of glaucoma relies on a comprehensive assessment that includes measuring intraocular pressure (IOP), evaluating visual function, and examining the retinal structure. The key diagnostic methods employed in clinical practice include tonometry, which is used to measure (IOP) and is crucial for glaucoma diagnosis. Elevated IOP is a significant risk factor for the development and progression of glaucoma, although it is important to note that glaucoma can occur even at normal IOP levels. Stereoscopic slit-lamp examination allows for detailed visualization of the optic nerve head, helping to

identify characteristic changes such as "cupping," which refers to the concavity of the optic nerve head that can indicate glaucomatous damage. Optical Coherence Tomography (OCT) is a non-invasive imaging technique that provides high-resolution cross-sectional images of the retina to assess the degeneration of the retinal nerve fiber layer (RNFL), which is primarily composed of axons from retinal ganglion cells (RGCs). Evaluation of the RNFL is essential for detecting the structural changes associated with functional impairment in vision. In conjunction with structural assessments, visual field testing is performed to evaluate functional impairment in vision and detect localized loss of peripheral vision, such as arcuate scotomas, which are indicative of glaucoma. Together, these diagnostic approaches enable clinicians to diagnose glaucoma accurately and monitor its progression, thereby ensuring timely intervention and management [20].

2.1.1. Optic Disk Photography

Stereoscopic optic nerve head (ONH) photography is a straightforward and cost-effective technique that offers a full-color, three-dimensional view of the optic nerve head. It is one of the most commonly used methods for objectively assessing morphological damage in patients at a risk of glaucoma. This technique allows clinicians to visualize structural changes in the optic nerve head, aiding the early detection and monitoring of glaucomatous damage. The high-resolution images obtained can be invaluable for tracking disease progression over time and for making informed treatment decisions [21].

2.1.2. Confocal Scanning Laser Ophthalmoscopy (CSLO)

Confocal Scanning Laser Ophthalmoscopy (CSLO) is an advanced imaging technology designed to provide quantitative, three-dimensional composite visualization of the optic nerve head (ONH) and posterior segment of the eye. This non-invasive technique allows for detailed assessment of the ONH and surrounding retinal structures, enabling clinicians to detect early glaucomatous changes. CSLO uses a laser to scan the eye and produces high-resolution images that can reveal subtle morphological alterations that may not be apparent with other imaging modalities. By analyzing these images, healthcare professionals can monitor disease progression and make informed treatment decisions based on precise structural changes[22].

2.1.3. Scanning Laser Polarimetry (SLP)

Scanning laser polarimeter (SLP) is a non-invasive imaging technique that objectively assesses the thickness of the retinal nerve fiber layer (RNFL). This measurement reflects the health of the ganglion cell layer, which extends from the fovea to optic disc. By analyzing RNFL thickness, clinicians can detect early signs of glaucomatous damage because reductions in RNFL thickness are indicative of retinal ganglion cell loss. SLP provides valuable information for monitoring disease progression and assessing the effectiveness of therapeutic interventions, making it an essential tool for the comprehensive evaluation of glaucoma patients [23].

2.1.4. Optical Coherence Tomography (OCT)

Optical Coherence Tomography (OCT) uses low-coherence interferometry to produce high-resolution cross-sectional images of tissue structures, thereby effectively providing optical biopsy. This non-invasive imaging technique allows for detailed visualization of the retinal layers, including the retinal nerve fiber layer (RNFL) and ganglion cell layer, which are crucial in the assessment of glaucoma. OCT enables clinicians to detect subtle structural changes associated with glaucoma, facilitating the early diagnosis and monitoring of disease progression. In addition, OCT technology has advanced to include retinal ganglion cell analysis and macular thickness measurements, further enhancing its utility in glaucoma management by providing comprehensive data on retinal health [24].

2.1.5. Role of AI in Glaucoma Diagnosis

With the accumulation of clinical data of healthy and glaucomatous eyes and the advent of the artificial intelligence (AI) revolution, deep/machine learning models can be developed to aid clinicians in diagnosis, treatment, and prognosis [25]. For example, Muhammed et al. developed a deep-learning diagnostic model capable of distinguishing between glaucomatous and healthy suspect eyes. This was done by leveraging the OCT scan data of 102 eyes; 57 and 45 of which were previously distinguished by clinicians as glaucomatous and healthy eyes. The model performed better than standard OCT and visual field assessments, with accuracies ranging from 63.7% to 93.1%. This indicates that with further improvement, similar models could potentially be used as

reliable diagnostic tools [26]. Similarly, Li et al. leveraged visual field data from 1,352 patients and developed a deep learning model that was able to distinguish between glaucomatous and healthy eyes, outperforming human clinician judgment [27].

2.2. Biomarkers in Glaucoma Diagnosis

2.2.1. Ciliary Neurotrophic Factor (CNTF)

Ciliary Neurotrophic Factor (CNTF) is a neurotrophic factor that plays a crucial role in supporting neuronal proliferation, differentiation, survival, and function. It exhibits neuroprotective properties, specifically in retinal ganglion cells (RGCs). However, the levels of CNTF were significantly diminished in the tear film and aqueous humor of glaucoma patients. This reduction correlates strongly with glaucoma severity, as indicated by the visual field loss, highlighting the potential of CNTF as a biomarker of disease progression. Monitoring CNTF levels may provide valuable insights into the neurodegenerative processes underlying glaucoma and may aid in assessing the effectiveness of therapeutic interventions [28].

2.2.2. Kallikrein and Angiotensin Converting Enzyme (ACE)

Kallikrein and angiotensin-converting enzyme (ACE) activities have been detected in the aqueous humor and tears of glaucoma patients. Furthermore, preclinical studies have suggested that ACE inhibitors, which inhibit the renin-angiotensin system, may effectively reduce intraocular pressure (IOP) when administered locally. This finding highlights the potential of targeting the renin-angiotensin system as a therapeutic strategy for managing glaucoma. By understanding the roles of kallikrein and ACE in the pathophysiology of glaucoma, clinicians can develop more effective treatment approaches for lowering IOP and preserving vision [29].

2.2.3. Superoxide Dismutase (SOD) and Glutathione Transferase (GST)

The levels of superoxide dismutase (SOD) and glutathione transferase (GST) in the aqueous humor were significantly reduced in patients with glaucoma compared with those in control subjects. Conversely, the levels of nitric oxide synthase and glutamine synthase are significantly elevated in patients with glaucoma [30]. Additionally, another study reported a notable increase in glutathione peroxidase activity and SOD levels in the aqueous humor of glaucoma patients. In parallel, low SOD-1 expression was detected in the serum of individuals with glaucoma [31]. Glutathione S-transferase (GST) is present in both glial and neuronal cells within the central nervous system and retina. Elevated levels of autoantibodies against GST observed in certain patients with primary open-angle glaucoma (POAG) may indicate a widespread response to tissue stress or damage caused by glaucomatous neurodegeneration, resulting in secondary production of GST-specific antibodies in the affected retina [32].

2.2.4. Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF)

The Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF), members of the neurotrophin family, play critical roles in regulating neuronal survival, growth, and function within the central and peripheral nervous systems, particularly the survival of retinal ganglion cells (RGC). A study [33] indicated that serum levels of BDNF and NGF were significantly lower in the early and moderate stages of glaucoma, suggesting that both factors may be further investigated as potential circulating biomarkers for the early detection of glaucoma [33]. Moreover, BDNF levels in the tears of patients with normal-tension glaucoma were significantly reduced compared to those in normal individuals, indicating its potential as a diagnostic biomarker for early identification of this condition. BDNF can cross the blood-brain barrier, allowing blood BDNF levels to reflect its concentration in the brain. Serum BDNF levels were measured using an enzyme-linked immunosorbent assay (ELISA) in patients with primary open-angle glaucoma (POAG) and controls, demonstrating that serum BDNF could serve as an effective biochemical marker for the early diagnosis of POAG [35].

2.2.5. Other Biomarkers

Various biomarkers have been implicated in glaucoma, including metalloproteinases (MMPs), tissue metalloproteinase inhibitors [36], S100-A8 [37], and pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-12, and tumor necrosis factor (TNF)-α. Additionally, T helper (Th)1 cytokines (Interferon (INF)-γ, IL-2) and Th2 cytokines (IL-5, IL-10, IL-4) have also been associated with this condition [38]. One study has demonstrated that

glaucoma is linked to elevated levels of ferritin, an iron-regulating protein. Furthermore, both inflammation and oxidative stress have been shown to correlate with serum ferritin levels [39].

2.3. Specific Diagnostic Tools for Different Types of Glaucoma

2.3.1. Primary Open Angle Glaucoma (POAG)

2.3.1.1. α-HSD

A study investigated the presence of decreased 3α-HSD activity in peripheral blood lymphocytes of patients with primary open-angle glaucoma (POAG). These findings indicate a correlation between reduced 3α-HSD activity in peripheral lymphocytes and POAG independent of antiglaucoma treatment. The study concluded that lower levels of 3α-HSD activity in readily obtainable peripheral blood lymphocytes could serve as a potential marker for POAG or for individuals at a risk of disease progression. [40].

2.3.1.2. Endothelin 1

endothelin-1 plays a functional role in the pathophysiology of glaucoma by promoting vasoconstriction and reducing the outflow of the aqueous humor. Increased levels of endothelin-1 have been observed in the tear film of patients with primary open-angle glaucoma (POAG) compared to healthy controls. Specifically, tear endothelin-1 levels were elevated 2-3 times in patients with POAG as well as in those with proliferative diabetic retinopathy [41].

2.3.1.3. ANGPTL7

ANGPTL7 has been identified as potentially linked to primary open-angle glaucoma (POAG) in proteomic analysis of trabecular meshwork (TM) tissue [42]. The hypothesis that ANGPTL7 contributes to the pathophysiology of POAG is supported by findings indicating that ANGPTL7 concentrations are higher in the aqueous humor (AH) of eyes with POAG. The authors concluded that elevated TGF-β2 levels in glaucomatous aqueous humor might lead to increased ANGPTL7 expression, which could cause changes in collagen or contribute to the development of POAG through other mechanisms. [43].

2.3.1.4 Apoptosis Stimulating Fragment (FAS)

Interactions between the apoptosis-stimulating fragment (FAS) ligand and its receptor have been shown to play a significant role in the death of retinal ganglion cells (RGCs) and the onset and progression of primary open-angle glaucoma (POAG). Furthermore, a separate study observed differences in protein expression in the tears of patients with primary open-angle glaucoma and pseudoexfoliative glaucoma (PEXG), emphasizing the inflammatory pathways common to both conditions, while revealing a distinct pattern of phosphorylated Cystatin-S that differentiates the two diseases [44].

2.3.1.5. Transforming Growth Factor β2 (TGF-β2)

Given the critical role of the extracellular matrix (ECM) in the trabecular meshwork (TM) in regulating intraocular pressure (IOP), proteins in the aqueous humor associated with the TM ECM may serve as significant biomarkers for glaucomatous pathology. For example, transforming growth factor β2 (TGF-β2), which is integral to regulating ECM composition and the TM actin cytoskeleton, has been detected at elevated levels in the aqueous humor of patients with primary open-angle glaucoma (POAG). Furthermore, higher concentrations of TGF-β2 correlate with increased resistance to aqueous outflow from the TM, thereby contributing to elevated IOP [45-46].

2.3.1.6. Glycosaminoglycans

Researchers have assessed serum immunoreactivity to glycosaminoglycans and used immunohistochemistry to analyze the distribution patterns of glycosaminoglycans in the optic nerve head of eyes with primary open-angle glaucoma (POAG) compared with control subjects. The authors found that these autoantibodies increased the susceptibility of the optic nerve head to damage by altering the functional properties of the lamina cribrosa, blood vessels, or both [43].

2.3.1.7. Antibody Against Neuron Specific Enolase (NSE)

It has been proposed that anti-NSE antibodies reach the retina via the bloodstream, contributing to retinal ganglion cell damage, exacerbating the loss of visual fields, and increasing intraocular pressure (IOP) [47].

2.3.1.8. AP4A

AP4A protects against ischemic injury in the cerebral cortex via anti-apoptotic mechanisms. In addition, AP4A exerts positive effects on dopaminergic neurons. Selective binding sites for AP4A have been identified in the substantia nigra and striatum [48]. A recent study investigated the role of AP4A in POAG, revealing that AP4A is present in the human aqueous humor (AH), with significantly elevated concentrations in patients with POAG compared to controls. [49].

2.3.1.9. Caspase-14

Caspase-14 is a member of a highly conserved family of cysteinyl aspartate-specific proteinases, which primarily play roles in inflammation and apoptosis. Unlike most caspases, which are widely expressed, caspase-14 is predominantly localized in cornifying epithelia such as the skin. Its stimulation is associated with cornification, suggesting its involvement in the final stages of keratinocyte differentiation. Recent research indicates that caspase-14 may also contribute to the apoptosis of ocular tissues in primary open-angle glaucoma (POAG) by directly inducing the activation of caspase-8 and caspase-9 in vitro [50].

2.3.2. Normal Tension Glaucoma

2.3.2.1. Axonal Transport

Research on glaucoma in humans has demonstrated compromised axonal transport in retinal ganglion cells (RGCs). It is widely recognized that axonal transport is crucial for survival [40].

2.3.2.2. Alcadein (Alc) and Retinal Ganglion Cell

Both Alcα and amyloid precursor protein (APP) function as cargo receptors for the kinesin-1 motor protein, which plays a crucial role in fast anterograde axonal transport. A significant loss of retinal ganglion cells (RGCs) was observed in Alcα-deficient adult mice [51].

3. Treatment Approaches for Glaucoma

3.1. Managing Primary Open-Angle Glaucoma (POAG))

3.1.1. Treatment Goals and Target IOP

Given that glaucoma currently has no cure, its primary goal is to delay the progression of neuropathy and further deterioration of the visual field to a level where the patient's quality of life remains stable and unimpaired over time. It has long been accepted that this can be achieved by decreasing intraocular pressure (IOP), the only modifiable risk factor for POAG [52-56, 63, 86]. It has been estimated that every 1 mmHg reduction in IOP correlates with a 10-19% reduction in the risk of further deterioration of neuropathy [60-62]. Thus, sustaining IOP within a specified range, along with stabilizing the optic nerve, retinal nerve fiber layer (RNFL), and visual fields, constitutes the main treatment goal according to the most recent guidelines [54, 64, 86].

Reduction in IOP is accepted as the major treatment goal for POAG, regardless of whether the IOP is elevated [54, 55, 64]. However, for normal-tension glaucoma (NTG), a growing body of evidence suggests that multiple modifiable factors are involved, indicating that NTG is a multifactorial disease [57]. This finding challenges the belief that IOP is the sole modifiable risk factor of NTG.

Various factors other than IOP, such as oxidative stress, endothelial dysfunction, ocular blood flow, abnormal regulation of blood vessels, and disruption of the connection between nerves and blood vessels, can lead to optic nerve damage, similar to that observed in small-vessel diseases [57]. Moreover, the "Dual-pressure theory" has recently been proposed, suggesting that low intracranial pressure (ICP) levels relative to IOP might be an additional risk factor worth addressing [58]. These factors indicate the need for new treatment approaches targeting IOP, ICP, and vascular factors, which have already been recognized as important [57, 58]. However, none of these approaches have been clinically proven, and the gold standard for POAG treatment is the lowering of IOP, even when it is not above the statistical baseline [59, 64].

When setting the target IOP range, it is assumed that the patient’s current IOP contributes to optic neuropathy, and could result in further visual field loss if left untreated. Therefore, IOP should be lowered and maintained within

Table1: Types of Glaucoma and their causes.

Type of Glaucoma	Etiology (Causes)
A) Most Common	
Open-Angle Glaucoma (OAG)	- Multifactorial: Age-related changes in drainage system (trabecular meshwork), genetics, race (African Americans at higher risk), medical conditions (diabetes, high blood pressure, sleep apnea), eye injuries/inflammation [11].
Angle-Closure Glaucoma (ACG)	- Narrow angle between iris and cornea obstructs drainage, causing sudden IOP rise. Anatomic factors (shallow anterior chamber, farsightedness), medications dilating the pupil (pupillary block) [12].
Childhood Glaucoma	- Congenital anomalies in the eye's drainage system andConditions like Sturge-Weber syndrome or neurofibromatosis [12].
Normal-Tension Glaucoma (NTG)	- Poor blood flow to the optic nerve, possibly due to vascular dysregulation. Susceptibility of the optic nerve to damage even at normal IOP [13].
B) Less Common (Rare)	
Exfoliative Glaucoma	- Pigment flakes from iris clog drainage channels [14].
Neovascular Glaucoma	- Abnormal blood vessel growth on iris/drainage angle disrupts fluid outflow (complication of diabetic retinopathy, severe uveitis, retinopathy of prematurity) [15].
Phacolytic Glaucoma	- Lens fragments after cataract surgery obstruct drainage angle [16].
Pseudoexfoliative Glaucoma	- Protein material within the eye (not just iris) obstructs drainage (likely genetic and environmental factors) [17].
Infantile Glaucoma	- Congenital drainage angle abnormalities prevent proper fluid drainage [18].
Uveitic Glaucoma	- Chronic eye inflammation (uveitis) causes scarring, blocking drainage channels [19].

an estimated range in which significant visual field loss is less likely to impair the quality of life. This target should be individualized for each patient, and can be adjusted during the course of treatment based on specific circumstances. Generally, an IOP reduction of 20-30% has been proven to be efficacious. Greater or lesser

reductions may be justified depending on the existence of additional risk factors, extent of neuropathy, patient tolerance for treatment, and estimated life expectancy. Unfortunately, no high-quality evidence comparing different target IOP levels is available, nor is there a consensus on an algorithm to guide clinical decisions regarding lowering or increasing the designated target IOP [54, 55, 64, 86].

3.1.2. Treatment Options

There are three well-established treatment modalities available to practitioners: pharmacotherapy, laser therapy, and incisional surgery. The initial treatment regimen should be based on a personalized approach, considering factors such as target IOP, degree of neuropathy, patient preference, existing comorbidities, and potential side effects.

3.1.3. Pharmacotherapy

Pharmacotherapy, the least invasive option, is the first-line treatment for most patients [54,64]. There are two primary mechanisms by which pharmacotherapy can reduce intraocular pressure (IOP): enhancing aqueous humor (AH) outflow through either conventional or unconventional pathways or decreasing AH production in the ciliary bodies [63]. Pilocarpine and systemic oral carbonic anhydrase inhibitors (CAIs) are the mainstay of glaucoma pharmacotherapy. We have developed safer and more effective alternatives, including prostaglandin analogs, beta-blockers, topical CAIs, alpha agonists, and Rho kinase inhibitors. These newer options facilitate the successful maintenance of the desired IOP with fewer medications and side effects [55]. The most prominent FDA-approved medications are shown as follows: (Table 1)

American and Japanese guidelines recommend initiating therapy with a single medication (monotherapy), because multiple-drug therapies may increase side effects and reduce patient adherence [54,64]. If the initial monotherapy fails to achieve the target IOP or becomes intolerable, switching to another monotherapy is advised. If the target IOP remains unachieved or intolerable, fixed combination therapy should be considered. It is essential to recognize that when multiple medications are required to maintain IOP, alternative treatment modalities (lasers or surgery) should also be evaluated.

Prostaglandin analogs (PGAs) are typically used as first-line therapy due to their excellent efficacy, tolerability, and suitability for many patients (once-daily dosing regimen) [54,64]. A recent meta-analysis showed that PGAs confer the strongest IOP-lowering effect as monotherapy compared with other options [65-67]. Generally, PGAs reduce IOP by enhancing the outflow of aqueous humor via an unconventional pathway, which is a significant advantage. They promote aqueous humor outflow instead of inhibiting its production, ensuring that vital nutrients continue to reach avascular structures of the anterior segment. This not only lowers IOP, but also stabilizes IOP fluctuations, which is a critical factor in reducing the risk of further neuropathy deterioration [63].

The first PGA (latanoprost) was approved by the FDA in 1996, and is often considered a benchmark for other prostaglandin analogs. Following latanoprost, additional PGAs such as bimatoprost, travoprost, and tafluprost have been introduced, each with unique structural modifications that enhance their efficacy and tolerability [60,63].

Generally, PGAs are well tolerated with fewer systemic adverse effects; however, they can cause localized side effects, such as excessive eyelash growth and iris and eyelid pigmentation [54,63,64]. Concerns have also been raised regarding their long-term efficacy since most PGAs do not target the primary outflow pathway through the trabecular meshwork (TM). To address this, a new PGA, latanoprostene bunod (LBN), was introduced in 2017, incorporating an NO-donating moiety that enhances AH outflow through both TM and unconventional pathways. A recent meta-analysis indicated that LBN numerically outperformed latanoprost, and was comparable to bimatoprost. Additionally, a novel PGA selective for the EP2 receptor, omidenepag isopropyl (OMDI), was introduced in 2022, significantly reducing the side effects associated with previous PGAs (FP receptor agonists) [63]. Selective EP2 agonists have been shown to be non-inferior to FP agonists and may serve as effective first-line monotherapies. However, it is important to note that the concomitant use of both combination therapy regimens is not recommended [64].

Beta-adrenergic receptor blockers (β-blockers) can also be employed as first-line monotherapies because of their efficacy and relatively low cost [64]. They primarily

reduce IOP by decreasing AH production via blocking sympathetic receptors in the ciliary body epithelium. Selective β1 blockers may be preferred over their non-selective counterparts in patients with asthma or obstructive pulmonary disease. Notably, nighttime dosing of beta-blockers correlates with reduced efficacy and further visual field deterioration [54]. Additionally, traces of topical beta-blockers may enter systemic circulation, leading to unwanted side effects. This can be mitigated by gentle punctal occlusion or eyelid closure for 2 min after administration [55].

Rho kinase inhibitors represent a new class of medications that has recently been introduced for glaucoma treatment. They lower IOP by targeting the Rho kinase pathway, leading to increased AH outflow through the conventional pathway, and reduced episcleral venous pressure. One notable example is netarsudil, which gained the FDA approval in 2017. A recent meta-analysis revealed that netarsudil is not only clinically non-inferior to well-established β-blockers but also has a superior safety profile [68]. Another meta-analysis comparing the efficacy of netarsudil/latanoprost combination therapy with latanoprost monotherapy demonstrated that the former was more effective [69]. Ripasudil is another Rho kinase inhibitor available as an option [64]; however, unlike netarsudil, no study has compared its efficacy with that of β-blockers as monotherapy [68].

Topical alpha2 adrenergic agonists (apraclonidine, brimonidine) and topical CAIs (brinzolamide and dorzolamide) are also available as pharmacotherapies, but their use is typically limited to second-line combinations [54,55,64]. Notably, CAI/PGA combinations are more frequently prescribed than α2 agonist/PGA combinations, suggesting that CAIs may be better tolerated than α2 agonists [55].

Table2: Different pharmacotherapeutic options available for POAG treatment.

Class	Sub-Class	Generic Name	Action Principle	Relative Efficacy as initial monotherapy	Prominent Side effects	Possible Contraindications
Prostaglandin analoges (PGAs)	FP Agonist	Latanoprost (1996)	Enhance AH Outflow Via Unconventional Pathway	–	•Conjunctival hyperemia •Excessive eye-lash growth •Iris and eyelid pigmentations	•Herpetic keratitis history •Active uveitis •Macular edema
		Bimatoprost (2001)		More effective IOP control than Latanoprost, but with more side effects. [15]		
		Travoprost (2001)		Comparable to Latanoprost. [12]		
		Tafluprost (2012)				
		Latanoprostene bunod (2017)	Enhance AH Outflow Via Both the Conventional and Unconventional Pathways	Numerically outperformed latanoprost and travoprost and was similar to bimatoprost. [16]		
	Selective EP2 Agonist	Omidenepag isopropyl (2022)		Non inferior to Latanoprost. Potential alternative to patients unresponsive to Latanoprost. [12]	•Conjunctival hyperemia	

β-adrenergic blockers	**Non-selective**	**Timolol**	**Supressing AH production**	**Inferior to PGAs as initial monotherapy [14]**	**•Bronchial constriction** **•Blepharitis** **•Bradycardia** **•Decreased blood pressure**	**•Cardiovascular diseases** **•Asthma** **•Diabetes mellitus** **•Chronic obstructive pulmonary disease**
		Levobunolol				
		Carteolol				
		Metipranolol				
	β1-selective	Betaxolol				
	α1βblocker	Nipradilol	SpressingAH production and enhancing its outflow Decrease episcleral venous pressure	No evidence supports their use as monotherapy. Can be used in combinations.		
α2-adrengergic agonists	-	Apraclonidine			•Allergic conjunctivitis •follicular conjunctivitis	Concomitant use of Monoamine oxidases
		Brimonidine				
Carbonic anhydrase inhibitors	Systemic	•Acetazolamide •Methazolamide •Dichlor-phenamide	Supressing AH production		•Renal calculi •Serum electrolyte imbalance	Adrenal diseases
	Topical	•Brinzolamide •Dorzolamide			•Corneal edema •Metallic taste	Sickle Cell disease
Rho Kinase Inhibitors (ROCK)	-	•Netarsudil	SpressingAH production and enhancing its outflow Decrease episcleral venous pressure		•Keratitis •Conjunctival hemorrhage •Corneal verticillata	None
		•Ripasudil	Enhancing AH outflow via the conventional pathway		•Blepharitis •Conjunctival hyperemia	

Although pharmacotherapy is an effective treatment modality for many patients, concerns regarding long-term efficacy, tolerability, cost, and adherence persist. Many studies have highlighted poor adherence as a significant barrier to effective treatment; in one study, nearly half of the patients took less than 75% of their prescribed doses [54]. This prompted the development of novel devices and drug delivery options. A recent example is the intracameral bimatoprost SR ocular implant (Durysta®) approved by the FDA [72]. For more details regarding devices and novel drug delivery approaches for glaucoma, readers are encouraged to consult other excellent reviews [70-72].**3.1.4. Laser trabeculoplasty**

Laser trabeculoplasty (LT) is indicated when pharmacotherapy fails to maintain the target intraocular pressure (IOP), and may also be utilized as an initial therapy for some patients [54,64]. There are various types of LT, with Argon laser trabeculoplasty (ALT) being the earliest, introduced in 1979 [73]. The efficacy of ALT is well-established, with an estimated reduction in IOP of 6.4 to 9.7 mmHg following treatment [73]. Moreover, multiple studies, including The Glaucoma Laser Trial (GLT), have demonstrated that clinically significant reductions in IOP occurred in over 75% of previously untreated eyes, thereby reducing the need for medications to control IOP [54]. However, long-term studies indicate

that after 5 years, 30-60% of eyes that underwent ALT may require surgical intervention [54].

The use of LT gradually declined until the development of selective laser trabeculoplasty (SLT) in 1995, which led to a resurgence in its use in 2001 [54]. SLT employs a low-energy laser selectively absorbed by pigmented cells, thereby minimizing collateral damage [54]. Subsequent LT procedures included transscleral SLT, pattern-scanning LT, micropulse LT, and titanium sapphire LT [55]. A recent network meta-analysis comparing the efficacy of different LT techniques found similar IOP reduction at 6 to 12 months; however, medication usage after 12 months of SLT appeared to decrease compared to ALT [73].

Generally, LT is preferred over surgery because of its less invasive nature and improved safety profile. Additionally, a recent Cochrane review indicated that, while LT may be comparable to pharmacotherapy for IOP reduction, it can be more effective in slowing visual field deterioration without causing serious adverse events [74].

3.1.5. Surgery

Surgery is indicated when neither pharmacotherapy nor laser therapy effectively reduces the intraocular pressure (IOP). It may also be considered the initial therapy in select cases. Surgical intervention for primary open-angle glaucoma (POAG) can be achieved through two main approaches: creating a new drainage pathway for aqueous humor (AH) via incisional surgeries (trabeculectomy, minimally invasive glaucoma surgeries [MIGS], and aqueous shunts) or reducing AH production rate through cyclodestructive surgeries [54].

For many years, trabeculectomy has been regarded as the "gold standard" for POAG surgery. This procedure involves excising a segment of the trabecular meshwork (TM) and creating a partial-thickness scleral flap to establish an alternative drainage channel from the anterior chamber to the subconjunctival space [55]. However, recent trends indicate a gradual decline in the popularity of trabeculectomy in favor of MIGS and aqueous shunts, as evidenced by a survey conducted by the American Glaucoma Society in 2017 [75].

Aqueous shunts, often referred to as glaucoma drainage devices (GDDs), tube shunts, or setons, consist of a tube that serves as a permanent drain to divert AH into the subconjunctival area. The advantages of GDDs over trabeculectomy include reduced conjunctival scarring (due to drainage being diverted to the equatorial region of the eye away from the limbus) and the creation of a persistent bleb [76].

MIGS encompasses a range of surgical techniques that utilize an ab interno approach to minimize harm to the ocular structures. Although MIGS appears to offer a better short-term safety profile than trabeculectomy and aqueous shunt surgery, it is generally less effective in reducing IOP [54].

3.2. Primary Angle Closure Diseases (PACD)

In contrast to primary open-angle glaucoma (POAG), which is characterized by elevated intraocular pressure (IOP), primary angle-closure disease (PACD) encompasses a spectrum of conditions related to angle closure. The main goals of treatment for PACD are to reverse angle closure, control IOP, and prevent optic nerve damage [77].

3.3. Primary Angle Closure Suspect (PACS)

Patients with iridotrabecular contact (ITC) ≥180 °, normal intraocular pressure (IOP), and no optic nerve damage may be at risk of developing primary angle closure (PAC). Therefore, prophylactic laser iridotomy (LI) should be considered [74]. However, recent trends have indicated a decline in the inclination to perform prophylactic LI. A large population-based randomized clinical trial known as the ZAP trial found that while LI has a significant prophylactic effect, progression to PAC is rare (occurring in only 4% of cases), leading the authors to conclude that prophylactic LI may be unjustified [78].

In contrast, a recent review challenged this conclusion, suggesting that patients treated with prophylactic LI in clinical settings may possess additional risk factors such as older age, presence of symptoms, and reduced anterior chamber depth, which were not considered in the ZAP trial. These factors may place patients at higher risk of developing PAC [79].

Other factors that may guide ophthalmologists in making clinical decisions regarding prophylactic LI include the presence of symptoms, use of medications with

Table 3: Classifications of PACD.

Term	Defined as:
Primary angle-closure suspect (PACS)	≥180 degrees iridotrabecular contact (ITC), normal IOP, and no optic nerve damage
Primary angle closure (PAC)	≥180 degrees ITC with peripheral anterior synechiae (PAS) or elevated IOP but no optic neuropathy
Primary angle-closure glaucoma (PACG)	≥180 degrees ITC with PAS, elevated IOP, and optic neuropathy
Acute angle-closure crisis (AACC)	Occluded angle with symptomatic high IOP
Plateau iris configuration (PIC)	Narrow angle due to an anteriorly positioned ciliary body, with deep central anterior chamber
Plateau iris syndrome (PIS)	Narrow angle due to an anteriorly positioned ciliary body, with deep central anterior chamber, and any ITC persisting after patent peripheral iridotomy

anticholinergic activity, and patient accessibility to immediate ophthalmic care [77].

3.4. Primary Angle Closure and Primary Angle Closure Glaucoma (PAC, PACG)

In patients with primary angle closure (PAC), intraocular pressure (IOP) elevation can occur because of obstruction of aqueous humor (AH) outflow resulting from angle closure or as a consequence of damage to the trabecular meshwork (TM) following previous acute angle-closure crisis (AACC) attacks.

Laser iridotomy (LI) is generally indicated for the treatment of both PAC and primary angle closure glaucoma (PACG) [77, 80, 81]. However, there are cases in which LI may not achieve the desired treatment outcomes, in which case latanoprost may be prescribed to help control IOP [80].

Complications following LI can include IOP elevation, laser burns, and ocular light-induced visual disturbances [77]. An alternative treatment option is clear lens extraction, which includes cataract surgery or phacoemulsification [77]. A recent clinical trial [82] demonstrated that lens extraction might provide better IOP control than LI, particularly in advanced cases of optic nerve damage that are less likely to benefit from LI [81]. Furthermore, lens extraction has been shown to confer even greater IOP control when combined with trabeculectomy [77, 83].

If additional IOP reduction is required after LI, further treatment options can be considered, mirroring the approach used to manage primary open-angle glaucoma (POAG) [77].

3.5. Acute Angle Closure Crisis (AACC)

The primary treatment goal for acute angle-closure crisis (AACC) is to lower intraocular pressure (IOP) and alleviate accompanying symptoms as quickly as possible. Although several treatment options have been shown to be effective, pharmacotherapy is typically the first-line treatment [77]. Pharmacotherapy options include topical β-blockers, α2 agonists, parasympathomimetics, and carbonic anhydrase inhibitors (CAIs). Additionally, oral or intravenous CAIs and hyperosmotic agents should be administered [84].

Parasympathomimetics may be ineffective in cases of severely elevated IOP or a secondary pupillary block.

Moreover, if ischemic ciliary bodies are present, agents that suppress AH formation, such as β-blockers and CAIs, may not produce the desired effect [84].

Once symptoms are alleviated and the acute attack resolves, laser iridotomy (LI) should be performed as soon as possible to equalize the pressure between the anterior and posterior chambers. If pharmacotherapy fails or LI is not feasible, paracentesis or incisional iridectomy may be indicated [77].

Following treatment, it is essential to examine fellow eyes of patients with AACC. If the chamber angle is narrow, prophylactic LI should be promptly considered given the high risk of developing AACC in that eye [77].

3.6. Childhood and Infantile Glaucoma

The management of childhood glaucoma primarily involves surgical intervention, with pharmacotherapy serving a supportive role either temporarily before surgery or as an adjunct after surgery. First-line pharmacotherapeutic options typically include topical β-blockers with other alternatives such as pilocarpine, carbonic anhydrase inhibitors (CAIs), or prostaglandin analogs (PGAs). Special attention must be paid to the potential complications and adverse events associated with each medication class, as children are more susceptible to side effects.

Angle surgery is commonly performed and often followed by trabeculectomy or other filtration-enhancing procedures. In cases where the initial treatment is insufficient, cyclodestruction may be considered a second-line option [85]. Goniotomy, trabeculotomy, and trabeculectomy with anti-scarring agents are regarded as the most effective treatment strategies [97].

3.7. Other Forms of Glaucoma

3.7.1. Pseudoexfoliative Glaucoma (PXFG)

Pseudoexfoliative Glaucoma (PEG), commonly referred to as exfoliative glaucoma, is the most prevalent type of secondary glaucoma. Research indicates that approximately 20% of eyes affected by pseudoexfoliation syndrome (PXF) develop elevated intraocular pressure (IOP), subsequently leading to PXFG within five years [86].

The treatment objectives and modalities for PXFG mirrors are used for primary open-angle glaucoma (POAG). However, there is a notably higher risk of disease progression in patients with PXFG. Consequently, a greater reduction in IOP may be necessary, often necessitating a higher number of medications or more invasive initial therapies, such as laser treatments or surgical interventions [87]. Notably, findings from the Glaucoma Laser Trial (GLT) suggest that initial therapy with laser trabeculoplasty (LT) may be more effective than medication alone, such as timolol [88].

Surgical procedures, including cataract surgery and trabeculectomy, are recommended in certain patients. A prospective multicenter study demonstrated that cataract surgery significantly lowered IOP in patients with POAG, PXF, and PXFG [89]. Interestingly, the IOP-lowering effect was more pronounced in patients with PXF and PXFG than in those with POAG, although the reasons for this discrepancy are not yet fully understood [89].

Trabeculectomy remains the most common surgical approach for PXFG, with success rates and complication profiles comparable to those observed in POAG [88].

3.7.2. Phacolytic Glaucoma

Phacolytic Glaucoma arises from the microleakage of lens proteins in eyes with advanced or hypermature cataracts. Leaked proteins attract macrophages and other inflammatory cells that accumulate in the trabecular meshwork (TM) and obstruct aqueous humor (AH) outflow, leading to elevated intraocular pressure (IOP). The primary treatment for Phacolytic Glaucoma involves lens extraction (cataract surgery), often supplemented with topical anti-inflammatory medications [86, 91].

In some cases, trabeculectomy may be indicated following lens extraction, as it has been demonstrated to effectively reduce postoperative IOP and decrease the need for additional medications [90].

3.7.3. Uveitic Glaucoma

Uveitic glaucoma (UG) is characterized by uveitis (inflammation within the eye) and elevated intraocular pressure (IOP) [92]. Uveitis may occur due to viral infections, such as herpes simplex and varicella-zoster viruses, or other inflammatory conditions, such as Posner-Schlossman syndrome. The resulting inflammatory debris

can accumulate in the trabecular meshwork (TM) and obstruct aqueous humor (AH) outflow. This may lead to TM scarring or secondary angle closure [86]. Notably, both angle-closure and open-angle pathological mechanisms may manifest concurrently within the same eye, complicating treatment strategies [92]. Successful management requires addressing uveitis and secondary glaucoma (s). Aggressive initial anti-inflammatory treatment is essential, as studies have shown that it yields better clinical outcomes than conservative approaches [92, 93]. The choice of anti-inflammatory agent is guided by the underlying cause of uveitis [86]. For example, topical or systemic corticosteroids are typically indicated during acute inflammatory episodes, whereas acyclovir is used for the herpes simplex virus [86, 92]. Topical non-selective β-blockers and carbonic anhydrase inhibitors (CAIs) are generally considered first-line treatments [86]. The use of prostaglandin analogs (PGAs) is controversial because of the potential complications that could exacerbate uveitis; however, they may be prescribed in cases where uveitis is well-controlled [92, 86]. If pharmacological treatments fail to adequately lower IOP, surgical interventions tailored to underlying inflammatory conditions may be necessary. It is crucial to note that current clinical evidence does not strongly support the use of laser trabeculoplasty (LT) in the context of UG, leading to its recommendation for LT [86, 92]. Various surgical options exist for UG, and further details can be found in specialized reviews [92].

3.7.4. Neovascular glaucoma

Neovascular glaucoma (NVG) can develop in patients with ischemic retinal diseases (posterior segment ischemia) owing to an imbalance between proangiogenic and antiangiogenic factors. This imbalance leads to the proliferation of new blood vessels on the anterior surface of the iris and within the anterior chamber angle, thereby obstructing aqueous humor (AH) outflow. Consequently, this mechanism elevates intraocular pressure (IOP) through an open-angle pathway, which may progress to synechial angle closure [94].

The management of NVG focuses on reducing IOP while addressing the underlying ischemia and angiogenesis. The initial approach involves lowering IOP to alleviate symptoms and protecting optic nerve function. This can be accomplished using topical β-blockers, α2-agonists, or carbonic anhydrase inhibitors (CAIs). It is advisable to avoid prostaglandin analogs (PGAs) and anticholinergic agents, as these may worsen inflammation [94]. Additionally, topical corticosteroids may be introduced early in the treatment process to mitigate inflammation [86, 94]. If further IOP reduction is necessary, surgical options such as trabeculectomy, aqueous drainage devices, and cyclodestructive procedures can be considered [86, 94].

To treat the underlying ischemia associated with NVG, pan-retinal photocoagulation, a laser therapy technique, is the cornerstone of management and should be promptly performed [94]. A new treatment modality involves intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors as adjunctive therapy. Although these anti-VEGF agents are recommended by the European Glaucoma Society guidelines [86], their efficacy remains uncertain according to a recent systematic Cochrane review [95, 96].

3.8. Artificial Intelligence in Glaucoma Treatment

Theoretically, AI models can also be extremely valuable for precision medicine in glaucoma treatment. Despite being still far from reach, each individual patient's clinical data and risk profile could be utilized by an AI model to suggest the most effective treatment modality, aiding clinicians in providing a personalized plan [25, 106] However, promising attempts have been made in this direction. For example, by utilizing a machine learning model, Kurysheva et al. concluded that lens extraction is more effective for PAC treatment than laser peripheral iridotomy based on postoperative clinical data [107]. Similarly, Qidwai et al. developed an AI-based algorithm (adaptive neuro-fuzzy inference system) based on postoperative data of 372 patients who had one of four MIGS to predict which one was more effective for a given set of baseline clinical characteristics [108].

4. Prognosis of Glaucoma

The primary treatment objective in glaucoma management is to preserve vision-related quality of life and prevent further visual field loss [54, 64, 86]. Accurate prediction and continuous monitoring of glaucoma progression are crucial for tailoring individualized treatment plans and determining appropriate follow-up intervals, particularly for patients with high-risk profiles [98,99].

The prognosis of glaucoma is highly variable among patients. A 20-year cohort study by King et al. indicated that with timely diagnosis and proper treatment, most patients retain significant vision, with 80% of glaucomatous eyes preserving visual acuity two decades after follow-up [100]. However, the study also revealed that 20% of the eyes of deceased patients suffered severe visual acuity damage at the final follow-up, and visual field deterioration was noted in 44% of surviving patients despite adequate IOP control. Additionally, a systematic review by Mokhles et al. highlighted that a significant proportion of patients experienced partial or total vision loss during their lifetime despite treatment efforts [101].

Progression of glaucoma is influenced by a multitude of prognostic factors. A systematic review identified 41 such factors, categorizing them into two definite (older age in OAG and disc hemorrhage in NTG), nine probable (such as higher baseline IOP and exfoliation), and 30 possible factors [102]. Further research involving large datasets from AGIS and UCLA underscored that African ancestry, older age, larger cup-to-disc ratios, and poorer baseline visual field values were associated with faster deterioration [103]. Interestingly, children with primary congenital glaucoma tend to have a more favorable prognosis than those with other congenital ocular abnormalities such as aniridia or Peters/Rieger syndrome, likely because of better treatment responses [104].

Currently, techniques for monitoring glaucoma progression can be divided into functional and structural assessment tools. These include clinical judgment, event analysis, and trend analysis [99,105]. Although no universally accepted standard has been established, trend analysis, which employs regression methods to assess changes over time, offers the advantage of detecting both the extent and rate of progression [99]. Event analysis compares the visual field results with the baseline tests to identify significant deviations. However, the subjectivity of clinical judgment and the lack of standardization remain concerns, particularly in busy clinical settings. Emerging technologies, such as artificial intelligence (AI) and machine learning, hold promise for enhancing prognostic accuracy. AI algorithms can integrate data from genetic profiles, IOP trends, and visual field assessments to provide more robust predictions of glaucoma progression. Although the field is still evolving, these innovations could revolutionize personalized treatment strategies in the future [25]. Likewise, the predictive potential of AI could be harnessed to forecast disease progression and risk assessment. In an unprecedented study, Li et al. utilized color fundus photographs of 17,497 eyes to develop two deep learning algorithms (DiagnoseNet and PredictNet) capable of distinguishing patients with a high risk of disease progression from low-risk patients. The predictive performance of these models is promising and could pave the way for breakthroughs in early glaucoma treatment [109]. Similarly, Hussain et al. utilized OCT, visual field, and demographic data from 86 glaucoma patients to develop a multimodal deep learning model capable of predicting further visual loss with impressive accuracy [110]. For further insight into prognostic models and assessment methods, readers are encouraged to conduct comprehensive reviews on the subject [99,105].

Conclusion

Glaucoma is a complex and poorly understood condition that potentially involves multiple factors or diseases, with similar outcomes. Current treatments focus on lowering the intraocular pressure (IOP). However, further improvements are required, particularly in targeting trabecular outflow and protecting the retinal neurons and glia. Future advancements will require a deeper understanding of genetic and molecular mechanisms, development of precise diagnostic tools, and enhancement of neuroprotective strategies. Innovations in technology and research on IOP-independent factors are crucial for advancing the prevention and treatment of glaucoma and paving the way for more effective management. AI has demonstrated immense potential for enhancing glaucoma care through more accurate diagnostics, personalized treatment strategies, and robust predictions of disease progression. Although challenges remain in integrating these models into clinical practice, ongoing advancements and evaluations are likely to establish AI as a cornerstone in the future of ophthalmology.

Disclosure

The authors report no conflict of interest.

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