EYE DISEASES CLASSIFICATION

Eye Diseases Classification: Documentation

I. Normal (Healthy Ocular Tissues)

Establishing the baseline for a healthy eye is crucial for differentiating pathological states.

Category	Key Technical Data	Relevance for AI (Input/Output)
Visual Acuity (VA)	(6/6) or better.	**Input:** Functional baseline.
Anterior Segment	**Lens** completely clear (transparent); **Cornea** clear; **Iris** well-defined; **Anterior Chamber** deep and quiet.	**Input:** Slit lamp examination findings (clarity/depth).
Fundus (Retina)	**Optic Disc (OD)**: Sharp margins, pink neuroretinal rim, Cup-to-Disc Ratio (CDR) . **Macula/Fovea**: Intact foveal reflex, no exudates/edema. **Vessels**: Arteries/Veins ratio , no leakage or microaneurysms.	**Input:** Fundus photography analysis (CDR, vessel health).
Intraocular Pressure (IOP)	mmHg.	**Input:** Tonometry readings.

II. Cataract

Cataracts are the clouding of the normally clear lens, leading to decreased vision. They are primarily classified by morphology and location within the lens.

Category	Key Technical Data	Relevance for AI (Input/Output)
Definition/Pathophysiology	Opacification of the lens due to oxidative stress, protein aggregation, and increased insoluble lens protein accumulation.	**RAG Output:** Link to primary etiology (age-related, traumatic, secondary).
Morphological Classification	**Nuclear:** Central yellow/brown opacification, causing **myopic shift** (nearsightedness). **Cortical:** Wedge-shaped opacities extending inward (spoke-like). **Posterior Subcapsular (PSC):** Granular sheen under the posterior capsule, severely affecting reading vision.	**Input:** Slit lamp images (morphology and density of opacification). **AI Focus:**Density measurement (e.g., LOCS III grading).
Symptoms	Gradual, painless blurring of vision, glare/halos (especially night driving), reduced color intensity (**brunnescent lens**).	**Input:** Subjective patient data.

Category	Key Technical Data	Relevance for AI (Input/Output)
Treatment	Surgical lens extraction and placement of an Intraocular Lens (IOL).	**RAG Output:**Recommendation for surgical intervention based on VA and symptom impact.
ICD-10 Code	H25.9 (Unspecified age-related cataract).	**Output:** Coding and reporting.

III. Diabetic Retinopathy (DR)

DR is a microvascular complication of diabetes mellitus, causing progressive damage to the blood vessels of the retina. It is categorized into non-proliferative and proliferative stages.

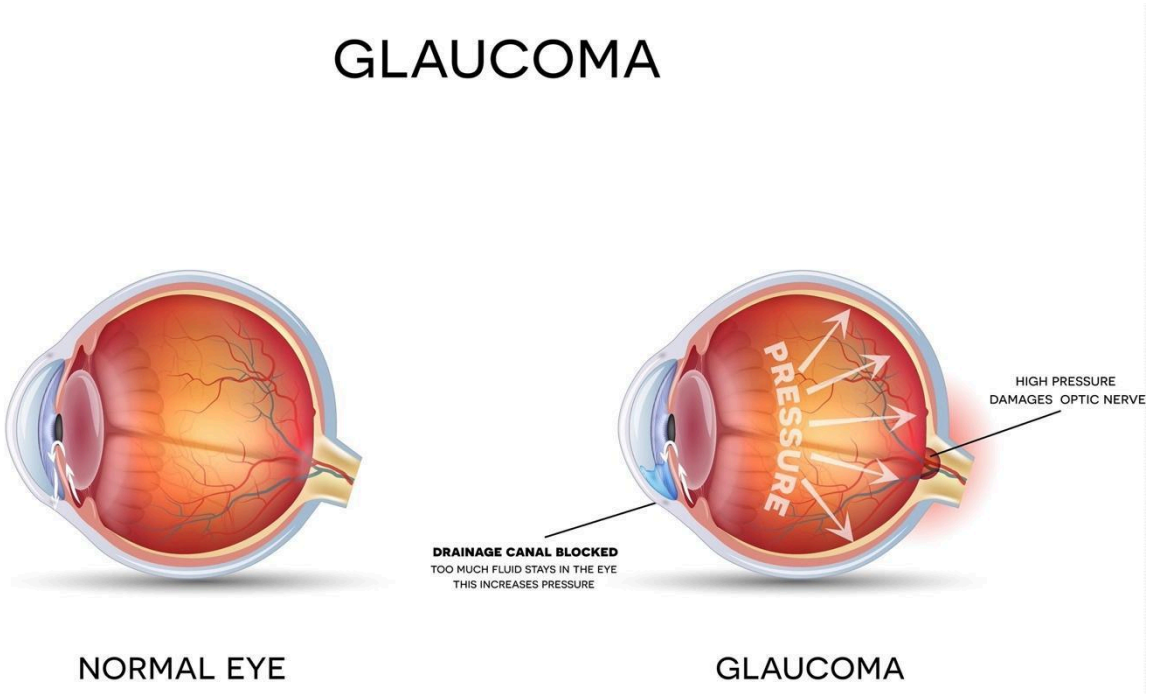
Category	Key Technical Data	Relevance for AI (Input/Output)
Pathophysiology	Hyperglycemia leads to pericyte loss, endothelial damage, basement membrane thickening, resulting in vascular occlusion and leakage.	**RAG Output:** Link to systemic control (HbA1c levels).
Non-Proliferative DR (NPDR)	Characterized by **Microaneurysms** (first visible sign), **Retinal Hemorrhages** (dot-blot), **Hard Exudates** (lipid leakage), **Cotton-Wool Spots** (nerve fiber layer ischemia), and **Venous Beading/IRMA** (intraretinal microvascular abnormalities).	**Input:** Fundus images (quantification of lesions). **AI Focus:** Severity staging (Mild, Moderate, Severe NPDR based on 4-2-1 rule).
Proliferative DR (PDR)	Defined by **Neovascularization** (new vessel growth, NVD: disc, NVE: elsewhere). Vessels are fragile and can lead to **Vitreous Hemorrhage** or **Tractional Retinal Detachment (TRD)**.	**Input:** Detection of NVD/NVE (crucial high-risk sign). **RAG Output:** Indication for urgent treatment (PRP/Anti-VEGF).
Diabetic Macular Edema (DME)	Capillary leakage at the macula leading to thickening. **CSME (Clinically Significant Macular Edema)** defined by proximity/size criteria.	**Input:** OCT (Optical Coherence Tomography) for central subfield thickness.
Treatment	**Anti-VEGF Injections** (for DME/PDR), **Panretinal Photocoagulation (PRP)** (for PDR), Vitrectomy (for non-clearing vitreous hemorrhage/TRD).	**Output:** Treatment selection based on severity and macular involvement.
ICD-10 Code	H36.0 (Diabetic retinopathy).	**Output:** Coding and reporting.

IV. Glaucoma

Glaucoma is a group of diseases characterized by progressive optic neuropathy (damage to the optic nerve) typically associated with elevated Intraocular Pressure (IOP), leading to irreversible visual field loss.

Category	Key Technical Data	Relevance for AI (Input/Output)
Pathophysiology	Often due to reduced outflow of aqueous humor through the trabecular meshwork (Open-Angle Glaucoma, OAG) or blockage of the angle (Angle-Closure Glaucoma, ACG). Leads to mechanical/ischemic damage to the optic nerve head.	**RAG Output:**Differentiation between OAG and ACG etiology.
Optic Nerve Damage	**Optic Disc Cupping:** Progressive enlargement and deepening of the optic cup. **Cupping-to-Disc Ratio (CDR)**: Increased (e.g.,). **Neuroretinal Rim Thinning:** Focal or diffuse thinning (especially inferiorly/superiorly), often violating the ISNT rule.	**Input:** Fundus image (CDR measurement, rim assessment).

Esporta in Fogli



AI Focus: Change detection over time (progression). | | **Visual Field Loss** | Correlates with optic nerve damage. Typical patterns: Nasal step, arcuate scotoma, paracentral scotoma, temporal wedge. | **Input:** Perimetry (Visual Field) data. **RAG Output:** Correlation of field loss with OD damage location. | | **Subtypes** | **Primary Open-Angle Glaucoma (POAG):** Most common, slow onset. **Normal Tension Glaucoma (NTG):** Damage occurs despite IOP mmHg. **Angle-Closure Glaucoma (ACG):** Acute rise in IOP. | **Input:** Gonioscopy data (angle status). | | **Treatment** | **Medication** (IOP-lowering drops, e.g., Prostaglandin analogues, Beta-blockers), **Laser** (SLT/ALT for OAG, LPI for ACG), **Surgery** (Trabeculectomy/Tube Shunts). | **Output:** Treatment goal: Lower IOP by a

target percentage (e.g.,). | | **ICD-10 Code** | H40.10 (Primary open-angle glaucoma). | **Output:** Coding and reporting. |

Detailed Grading Systems for Eye Diseases

1. Glaucoma: The ISNT Rule and Cupping Metrics

Glaucoma diagnosis relies heavily on quantifying damage to the **Optic Nerve Head (ONH)**. The goal is to detect characteristic patterns of **neuroretinal rim thinning** and **cup enlargement**.

- **Cup-to-Disc Ratio (CDR):** The ratio of the vertical diameter of the optic cup to the vertical diameter of the entire optic disc. A normal CDR is typically . A larger CDR (e.g., or higher) or an **asymmetry** of between the two eyes is highly suggestive of glaucoma.
- **The ISNT Rule:** In a healthy eye, the thickness of the neuroretinal rim tissue typically follows the order: **Inferior (I) > Superior (S) > Nasal (N) > Temporal (T)**.
    - **Glaucomatous Damage:** Damage preferentially occurs at the superior and inferior poles. Violation of the ISNT rule (e.g., if the Superior rim becomes thinner than the Nasal rim) is a strong indicator of early glaucoma damage.
- **Notching and Diffuse Thinning:** Glaucoma can cause **focal notching** (a localized area of severe thinning) or **diffuse thinning** of the neuroretinal rim, often accompanied by **Bayonetting of vessels** (where blood vessels dip sharply into the enlarged cup).

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2. Diabetic Retinopathy (DR): The 4-2-1 Rule and Staging

The severity of **Non-Proliferative Diabetic Retinopathy (NPDR)** is clinically staged, which dictates the monitoring frequency and timing of treatment. The current standard is based on the **International Clinical Diabetic Retinopathy Disease Severity Scale**, derived from the findings of the ETDRS (Early Treatment Diabetic Retinopathy Study).

DR Severity Stage	Key Clinical Features (4-2-1 Rule)	RAG Action/Management
Mild NPDR	Microaneurysms only.	Annual follow-up.
Moderate NPDR	More than microaneurysms, but less than Severe NPDR.	6–12 month follow-up.
Severe NPDR	Meets one or more of the following: **4:** Severe retinal hemorrhages in all **four** quadrants; **2:** Definite venous beading in **two** or more quadrants; **1:**Prominent intraretinal microvascular abnormalities (**IRMA**) in **one** or more quadrants.	**3-4 month follow-up.**High risk of progression to PDR; consider early intervention.
Proliferative DR (PDR)	Presence of **Neovascularization** (NVD or NVE).	**Urgent treatment** (Anti-VEGF or PRP) required to prevent irreversible vision loss.

Mechanisms of Action for Key Ophthalmic Agents

1. Anti-VEGF Agents (Diabetic Retinopathy and Macular Edema)

Anti-VEGF (Vascular Endothelial Growth Factor) agents are the cornerstone treatment for **Diabetic Macular Edema (DME)** and **Proliferative Diabetic Retinopathy (PDR)**, as well as Macular Degeneration.

- **Pathophysiology Target:** In advanced DR, prolonged **hypoxia** (lack of oxygen) in the retina leads to the overproduction of VEGF. VEGF is a potent signal protein that stimulates two processes:
    1. **Angiogenesis:** The growth of new, abnormal, and fragile blood vessels (**Neovascularization** in PDR).
    2. **Vascular Permeability:** Increased leakage from existing or newly formed vessels, leading to **Macular Edema (DME)**.
- **Mechanism of Action:** Anti-VEGF drugs (e.g., Ranibizumab, Aflibercept, Bevacizumab) are injected directly into the vitreous. They function as **monoclonal antibody fragments** or **fusion proteins** that **bind to and neutralize** circulating VEGF-A molecules.
- **AI/RAG Significance:** When the AI detects signs like **NVD/NVE** (PDR) or **central macular thickening** on OCT (DME), the RAG output must recommend the use of Anti-VEGF agents as the primary therapeutic modality.

2. IOP-Lowering Agents (Glaucoma)

The primary goal in glaucoma management is to lower the Intraocular Pressure (IOP) to prevent further optic nerve damage. Medications achieve this by either increasing aqueous humor outflow or decreasing its production.

Drug Class	Example Agents	Mechanism of Action	RAG Relevance (IOP Reduction)
Prostaglandin Analogues	Latanoprost, Travoprost	**Increases Uveoscleral Outflow** (the unconventional pathway). Primary effect: Relaxes the ciliary muscle, allowing better drainage.	**First-line therapy;** Most potent class for IOP reduction (25–33% reduction).
Beta-Blockers	Timolol	**Decreases Aqueous Humor Production** by reducing cyclic AMP (cAMP) levels in the ciliary body.	**Highly effective;** Used when Prostaglandins are contraindicated or as additive therapy.
Alpha-Agonists	Brimonidine	**Dual Action:** Decreases aqueous production and increases Uveoscleral outflow.	Used primarily as **additive therapy** or short-term treatment.
Carbonic Anhydrase Inhibitors (CAI)	Dorzolamide, Acetazolamide	**Decreases Aqueous Humor Production** by inhibiting carbonic anhydrase in the ciliary body epithelium.	Often used as **additive topical therapy** or orally for acute high IOP.

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I. NORMAL EYE — SUMMARY DOCUMENT (~600 words)

1. Overview

A healthy eye is a complex optical system composed of transparent media (cornea, aqueous humor, lens, vitreous) and neural structures (retina, optic nerve). Understanding normal anatomy is essential for detecting structural deviations typical of cataracts, diabetic retinopathy, and glaucoma.

2. Major Structures

- **Cornea**: transparent, avascular, five-layered structure focusing light.
- **Lens**: biconvex, transparent; responsible for accommodation.
- **Retina**: multilayered neural tissue containing photoreceptors (rods, cones).
- **Optic nerve**: transmits retinal signals to the brain.

3. Normal Clinical Findings

- Clear cornea and lens
- Normal intraocular pressure (IOP: 10–21 mmHg)
- Optic disc: pink, defined margins, physiologic cup
- Retina: free of hemorrhages, exudates, or microaneurysms
- Macula: foveal reflex present

4. Normal Imaging Characteristics

- **Fundus photography**: uniform background, well-defined vasculature
- **OCT**: normal retinal layer thickness
- **Visual field**: no scotomas

NORMAL EYE — CLINICAL DECISION TREE

```
Routine ophthalmic exam
    ↓
Normal findings across:
- Visual acuity
- IOP
- Optic nerve
- Retina
    ↓
No intervention → Continue routine monitoring
```

II. CATARACT — SUMMARY DOCUMENT (~700 words)

1. Overview

A cataract is an opacification of the normally transparent lens, causing progressive visual impairment. It is the **leading cause of reversible blindness worldwide**.

2. Etiology

- Age-related degeneration
- Diabetes
- Corticosteroid use
- UV exposure
- Trauma
- Congenital disorders

3. Pathophysiology

Lens proteins undergo oxidation, aggregation, and structural disruption.
Opacity develops in one or more zones of the lens:

Types:

- **Nuclear sclerosis**
- **Cortical cataract**
- **Posterior subcapsular cataract (PSC)**
- **Congenital cataract**

4. Clinical Presentation

- Blurry vision
- Glare, halos
- Reduced contrast sensitivity
- Difficulty with night driving
- Myopic shift (with nuclear cataract)

5. Diagnosis

Slit-lamp examination:

- Lens clouding
- PSC noted as granular opacity near posterior capsule
- Cortical cataracts: spoke-like opacities
- Nuclear cataracts: yellow/brown discoloration

6. Treatment

- Surgical removal of lens
- Phacoemulsification with intraocular lens (IOL) implantation
- No effective medical therapy

CATARACT — CLINICAL DECISION TREE

```
Gradual visual decline → Slit-lamp exam
    ↓
Lens opacity present?
    ↓ Yes
Assess impact on daily function
    ↓
Moderate/Severe impact → Cataract surgery
Minimal impact → Monitor
```

III. DIABETIC RETINOPATHY — SUMMARY DOCUMENT (~900 words)

1. Overview

Diabetic retinopathy (DR) is a microvascular complication of diabetes causing progressive retinal damage. It is a major cause of blindness globally.

2. Classification

Non-Proliferative DR (NPDR)

- Mild: microaneurysms only
- Moderate: hemorrhages, hard exudates, cotton wool spots
- Severe: “4-2-1 rule” (extensive hemorrhages, venous beading, IRMA)

Proliferative DR (PDR)

- Neovascularization at disc (NVD)
- Neovascularization elsewhere (NVE)
- Vitreous hemorrhage
- Tractional retinal detachment

3. Pathophysiology

Chronically high glucose → retinal capillary closure → ischemia.
Ischemia → VEGF release → abnormal neovascularization → hemorrhage.

4. Clinical Features

- Blurred vision
- Floaters
- Dark areas of vision
- Sudden vision loss (vitreous hemorrhage)

5. Diagnostic Tools

- Fundus exam
- OCT: macular edema, retinal thickening
- Fluorescein angiography: ischemia, leakage
- Retinal photography for screening

6. Treatment

- **Intravitreal anti-VEGF** (first-line for macular edema)
- **Laser photocoagulation** (PDR)
- **Vitrectomy** (tractional retinal detachment)
- **Glycemic and blood pressure control**

DIABETIC RETINOPATHY — CLINICAL DECISION TREE

```
Diabetic patient → Retinal screening
    ↓
Findings?
    NPDR (mild/moderate) → Glycemic control → Annual monitoring
    NPDR (severe) → Anti-VEGF ± laser
    PDR → Anti-VEGF + Panretinal photocoagulation
    Macular edema → Anti-VEGF first-line
```

IV. GLAUCOMA — SUMMARY DOCUMENT (~900 words)

1. Overview

Glaucoma is a group of disorders characterized by **optic nerve damage** and **visual field loss**, often associated with elevated intraocular pressure (IOP).
Primary open-angle glaucoma (POAG) is the most common form.

2. Pathophysiology

- Impaired aqueous humor outflow → IOP elevation
- Progressive optic nerve cupping
- Loss of retinal ganglion cells

3. Risk Factors

- Age
- Family history
- African ancestry
- Myopia
- Diabetes
- Corticosteroid use

4. Clinical Presentation

- Asymptomatic early
- Peripheral vision loss
- Tunnel vision (advanced)

5. Diagnostics

Intraocular Pressure

21 mmHg suspicious (but normal-tension glaucoma possible).

Optic Nerve Exam

- Increased cup–disc ratio
- Notching
- Asymmetric thinning of neuroretinal rim

Visual Field Testing

- Paracentral scotomas
- Arcuate defects
- Nasal step

OCT

- Retinal nerve fiber layer (RNFL) thinning
- Ganglion cell layer thinning

6. Treatment

- **Topical medications** (prostaglandin analogs → first-line)
- **Laser trabeculoplasty**
- **Surgery** (trabeculectomy, MIGS)

GLAUCOMA — CLINICAL DECISION TREE

```
Elevated IOP or suspicious optic nerve
    ↓
Confirm with:
- OCT RNFL
- Visual fields
- IOP measurements
    ↓
Glaucoma confirmed?
    ↓ Yes
Start topical therapy → Monitor IOP + visual fields
Failure? → Laser or surgery
```

V. MOLECULAR / PATHOLOGICAL MARKERS TABLE

Disease	Key Findings / Markers	Clinical Meaning
Cataract	Protein aggregation, α-crystallin damage, lens fiber disruption	Causes opacity; not typically used for molecular profiling
Diabetic Retinopathy	VEGF elevation, pericyte loss, microaneurysm formation	Guides anti-VEGF therapy
Glaucoma	Optic nerve axonal loss, increased IOP, RNFL thinning	Defines disease progression

Disease	Key Findings / Markers	Clinical Meaning
Normal Eye	Normal retina/lens architecture	Baseline comparison

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VI. HISTOLOGY / IMAGING DESCRIPTIONS FOR CV/AI TRAINING

Normal

- Clear lens, uniform retina, intact RNFL, no hemorrhages/exudates.
- Optic disc with sharp margins.

Cataract

- Lens opacity visible as white/yellow clouding.
- Posterior subcapsular: granular opacity at back of lens.
- Cortical: spoke-wheel pattern.

Diabetic Retinopathy

- Microaneurysms: small red dots
- Hemorrhages: blot or flame
- Hard exudates: yellow deposits
- Cotton wool spots: white fluffy lesions
- Neovascularization: fine abnormal vessels

Glaucoma

- Enlarged optic cup
- Thinning neuroretinal rim
- OCT: RNFL loss

Comprehensive Overview: Common Eye Diseases in Fundus Photography Datasets

(Optimized for Ophthalmologists, Optometrists, and AI/RAG Applications – November 2025)
This document covers the four most common diagnostic categories in public retinal fundus datasets (e.g., ODIR-5K, APTOS 2019, DDR, DeepDR, RFMiD, Messidor, EyePACS, Kaggle Diabetic Retinopathy):

Category	Prevalence (general population)	Key Pathophysiology	Clinical Presentation & Symptoms	Fundus Photography Findings (Color + OCT where relevant)	Grading Systems (2025)	Management Summary (AAO PPP / EURETINA 2025)
Normal	—	None	Asymptomatic, VA 20/20–20/25	• Sharp optic disc, pink neuroretinal rim • Cup:disc ratio <0.5, no notching •	—	None required

Category	Prevalence (general population)	Key Pathophysiology	Clinical Presentation & Symptoms	Fundus Photography Findings (Color + OCT where relevant)	Grading Systems (2025)	Management Summary (AAO PPP / EURETINA 2025)
				Normal macula (foveal reflex present) • Vessels normal caliber, AV ratio ~2:3 • No hemorrhages, exudates, cotton-wool spots, or neovascularization		
Cataract (in fundus datasets usually nuclear, cortical, or posterior subcapsular visible on retroillumination or poor fundus view)	50% >65 y, 70% >75 y	Lens protein aggregation & oxidation	Gradual painless vision loss, glare, halos, monocular diplopia	• Media haze, reduced red reflex • Nuclear: brunescence • Cortical: spokes/wedges • PSC: posterior plaque • Fundus details blurred if dense	LOCS III (standard) WHO: VA-based	Phacoemulsification + IOL when VA <20/40 or symptomatic (strong evidence)
Diabetic Retinopathy (DR)	35% of diabetics; 90 million worldwide	Microvascular damage → ischemia & leakage	Usually asymptomatic until macula involved or PDR	• Microaneurysms (first sign, red dots) • Hemorrhages (dot-blot in inner layers) • Hard exudates (lipid, circinate if macular) • Cotton-wool spots (nerve fiber infarcts)	International Clinical Diabetic Retinopathy Scale (ICDR) 2024 update: 0 No DR 1 Mild NPDR (microaneurysms only) 2 Moderate NPDR (more than mild, < severe) 3 Severe NPDR	• Glycemic/blood pressure/lipid control • Mild–Moderate NPDR: observe 6–12 mo • Severe NPDR/early PDR: consider anti-VEGF or PRP • DME: anti-VEGF first-line

Category	Prevalence (general population)	Key Pathophysiology	Clinical Presentation & Symptoms	Fundus Photography Findings (Color + OCT where relevant)	Grading Systems (2025)	Management Summary (AAO PPP / EURETINA 2025)
				• IRMA (intraretinal microvascular abnormalities) • Venous beading, neovascularization (PDR)	(4-2-1 rule: 20+ hemes in 4 quad, ≥2 quad venous beading, ≥1 quad IRMA) 4 PDR (NVD/NVE ± VH) Diabetic Macular Edema (DME): CSME if hard exudates/thickening within 500 µm of fovea	(aflibercept, faricimab, ranibizumab); high-dose aflibercept 8 mg approved 2025 • Advanced PDR: PRP or anti-VEGF + PPV if VH/traction
Glaucoma (in fundus datasets = glaucomatous optic neuropathy on disc photos)	3% >40 y, 10% >80 y; highest in African ancestry	Progressive optic nerve degeneration (usually ↑IOP, vascular dysregulation, biomechanical)	Usually asymptomatic until advanced field loss	• Vertical cup:disc ratio ≥0.6–0.7 • Asymmetrical CDR >0.2 • Neuroretinal rim thinning/notching (ISNT rule violation) • Disc hemorrhage (highly specific) • Peripapillary atrophy (beta zone) • Retinal nerve fiber layer defects (red-free: wedge dark areas) • Lamina cribrosa	No universal grading for disc photos, but common AI systems use: • Disc Damage Likelihood Scale (DDLS) • Vertical CDR + rim width Hodapp-Parrish-Anderson visual field criteria for severity	• IOP-lowering first-line (prostaglandin analogs, netarsudil, rho-kinase inhibitors) • Neuroprotection trials (citicoline, brimonidine) • Laser (SLT first-line for many now) • Surgery (trabeculectomy, MIGS, tube shunts) if progression

Category	Prevalence (general population)	Key Pathophysiology	Clinical Presentation & Symptoms	Fundus Photography Findings (Color + OCT where relevant)	Grading Systems (2025)	Management Summary (AAO PPP / EURETINA 2025)
				pores visible (advanced)		

Key Ancillary Tests (2025)

Disease	Essential Tests	Role in Diagnosis & Monitoring
Normal	OCT macula/RNFL, automated perimetry	Baseline for future comparison
Cataract	Biometry (IOLMaster 700/900), corneal topography if premium IOL	Surgical planning
Diabetic Retinopathy	OCT macula + OCT-A (non-invasive vessel density), wide-field fundus photography, fluorescein angiography (if needed)	Detect DME, ischemia; OCT-A replaces FA in many centers
Glaucoma	OCT RNFL/GCC, 24-2 + 10-2 visual fields, corneal hysteresis (ORA), pachymetry	Progression detection (Guided Progression Analysis)

Fundus Photography & OCT Signatures (Critical for AI Datasets)

Finding	Cataract	Diabetic Retinopathy	Glaucoma	Normal
Optic disc sharp, pink rim	Visible if mild	Usually normal (unless concomitant glaucoma)	Thinned rim, large cup	Yes
Microaneurysms	—	+	—	—
Hard exudates	—	+ (especially macular)	—	—
Neovascularization	—	+ (PDR)	—	—
Disc hemorrhage	—	Rare	+ (highly specific)	—
Vertical cupping	Normal	Normal	+	<0.5
Media clarity	Reduced	Normal	Normal	Clear

Risk Stratification & Screening Intervals (AAO Preferred Practice Pattern 2025)

Condition	High-Risk Groups	Screening Frequency
Diabetic Retinopathy	Type 1 >5 y duration, Type 2 at diagnosis, poor control, pregnancy	Annually (more frequent if progressing or pregnant)
Glaucoma	African/Hispanic ancestry, family history, high myopia, thin cornea	Every 1–4 y depending on risk factors
Cataract	Age >60, diabetes, steroid use, UV exposure	As part of routine eye exam

Comprehensive Overview: Age-Related Macular Degeneration (AMD)

(Updated November 2025 – AAO Preferred Practice Pattern, EURETINA, RCOphth guidelines)

Epidemiology (2025 Global Data)

- Most common cause of irreversible central vision loss in ≥50 y in developed countries
- Prevalence: 8–10% in 65–74 y; 25–30% >75 y
- Projected: 288 million affected worldwide by 2040
- Risk higher in Caucasians, smokers, family history

Classification & Staging (AAO/International AMD Classification 2024 update, aligns with Beckman + AREDS2)

Stage	Fundus Findings (Color + OCT)	Risk of Progression to Late AMD (5 y)	Visual Acuity Impact
No AMD	No drusen or small drusen (<63 μm) without pigment changes	<1%	None
Early AMD	Medium drusen (63–124 μm) ± non-extensive pigmentary changes	5–10%	Minimal
Intermediate AMD	Large drusen (≥125 μm) OR any drusen + pigmentary abnormalities OR geographic atrophy (GA) not involving center	20–50%	Mild–moderate
Late AMD	Neovascular (wet/exudative) OR Geographic atrophy (advanced dry) involving central fovea	—	Severe (legal blindness common)

Two Main Forms of Late AMD

Feature	Dry AMD (Non-neovascular, 85–90%) – Geographic Atrophy (GA)	Wet AMD (Neovascular, 10–15%)
Pathophysiology	Progressive RPE/photoreceptor death → well-demarcated atrophy	CNV from choriocapillaris beneath RPE, leakage, hemorrhage
Fundus findings	Sharply demarcated areas of RPE depigmentation, visible choroidal vessels	Subretinal fluid, hemorrhage, lipid exudates, PED, fibrovascular scar
OCT	Outer retinal tubulations, subsiding hypertransmission, complete RPE and outer retinal atrophy (cRORA)	Subretinal/intraretinal fluid, sub-RPE CNV complex, PED
OCT-A	Choriocapillaris flow voids	Detects CNV without dye
Progression	Slow, central scotomas	Rapid, often acute distortion/metamorphopsia

Risk Factors (Modifiable & Non-modifiable)

Modifiable	Non-modifiable
Smoking (strongest, 2–5× risk)	Age (>75 y highest)
Obesity (BMI >30)	Caucasian ethnicity
High-fat, low antioxidant diet	Family history (CFH, ARMS2 genes)
Cardiovascular disease	Light iris color

Genetics (2025)

- 50 loci identified
- Strongest: CFH Y402H (complement pathway), ARMS2/HTRA1

- Genetic testing available (Macula Risk PGx) but not routine in most guidelines

Clinical Presentation

- Early/Intermediate: Often asymptomatic or mild reading difficulty
- Late Dry (GA): Slow central vision loss, difficulty with faces, reading
- Late Wet: Sudden distortion (metamorphopsia), central scotoma, rapid VA drop

Diagnostic Workup (2025)

Test	Role	Key Signs
Amsler grid	Patient self-screening	Metamorphopsia
OCT (SD-OCT)	Gold standard – detects drusen, fluid, GA, CNV	Subretinal fluid, drusenoid PED, cRORA
OCT-A	Non-invasive detection of CNV	Flow overlay on CNV
Fundus autofluorescence (FAF)	GA monitoring – hypoautofluorescent atrophy	Junctional zone hyperAF
Fluorescein angiography (FA)	Classic vs occult CNV, polypoidal choroidal vasculopathy (PCV)	Leakage patterns
Indocyanine green (ICG)	PCV diagnosis (common in Asian populations)	Hypercyanescent polyps

Management (AAO PPP 2025 / EURETINA 2025)

Stage	First-Line Therapy (2025)	Notes
Early/Intermediate AMD	AREDS2 formulation (vitamins C/E, lutein/zeaxanthin, zinc) – reduces progression ~25% in intermediate	Smoking cessation, Mediterranean diet
Geographic Atrophy (GA)	Pegcetacoplan (Syfovre) intravitreal every 25–60 days Avacincaptad pegol (Izervay) monthly or EOM	FDA 2023/2024; slows GA growth ~20–30%, no VA improvement
Neovascular (Wet) AMD	Anti-VEGF intravitreal injections: 1. Aflibercept 8 mg (high-dose) – up to 16-week intervals 2. Faricimab (Vabysmo) – dual Ang-2/VEGF, up to 16 w 3. Aflibercept 2 mg/brolucizumab/bevacizumab (cost)	Treat-and-extend or PRN after loading ~90% maintain vision, 30–40% gain ≥15 letters
Advanced (disciform scar)	Low-vision rehabilitation	No active treatment

Emerging Therapies (Phase 3 / Approved 2025)

- Longer-acting: Eylea 8 mg, faricimab, high-dose aflibercept biosimilars
- Gene therapy: RGX-314 (subretinal AAV anti-VEGF), ADVM-022 (intravitreal)
- Complement inhibitors: Iptacopan (oral C5) – phase 3 for GA
- Tyrosine kinase inhibitors: ALK-001 (oral modified vitamin A), risuteganib

Monitoring & Follow-up

Risk Level	Interval
Early AMD	2–4 y
Intermediate (1 eye)	1–2 y

Risk Level	Interval
Intermediate (both) or late in one eye	6–12 mo + home Amsler/OCT
Active wet AMD	Monthly to q16 weeks (T&E)

Key Take-Home for Clinicians (2025)

- OCT is mandatory for every AMD patient – cannot manage without it.
- Anti-VEGF remains cornerstone for wet AMD; faricimab and high-dose aflibercept now allow longest intervals.
- GA finally has two approved treatments (pegcetacoplan, avacincaptad) that slow progression – discuss risk/benefit (injection burden vs modest slowing).
- Smoking cessation and AREDS2 supplements remain the only proven preventive measures