

Retinitis Pigmentosa

Inherited photoreceptor degeneration

Pathogenesis | Morphology | Clinical diagnosis

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Learning objectives

- Explain why rod degeneration produces nyctalopia and field constriction.
- Distinguish nonsyndromic from syndromic RP and recognize inheritance patterns.
- Relate photoreceptor and RPE injury to the characteristic fundus signs.
- Select investigations that establish phenotype and enable molecular diagnosis.

Retinitis pigmentosa: An inherited retinal dystrophy

- A heterogeneous group of progressive disorders affecting retinal photoreceptors.
- Pathogenic variants can impair rods, cones, or the retinal pigment epithelium (RPE).
- Functional decline can range from mild impairment to profound visual loss.

Why the name “retinitis” is misleading

Historical label

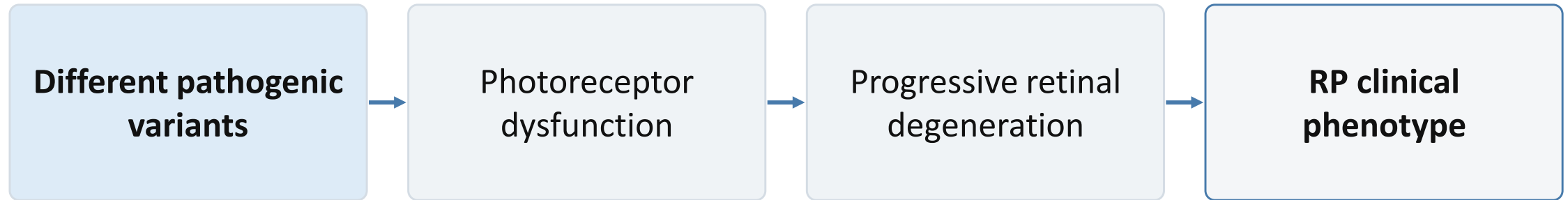
- “Retinitis” implied inflammation
- “Pigmentosa” described the fundus

Current concept

- Inherited photoreceptor dystrophy
- Secondary pigment redistribution

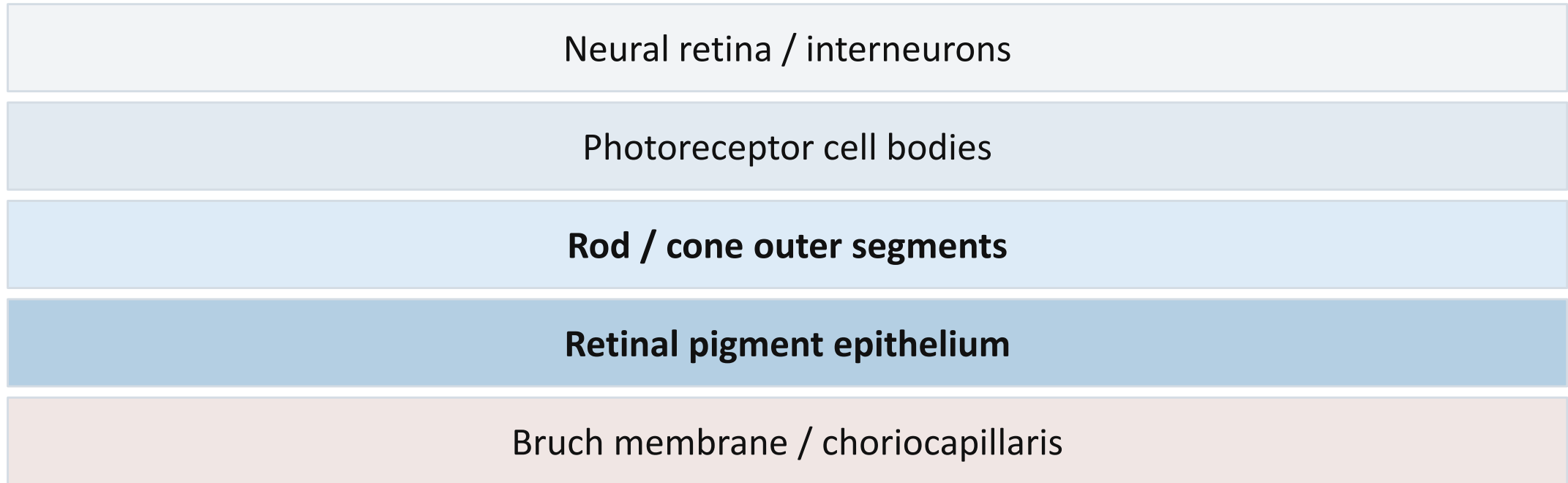
The historical name predates recognition of its genetic, degenerative basis.

RP is a phenotype, not a single genotype



- Different genetic defects may converge on progressive retinal dysfunction.
- The age at onset, severity, and clinical course vary.
- A similar retinal phenotype does not establish the same molecular diagnosis.

Retinal architecture: Where RP begins



Conceptual retinal-layer schematic — not a histologic section

- Photoreceptor outer segments contact the apical RPE.
- The RPE supports photoreceptor homeostasis and visual-cycle function.

Rod and cone functions

Rod pathway

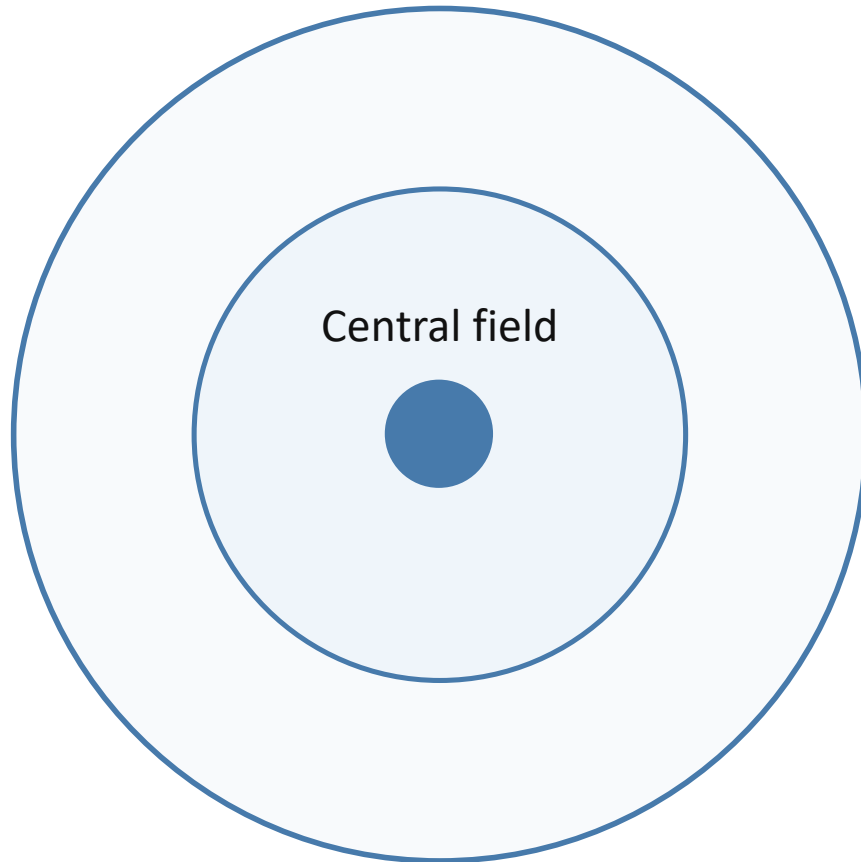
- Dim-light sensitivity
- Peripheral field function
- Night-vision symptoms

Cone pathway

- Fine central acuity
- Color and daylight vision
- Later central impairment

Rods support dim-light vision and contribute strongly to peripheral vision.

Spatial distribution matters



More vulnerable peripheral function

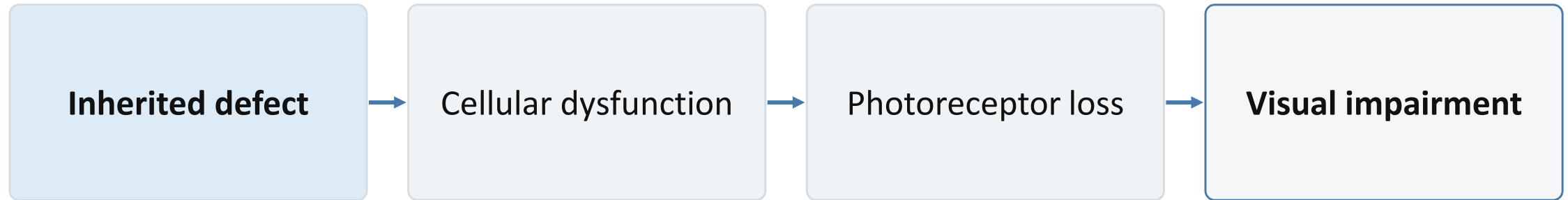
Rods are abundant in the extrafoveal retina.

The central fovea is cone-rich.

Early rod-predominant injury can reduce peripheral function despite useful central acuity.

Conceptual field schematic — not a patient perimetry plot

A common endpoint of genetically diverse insults



- Pathogenic variants disturb essential photoreceptor or RPE functions.
- Cellular dysfunction is followed by photoreceptor loss.
- Clinical dysfunction may precede conspicuous pigmentary signs.

Isolated and syndromic disease

Nonsyndromic RP

- Retinal phenotype predominates
- Gene-specific inheritance
- Eye-focused assessment

Syndromic RP

- Retinal plus systemic findings
- Examples: Hearing, metabolic, renal
- Multidisciplinary assessment

Nonsyndromic RP predominantly affects the retina.

Three major Mendelian patterns

Autosomal patterns

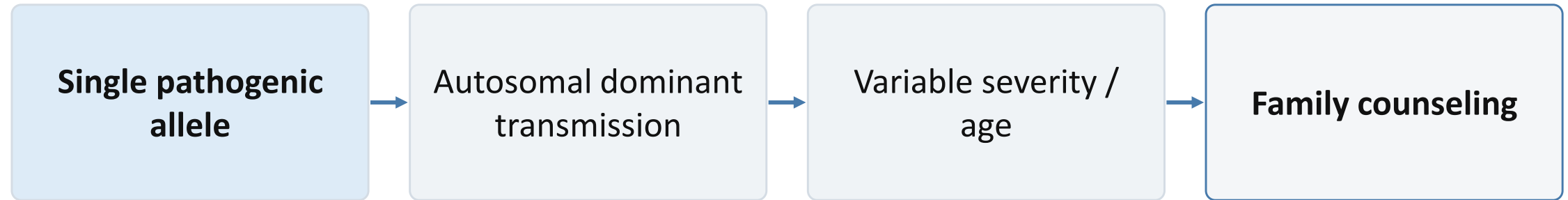
- Dominant: One disease allele may suffice
- Recessive: Biallelic disease variants
- Family history may be negative

X-linked pattern

- Variant on the X chromosome
- Often more severe in hemizygous males
- Female carrier expression varies

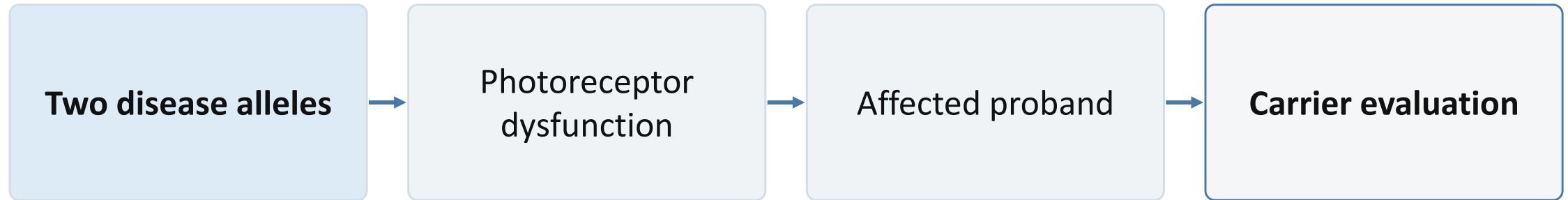
Autosomal dominant RP is transmitted vertically in some pedigrees.

Autosomal dominant RP: Pedigree implications



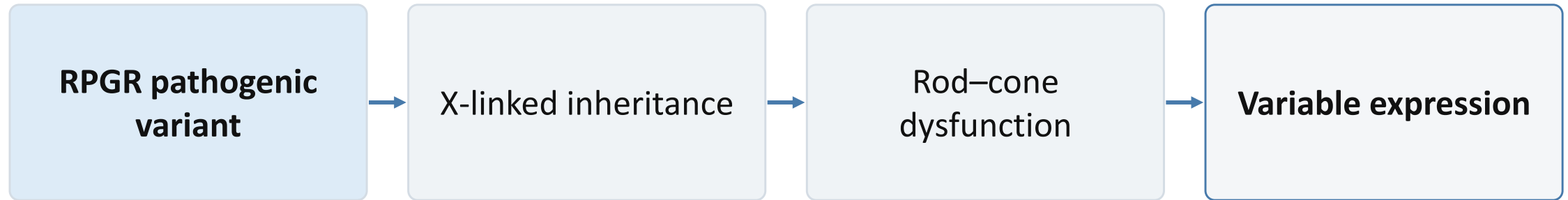
- A pathogenic variant in one allele may cause disease.
- Affected individuals may appear in successive generations.
- Variable expressivity and incomplete penetrance can complicate pedigree interpretation.

Autosomal recessive RP: Pedigree implications



- Biallelic pathogenic variants are generally required.
- Parents can be clinically unaffected carriers.
- Apparently sporadic disease does not exclude a monogenic recessive disorder.

X-linked RP: A distinct clinical pattern



- RPGR is an important gene in X-linked RP.
- Hemizygous males may present with early, severe rod-cone dysfunction.
- Heterozygous females can have widely variable phenotypes.

Onset and severity are not fixed by inheritance alone

- A tendency toward later onset in autosomal dominant RP.
- Genotype, specific variant, and individual context influence expression.
- Avoid assuming inheritance pattern from age at presentation alone.

Genetic heterogeneity has two dimensions

Locus heterogeneity

- Many genes
- Convergent retinal phenotype
- Panel-based testing helps

Allelic heterogeneity

- Different variants in one gene
- Variable severity or phenotype
- Variant-level interpretation matters

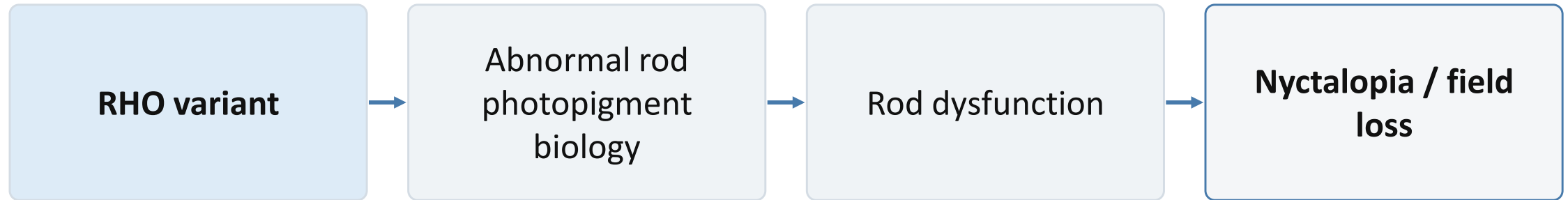
Locus heterogeneity: Disease variants in different genes produce RP.

Core genes emphasized

Gene	High-yield association
RHO	Rhodopsin / rod function
USH2A	RP ± hearing phenotype
RPGR	X-linked RP
EYS	Autosomal recessive RP

RHO — encodes rhodopsin, a major rod photopigment.

RHO: Linking phototransduction to degeneration



- Rhodopsin mediates light detection in rods.
- Disease-causing RHO variants perturb normal rod biology by variant-dependent mechanisms.
- Rod dysfunction can therefore be an early clinical feature.

USH2A: Retinal disease with or without hearing loss

Isolated retinal phenotype

- Typical RP features
- No recognized hearing phenotype
- Ongoing phenotype assessment

Usher-associated phenotype

- RP plus sensorineural hearing loss
- Additional evaluation indicated
- Genotype–phenotype nuance

USH2A variants can cause nonsyndromic RP or Usher syndrome.

RPGR: An important X-linked locus

- RPGR is a recognized cause of X-linked RP.
- Some RPGR regions are technically challenging for sequencing.
- Molecular assay limitations should be considered if suspicion remains high.

EYS: Structural maintenance and recessive RP

- Biallelic EYS pathogenic variants are associated with retinal degeneration.
- The clinical presentation overlaps other forms of rod–cone dystrophy.
- Phenotype alone generally cannot assign EYS as the cause.

Source-text quality control: RPGR versus RGPR

Extracted wording

- “RGPR” in supplied conversion
- Not the standard disease gene symbol

Verified nomenclature

- RPGR
- Retinitis pigmentosa GTPase regulator

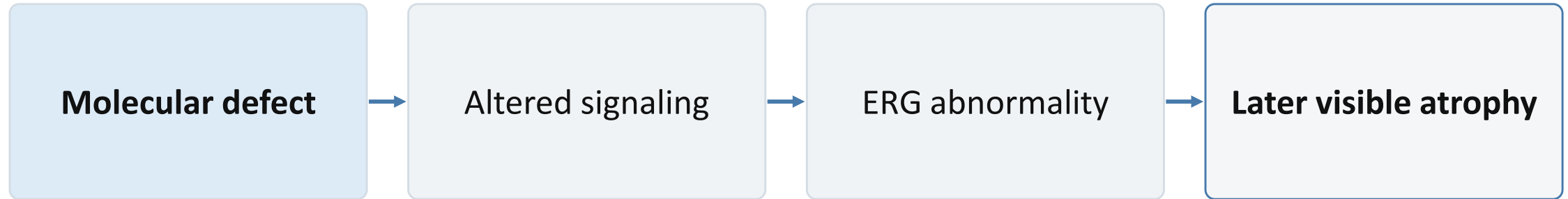
The extracted Robbins paragraph spells the gene “RGPR”.

Functional categories of RP-associated genes

Functional domain	What can fail
Phototransduction	Normal conversion of light into signal
Visual cycle / RPE support	Photopigment regeneration and homeostasis
Structure / transport	Outer-segment maintenance
Gene expression	Photoreceptor protein regulation

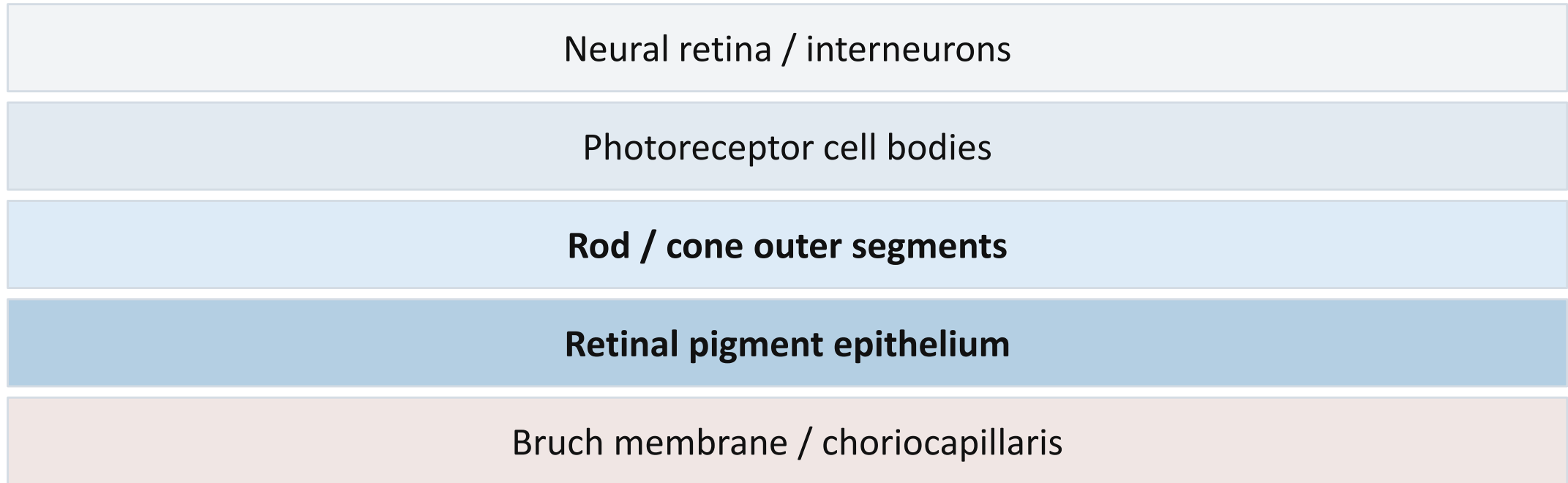
Phototransduction: Processing the light signal.

Phototransduction failure can precede cell loss



- Mutated pathway components can impair retinal response before overt structural atrophy.
- Functional testing is therefore complementary to structural examination.
- A normal-looking early fundus does not exclude inherited retinal dysfunction.

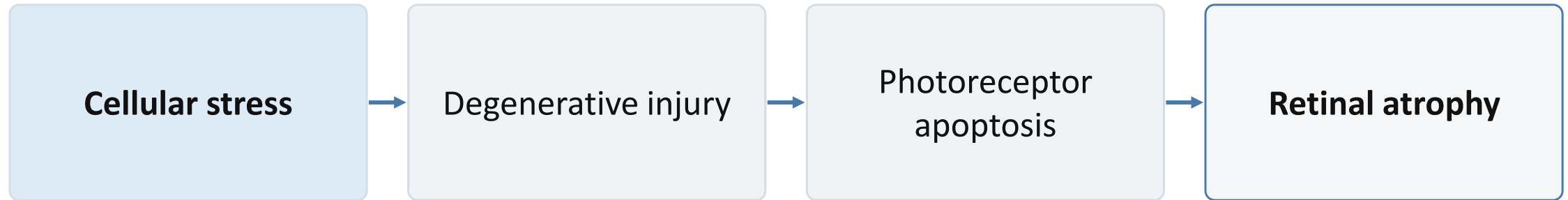
The photoreceptor–RPE relationship



Conceptual retinal-layer schematic — not a histologic section

- Photoreceptors depend on an intact supporting RPE.
- Variants may primarily affect photoreceptor cells or RPE-associated pathways.

Programmed cell death in retinal degeneration

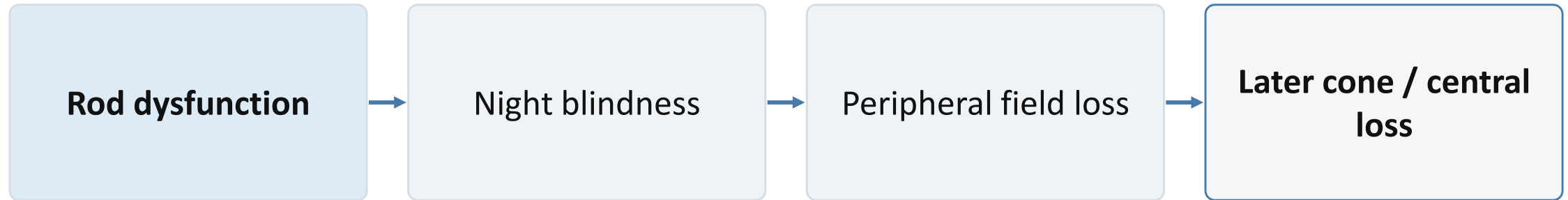


- The Robbins account identifies apoptosis as a mechanism of rod and cone death.
- Progressive cell depletion explains irreversible loss of light-sensing capacity.
- Different causal mutations may converge on this tissue-level outcome.

RIP kinase and cone cell death

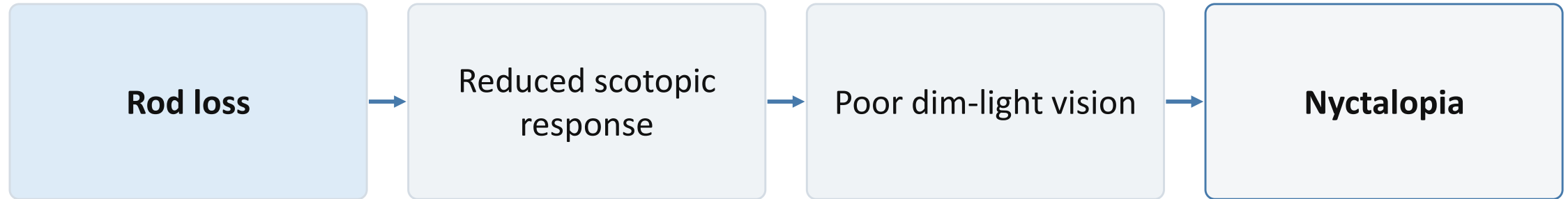
- RIP kinase activation as a partial mediator of cone death.
- This is a mechanistic observation, not a clinical diagnostic criterion.
- It does not establish a routinely available RP treatment target.

Typical rod–cone progression



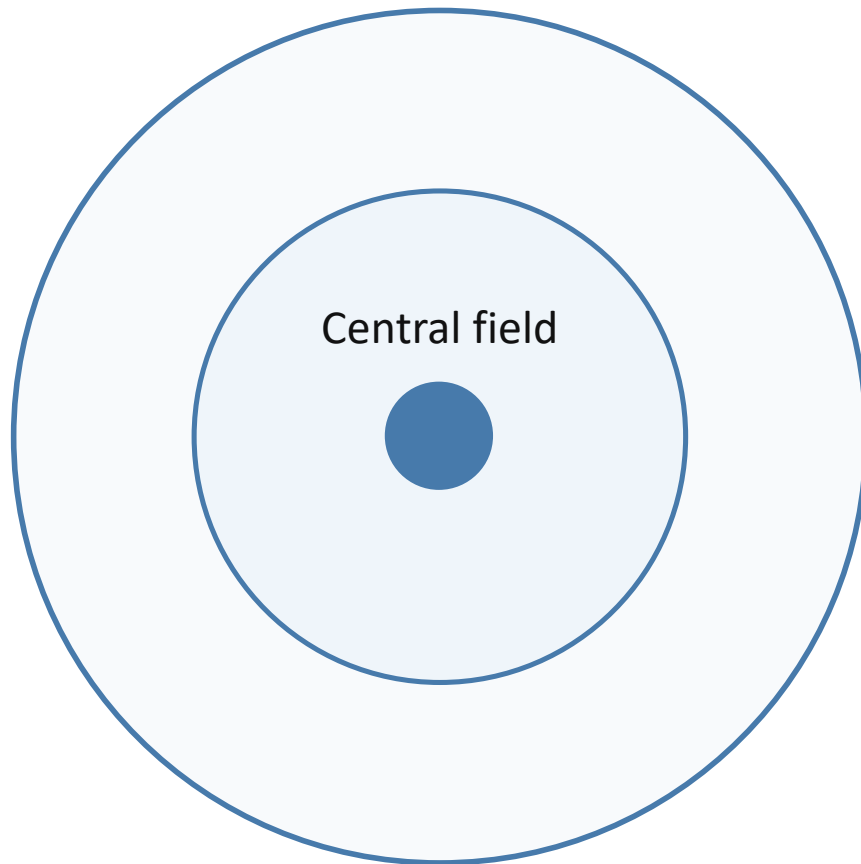
- Rod dysfunction often dominates early manifestations.
- Peripheral field reduction develops as rod-mediated function deteriorates.
- Progression to cone involvement may reduce central acuity.

Why night blindness appears early



- Rods are specialized for low-light vision.
- Loss of rod-mediated sensitivity impairs dark adaptation and navigation in dim environments.
- Nyctalopia is a functional manifestation, not an inflammation-related symptom.

Why visual fields constrict



Central field

More vulnerable peripheral function

Photoreceptor dysfunction may be pronounced outside the central macula.

Peripheral or ring scotomas can expand with disease progression.

Preserved central acuity can coexist with disabling field loss.

Conceptual field schematic — not a patient perimetry plot

Why central acuity may decline later

Earlier phase

- Night-vision complaints
- Constriction of side vision
- Central acuity may remain good

Advanced phase

- More extensive cone dysfunction
- Central visual impairment
- Major daily-living consequences

The cone-rich central retina may initially remain relatively functional.

Clinical trajectories vary substantially

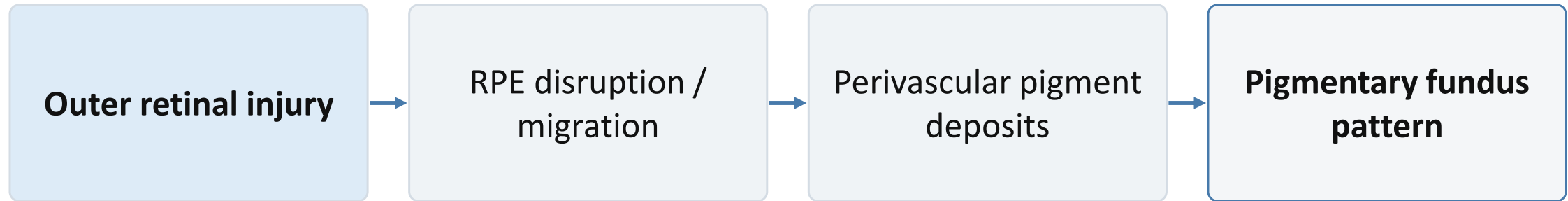
- Age of onset and rate of progression differ between genotypes and individuals.
- Symptoms, function, and retinal appearance are not always synchronous.
- Prognosis requires longitudinal measurements rather than a single snapshot.

Funduscopy morphology: Classic triad

Finding	Pathologic interpretation
Bone-spicule pigmentation	Pigment redistribution around retinal vessels
Vessel attenuation	Reduced caliber with retinal atrophy
Waxy disc pallor	Optic nerve head pallor in advanced disease

Bone-spicule–like intraretinal pigment clumping.

Bone-spicule pigmentation: Why the pattern forms



- Degeneration accompanies migration or redistribution of RPE pigment.
- Dark pigment clumps become conspicuous along retinal vessels.
- Pigment location is a consequence of chronic injury, not evidence of active retinitis.

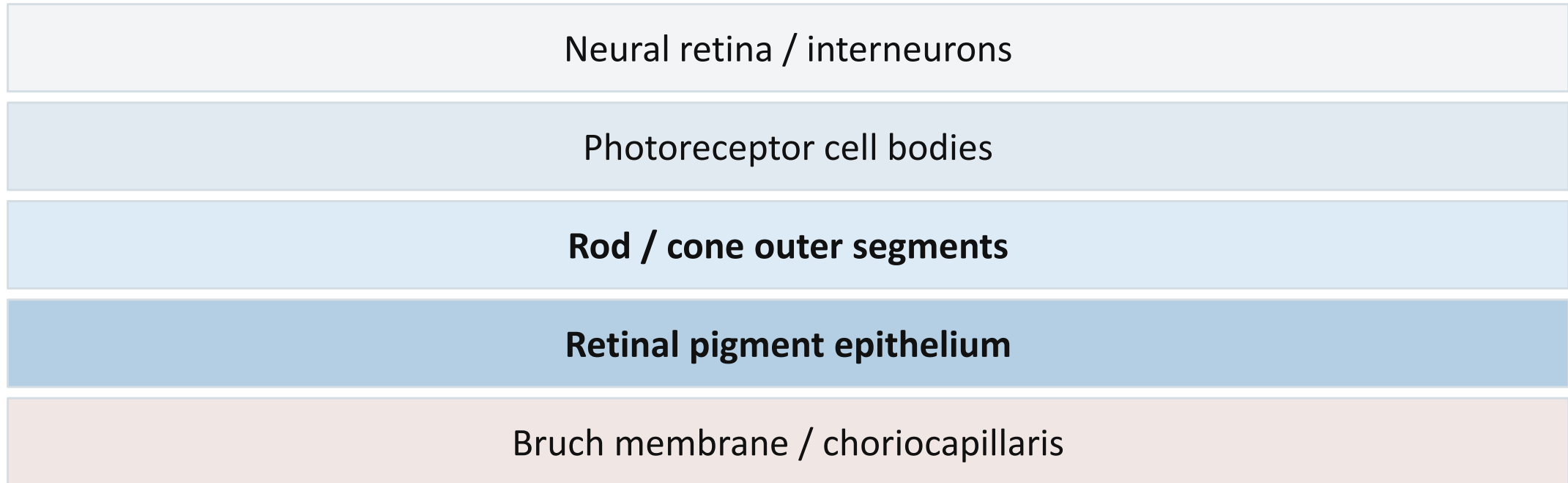
Retinal vessel attenuation

- Narrowed retinal vessels accompany chronic retinal atrophy.
- Attenuation should be interpreted together with functional and other fundus findings.
- Vessel narrowing is not specific enough to establish RP by itself.

Waxy optic-disc pallor

- A pale optic nerve head can develop in longstanding RP.
- It belongs to the classic phenotypic triad with pigmentation and vessel attenuation.
- It should not be confused with proof of primary optic neuropathy.

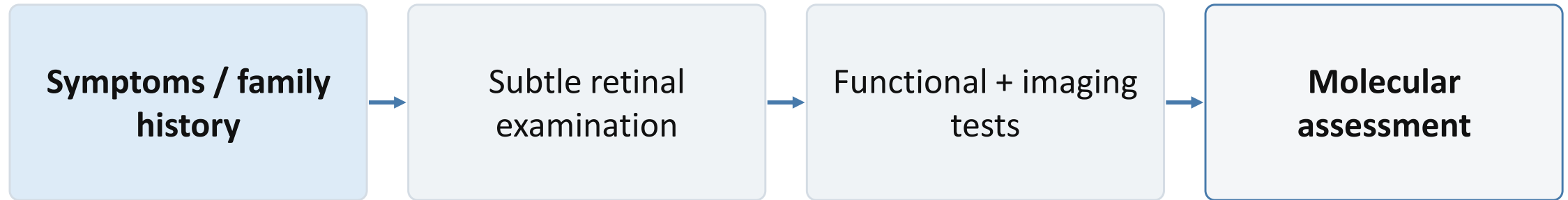
Tissue-level consequence: Outer retinal atrophy



Conceptual retinal-layer schematic — not a histologic section

- Photoreceptor loss primarily affects the outer neural retina.
- Associated RPE changes alter the overlying retinal appearance.

Early RP may lack the classic appearance



- Photoreceptor dysfunction can be detectable before extensive pigmentation develops.
- Normal or subtle fundus appearance does not rule out early RP.
- ERG, visual fields, multimodal imaging, and genetics may clarify the diagnosis.

Systemic clues can redefine the diagnosis

Clinical clue	Consider
Hearing impairment	Usher syndrome
Obesity, polydactyly, renal issues	Bardet–Biedl syndrome
Neuropathy / ataxia / hearing symptoms	Refsum disease

Ask about hearing loss, vestibular symptoms, developmental findings, and multisystem disease.

Usher syndrome: Retina and hearing

Ophthalmic phenotype

- Progressive rod–cone dysfunction
- Night blindness / field loss
- Pigmentary degeneration

Systemic phenotype

- Sensorineural hearing impairment
- Vestibular findings vary by type
- Multidisciplinary counseling

RP is associated with sensorineural hearing loss in Usher syndrome.

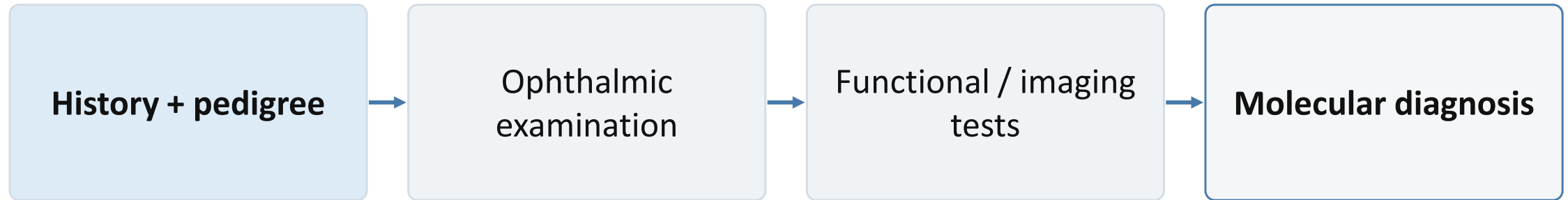
Bardet–Biedl syndrome: A multisystem disorder

- Retinal dystrophy may occur with obesity, polydactyly, and renal or developmental features.
- A syndromic diagnosis has implications beyond visual prognosis.
- Recognition prompts comprehensive systemic assessment.

Refsum disease: A relevant syndromic differential

- RP-like retinal degeneration can occur in Refsum disease.
- Neurologic, hearing, and other systemic clues should prompt targeted evaluation.
- Unlike many inherited retinal dystrophies, identifying its metabolic cause can influence management.

Diagnostic approach: Phenotype first



- Document symptoms, visual acuity, and family history.
- Evaluate retinal appearance and distribution of dysfunction.
- Combine fields, ERG, retinal imaging, and genetic analysis as indicated.

History: Questions that discriminate

- When did night blindness or dark-adaptation difficulty begin?
- Is field loss progressive and bilateral?
- Are relatives affected or are there consanguineous relationships?
- Are hearing, neurologic, renal, or metabolic manifestations present?

Pedigree analysis guides—not replaces—testing

Pedigree information

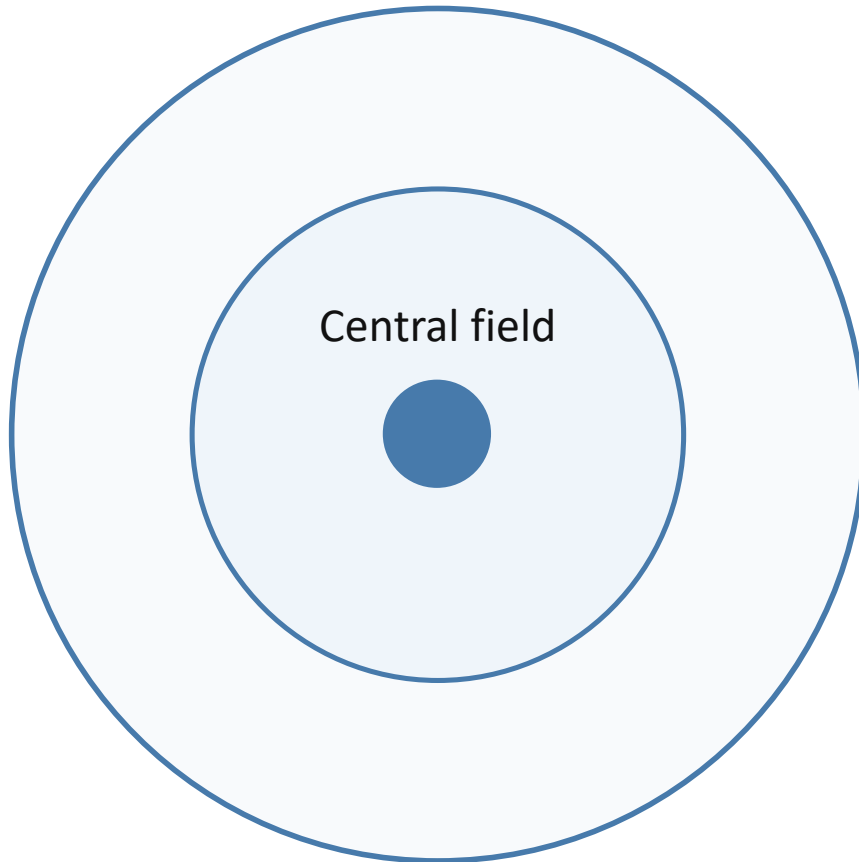
- Affected relatives
- Sex distribution
- Age at symptom onset

Limitations

- Small pedigrees
- Reduced penetrance
- Variable expressivity / de novo variants

Vertical transmission raises suspicion for autosomal dominant disease.

Visual fields document peripheral impairment



More vulnerable peripheral function

Perimetry detects constriction and scotomas that acuity tests can miss.

Field mapping can establish functional impairment at baseline.

Serial assessments support evaluation of progression.

Conceptual field schematic — not a patient perimetry plot

Full-field ERG: Evidence of generalized dysfunction

Scotopic / dark adapted

- Rod-mediated response
- Often reduced early
- Useful for rod–cone distinction

Photopic / light adapted

- Cone-mediated response
- May be relatively preserved early
- Can decline with progression

Dark-adapted responses assess rod-mediated function.

Optical coherence tomography

Neural retina / interneurons

Photoreceptor cell bodies

Rod / cone outer segments

Retinal pigment epithelium

Bruch membrane / choriocapillaris

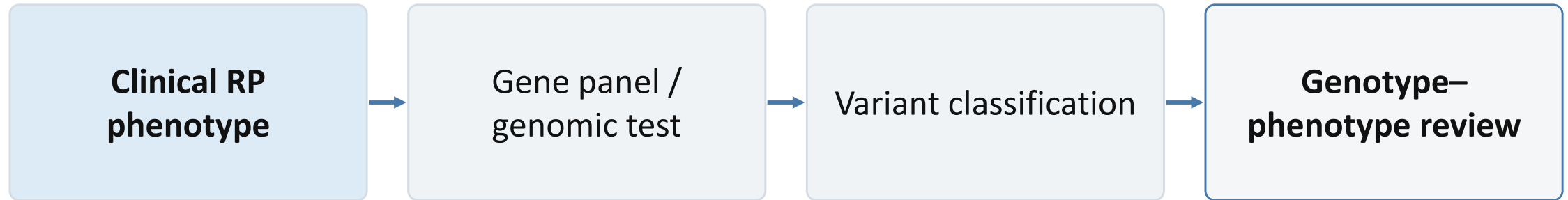
Conceptual retinal-layer schematic — not a histologic section

- OCT delineates retinal layers and outer-retinal structural loss.
- It can document macular integrity and associated complications such as cystoid macular edema.

Fundus autofluorescence

- Fundus autofluorescence provides an indirect view of RPE-associated signal patterns.
- It can map retinal changes beyond what color photography shows.
- Findings need interpretation alongside fundus examination, OCT, and function.

Genetic testing: Why broad panels are useful



- Many genes can produce similar clinical RP phenotypes.
- A well-designed inherited retinal dystrophy gene panel is often appropriate.
- Assay coverage and copy-number / difficult-region limitations matter.

Interpreting a molecular result

Result category	Clinical use
Causal variant(s)	Supports gene-specific diagnosis
VUS	Not proof of causality
Negative / inconclusive	Revisit assay coverage and phenotype

“Pathogenic” and “likely pathogenic” differ from a variant of uncertain significance.

Differential: Rod–cone versus cone–rod dystrophy

Feature	Typical RP	Cone–rod dystrophy
Early problem	Night / side vision	Central / color vision
Early function	Rod-predominant	Cone-predominant
Testing	ERG rod deficit	ERG cone deficit

RP usually has a rod-predominant initial dysfunction.

Differential: Choroideremia

- Choroideremia can also cause night blindness and progressive peripheral field loss.
- Its characteristic RPE and choroidal atrophy differs from typical RP patterns.
- Fundus structure, inheritance, and genetics support distinction.

Differential: Inherited retinal dystrophy is broader than RP

RP pattern

- Rod–cone dysfunction
- Classic triad may appear
- Progressive bilateral phenotype

Alternatives

- Cone–rod dystrophy
- Choroideremia
- Other retinal dystrophies / mimics

Other inherited retinal disorders may share night blindness or pigmentary changes.

Differential: RP versus age-related macular degeneration

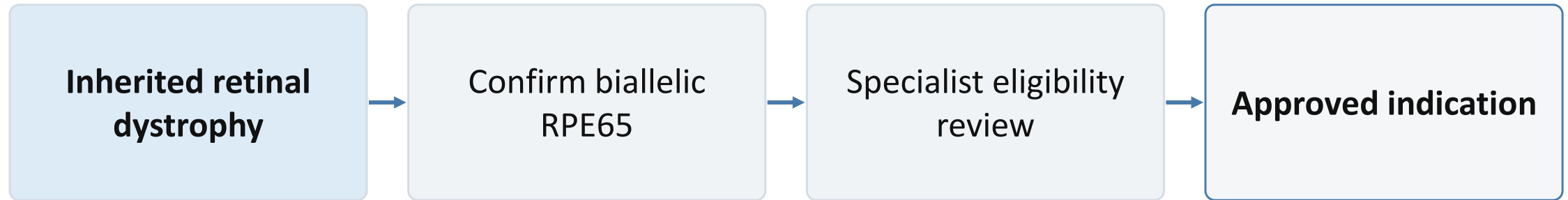
Feature	Retinitis pigmentosa	AMD
Main early phenotype	Night / peripheral dysfunction	Central macular dysfunction
Distribution	Generalized rod–cone retina	Macula-centered
Hallmark morphology	Spicules / vessel attenuation	Drusen / atrophy or neovascularity

RP: Inherited, typically rod–cone retinal degeneration with peripheral symptoms.

Management: Preserving function and independence

- No general cure exists for the heterogeneous group of RP disorders.
- Visual rehabilitation, appropriate aids, and support services can mitigate disability.
- Management should address treatable complications and systemic syndromic disease.

Gene-specific therapy is not a universal RP treatment



- The FDA-approved voretigene neparvovec indication is specific to confirmed biallelic RPE65 mutation-associated retinal dystrophy.
- Eligibility is molecularly defined and requires specialist assessment.
- This approval must not be extrapolated to RHO-, RPGR-, USH2A-, or EYS-related RP.

Separating approved care from investigational approaches

Available care

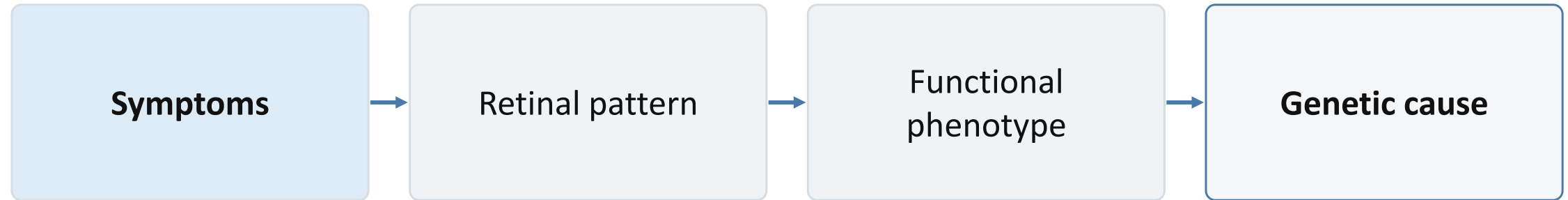
- Diagnostic assessment
- Low-vision rehabilitation
- RPE65-specific treatment in eligible patients

Research directions

- Additional gene-based interventions
- Cell therapies
- Other experimental approaches

Gene-based, cellular, and neuroprotective strategies remain under study for many genotypes.

Integrated clinicopathologic reasoning



- Night blindness suggests rod dysfunction.
- Progressive constricted fields support diffuse photoreceptor involvement.
- Pigmentary migration, arteriolar attenuation, and disc pallor reflect chronic retinal degeneration.

Teaching case: Progressive night blindness

Hypothetical teaching case

- Hypothetical case: Adolescent with difficulty walking in dim light and slowly narrowing side vision.
- Central acuity remains useful; Family history is initially unrevealing.
- Question: Which photoreceptor population is most likely to be impaired first?

Teaching case: Retinal dystrophy plus hearing loss

Hypothetical teaching case

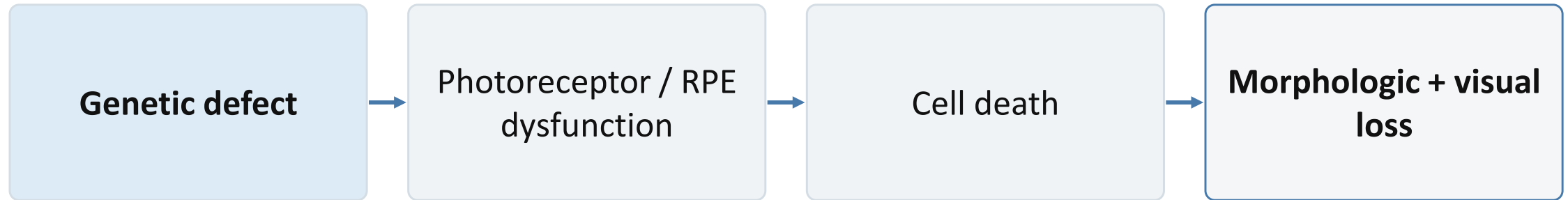
- Hypothetical case: Young adult with night blindness and sensorineural hearing impairment.
- Retinal examination suggests generalized pigmentary degeneration.
- Question: Which category of inherited disease must be evaluated?

Teaching case: Central impairment precedes nyctalopia

Hypothetical teaching case

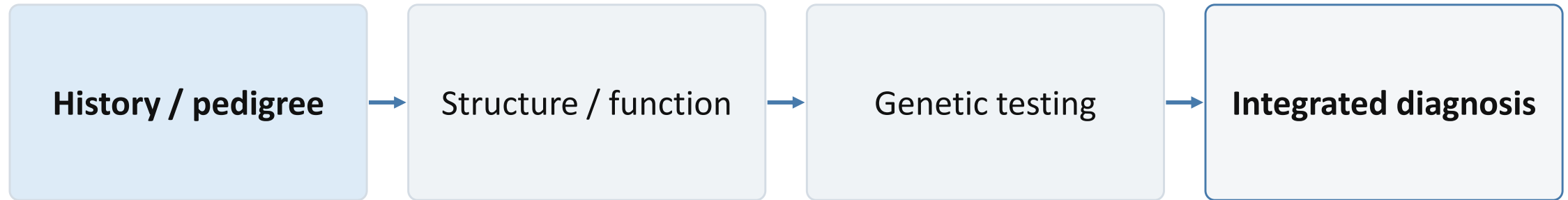
- Hypothetical case: Early color difficulty and photophobia, followed later by peripheral symptoms.
- Full-field ERG shows disproportionately impaired cone responses.
- Question: Does this sequence favor classic rod–cone RP or cone–rod dystrophy?

Pathogenesis: The core causal chain



- Inherited defects can impair rod/cone and RPE function.
- Photoreceptor loss drives progressive loss of visual sensitivity.
- Secondary retinal atrophy and pigment migration produce classic morphology.

Diagnosis: The core evidence chain



- Clinical history and pedigree establish the suspected phenotype.
- Fundus examination, fields, OCT/FAF, and ERG provide complementary evidence.
- Molecular testing identifies genotype when an interpretable causal variant is found.

Key discriminators to retain

- Night blindness with field constriction indicates rod-predominant dysfunction.
- Bone-spicule pigmentation is secondary and may be absent early.
- Syndromic clues—especially hearing or multisystem findings—must not be overlooked.
- A molecularly defined treatment for one genotype is not treatment for all RP.

Selected sources and scientific provenance

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 29, p 1206.

GeneReviews: Nonsyndromic Retinitis Pigmentosa Overview (NCBI Bookshelf NBK1417).

National Eye Institute: Retinitis Pigmentosa (2025).

U.S. Food and Drug Administration: LUXTURN A prescribing/indication information.