

Retinal Lymphoma

Clinicopathologic diagnosis, ocular imaging and CNS implications

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Learning objectives

- Localize neoplastic infiltrates to vitreous, neural retina and retinal pigment epithelium.
- Recognize the clinical masquerade and select a diagnostic specimen.
- Integrate cytology, immunophenotyping and molecular evidence with CNS evaluation.
- Interpret contemporary treatment and follow-up principles without overclaiming evidence.

Scope and terminology

Retinal lymphoma

Aggressive intraocular B-cell neoplasm

Predilection for neurosensory retina and RPE

Characteristically associated with brain disease

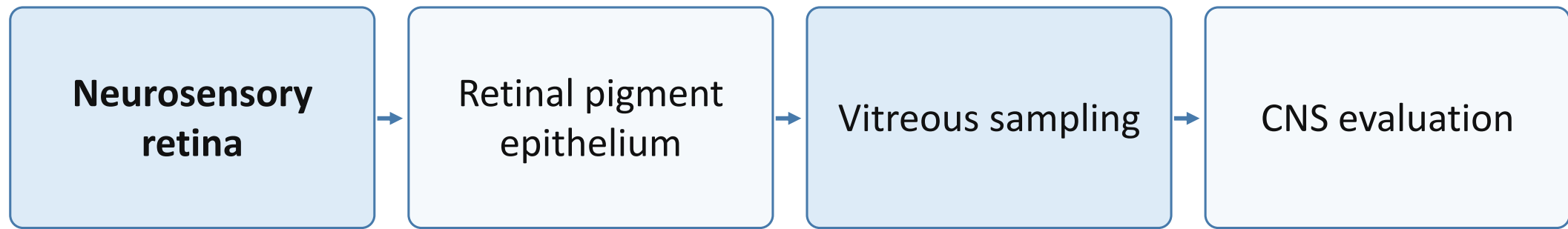
Contemporary clinical designation

Primary vitreoretinal lymphoma (PVRL)

Predominantly large B-cell lymphoma

Within the primary CNS lymphoma spectrum

The eye as a CNS-associated compartment



The anatomic localization of ocular lesions guides sampling and staging; These steps are not a biological lineage.

Retinal layers relevant to lymphoma

Vitreous cavity

Neurosensory retina

Retinal pigment epithelium

Bruch membrane

Choroid

PVRL commonly involves vitreous, retina and the RPE interface; Choroidal lymphoma occupies a different anatomic compartment.

Why the RPE interface matters

Lesions at or above the RPE

Sub-RPE deposits and retinal infiltrates

OCT: RPE nodularity or outer retinal signal

Supports the vitreoretinal pattern

Lesions deep to Bruch membrane

Primarily choroidal distribution

Different imaging contour/depth

Suggests a choroidal process in the differential

Retinal lymphoma is not retinoblastoma

Retinal lymphoma

Typically older adult

Large B-cell hematolymphoid neoplasm

Common CNS association

Vitreous cytology often key

Retinoblastoma

Typically young child

Retinal embryonal neoplasm

RB1 pathway relevant

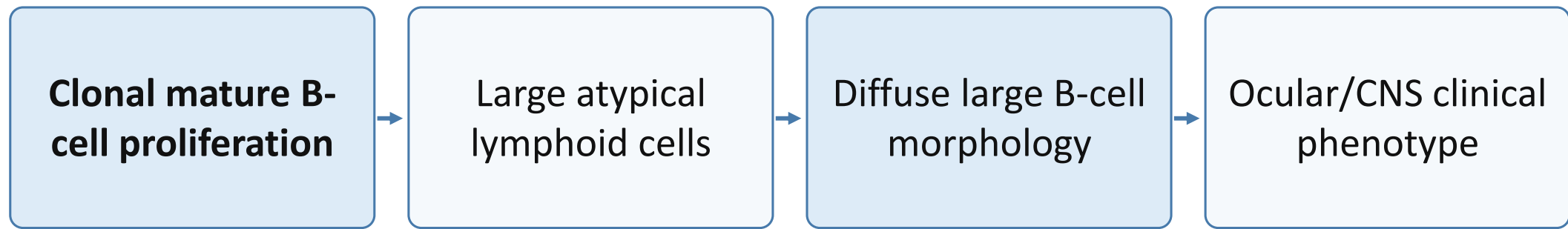
Retinal mass with rosettes in some tumors

Age and host context

- PVRL classically presents in older adults, but age alone never determines the diagnosis.
- Immunocompromised patients warrant evaluation for CNS/ocular lymphoma and infectious mimics.
- A prolonged “uveitis” history does not exclude malignancy.

Do not use patient age or steroid responsiveness as a substitute for tissue diagnosis.

Histologic identity: Large B-cell lymphoma



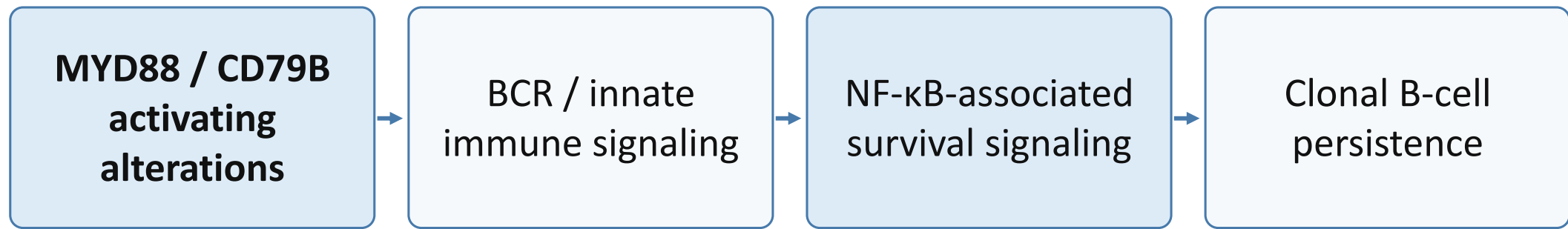
Most cases are large B-cell lymphomas; Uncommon non-B-cell intraocular lymphomas require separate classification.

Lymphoma phenotype is not defined by one stain

- Lineage markers such as CD20, PAX5 and CD79a support B-cell differentiation.
- CD3 highlights accompanying T cells and helps assess reactive components.
- An integrated morphology–immunophenotype–molecular interpretation is required.

Marker expression is supportive; Histologic subtype is a composite diagnosis.

Molecular context: B-cell receptor signaling



Conceptual pathway only. Mutations are common in PVRL, but not present in every case and not sufficient alone for diagnosis.

MYD88 p.L265P: Role and limits

What a positive assay adds

Supports an ocular B-cell lymphoma

Useful on paucicellular specimens

May complement cytology and clonality

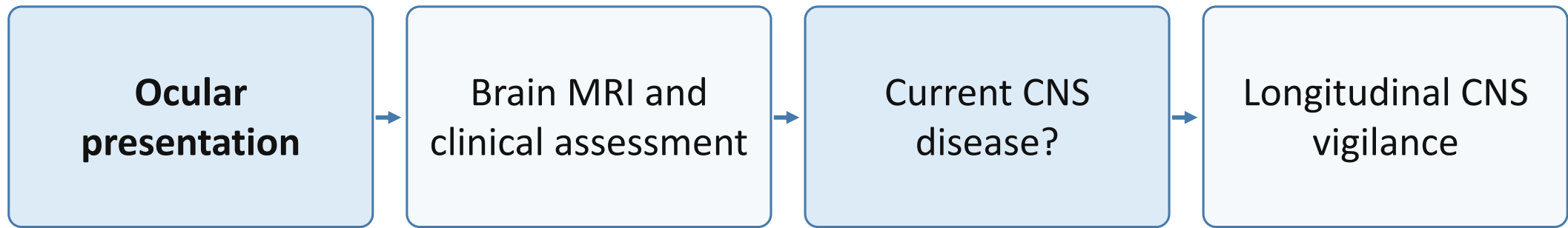
What it does not establish

Not positive in all confirmed cases

Does not independently localize tumor

Must be interpreted in the clinical context

CNS connection defines the clinical stakes



PVRL can precede, accompany or follow CNS lymphoma; The time sequence varies by patient.

The optic nerve as a route of extension

Neurosensory retina

Optic nerve head

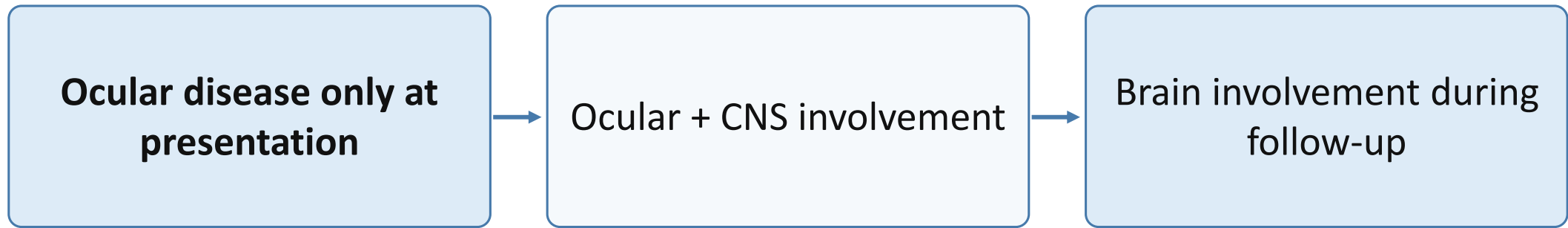
Optic nerve

Intracranial visual pathway

Brain

Possible spread to the brain along the optic nerve; Clinical CNS disease can also reflect the broader PCNSL spectrum.

Possible clinical trajectories



Alternative patterns are shown, not a deterministic progression for every patient.

Early symptoms are nonspecific

- Floaters and painless blurred vision are characteristic presenting complaints.
- Symptoms may fluctuate despite persistent neoplastic disease.
- Unilateral symptoms do not exclude bilateral involvement on careful examination.

Persistent unexplained floaters plus posterior segment inflammation warrant a malignancy-aware differential.

A classic masquerade: Chronic uveitis

Features that resemble uveitis

Vitreous cells and haze

Blurred vision and floaters

Variable retinal inflammation-like lesions

Features that raise suspicion

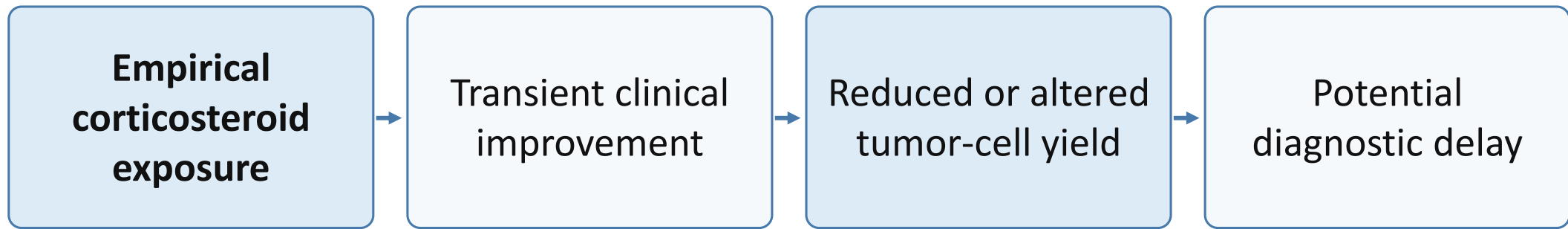
Older patient with atypical course

Relapsing or treatment-resistant disease

Creamy outer retinal/RPE infiltrates

Limited macular edema despite vitritis

Corticosteroids can obscure the diagnosis



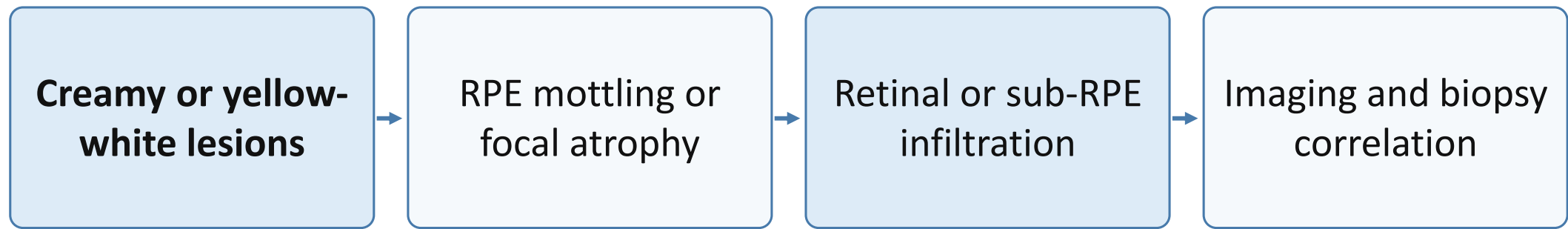
Consensus recommends withholding systemic corticosteroids before diagnostic vitrectomy when clinically feasible; Coordinate this decision with treating specialists.

Slit-lamp observations

- Vitreous cells may appear in sheets, clusters or dense haze.
- Anterior segment inflammation may be relatively modest compared with vitreous infiltration.
- Evaluate both eyes; Absence of striking retinal lesions does not exclude lymphoma.

A normal-appearing fundus through dense vitritis is not reassuring.

Fundus: Creamy retinal and subretinal lesions



Findings are suggestive rather than pathognomonic; Avoid diagnosing lymphoma solely from fundus color.

Patterns beyond a discrete lesion

- Optic disc edema, perivascular changes and serous retinal detachment may occur.
- RPE pigment disturbance can persist after an active infiltrate resolves.
- Retinitis-like presentations require exclusion of infection and other mimics.

Document anatomic distribution, not just the presence of “white spots”.

Multimodal imaging has complementary roles

Modality	Primary information	Key limitation
Color fundus	Vitreous haze; Lesion distribution	Subtle lesions may be missed
OCT	Layer and sub-RPE localization	Imaging is not tissue proof
FAF	RPE metabolic disturbance	Signal varies with activity/damage
Angiography	Staining, blockage, leakage	Findings are nonspecific

OCT: Anatomic localization

Inner retina

Outer retina

Subretinal space

RPE

Bruch membrane

Hyperreflective material may involve outer retina, subretinal space, or the sub-RPE interface. This drawing is schematic, not an OCT scan.

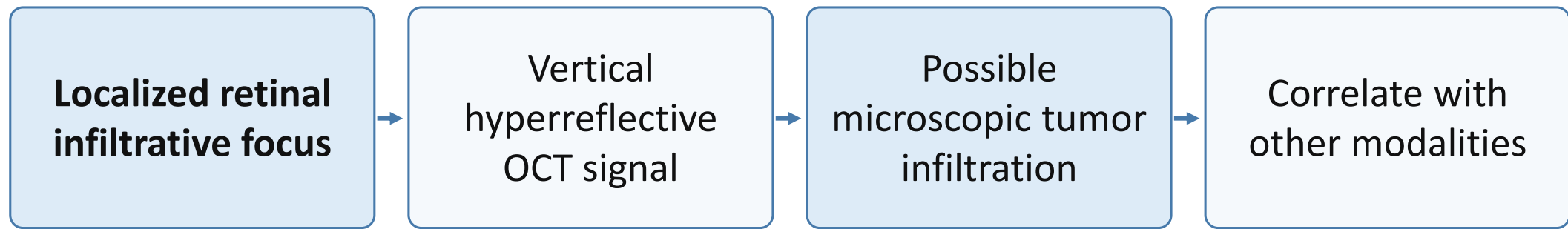
Schematic (not histology)

OCT signs that increase suspicion

- Nodular elevation or irregularity of the retinal pigment epithelium.
- Outer retinal hyperreflective foci and subretinal infiltrative material.
- Vitreous cellular echoes and occasional pigment epithelial detachment.

Interpret OCT in combination with fundoscopy, FAF and clinical context.

Vertical hyperreflective columns



Proposed association, not a stand-alone diagnostic sign; Exact mechanism remains inferential.

Fundus autofluorescence patterns

Hyperautofluorescence

May accompany active sub-RPE lesions

Related to disturbed RPE function

Often paired with OCT nodularity

Hypoautofluorescence

May reflect masking by infiltrate

Can follow RPE atrophy or injury

Does not alone establish inactivity

Fluorescein angiography: What it adds

- Granular or mottled RPE-level fluorescence changes may be seen.
- Blocking and late staining can coexist at different lesion sites.
- Angiography assesses morphology and activity but cannot classify lymphoid cells.

If imaging and clinical course remain suspicious, tissue-based evaluation is still necessary.

An imaging finding is not a tumor diagnosis

Imaging can

Locate abnormalities by retinal layer

Map burden and possible response

Select an accessible biopsy target

Imaging cannot

Establish B-cell clonality alone

Replace cytologic/molecular analysis

Prove absence of microscopic disease

Differential: Inflammatory posterior uveitis

Question	Inflammatory uveitis	PVRL concern
Course	Often follows recognized syndrome	Chronic atypical or relapsing
Vitreous	Inflammatory cells	Clumped atypical cells possible
Retina	Inflammatory/chorioretinal lesions	Creamy infiltrates / RPE deposits
Next step	Cause-directed tests	Ocular biopsy if unexplained

Differential: Infectious retinitis

Infectious considerations

Herpetic necrotizing retinitis

Toxoplasma retinochoroiditis

Opportunistic infection in at-risk hosts

Why lymphoma remains in the differential

Retinitis-like lesions may occur

Nonresponse despite adequate antimicrobial therapy

Negative pathogen evaluation with atypical course

Differential: Choroidal lymphoma

Neural retina

RPE

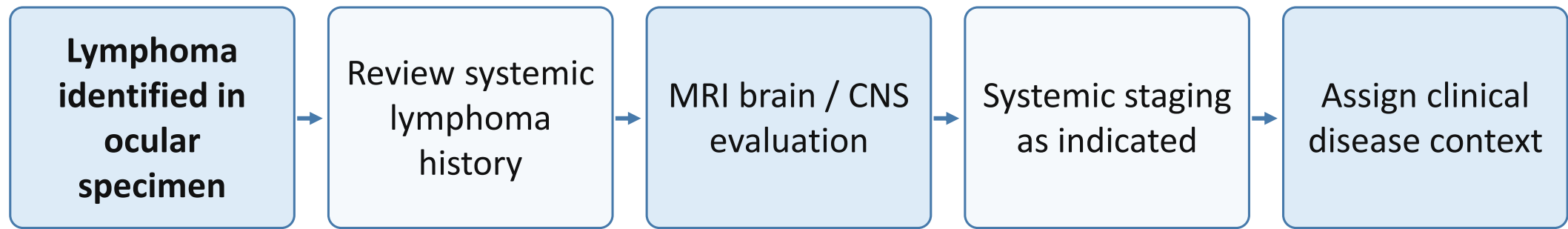
Bruch membrane

Choroidal stroma

Sclera

A primarily choroidal lymphoma is centered below Bruch membrane; PVRL often occupies retinal and sub-RPE compartments.

Differentiate primary from secondary ocular disease



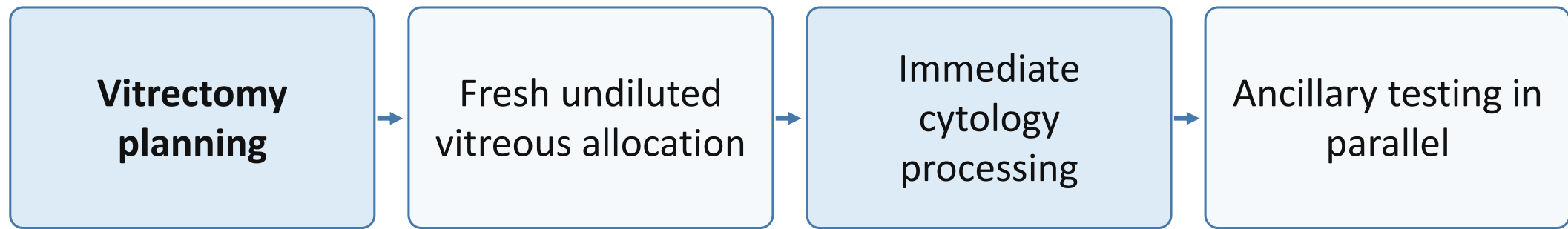
PVRL is used for eye-predominant disease in the PCNSL spectrum after appropriate evaluation;
Secondary intraocular involvement is a separate context.

When to proceed to diagnostic vitrectomy

- Sustained suspicion persists despite noninvasive evaluation and appropriate differential testing.
- Sampling should be planned with ophthalmology and an experienced cytopathology laboratory.
- Specimen volume, priorities, transport conditions and ancillary tests should be agreed before surgery.

A vitrectomy intended for diagnosis is a coordinated tissue-acquisition procedure.

The diagnostic specimen is fragile



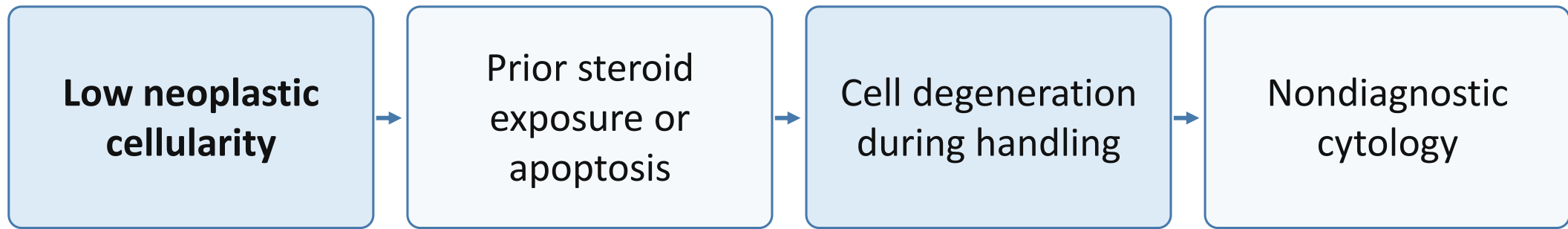
Neoplastic cells can degenerate quickly; Fixation and handling must follow local ocular-cytopathology protocols.

Vitreous cytology: Hallmark morphology

- Large atypical lymphoid cells with irregular nuclear contours and prominent nucleoli.
- Variable cytoplasmic volume, apoptosis and background necrotic debris may be present.
- Reactive small lymphocytes and macrophages can obscure sparse malignant cells.

The diagnosis is morphological and multimodal; This slide does not substitute for a real cytology image.

Why diagnostic yield may be low



False-negative vitreous cytology does not exclude lymphoma when clinical suspicion remains high.

The core immunocytochemical panel

Marker	Interpretive use	Caution
CD20 / PAX5	B-cell lineage	Expression can vary
CD3	Reactive T-cell component	Not equivalent to tumor lineage
CD79a	Additional B-lineage support	Integrate with phenotype
Ki-67	Proliferation pattern	Not independently diagnostic

Typical immunophenotypic pattern

- Many tumors express B-cell markers with MUM1/IRF4 and other activated B-cell–associated features.
- BCL2 and BCL6 may be expressed; CD10 is often absent.
- There is no single immunophenotypic profile that replaces integrated classification.

Phenotypic expectations should guide, not dictate, interpretation of an individual small specimen.

Flow cytometry: Strength and limitation

Strengths

Detects aberrant B-cell populations

Can assess light-chain restriction

Phenotypes multiple markers in parallel

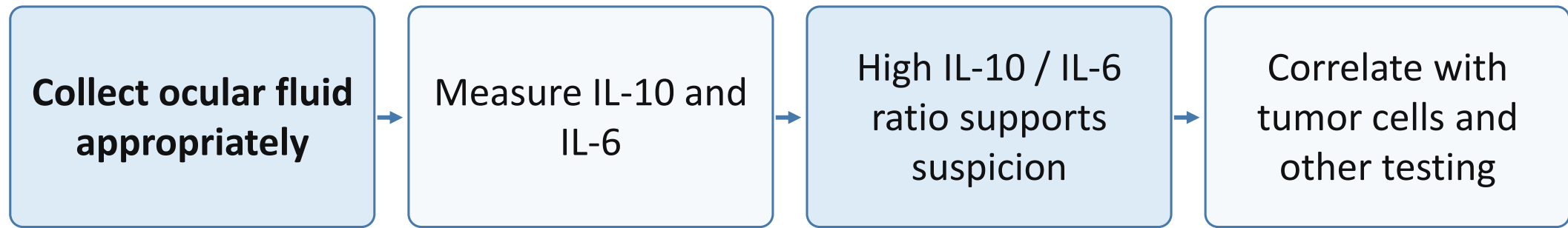
Limitations

Needs viable, adequate cellular material

May miss sparse or fragile tumor cells

Clonality alone is not whole diagnosis

Interleukin-10 and interleukin-6



An IL-10:IL-6 ratio >1 is a consensus-supported indicator, not independently definitive proof.

Interpret a cytokine-positive sample carefully

Reasonable conclusion

Lymphoma becomes more likely

Prioritize morphology and clonality

Reassess imaging and CNS staging

Unwarranted conclusion

Ratio alone proves malignancy

Specimen handling is irrelevant

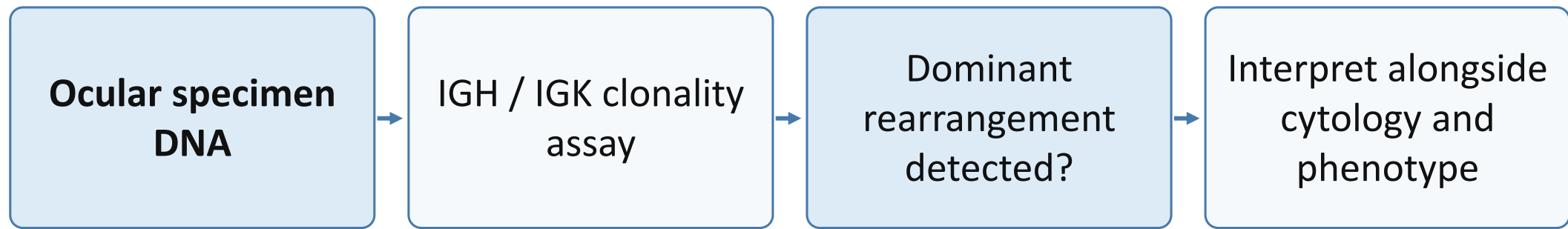
Negative cytology can be ignored

MYD88 mutation testing

- Targeted detection of MYD88 p.L265P can reinforce suspicion for PVRL.
- The mutation is absent from a meaningful subset of confirmed cases.
- Positive testing should be integrated with morphology, lineage and presentation.

A negative result is not a rule-out test; Mutation positivity alone is not sufficient.

Immunoglobulin gene rearrangements

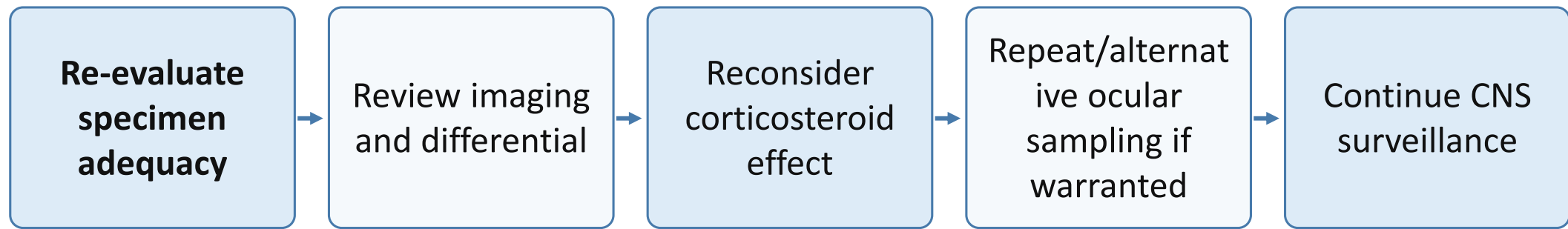


A clonality result supports an expanded population but must be evaluated against small-sample artifacts and biologic context.

Evidence integration rather than one-test diagnosis

Evidence level	Contribution	Interpretation
Direct malignant cytology	Morphologic evidence	Central to diagnosis
B-cell phenotype / clonality	Establish lineage and restricted clone	Strong corroboration
MYD88 / cytokines	Supportive molecular / soluble markers	Not sufficient in isolation
Imaging / clinical pattern	Localization and suspicion	Guides sampling

When a vitreous biopsy is negative



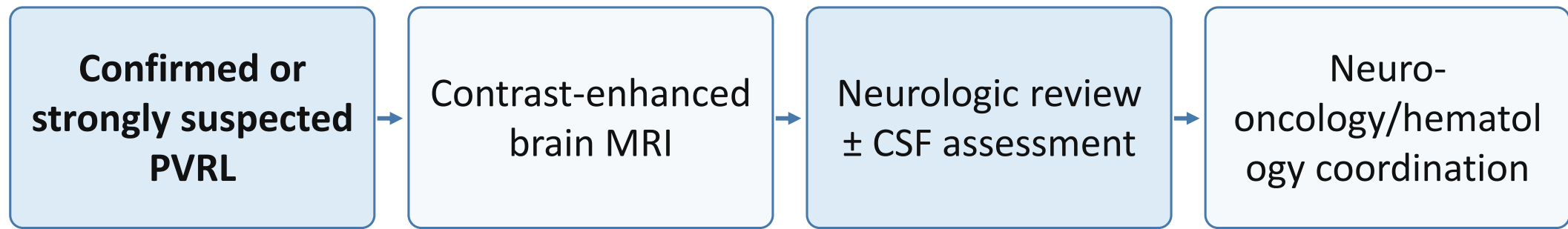
Decisions require a multidisciplinary risk–benefit assessment; Do not declare lymphoma excluded on one negative sample.

Retinal/subretinal tissue biopsy

- May be considered when vitreous testing is nondiagnostic and accessible retinal lesions persist.
- Targets should correspond to the demonstrated site of disease.
- Retinal biopsy has procedural risks and requires specialist planning.

Biopsy site and tissue allocation are clinical decisions, not automatic next steps.

CNS evaluation is part of the diagnosis



A normal initial MRI does not eliminate the need for subsequent surveillance.

Why systemic staging still matters

Primary vitreoretinal pattern

Ocular disease within PCNSL spectrum

No demonstrated systemic primary after assessment

CNS risk remains central

Secondary ocular lymphoma

Ocular infiltration by systemic lymphoma

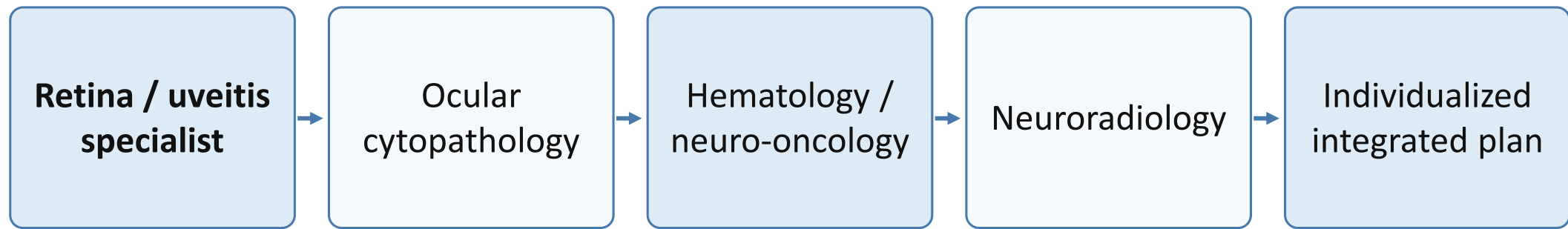
Different staging and therapeutic context

Requires systemic disease evaluation

Pathology report: Essential components

- Specimen type, preservation and diagnostic adequacy.
- Atypical-cell morphology, B-cell markers and cytologic interpretation.
- Ancillary test results with assay-specific limitations.
- Integrated diagnosis and recommendation for clinicoradiologic correlation.

Clinical decision-making is multidisciplinary



Eye control and CNS disease prevention/control are related but distinct clinical goals.

Treatment goals

Ocular objectives

Regress vitreoretinal infiltration

Preserve visual function

Monitor local relapse

Systemic / CNS objectives

Treat or prevent CNS progression when feasible

Address current CNS involvement

Balance toxicity against fitness

Systemic therapy: 2024 guideline emphasis

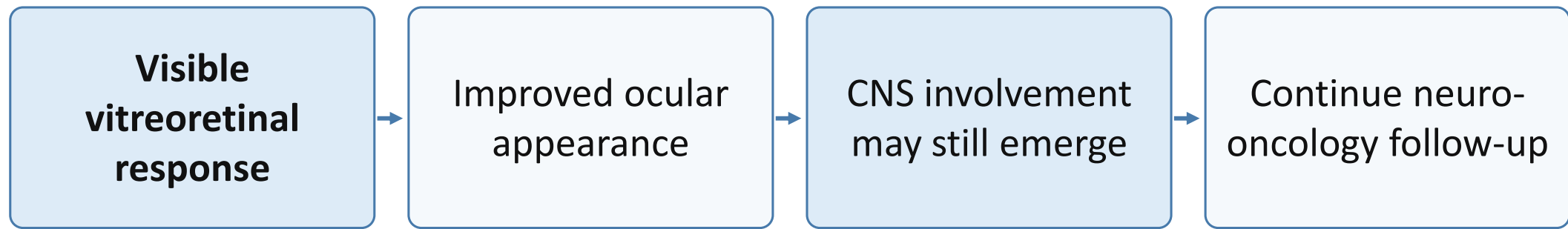
- EHA–ESMO recommends high-dose methotrexate–based induction for fit patients with PVRL.
- Regimen selection parallels primary CNS lymphoma and depends on systemic fitness.
- Evidence is limited by disease rarity; Recommendations include expert consensus.

Treatment choices should follow specialist multidisciplinary assessment, not a generic fixed regimen.

Local ocular treatment

Modality	Clinical intent	Important trade-off
Intravitreal methotrexate	Rapid local tumor control	Injection burden / ocular toxicity
Intravitreal rituximab	Local CD20-targeted therapy	Limited comparative evidence
Ocular radiotherapy	Local consolidation / control	Potential late ocular toxicity

Local control is not CNS assurance



An apparently quiet eye does not establish systemic or CNS remission.

Treatment must reflect patient fitness

Fit for intensive systemic treatment

HD-MTX-based induction in guidelines

Consolidation discussed individually

Ocular treatment added when appropriate

Frailty or contraindications

Local treatment may play larger role

Alternative systemic approaches considered

Toxicity and visual goals prioritized

Assessing response

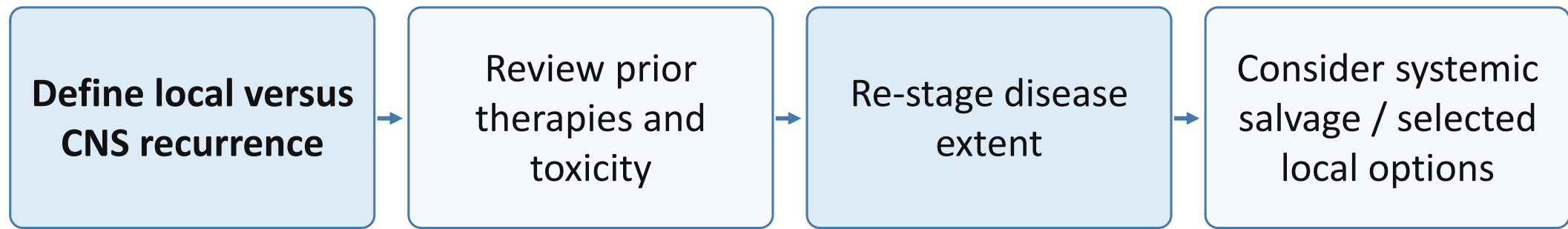
Assessment	What it can track	Why it is insufficient alone
Slit lamp / fundus	Vitreous cells and visible lesions	Microscopic persistence possible
OCT / FAF	Retinal structure and RPE change	Damage may remain after control
MRI brain	Parenchymal CNS involvement	Does not replace ocular exam
Aqueous biomarkers	Potential molecular activity	Standardization varies

Relapse and follow-up

- Ocular and CNS disease require coordinated follow-up even after apparent response.
- New floaters, reduced vision or new neurologic symptoms merit prompt reassessment.
- Repeat imaging, biomarkers and tissue testing may be indicated depending on context.

Follow-up intervals and modalities are individualized; No single universal timetable is implied.

Relapsed disease: Concept and limitations



Guideline salvage choices depend on performance status, prior regimens and CNS involvement;
Efficacy evidence remains heterogeneous.

Case A: An apparent posterior uveitis

A 71-year-old has 9 months of floaters, blurred vision, fluctuating vitreous haze, and recurrent “uveitis” after corticosteroids. OCT shows nodular RPE changes.

What is the highest-value next diagnostic action?

Arrange a planned diagnostic vitrectomy with ocular cytology and ancillary testing, while initiating CNS assessment. Treatable infections still require consideration.

Case A: Dissect the decision

Finding	Interpretation	Action
Older adult + recurrent vitritis	Masquerade phenotype	Keep PVRL on differential
RPE nodularity	Anatomic clue	Guide multimodal imaging
Temporary steroid response	Not exclusionary	Plan appropriate sampling
CNS association	Potential systemic consequence	MRI and referral

Case B: A nondiagnostic aspirate

A patient with multifocal creamy retinal lesions has nondiagnostic vitreous cytology. OCT remains suspicious. An ocular-fluid MYD88 assay is negative.

Does this exclude vitreoretinal lymphoma?

No. Reassess sample quality, previous treatment, imaging and mimics; Consider repeat or targeted retinal sampling after multidisciplinary review.

Case B: Interpret discordant tests

What is known

Clinical localization remains suspicious

One ocular specimen lacked diagnostic cells

MYD88 assay did not detect the mutation

What remains unresolved

Whether tumor cells were sampled

Whether another subtype/molecular profile is present

Which specimen has best next yield

Case C: Ocular control with later CNS lesion

After treatment, fundus lesions regress and vision stabilizes. Several months later, the patient develops new focal neurologic symptoms.

What is the most important clinical inference?

Ocular improvement does not exclude CNS lymphoma. Urgent neurological assessment and brain imaging are required.

What the original textbook establishes

- Primary retinal lymphoma targets neurosensory retina and RPE.
- It usually presents in older individuals and can mimic uveitis.
- Most cases are diffuse large B-cell lymphoma.
- Brain involvement is frequent; Vitreous aspirate demonstrates malignant cells.

What specialist literature adds

Diagnostic refinement

OCT / FAF and layer-specific signs

Coordinated vitrectomy specimen triage

MYD88, cytokines and clonality as adjuncts

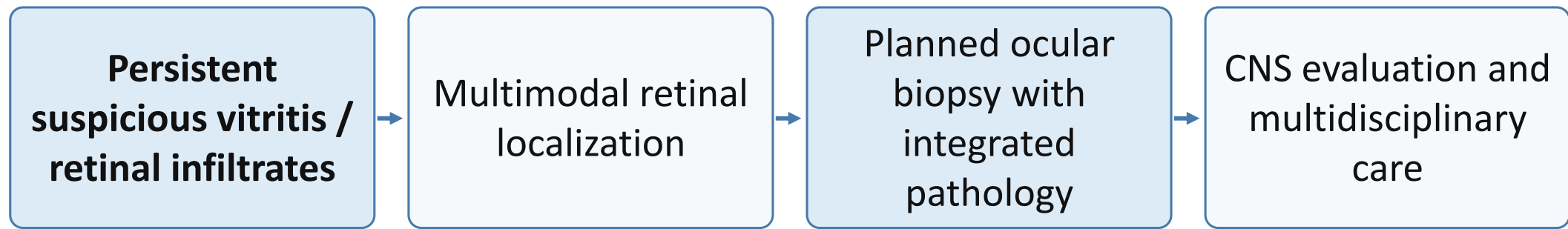
Clinical management refinement

MRI and systemic context

Individualized CNS-directed / ocular therapy

Structured recurrence surveillance

Diagnostic synthesis



Consider infection, inflammatory disease and alternative ocular lymphoma throughout the pathway.

Five defensible conclusions

- Atypical “uveitis” may be an ocular presentation of large B-cell lymphoma.
- The vitreous–retina–RPE distribution helps direct imaging and biopsy.
- Cytology is central; Immunophenotype and molecular tests increase confidence.
- Negative sampling does not automatically exclude the disease.
- CNS evaluation and prolonged coordinated follow-up are integral.

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