
Uveal Nevi and Melanomas

Clinicopathologic foundations · molecular progression · prognosis

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

1

Distinguish common uveal nevi from malignant uveal melanoma.

2

Explain GNAQ/GNA11 initiation and BAP1-associated progression.

3

Interpret morphology, dissemination and prognostic features.

4

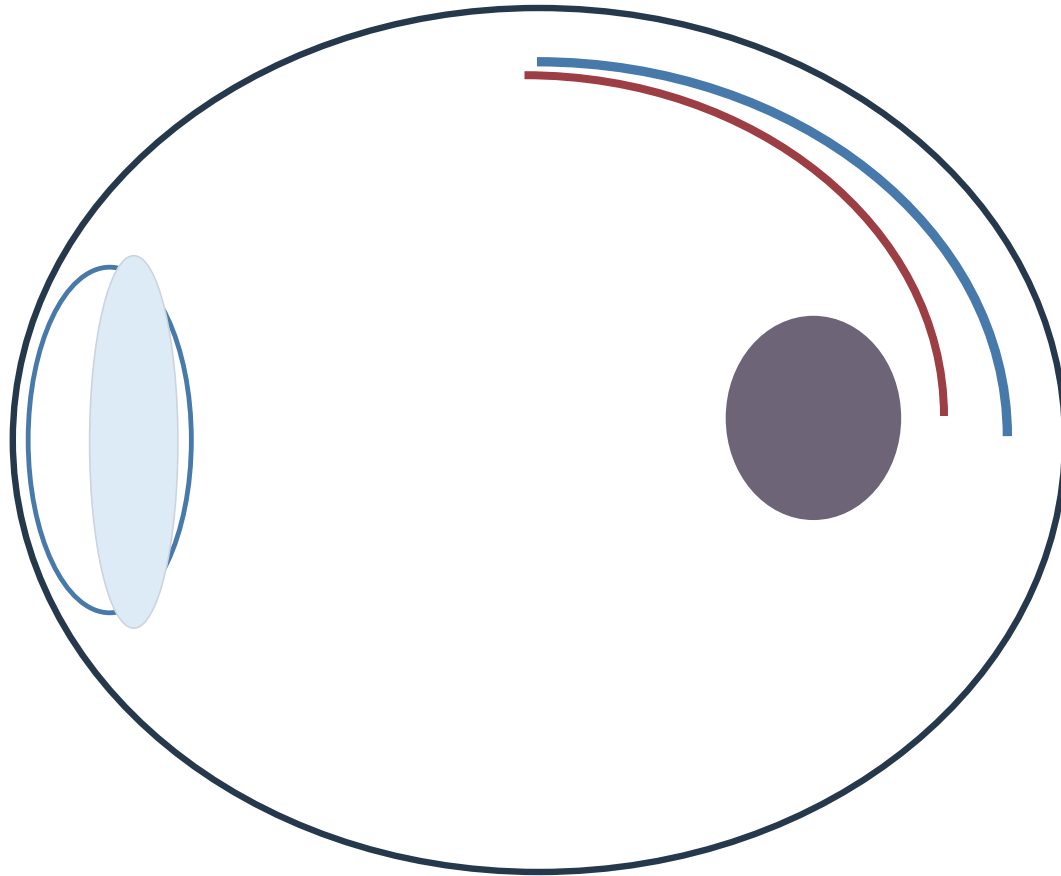
Relate pathology to presentation and management.

The uvea: Three connected tissues

Iris	Ciliary body	Choroid
Anterior uveal component; Melanoma limited to iris generally follows a less aggressive course.	Intermediate uveal component; Tumors here belong to the more aggressive group.	Posterior, highly vascularized uveal component; A frequent site for nevi and melanoma.

The vascular nature of the choroid is relevant to hematogenous dissemination.

Anatomic context of a posterior uveal tumor



Pigmented posterior uveal lesion

- Situated within the uveal wall.
- May affect adjacent retina.
- Schematic anatomy—not an observed specimen.

Uveal nevi: Common benign melanocytic lesions

- Uveal nevi are melanocytic lesions of the iris, ciliary body or choroid.
- Choroidal nevi are particularly common.
- Presence of a nevus does not, by itself, imply inevitable malignant transformation.

Benign lesions and melanoma may share early molecular alterations.

Uveal melanoma: Why it matters

- Most common PRIMARY intraocular malignancy in adults.
- Biologically and genomically distinct from cutaneous melanoma.
- Local control of the eye tumor does not abolish the risk of distant metastasis.

Primary intraocular malignancy $\neq$ most common intraocular malignancy overall.

Primary melanoma versus ocular metastasis

Uveal melanoma

- Primary adult intraocular cancer.
- Originates within uveal tissues.
- Characteristic molecular drivers.

Metastatic cancer to uvea

- Most common intraocular adult malignancy overall.
- Choroid is a frequent destination.
- Classically from lung or breast.

Site of origin is the essential distinction.

Epidemiologic scale of uveal melanoma

~5%

Approximate fraction of all melanomas represented by uveal melanoma in the United States.

5.1 / million / year

Age-adjusted U.S. Incidence reported in the Robbins source.

Adult malignancy

Predominant epidemiologic teaching context for primary intraocular melanoma.

Historical textbook estimates; Not a forecast of current population incidence.

Uveal nevi are much more frequent than melanoma

~5%

Estimated uveal nevi prevalence among people of European descent, especially choroidal nevi.

Rare malignancy

Uveal melanoma incidence is reported per million persons per year.

Do not compare a prevalence proportion directly with an annual incidence rate.

Incidence is relatively stable over time

Uveal melanoma

- Textbook describes stable incidence across many years.
- No clear UV–risk association established in this source.

Cutaneous melanoma

- The epidemiologic pattern differs.
- The underlying mutation spectrum also differs.

Do not extrapolate cutaneous melanoma trends to uveal melanoma.

Ultraviolet exposure: Avoid assumed causality

- The Robbins passage reports no clear link between UV exposure and uveal melanoma risk.
- This epidemiologic pattern is consistent with a distinct oncogenic mechanism.
- Absence of a clear population association is not proof that an exposure can never matter in an individual.

Molecular contrast with cutaneous melanoma

Molecular feature	Uveal melanoma	Cutaneous melanoma
Canonical example	GNAQ / GNA11	BRAF (common driver)
BRAF in initiation	Not a principal driver	Frequent in subsets
Risk interpretation	Uveal-specific biology	Cannot be transferred directly

Textbook juxtaposition: Tumor site and mutation spectrum matter.

GNAQ and GNA11 encode G-protein α subunits



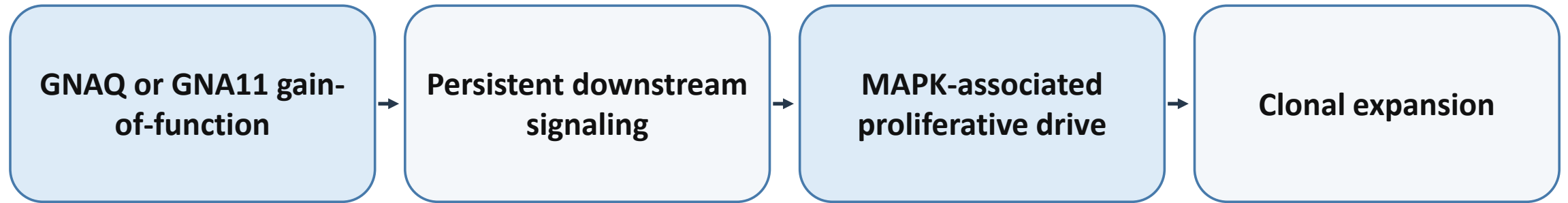
Correction to source wording: These genes do NOT encode the receptors themselves.

Activating mutations are frequent

- Approximately 85% of uveal melanomas have activating GNAQ or GNA11 mutations in the source.
- Both genes operate in a related G-protein signaling module.
- Mutation prevalence alone does not indicate metastatic risk.

Frequent early driver ≠ sufficient explanation of malignant progression.

How an activating G-protein mutation promotes growth



Original pathway abstraction. Receptor coupling and multiple downstream branches are simplified.

Uveal nevi can share the same initiating mutations

Benign nevus

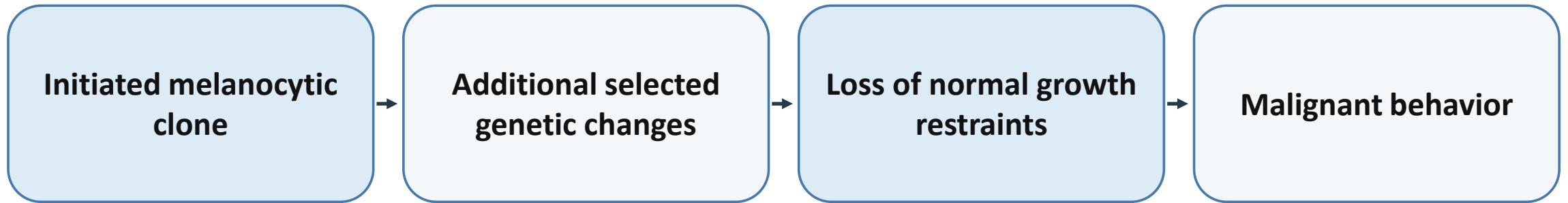
- May already contain GNAQ / GNA11 mutations.
- Common and rarely progresses to melanoma.

Malignant melanoma

- Often contains the same mutation class.
- Additional genetic alterations are implicated.

A driver mutation must be interpreted in its biologic context.

Why an early driver is not sufficient



Multistep oncogenesis is an explanatory model, not a claimed obligatory timeline.

Loss of chromosome 3 in progression

- Loss of chromosome 3 is a consequential event in many uveal melanomas.
- The deleted chromosome contains the tumor suppressor gene BAP1.
- The selection for chromosome 3 loss can therefore remove tumor-suppressive functions.

BAP1: A tumor-suppressive chromatin regulator

- BAP1 encodes a deubiquitinating enzyme.
- BAP1 participates in complexes involved in chromatin regulation.
- Loss of BAP1 function can disrupt epigenetic control of gene expression.

GNAQ/GNA11 activation and BAP1 loss represent different biological roles.

The epigenetic dimension of uveal melanoma



Conceptual relationship; Exact loci, chromatin marks and targets are not specified.

A two-stage molecular framework

Early signaling event

GNAQ / GNA11 activating mutation may be present in nevus or melanoma.

Additional progression event

Chromosome 3 loss and BAP1 dysfunction are implicated in malignant behavior.

Do not infer that every melanoma follows one fixed molecular sequence.

BAP1 alterations can be inherited

- Some patients carry a germline pathogenic BAP1 alteration.
- A germline variant creates cancer predisposition; It does not establish that a given ocular lesion is malignant.
- Tumor-only and constitutional variants are different interpretive categories.

Germline BAP1: Associated tumor spectrum

Uveal melanoma

Ocular melanocytic
malignancy

Renal cell carcinoma

Renal epithelial
malignancy

Mesothelioma

Malignancy of mesothelial
surfaces

The listed associations come from the textbook; No penetrance estimates are assumed.

Initiating drivers versus progression alterations

Interpretive category	GNAQ / GNA11	Chromosome 3 / BAP1
Main role	Activation of growth pathways	Loss of suppressor / chromatin regulation
Presence in nevi	Possible	Not established by the excerpt
Clinical inference	Supports pathobiology	Associated with progression and risk

Mutation presence must not be equated with a complete diagnosis or prognosis.

Histologic spectrum: Two classic cell patterns

Spindle cell type

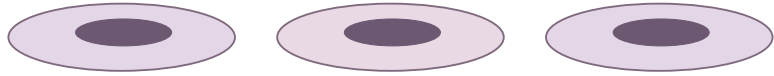
- Fusiform neoplastic cells.
- Elongated cytomorphology.
- Pure spindle tumors have more favorable prognosis relative to epithelioid-containing tumors.

Epithelioid cell type

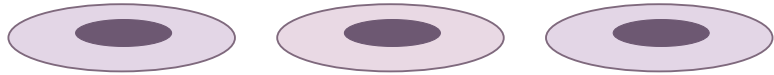
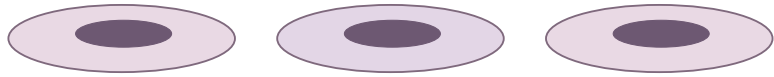
- Round to polygonal appearance.
- Greater cytologic atypia.
- An adverse morphologic prognostic feature.

Tumors may contain mixtures of both patterns.

Spindle-cell morphology: Schematic

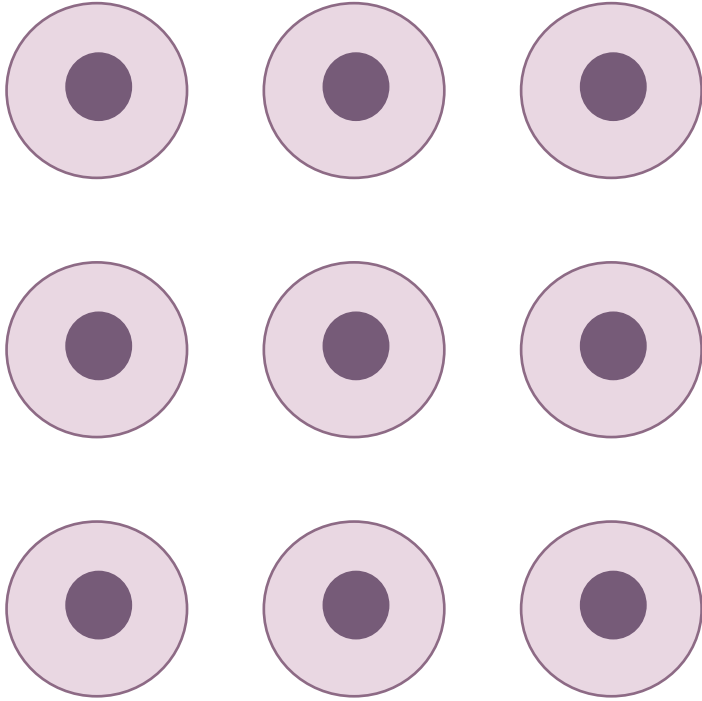


Fusiform profile



- Elongated cells with tapered ends.
- The spindle phenotype is one recognized uveal melanoma cell type.
- Illustration is schematic—not a histologic specimen.

Epithelioid morphology: Schematic



Greater cytologic atypia

- Larger, more rounded cellular silhouette.
- Epithelioid component is linked to worse prognosis.
- Schematic, not a genuine H&E section.

Mixed cellular composition is common

- Spindle and epithelioid tumor cells can occur in varying proportions within one lesion.
- Do not force a heterogeneous tumor into a purely spindle or purely epithelioid mental model.
- The presence of an epithelioid component has prognostic implications.

Tumor-infiltrating lymphocytes may be present

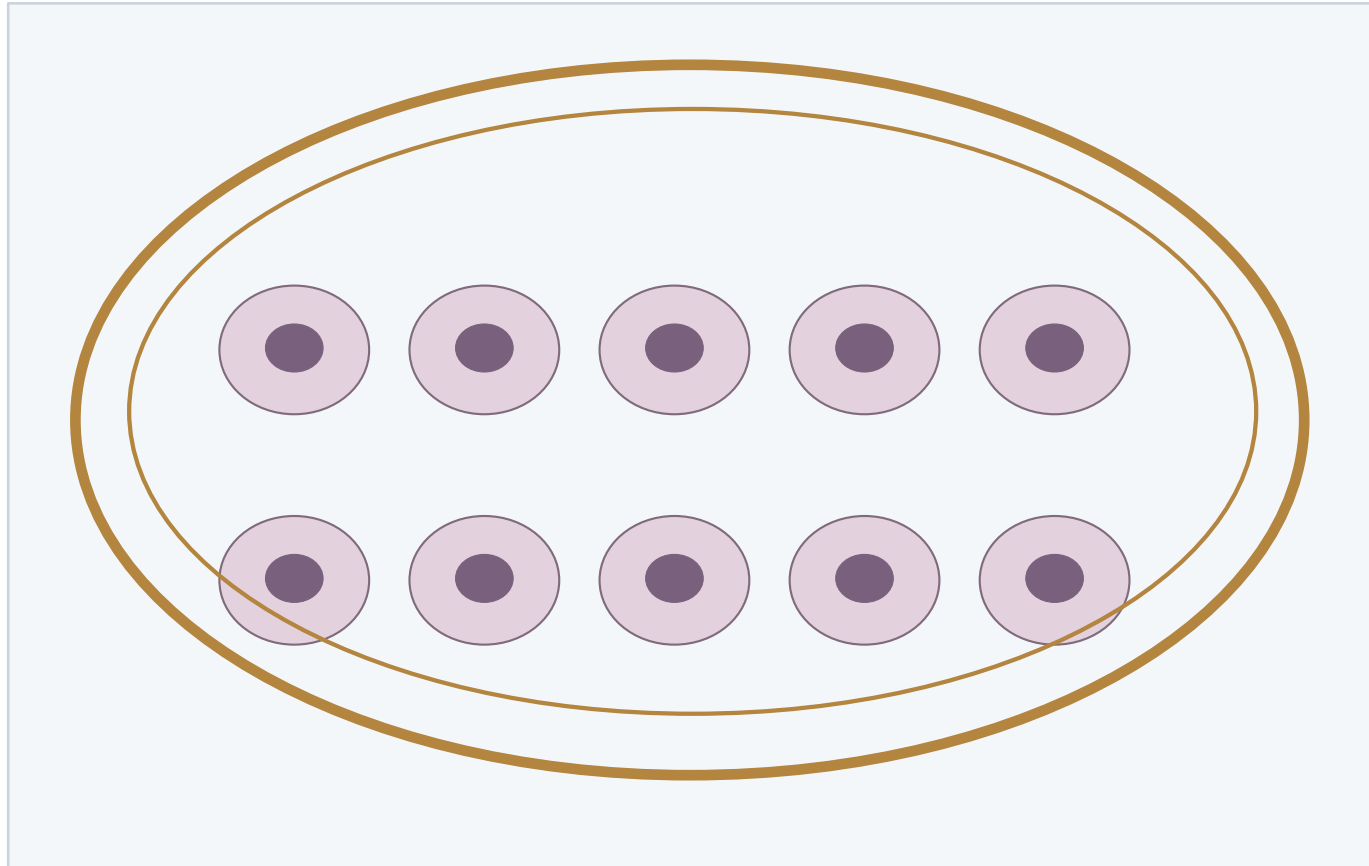
- Some uveal melanomas display numerous infiltrating lymphocytes.
- This histologic observation is also familiar in cutaneous melanoma.
- The excerpt does not provide a validated prognostic direction or numeric cutoff for lymphocytes.

Recognition of an immune infiltrate is not equivalent to prognostic classification.

Vasculogenic mimicry: The observed pattern

- Some lesions show looping, slit-like channels around packets of tumor cells.
- These spaces are lined by laminin and connect with blood vessels.
- They are not conventional endothelial-lined blood vessels.

Native schematic of laminin-lined tumor loops



Laminin-associated loop

Surrounds groups of melanoma cells

Schematic: NOT a blood vessel

Vasculogenic mimicry is not ordinary angiogenesis

Ordinary vascular lumen

- Endothelial vessel wall.
- Blood transport through vessel lumen.

Vasculogenic mimicry

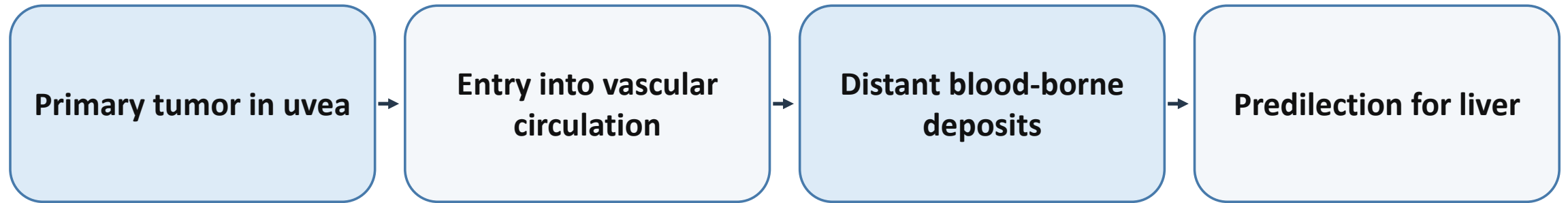
- Tumor-associated laminin-lined spaces.
- Connect to vessels; May conduct plasma or blood.

Do not label every loop as a capillary in a pathology diagram.

Interpreting vasculogenic mimicry cautiously

- In vitro studies and human tissues support tumor-cell participation in these growth patterns.
- The textbook uses the term vasculogenic mimicry.
- The precise functional contribution of each loop to perfusion cannot be inferred from morphology alone.

Uveal melanoma disseminates hematogenously

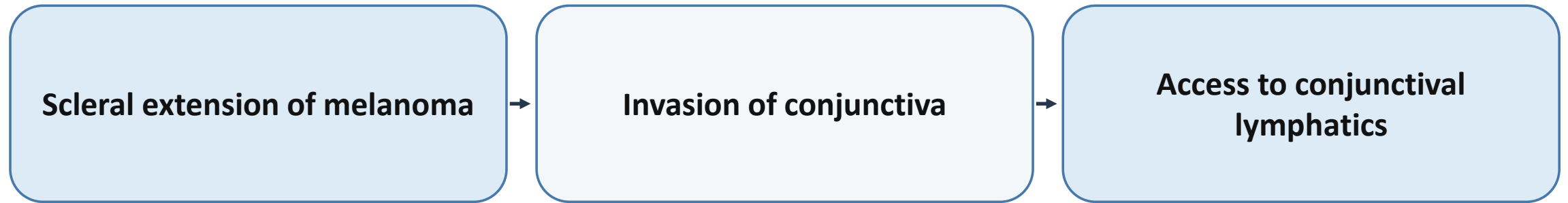


Hematogenous spread is the rule; Classic lymph-node-first modeling is inappropriate.

Liver tropism is a signature clinical feature

- The liver is usually the first metastatic destination for uveal melanoma.
- This is a classic example of organ-selective metastatic tropism.
- Controlling the primary ocular lesion does not remove all risk of an occult disseminated clone.

Rare exception: Access to conjunctival lymphatics

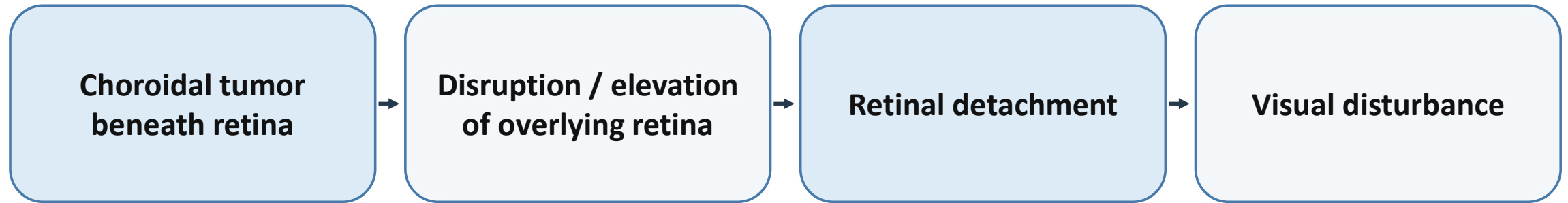


Lymphatic spread is exceptional in the source, not the dominant route.

Why melanomas may be detected incidentally

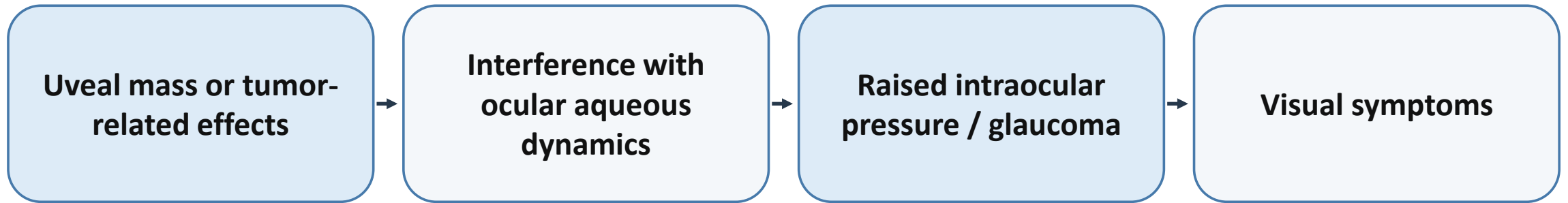
- Many uveal melanomas are discovered without tumor-specific symptoms.
- A clinically quiet primary lesion can nevertheless carry metastatic potential.
- Symptoms are therefore an unreliable surrogate for biologic aggressiveness.

Retinal detachment links mass to symptoms



Mechanism is a clinicopathologic interpretation of the source association.

Glaucoma is another route to visual symptoms



The exact glaucoma mechanism varies by tumor location and is not specified by the excerpt.

Primary site influences clinical behavior

Iris only	Ciliary body	Choroid
Often relatively indolent when confined to the iris.	More aggressive behavior than lesions confined to iris.	More aggressive behavior; Hematogenous metastatic risk.

Anatomic site modifies prognosis but does not replace other risk factors.

Tumor dimensions: What matters in uveal melanoma

- Larger choroidal and ciliary-body tumors have less favorable outcomes.
- The source emphasizes lateral tumor extent in contrast to the depth emphasis familiar in cutaneous melanoma.
- Anatomic measurements must be interpreted within the ocular staging framework, not by cutaneous melanoma rules.

Cell type is prognostically informative

Spindle-only lesions

- More favorable relative outcome in the classic morphologic comparison.
- Fusiform tumor cell population.

Epithelioid-containing lesions

- Worse relative prognosis.
- Rounder, more atypical tumor cells.

Morphologic phenotype complements rather than replaces molecular risk assessment.

Proliferative activity contributes to risk

- The proliferative index is a prognostic factor in the Robbins account.
- A higher index indicates greater tumor proliferative activity.
- No numeric cutoff or required assay is specified in this source section.

Avoid inventing Ki-67 thresholds or grading algorithms.

Gene expression profiling can stratify risk



The textbook supports prognostic stratification, not a claim that profiling predicts treatment response.

Risk requires integration across domains

Morphologic	Molecular	Anatomic
Tumor size, cell phenotype, proliferation.	Expression-profile risk; Chromosome 3 / BAP1 biology.	Iris-confined versus ciliary-body / choroidal location.

These are complementary dimensions, not an arithmetic score.

Long-term outcomes: Competing interpretations

Textbook endpoint	Estimate	Interpretation
Five-year survival	Approximately 80%	Survival to a defined time point
Ten-year cumulative melanoma mortality	About 40%	Disease-specific cumulative deaths
Late risk	Persists after treatment	Follow-up horizon matters

Do not equate five-year all-cause survival with ten-year melanoma-specific mortality.

Late metastasis raises the problem of tumor dormancy



Delayed detection does not prove when dissemination actually occurred.

Primary ocular therapy: Preserve the eye when suitable

Eye-sparing radiotherapy

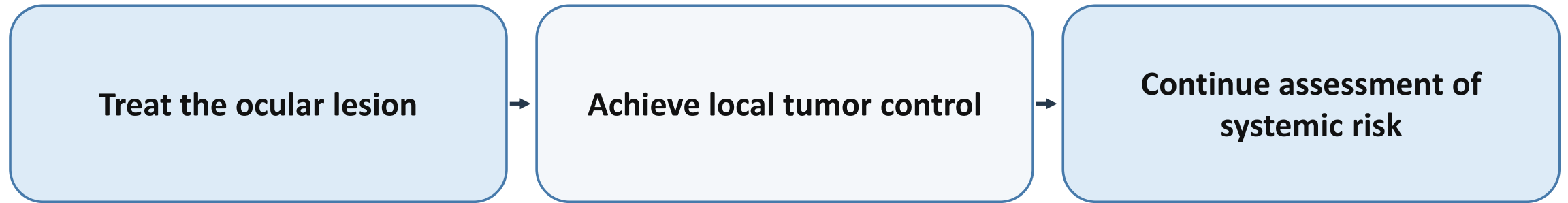
- Textbook identifies radiotherapy as preferred local treatment.
- Aims for local tumor control with ocular preservation.

Enucleation

- Surgical removal of affected eye.
- Retained for cases requiring removal.

Textbook reports no survival advantage for enucleation over radiotherapy.

Local control and metastatic risk are different endpoints



A successful local procedure cannot guarantee prevention of late liver metastases.

Updated metastatic treatment: Source correction

Textbook passage

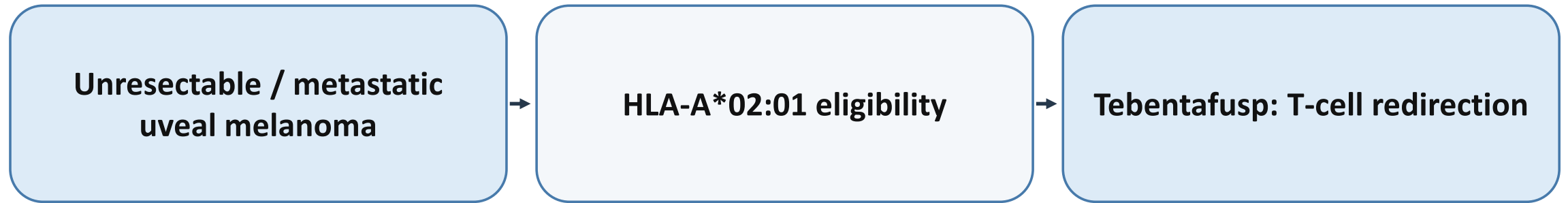
- States that no effective systemic treatment exists.
- This statement is obsolete as current practice guidance.

Verified FDA update

- Tebentafusp was approved in January 2022.
- Indication is restricted to HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma.

External, separately verified update—not a claim about the printed Robbins wording.

Tebentafusp requires an eligible HLA type



Therapy is for a molecularly defined subset—not every patient with uveal melanoma.

Nevus and melanoma: What this source supports

Feature	Uveal nevus	Uveal melanoma
Biology	Benign melanocytic lesion	Malignant melanocytic neoplasm
Frequency	Relatively common	Rare
GNAQ / GNA11	Can be mutated	Often mutated
Metastatic capacity	Not established	Characteristic systemic risk

This is conceptual comparison, not a validated clinical lesion-scoring system.

Uveal versus cutaneous melanoma: Pitfalls

Domain	Uveal	Cutaneous
Principal drivers	GNAQ / GNA11	BRAF in a major subset
UV association	No clear association	Biology differs; Avoid extrapolation
Size concept	Lateral extent emphasized	Depth important in cutaneous staging
Spread	Usually hematogenous to liver	Different patterns

Different biologic diseases despite sharing melanocytic lineage.

A pathology interpretation checklist

1

Confirm whether the lesion is intraocular and primary or metastatic.

2

Describe uveal site and morphology, including epithelioid component.

3

Characterize prognostic tumor dimensions and proliferation when available.

4

Interpret molecular findings by their diagnostic or prognostic role.

Clinical reasoning case: A pigmented lesion

- A choroidal pigmented lesion is found incidentally during routine examination.
- Molecular testing identifies a GNAQ activating alteration.
- Question: Does the mutation alone establish malignancy?

Apply the distinction between an initiating driver and malignant progression.

Case interpretation: Mutation alone is insufficient

- No: Benign uveal nevi can carry activating GNAQ / GNA11 mutations.
- Malignancy requires interpretation of the complete clinical and pathologic context.
- A driver mutation should not be converted into an unsupported binary diagnosis.

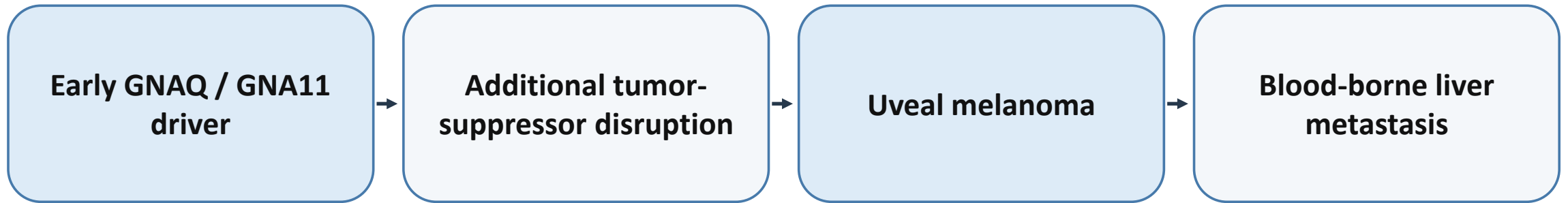
Clinical reasoning case: Recurrence after years

- A prior choroidal melanoma was treated locally years earlier.
- A new liver mass is found after a long clinically disease-free interval.
- Question: What dissemination mechanism and timing concept fit?

Case interpretation: Hepatic tropism and dormancy

- Uveal melanoma preferentially metastasizes to the liver via blood.
- Late clinical metastasis is compatible with tumor dormancy.
- A symptom-free interval does not prove absence of earlier dissemination.

Synthesis: Molecular and clinical trajectory



Conceptual sequence; Individual tumors vary and metastasis is not inevitable.

Five conclusions to retain

- Uveal melanoma is the commonest primary intraocular adult malignancy.
- GNAQ / GNA11 are early G-protein drivers; BAP1 participates in progression.
- Spindle and epithelioid cytomorphology informs prognosis.
- Systemic dissemination is predominantly blood-borne, commonly to liver.
- Therapy claims must distinguish the Robbins excerpt from current FDA approvals.

References and source clarification

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 29, p. 1197.
- GNAQ/GNA11 protein identity: Cancers. 2022;14:3066. PMID: 35804836.
- FDA: KIMMTRAK (tebentafusp) Drug Trials Snapshot; approval January 25, 2022.
- External updates are distinguished from the extracted textbook prose.