

Medulloblastoma

Malignant embryonal tumor of the cerebellum | Morphology,
molecular groups, dissemination and prognosis

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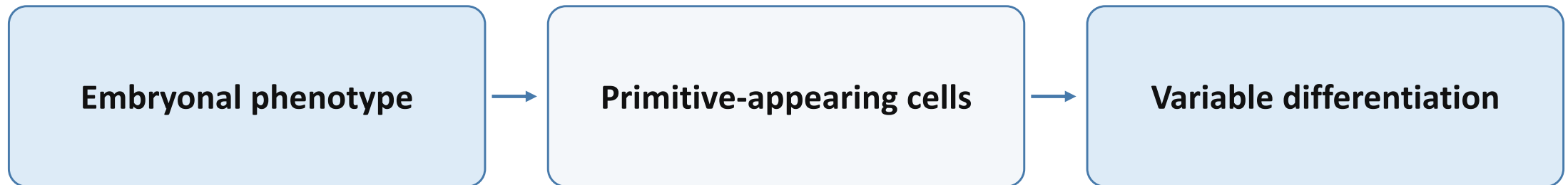
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Learning objectives

- Define medulloblastoma and explain its anatomic restriction.
- Recognize the morphologic patterns and immunophenotype.
- Relate molecular groups to location and clinical behavior.
- Explain CSF dissemination and the significance of risk heterogeneity.

Medulloblastoma is an embryonal CNS tumor

- Embryonal neoplasms have primitive or relatively undifferentiated cytology.
- Limited neuronal differentiation may be present; Glial differentiation is less common.
- Medulloblastoma is the most common embryonal CNS tumor.



Its pediatric importance is substantial

- Approximately 20% of pediatric brain tumors to medulloblastoma.
- This proportion describes the pediatric brain-tumor case mix, not all childhood cancers.

~20%

Of pediatric brain tumors (Robbins, 11th ed.)

The primary site is the cerebellum

- Medulloblastoma is cerebellar by definition.
- A similar primitive tumor elsewhere in the CNS should not automatically receive this designation.
- Anatomic site and morphology must be integrated.

Cerebellum

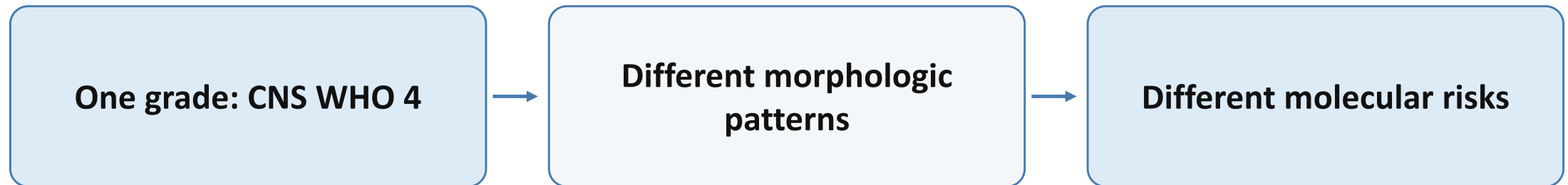
Fourth ventricle

Other CNS sites

Named regions only; Position is diagrammatic

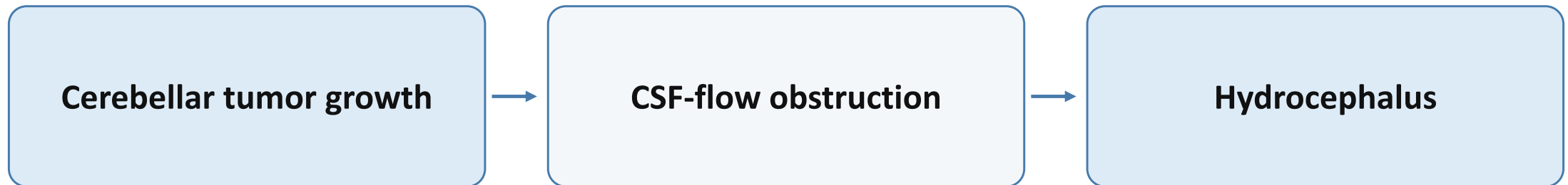
All medulloblastomas are CNS WHO grade 4

- The grade reflects the intrinsically malignant biologic category.
- Histologic variants and molecular groups remain clinically heterogeneous.
- Grade 4 alone does not resolve the major prognostic differences.



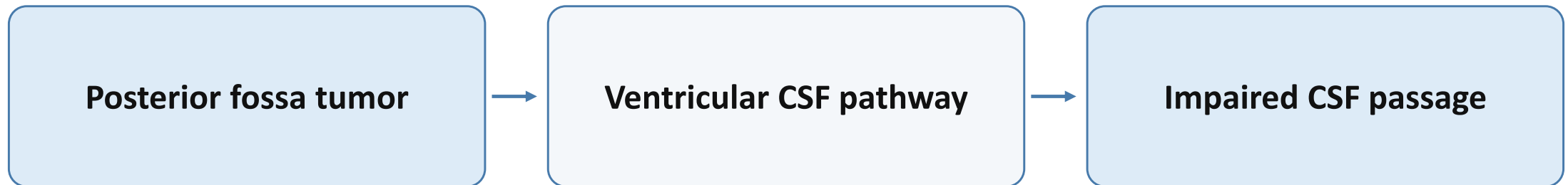
Rapid growth creates local mechanical danger

- Expanding tumor can obstruct cerebrospinal fluid flow.
- The consequence is hydrocephalus, independent of distant dissemination.
- Local mass effect and biologic subtype are different dimensions of disease.



Why the fourth ventricle matters

- Medulloblastoma arises in the posterior fossa near ventricular CSF pathways.
- Obstruction of CSF outflow provides the mechanism for hydrocephalus.
- This is a location-dependent consequence, not a unique histologic marker.



Two complementary dimensions of disease

- Local expansion explains CSF obstruction and hydrocephalus.
- Leptomeningeal dissemination explains deposits away from the cerebellum.
- Both phenomena can arise from the same primary tumor.

LOCAL

CSF obstruction

Hydrocephalus

DISSEMINATED

Subarachnoid spread

Spinal deposits

Classification requires more than one axis

- Molecular classification examines characteristic genetic alterations.
- Histologic classification examines cellular and architectural patterns.
- Clinical risk depends strongly on tumor subtype.

Molecular group

Histologic pattern

Clinical behavior

At least four molecular groups are recognized

- WNT-activated, SHH-activated, group 3 and group 4 are the principal categories described.
- The names refer to biologic classification rather than four gross appearances.

WNT-activated

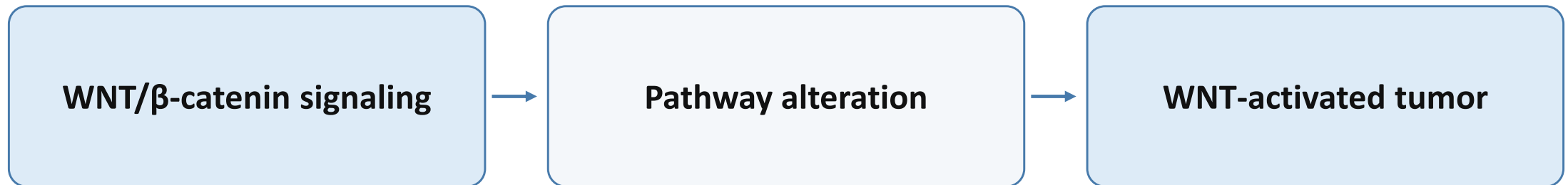
SHH-activated

Group 3

Group 4

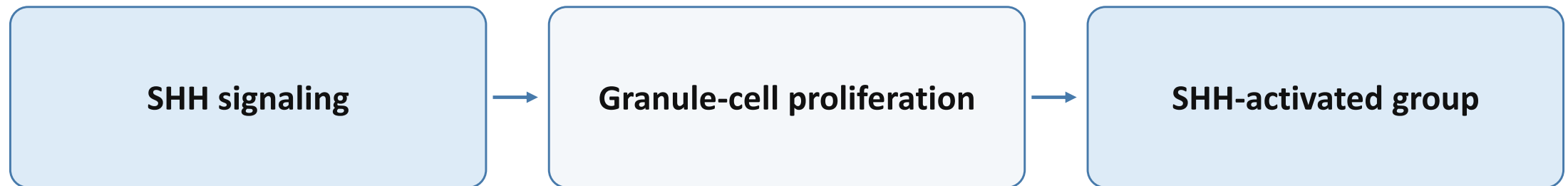
WNT-activated tumors involve a developmental pathway

- The WNT/ β -catenin pathway participates in embryogenesis and tissue homeostasis.
- Pathway alteration identifies one major medulloblastoma group.
- WNT activation has strong prognostic relevance in the cited classification.



SHH relates to cerebellar granule-cell proliferation

- Sonic hedgehog signaling participates in proliferation of cerebellar granule cells.
- Aberrant activity is implicated in the SHH-activated molecular group.
- This provides a developmental link between pathway biology and tumorigenesis.



Groups 3 and 4 are separate molecular categories

- Groups 3 and 4 alongside WNT and SHH tumors.
- They should not be relabeled as SHH-negative variants of a single entity.
- Their prognoses cannot be inferred from morphology alone.

GROUP 3

Distinct molecular group

Adverse overall prognosis

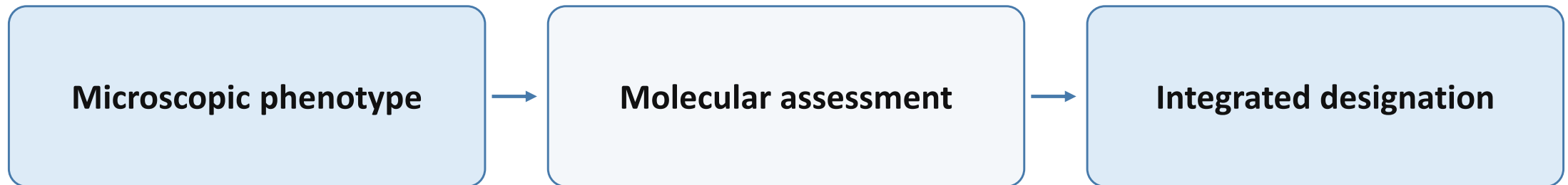
GROUP 4

Distinct molecular group

Do not infer risk from name alone

Molecular grouping is not a histologic stain

- A small-cell appearance does not itself establish WNT, SHH, group 3 or group 4.
- A molecular classification requires molecular evidence.
- Morphologic correlations provide clues, not complete molecular identity.



SHH activation does not imply uniform risk

- Robbins specifically highlights SHH-activated/TP53-mutant disease among the poorest-prognosis categories.
- The TP53 qualifier changes the interpretation of an otherwise broad SHH label.

SHH-activated

Molecular family

Heterogeneous outcome

SHH + TP53-mutant

Specified high-risk subset

Poorer prognosis

Group 3 is a poor-prognosis category

- Group 3 is identified among the categories with the worst outcomes.
- This is a group-level observation rather than a guarantee of outcome in an individual case.

Molecular subtype modifies prognosis

Group 3 is singled out as an unfavorable category.

WNT-activated tumors have the best overall prognosis

- The WNT group as the most favorable of the major categories.
- Overall group prognosis should not be conflated with a patient-specific prediction.

WNT-activated

Most favorable overall prognostic group.

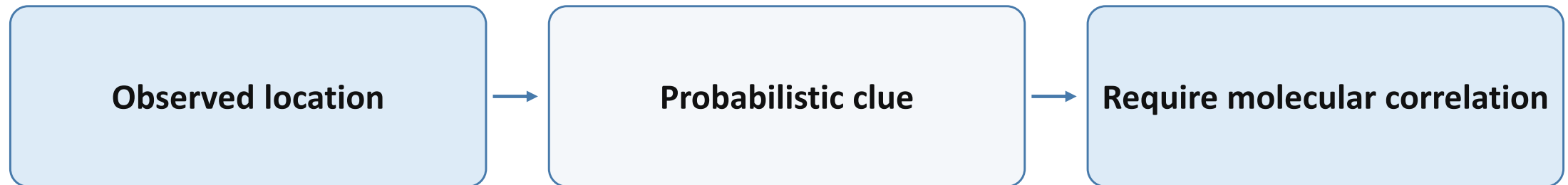
Anatomic preferences differ between groups

Molecular group	Location favored
WNT-activated	Anterior fourth ventricle / middle cerebellar peduncle
SHH-activated	Vermis / lateral cerebellum

WNT-activated tumors are often near the anterior fourth ventricle or middle cerebellar peduncle.

Location is supportive, not definitive

- A tumor near the fourth ventricle is not automatically WNT-activated.
- Vermian or lateral cerebellar position does not alone prove SHH activation.
- Integrated interpretation avoids a location-only molecular diagnosis.



Grossly, the tumor is gray and friable

- The lesion is often well circumscribed macroscopically.
- Gray color and friability are characteristic reported appearances.
- Circumscription does not make a WHO grade 4 tumor benign.

Well circumscribed $\neq$ biologically indolent

Gray, friable gross tumor; Malignant embryonal behavior.

Relationship to cerebellar folia has consequences

- The tumor may extend toward the surfaces of cerebellar folia.
- The leptomeninges may become involved.
- Surface extension offers a path toward meningeal/CSF dissemination.



Macroscopic boundaries do not define extent

- A grossly delineated cerebellar lesion may coexist with leptomeningeal spread.
- The primary mass and disseminated component must be conceptually distinguished.

PRIMARY MASS

Gray / friable

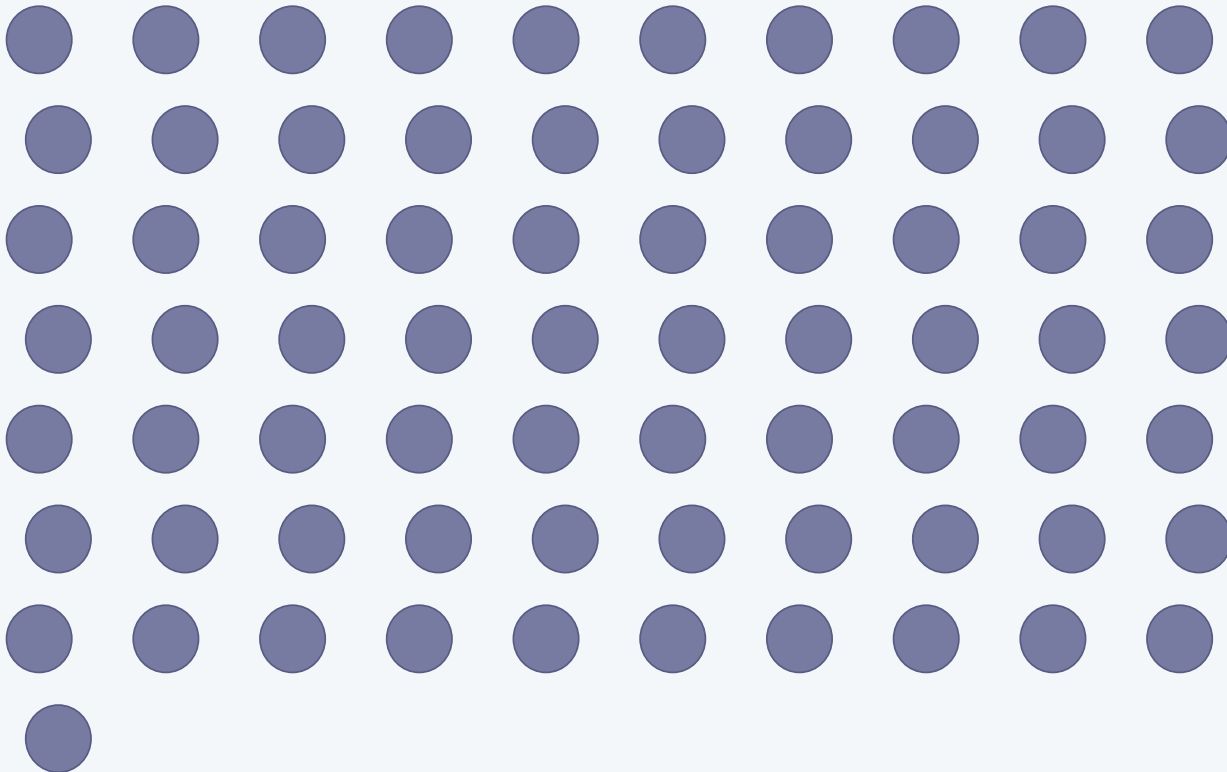
Often circumscribed

DISEASE EXTENT

Meningeal spread

May be more extensive

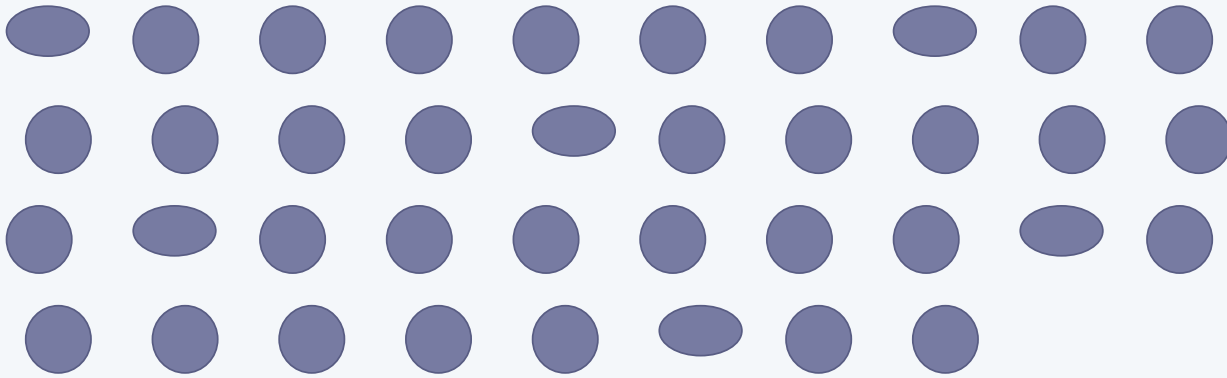
The dominant microscopic pattern is high cellularity



Schematic morphology — not a histologic specimen

- Dense sheets of primitive-appearing cells typify medulloblastoma.
- Little intervening cytoplasm gives a crowded blue-cell impression.
- Architectural patterns allow further histologic subclassification.

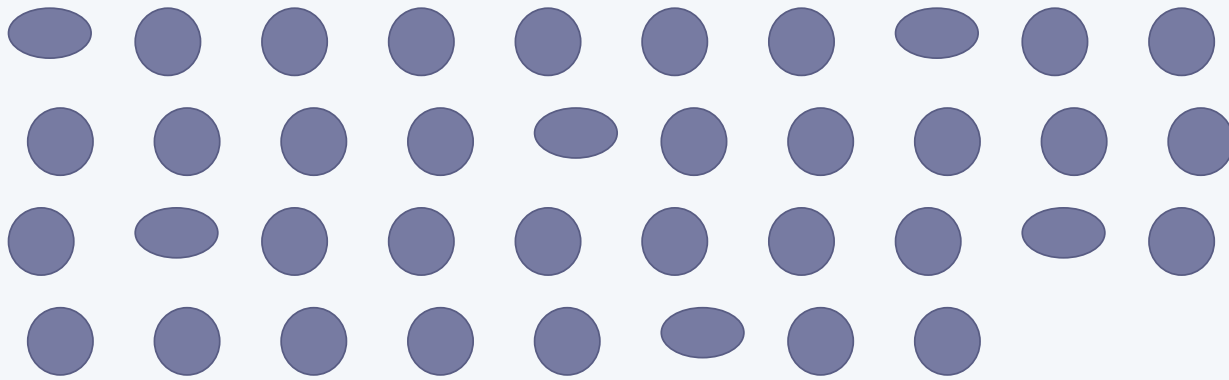
Small primitive cells have high nuclear-to-cytoplasmic ratios



Schematic morphology — not a histologic specimen

- The cytoplasm is scant relative to the nucleus.
- Nuclei are often hyperchromatic.
- Cells may be elongated or crescent shaped.

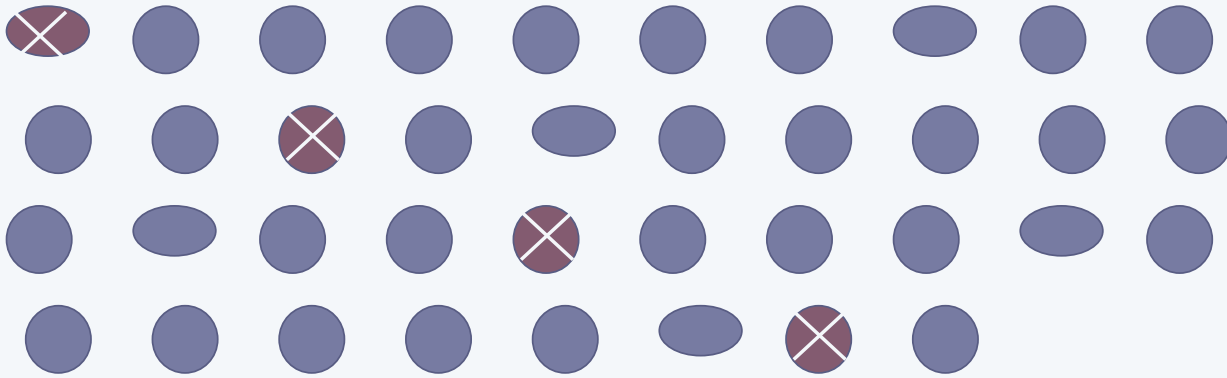
Nuclear shape is variable within the primitive-cell spectrum



Schematic morphology — not a histologic specimen

- Crescent-shaped and elongated nuclei are described alongside small dark nuclei.
- No single nuclear silhouette is sufficient to establish the diagnosis.

Frequent mitoses support aggressive proliferation

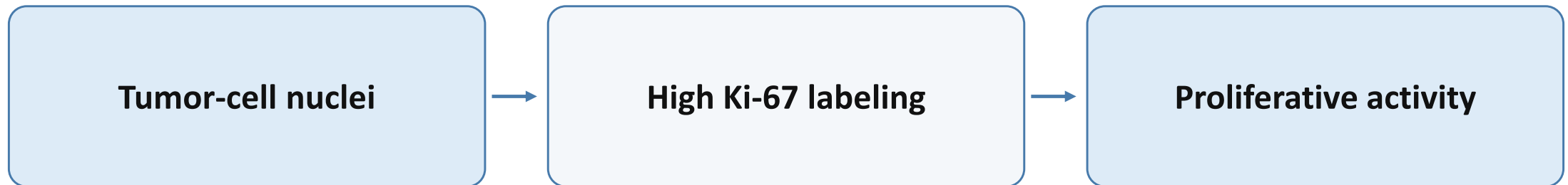


Schematic morphology — not a histologic specimen

- Mitoses are abundant in the classic small-cell sheets.
- This finding is compatible with the high-grade biology of the tumor.
- Mitotic activity is one component of morphology, not the molecular grouping.

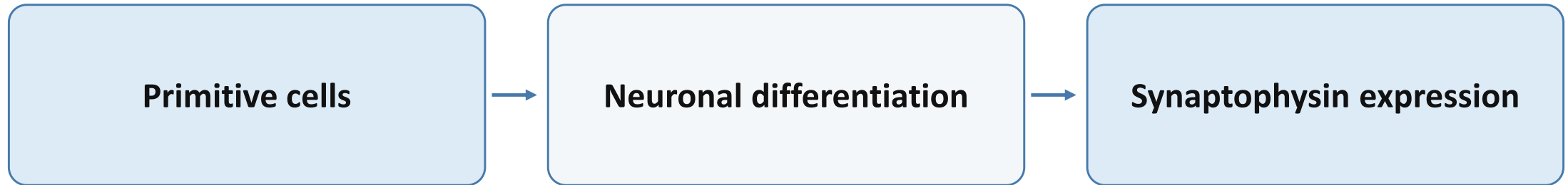
Ki-67 indexes the proliferative compartment

- A high proportion of Ki-67-positive tumor cells.
- Ki-67 is a proliferation marker, not proof of neuronal differentiation.
- The cited passage does not supply a universal diagnostic cutoff.



Synaptophysin supports neuronal differentiation

- Classic medulloblastoma often expresses synaptophysin.
- The finding is consistent with partial neuronal differentiation.
- Immunoreactivity must be interpreted with morphology and anatomic context.



GFAP expression is less common

- Glial markers such as GFAP are expressed less often than neuronal markers.
- The expected immunophenotype is not an absolute single-stain rule.

NEURONAL

Synaptophysin

Often expressed

GLIAL

GFAP

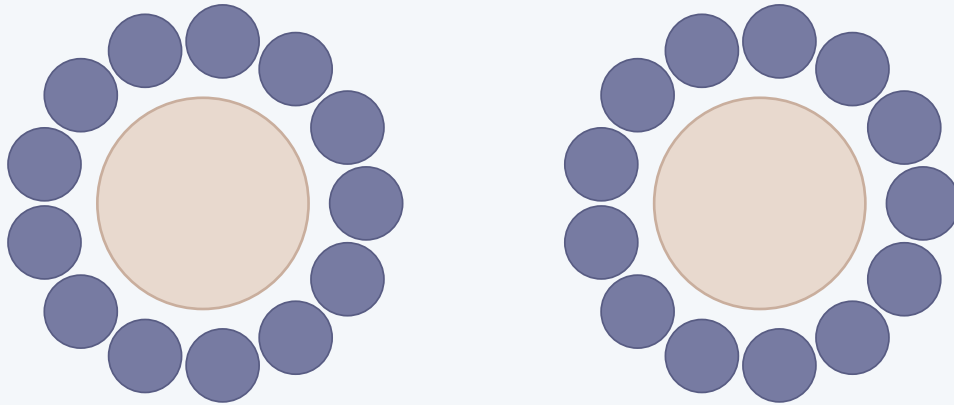
Less common expression

Interpret the stains by the question they answer

Assay / stain	Primary interpretive role
H&E	Cytology, density, architectural pattern
Ki-67	Proliferation assessment
Synaptophysin	Neuronal differentiation
GFAP	Glial differentiation (less common)

H&E shows cell morphology and architecture.

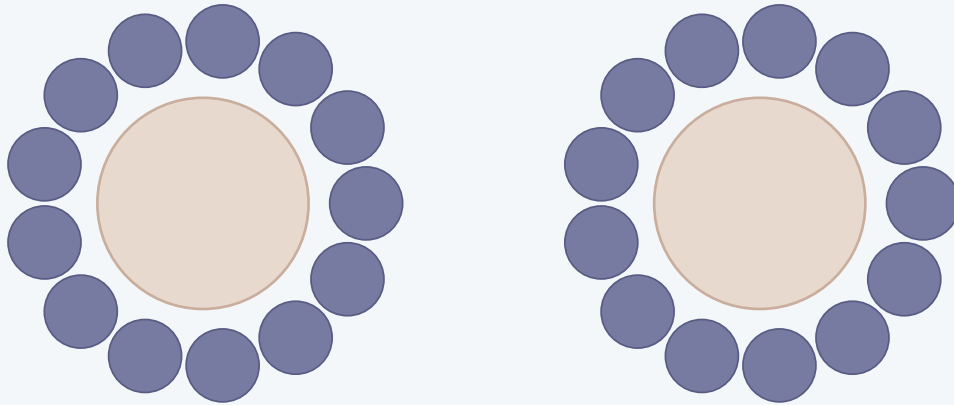
Homer Wright rosettes contain central neuropil



Schematic morphology — not a histologic specimen

- Classic medulloblastoma can form Homer Wright rosettes.
- Tumor cells are arranged around a central neuropil-rich zone.
- The center does not represent an epithelial or ependymal lumen.

Recognize the rosette construction



Schematic morphology — not a histologic specimen

- Look for a central fibrillary neuropil rather than an empty true lumen.
- Surrounding primitive cells form the recognizable rosette pattern.
- The structure expresses neuronal differentiation in a primitive tumor.

Homer Wright rosettes are not unique to medulloblastoma

- Robbins also notes Homer Wright rosettes in neuroblastoma.
- Therefore the rosette is a morphological pattern, not a site-independent diagnosis.
- Cerebellar location and other findings remain decisive context.

MEDULLOBLASTOMA

Cerebellar primary

Can show rosettes

NEUROBLASTOMA

Different primary context

Can show rosettes

The classic histologic pattern combines several findings

- Sheets of small primitive cells and high cellularity form the background.
- Homer Wright rosettes may be evident.
- Synaptophysin expression supports neuronal differentiation.

Primitive-cell sheets

Homer Wright rosettes

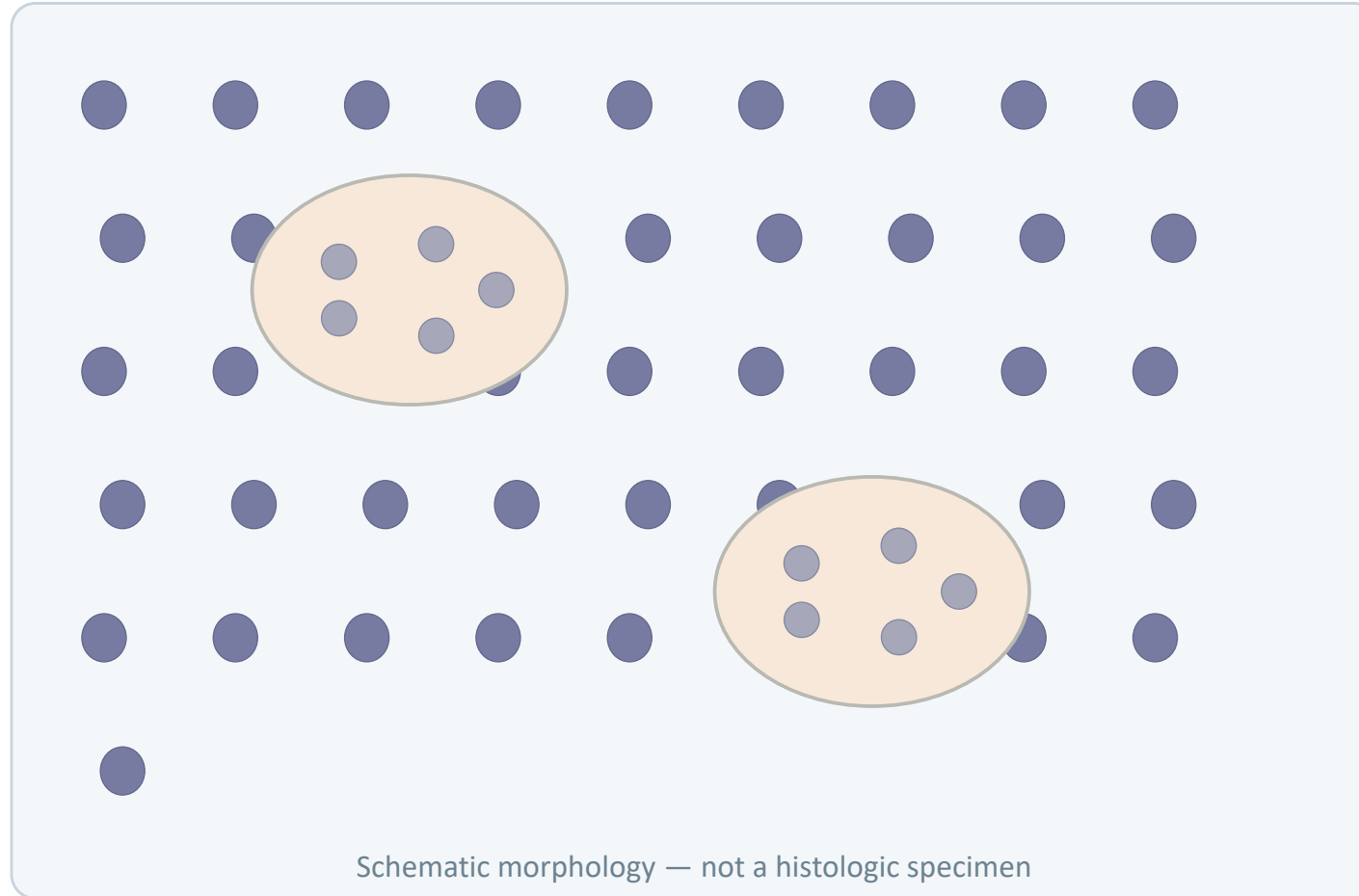
Neuronal immunophenotype

Do not reverse a histologic–molecular association

- The textbook associates classic morphology with WNT-activated tumors.
- That association does not establish WNT activation in an individual classic-appearing lesion.
- Molecular and histologic categories should be recorded separately.

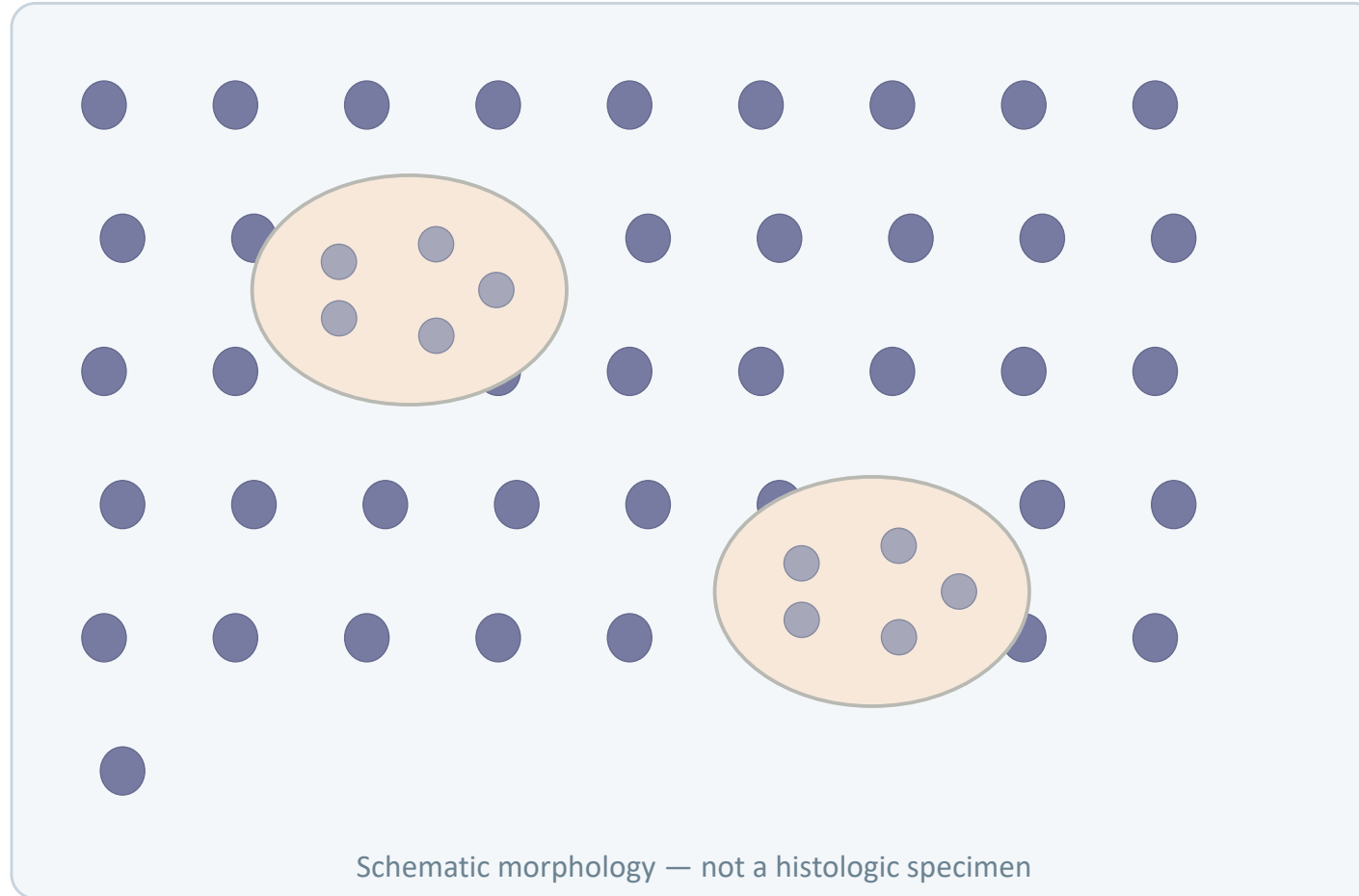


Desmoplastic/nodular architecture is biphasic



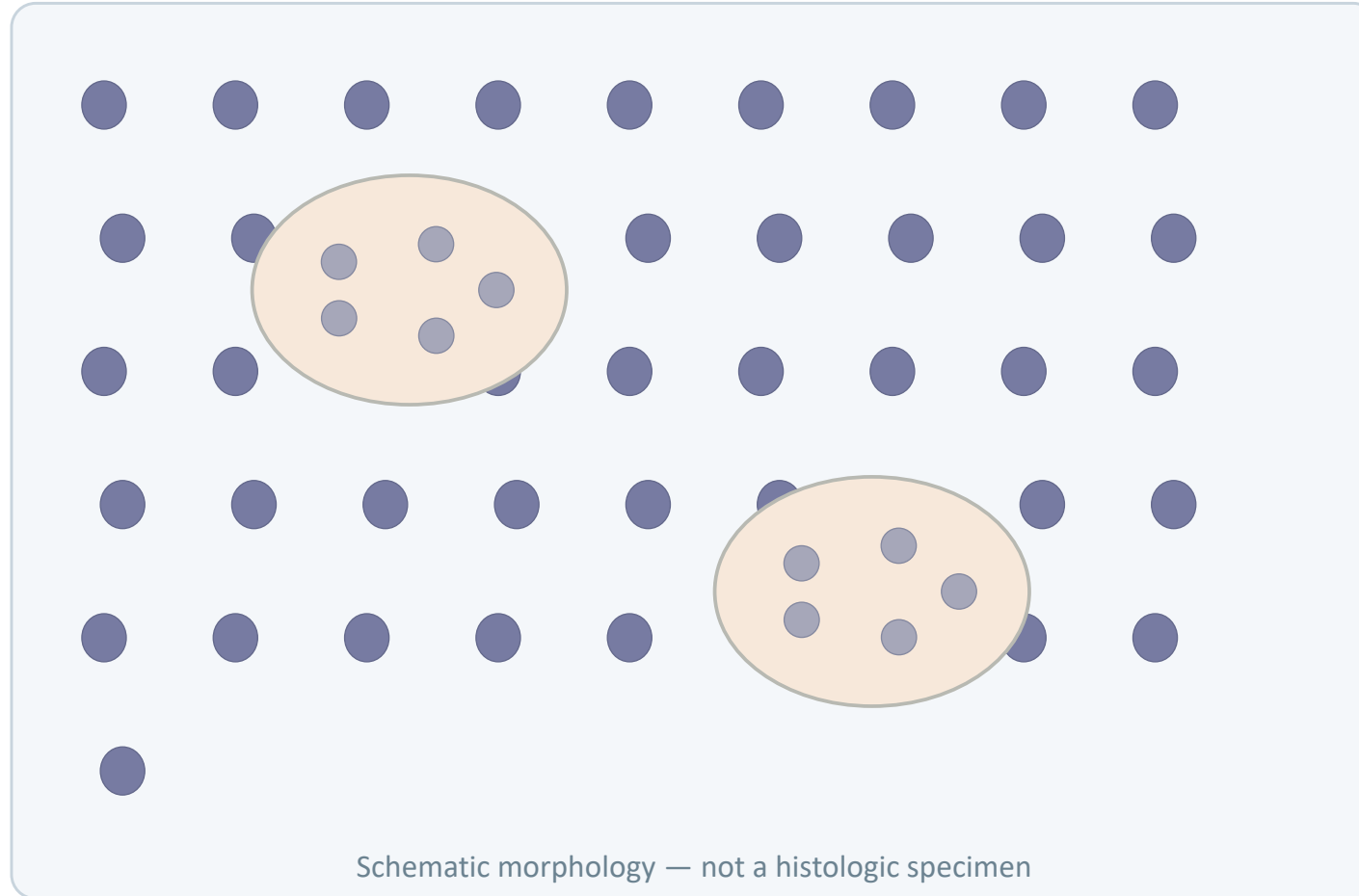
- Reticulin-rich internodular tissue contrasts with pale, more differentiated nodules.
- The two compartments differ in stromal response and cellular appearance.

Internodular zones contain a desmoplastic response



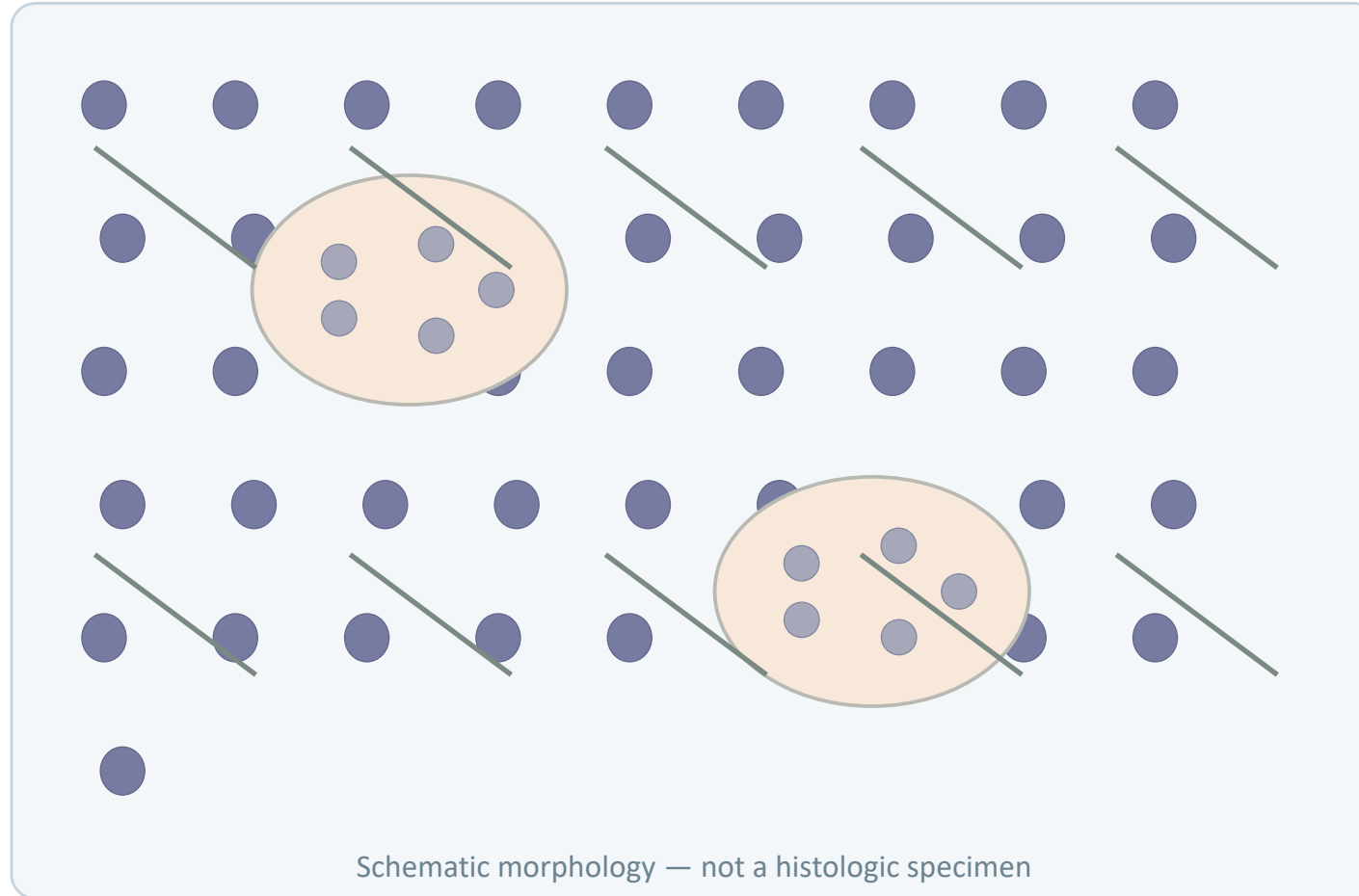
- Collagen and reticulin deposition mark the internodular areas.
- The stromal pattern is a defining diagnostic clue.
- It is the contrast with the nodules that creates the characteristic architecture.

Pale nodules represent partial neuronal maturation



- Pale islands contain more neuropil and show more advanced neuronal differentiation.
- The adjective “pale” reflects their appearance relative to the surrounding cellular tissue.

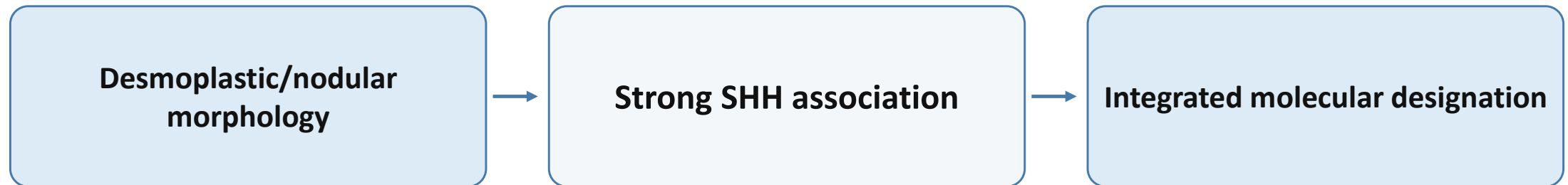
Reticulin distribution explains the nodular pattern



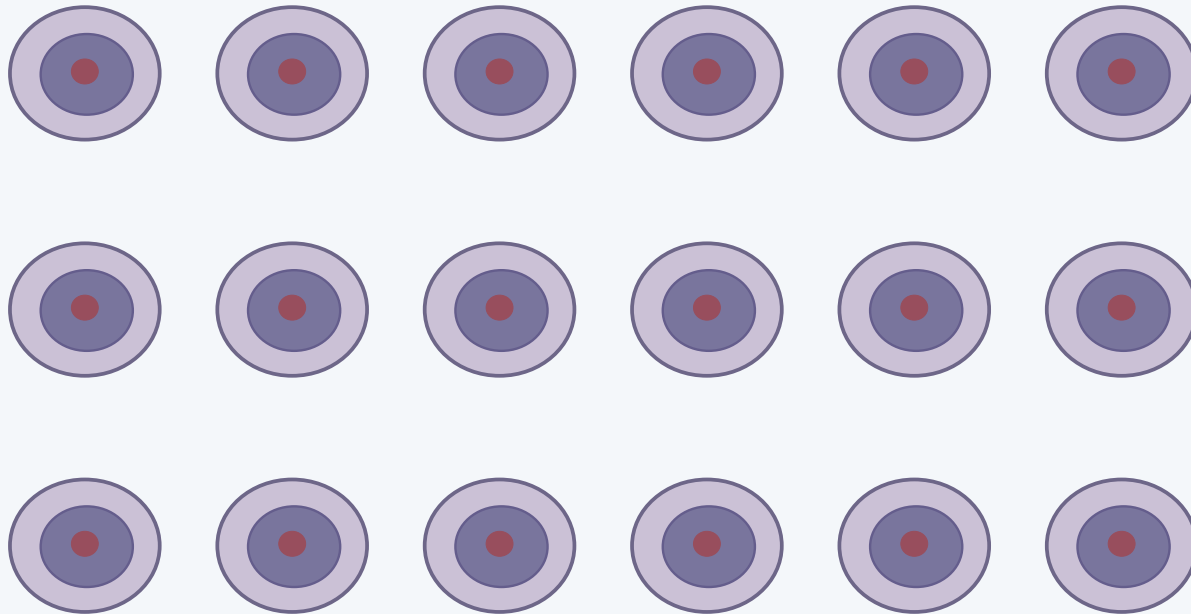
- Reticulin-rich internodular tissue is separated from more differentiated pale nodules.
- A reticulin stain can demonstrate the tissue-compartment distinction.

Desmoplastic/nodular tumors usually map to SHH

- Most desmoplastic/nodular cases with the SHH-activated group.
- This is a useful morphomolecular clue but molecular characterization retains independent value.



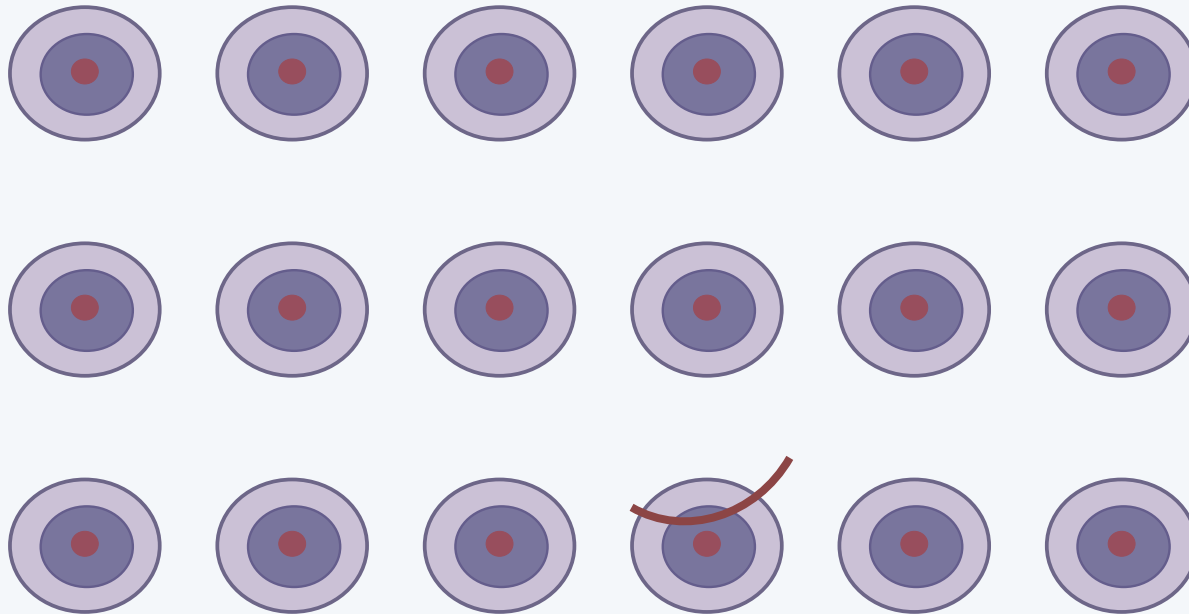
Large cell/anaplastic morphology changes nuclear appearance



Schematic morphology — not a histologic specimen

- Large and irregular vesicular nuclei contrast with the classic small hyperchromatic cells.
- Prominent nucleoli are characteristic of this histologic pattern.

Cell wrapping creates a cell-in-cell appearance



Schematic morphology — not a histologic specimen

- Tumor cells may appear to wrap around neighboring cells or dying-cell nuclei.
- Cell wrapping is among the described large cell/anaplastic features.

High turnover accompanies anaplastic morphology

- Mitotic and apoptotic indices are high.
- The pattern combines proliferative and cell-death features.
- The diagnosis is based on the aggregate histomorphology, not one feature.



Compare the principal histologic patterns

Pattern	Defining discriminators
Classic	Primitive-cell sheets; Homer Wright rosettes
Desmoplastic / nodular	Pale neuropil-rich islands; Reticulin-rich stroma
Large cell / anaplastic	Vesicular nuclei, prominent nucleoli, wrapping, high turnover

Classic: Sheets of primitive cells and Homer Wright rosettes.

Histology and molecular subtype answer different questions

- Histology describes what the cells and tissue look like.
- Molecular grouping classifies underlying oncogenic biology.
- Risk interpretation benefits from both rather than substituting one for the other.

HISTOLOGY

Architecture / cytology

Observed phenotype

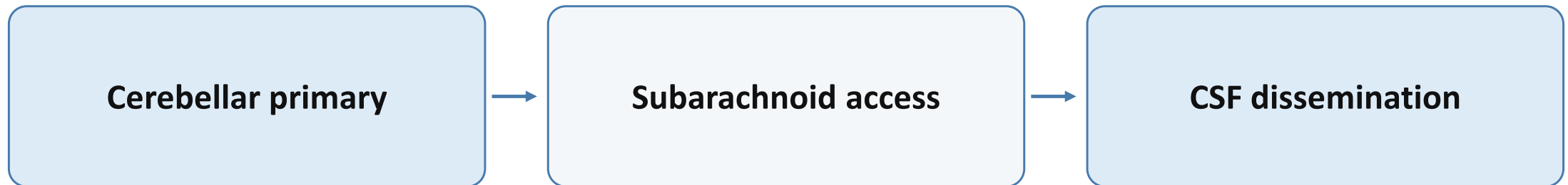
MOLECULAR

WNT / SHH / 3 / 4

Biologic subtype

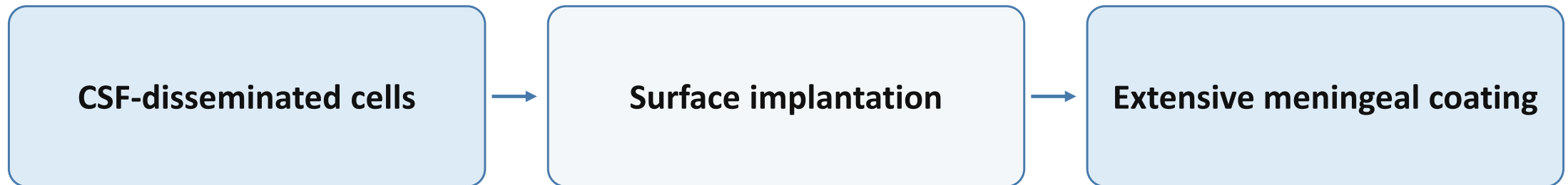
The subarachnoid space is a dissemination route

- Medulloblastomas tend to spread into the subarachnoid compartment.
- Tumor cells can disseminate within CSF rather than only expanding contiguously.



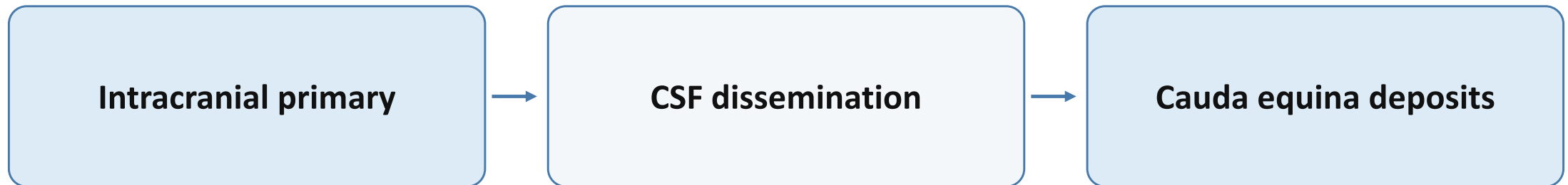
Dissemination may coat CNS surfaces

- Extensive surface growth is likened to “icing”.
- This is a descriptive growth pattern, not a separate molecular group.

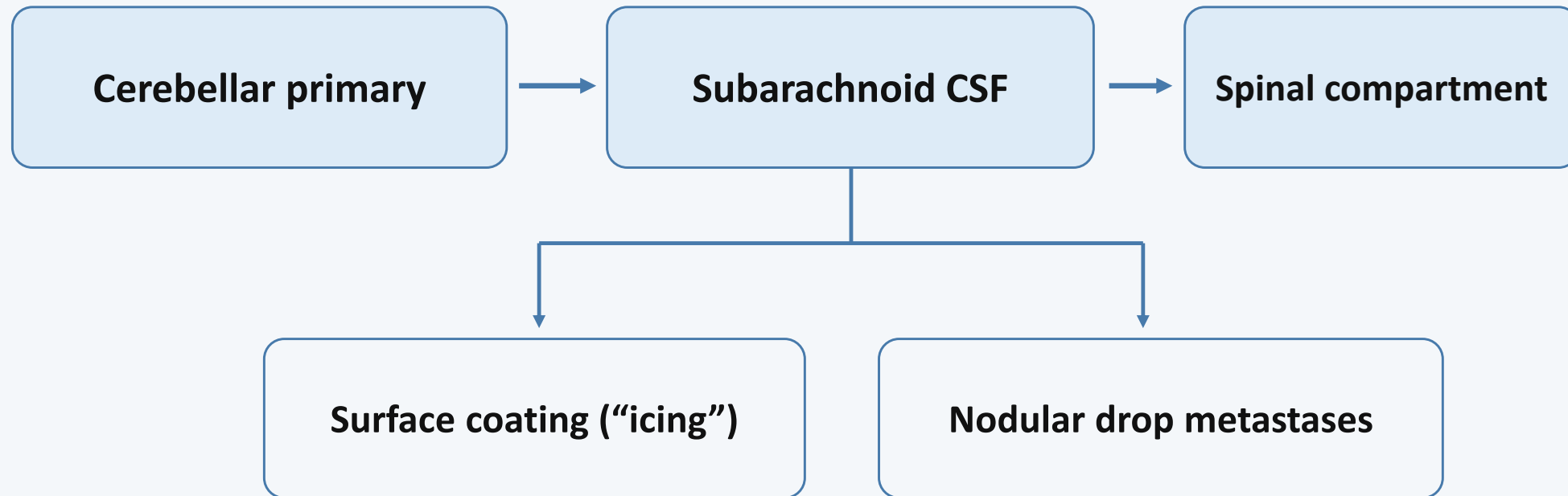


Drop metastases can involve the cauda equina

- Disseminated tumor may form nodular deposits along the neuraxis.
- The cauda equina as a favored location for drop metastases.



Primary tumor and spinal deposits share a route



Conceptual dissemination routes; Not an anatomic section

Two clinical consequences must be kept separate

Clinical consequence	Mechanism
Hydrocephalus	Local blockage of CSF pathways
Leptomeningeal deposits	Tumor-cell spread in subarachnoid CSF
Cauda equina nodules	Distant CSF-associated drop metastases

Hydrocephalus follows obstruction of CSF flow by rapid local growth.

Medulloblastoma is treatment-sensitive despite high grade

- Marked sensitivity to radiation and chemotherapy.
- Untreated disease nevertheless has a dismal prognosis.
- Therapeutic responsiveness should not be mistaken for indolent behavior.

NATURAL HISTORY

Highly malignant

Poor without treatment

TREATMENT RESPONSE

Radiation-sensitive

Chemotherapy-sensitive

Prognosis varies markedly by subgroup

- WNT-activated cases have favorable overall outcomes.
- SHH-activated/TP53-mutant and group 3 tumors are identified as unfavorable groups.
- Histologic pattern also contributes to prognostic assessment.

Histologic subtype

Molecular group

Clinical prognosis

Read the published survival figures as group estimates

- Nearly 100% five-year survival for WNT-activated disease.
- It contrasts this with approximately 20%–30% survival in more aggressive subtypes.
- These are textbook group-level estimates, not an individual prediction or a uniform contemporary cohort.

WNT-ACTIVATED

Nearly 100%

5-year survival reported

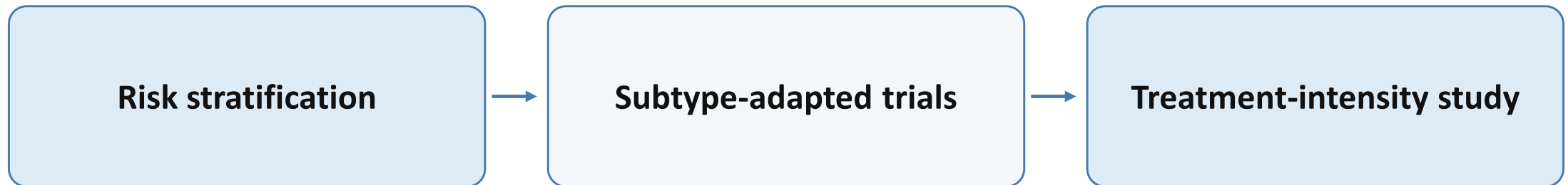
AGGRESSIVE SUBTYPES

20%–30%

Range reported

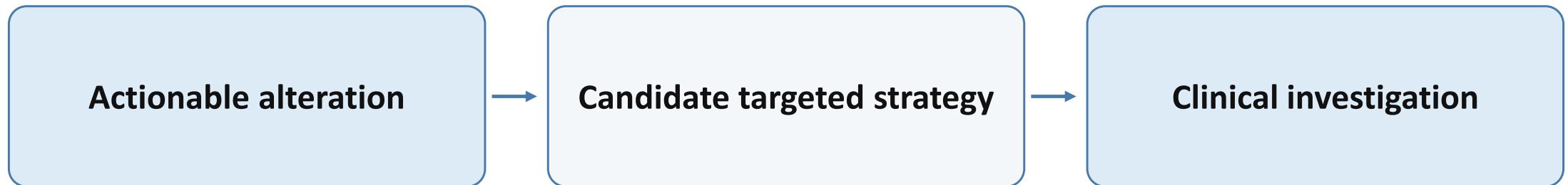
Treatment intensity is under subtype-based study

- Clinical trials explore de-escalation for some more favorable subtypes.
- Escalation is explored for biologically adverse disease.
- The source describes investigations rather than universal practice recommendations.



Targeted therapies remain an investigational direction

- Actionable molecular alterations motivate exploration of targeted agents.
- The textbook does not specify a universal targeted regimen for medulloblastoma.
- “Being explored” must not be presented as established efficacy.



Application: Rapid cerebellar growth

Illustrative pathology reasoning

- Illustrative question: A rapidly enlarging cerebellar tumor impedes CSF passage.
- What major complication follows from the mechanical obstruction?
- Name the causal chain rather than inferring a molecular subtype.

Teaching answer (speaker discussion)

CSF obstruction → hydrocephalus.

Application: Pale islands and reticulin

Illustrative pathology reasoning

- Illustrative question: A tumor contains pale neuropil-rich islands separated by reticulin-rich cellular zones.
- Which histologic pattern is suggested?
- Which molecular group is most strongly associated?

Teaching answer (speaker discussion)

Desmoplastic/nodular pattern; Associated with SHH activation.

Application: Prominent nucleoli and cell wrapping

Illustrative pathology reasoning

- Illustrative question: Primitive tumor cells show large irregular vesicular nuclei, nucleoli and cell wrapping.
- Which histologic pattern does this constellation support?

Teaching answer (speaker discussion)

Large cell/anaplastic medulloblastoma.

Application: Interpret a WNT-associated outcome

Illustrative pathology reasoning

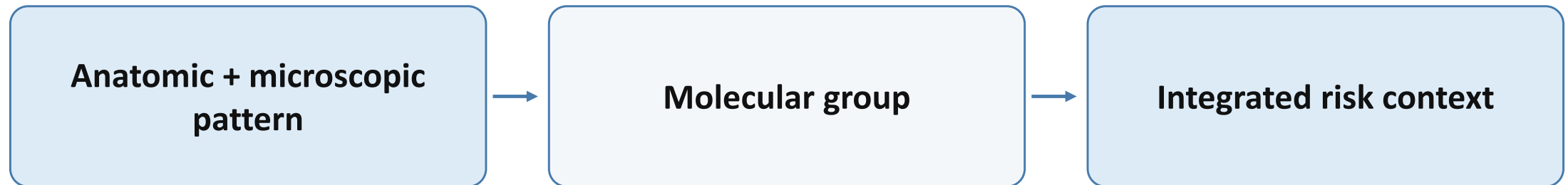
- Illustrative question: A molecularly confirmed WNT-activated tumor is identified.
- What is the direction of the group-level prognostic association?
- Why should a precise individual outcome not be promised?

Teaching answer (speaker discussion)

Favorable overall prognosis; Group estimates do not predict a specific patient.

An integrated pathology interpretation is layered

- Establish a cerebellar embryonal tumor with appropriate morphology.
- Describe classic, desmoplastic/nodular or large cell/anaplastic features.
- Integrate molecular classification and clinical dissemination/risk information.



Medulloblastoma: Essential distinctions

- Cerebellar malignant embryonal tumor; All are CNS WHO grade 4.
- Four molecular groups have different locations and prognoses.
- Histologic patterns are recognizable but not sufficient for molecular typing.
- The major hazards are CSF obstruction and leptomeningeal dissemination.

Primary reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 28: The Central Nervous System.
- Parent section: Embryonal Tumors; Medulloblastoma, printed p. 1182.
- For genuine gross and microscopic examples, see the original textbook Fig. 28.52A–D.