

Dysplastic Nevi

Melanocytic morphology, molecular pathogenesis, and melanoma-risk interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Define dysplastic nevi and distinguish a lesion-level precursor from a patient-level melanoma-risk marker.

Explain the contributions of RAS/BRAF signaling and p16–CDK4/6 cell-cycle control.

Identify the major clinical, architectural, cytologic, and stromal features.

Differentiate dysplastic nevi from ordinary nevi and melanoma using integrated findings.

Definition: A clinically and histologically atypical nevus

Dysplastic nevi are melanocytic neoplasms with atypical clinical appearance and microscopic architecture/cytology.

An individual lesion may rarely give rise directly to melanoma.

The presence of multiple lesions is most important as a marker of elevated melanoma risk.

Most individual dysplastic nevi are stable and never progress.

Two distinct meanings of “risk”

Risk carried by a lesion

Potential, but uncommon, direct progression to melanoma.

Most dysplastic nevi do not become melanoma.

Histologic atypia alone does not prove invasion.

Risk carried by a person

Multiple dysplastic nevi may indicate susceptibility to melanoma.

A familial syndrome can confer substantial lifetime risk.

Melanoma can arise independently of an existing nevus.

How the entity entered dermatopathology

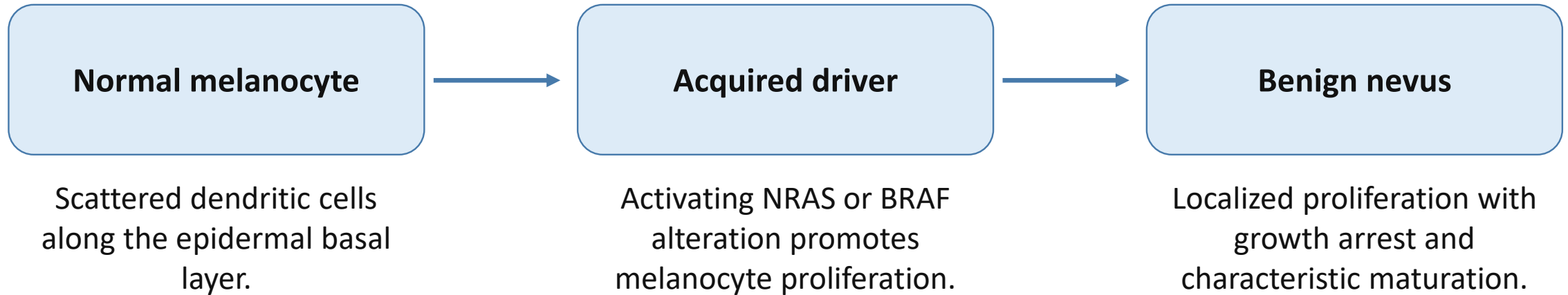
A link between melanocytic nevi and melanoma had long been recognized.

In 1978, Clark and colleagues described atypical lesions later termed dysplastic nevi.

The model connected atypical nevi, inherited susceptibility, and possible melanoma progression.

Contemporary interpretation must separate a plausible precursor pathway from the common outcome of clinical stability.

Biologic setting: Melanocytes to melanocytic nevi



A benign nevus is a true clonal neoplasm; Neoplasia is not synonymous with malignancy.

“Lentiginous” has a precise architectural meaning

Describes a linear increase in melanocytes along the epidermal basal layer.

Contrasts with cohesive, rounded nests concentrated near rete-ridge tips.

Dysplastic nevi frequently include lentiginous melanocytic hyperplasia.

Lentiginous growth is a pattern to interpret in context, not a stand-alone diagnosis.

Activating mutations can initiate benign nevi

NRAS / BRAF activation

Constitutively stimulates a growth-signaling circuit.

Initial proliferation

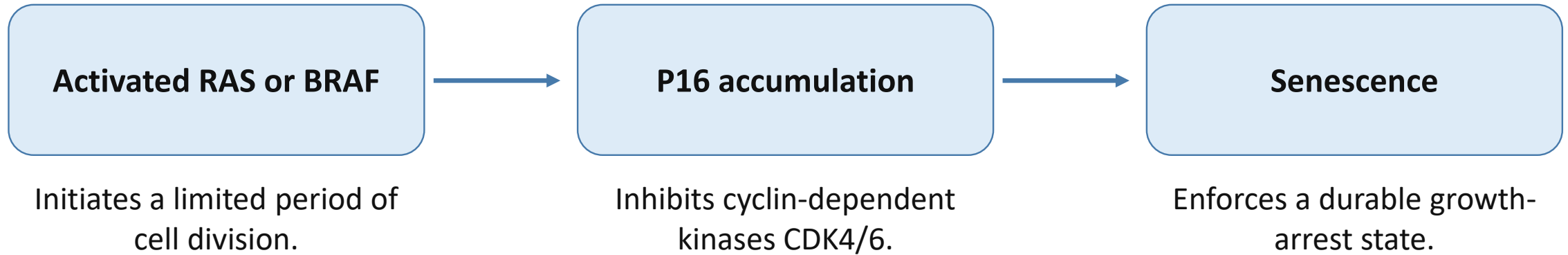
Melanocytes expand and form a local nevus.

Growth arrest

Oncogene-induced senescence limits progression.

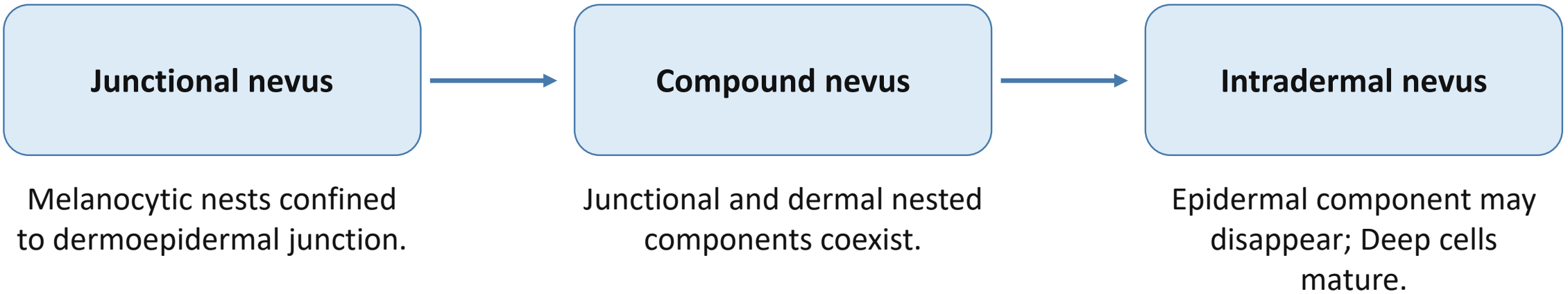
Driver activation alone is insufficient to imply melanoma.

Why ordinary nevi usually stop growing



Disruption of this safeguard is important in melanocytic progression.

Usual maturation sequence of a nevus



This is a common morphologic sequence, not a compulsory sequence for every nevus.

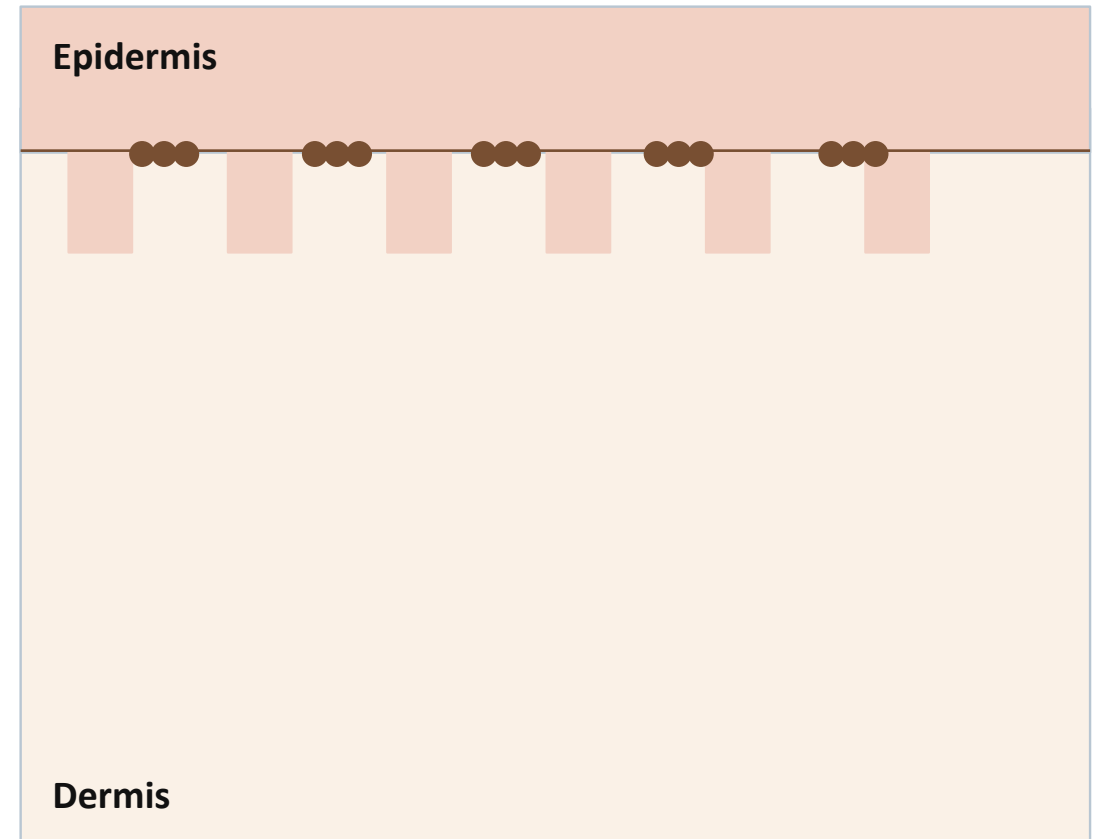
Junctional nevus: Nested basal proliferation

Histomorphologic interpretation

Round, relatively uniform nevus cells occupy junctional nests.

Nests typically arise near the tips of rete ridges.

Bland nuclei and limited mitotic activity support benign morphology.



Schematic — not a histologic specimen

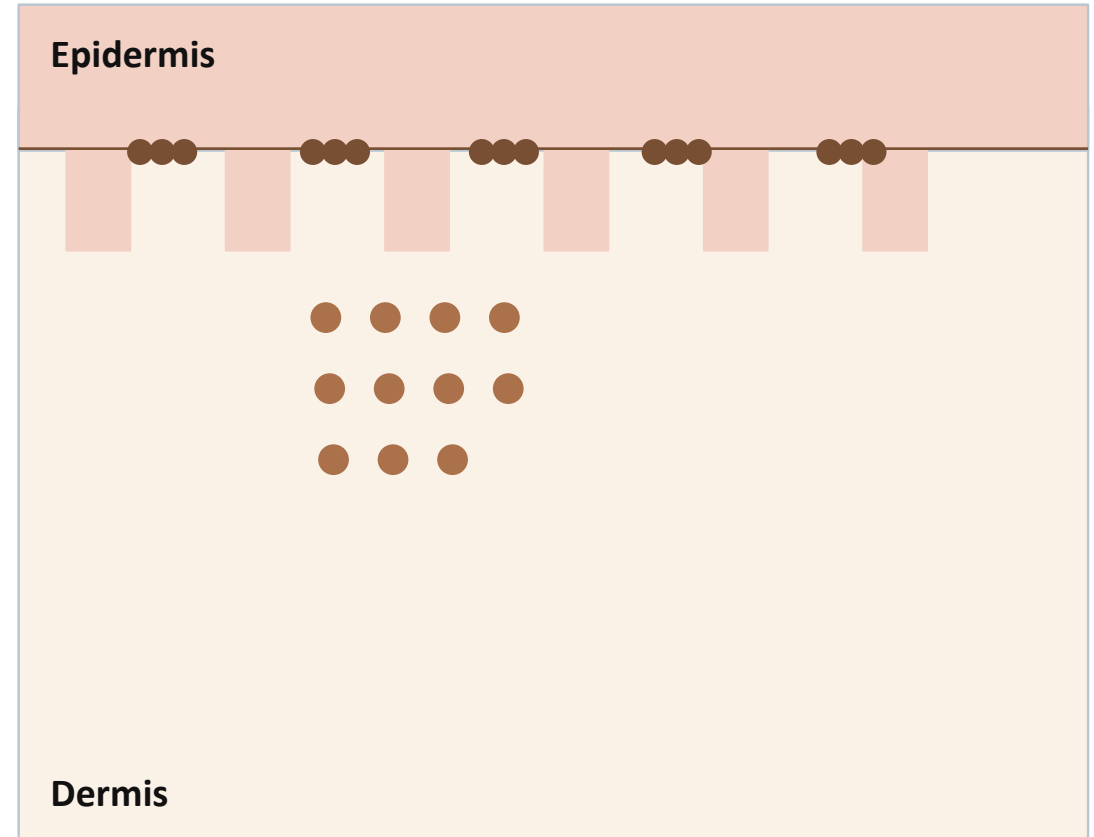
Compound nevus: Epidermal and dermal components

Histomorphologic interpretation

Junctional nests are accompanied by nevus-cell nests or cords in the dermis.

The clinical lesion may be dome-shaped and raised.

Symmetry and uniform pigment distribution favor an ordinary benign nevus.



Schematic — not a histologic specimen

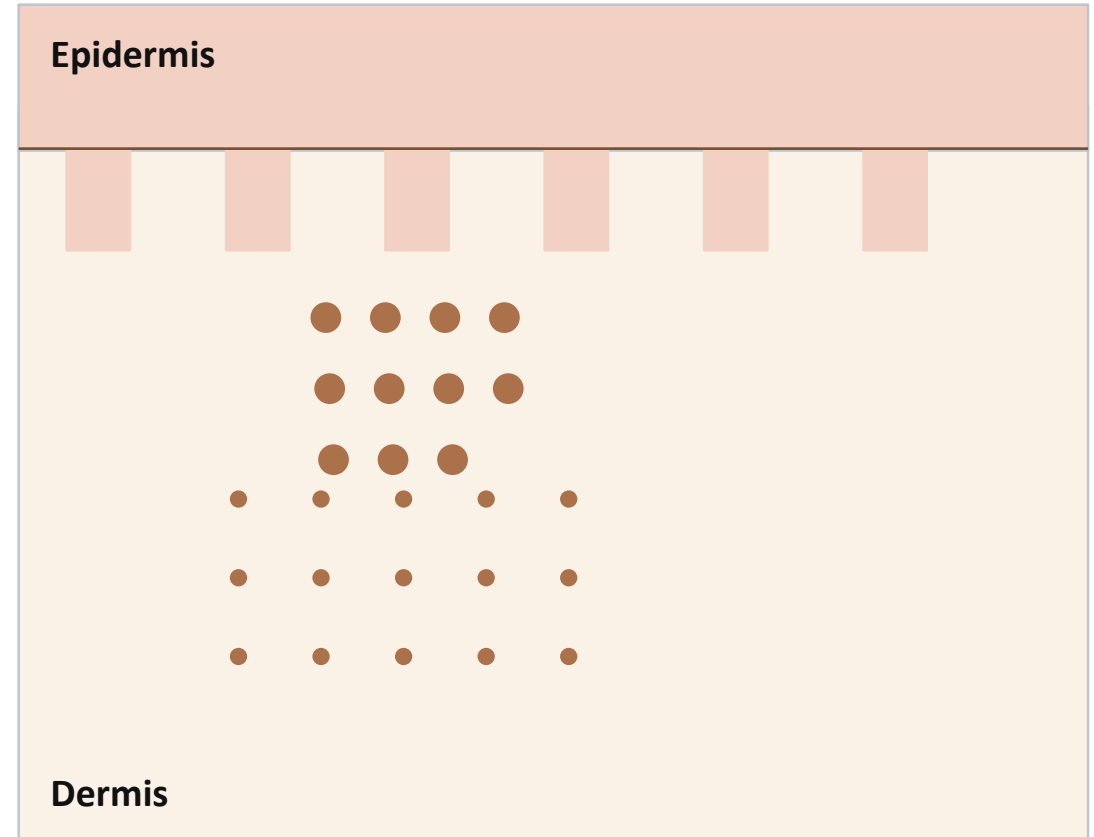
Maturation in the deeper part of an ordinary nevus

Histomorphologic interpretation

Deeper nevus cells become smaller and less pigmented.

Growth shifts from superficial nests toward smaller cords or single cells.

Deep fusiform “neurotization” may appear with reduced tyrosinase activity.



Schematic — not a histologic specimen

Ordinary versus dysplastic nevus: Orienting comparison

Feature	Ordinary acquired nevus	Dysplastic nevus
Surface appearance	Usually round; even pigmentation	May be irregular; variegated
Typical size	Often <6 mm	Frequently >5 mm
Histologic nesting	Bland, organized junctional nests	Enlarged and coalescent nests
Cytology	Uniform nuclei	Nuclear enlargement/irregularity
Dermal stroma	Maturation is characteristic	Lamellar fibrosis may be present

Why dysplastic nevi are a heterogeneous group

Isolated dysplastic nevus

Occurs in otherwise healthy individuals.

The risk that this single lesion becomes melanoma is very low.

An isolated diagnosis does not establish a familial syndrome.

Multiple dysplastic nevi

Can occur as a strong familial trait.

May signal elevated melanoma susceptibility.

Family history and the broader lesion population matter.

Dysplastic nevus syndrome

Also known as familial atypical multiple mole–melanoma syndrome.

An autosomal dominant susceptibility pattern may be observed in affected families.

A tendency to develop many dysplastic nevi and melanoma can be coinherited.

This syndrome should not be conflated with a solitary histologically atypical nevus.

Familial syndrome: What is transmitted?

Inherited susceptibility

A germline genetic predisposition is shared within a pedigree.

Multiple dysplastic nevi

Nevi may be numerous and morphologically atypical.

Melanoma risk

Some carriers develop melanoma, sometimes at multiple sites.

Autosomal dominant inheritance does not mean that every carrier must develop dysplastic nevi.

Magnitude of risk in the familial syndrome

>50% by age 60

A probability greater than 50% of melanoma by age 60 in people with dysplastic nevus syndrome—not a probability for every dysplastic nevus.

Risk of an isolated sporadic dysplastic nevus

Very low

In otherwise normal individuals, the risk of malignant transformation of a solitary dysplastic nevus is described as very low.

Evidence for occasional direct progression

Histologic observations document apparent transformation of dysplastic nevi into melanoma.

Such cases demonstrate precursor potential but do not establish routine progression.

Most dysplastic nevi remain stable over time.

A continuum model must be presented as a possible route rather than the expected fate.

Melanoma risk marker versus obligate precursor

Evidence supporting precursor potential

Occasional direct histologic transitions exist.

Morphologic progression has been proposed.

Additional oncogenic/epigenetic changes may accumulate.

Evidence against an inevitable sequence

Most dysplastic nevi never progress.

Some melanomas arise where no dysplastic nevus was present.

Multiple dysplastic nevi may mainly index host susceptibility.

The genetic overlap with ordinary nevi

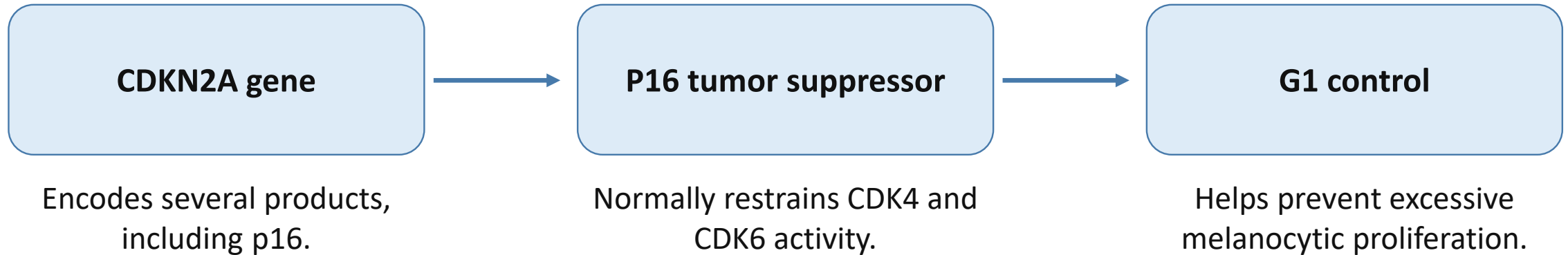
Dysplastic nevi, like ordinary acquired nevi, commonly contain acquired activating NRAS or BRAF mutations.

These shared alterations activate progrowth RAS-signaling pathways.

The overlap means a driver mutation by itself does not establish histologic dysplasia.

Additional checkpoint alterations and genetic context help explain susceptibility.

P16 connects the nevus to cell-cycle arrest



Loss of p16 function weakens a key growth-restricting checkpoint.

Pathogenic effect of inherited CDKN2A loss

Germline loss-of-function

Inherited reduction in a key cell-cycle suppressor.



Impaired p16 restraint

Less inhibition of CDK4/6.



Increased susceptibility

Cell-cycle progression is easier in a nevus-prone background.

Not every individual with a CDKN2A germline variant has clinically dysplastic nevi.

CDK4 mutation creates a different checkpoint lesion

Germline CDK4 variant

An alteration in CDK4 is inherited.

Resistance to p16

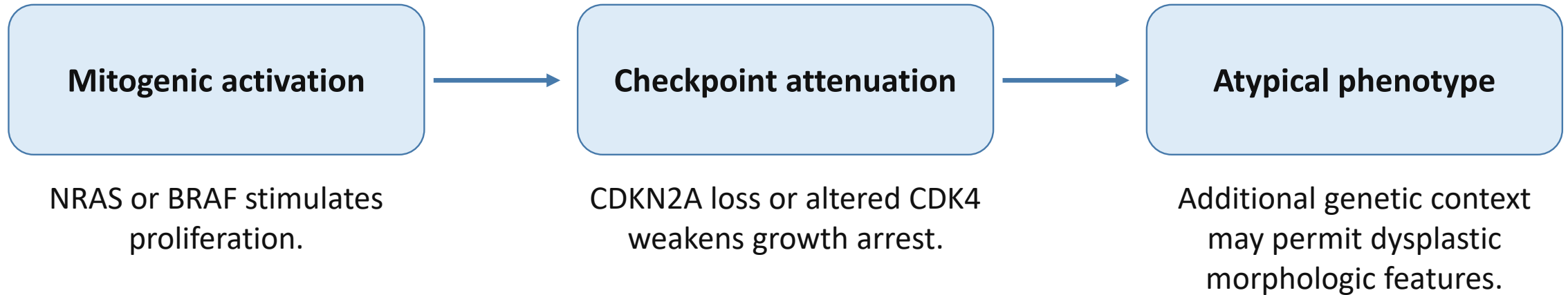
Mutant CDK4 is less susceptible to p16 inhibition.

Reduced growth control

Cell-cycle activity is less effectively restrained.

CDKN2A loss and p16-resistant CDK4 converge functionally but are different mutations.

A two-axis model of dysplastic nevus pathogenesis



Simplified conceptual model: Neither a single mutation nor a single morphology feature defines all lesions.

Modifier genes and incomplete phenotypic expression

Some CDKN2A or CDK4 mutation carriers do not develop dysplastic nevi.

Not all familial dysplastic nevi are explained by pathogenic variants in these genes.

Robbins infers additional genetic modifiers of nevus phenotype.

Do not present CDKN2A or CDK4 testing as a universal diagnostic test for dysplastic nevi.

Somatic drivers are not the same as inherited risk

Dimension	Acquired NRAS/BRAF change	Inherited CDKN2A/CDK4 change
Genetic compartment	Present in the nevus clone	Present constitutionally in the pedigree
Primary role	Proliferative signal	Cell-cycle checkpoint susceptibility
Diagnostic inference	Does not uniquely identify dysplasia	Does not guarantee dysplastic lesions
Teaching implication	Nevus-level event	Patient/family-level predisposition

No single pathway explains every dysplastic nevus

The clinical–histologic entity is not defined by one molecular alteration.

Several pathways may generate a similar atypical phenotype.

The absence of known familial variants does not disprove a familial clustering pattern.

Interpret molecular and morphologic findings at different levels: Lesion, patient, and family.

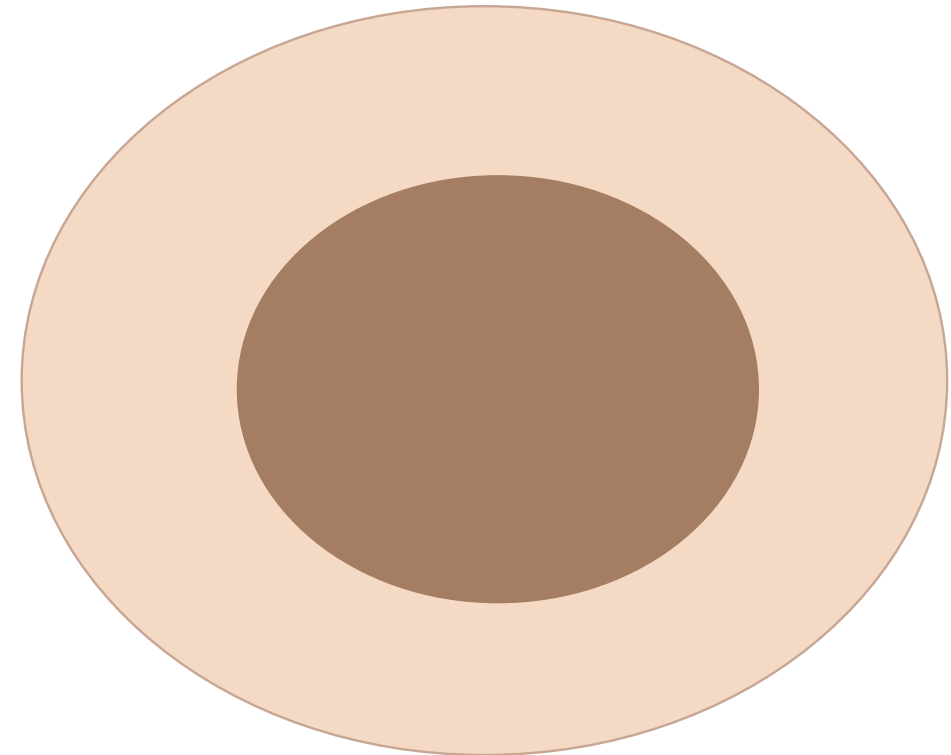
Clinical size: Often larger than ordinary nevi

Dysplastic nevi are frequently more than 5 mm across.

Ordinary acquired nevi are often less than 6 mm across.

These textbook ranges overlap: Diameter is a cue, not a stand-alone test.

Look for accompanying border, pigment, and evolution findings.



Schematic — not a clinical photograph

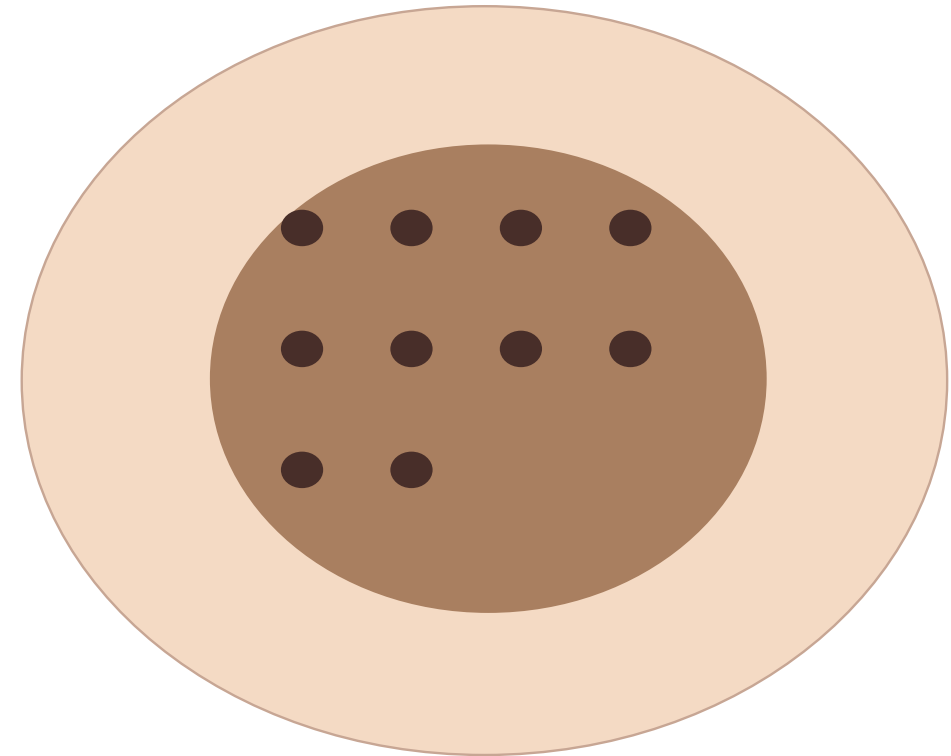
Clinical morphology: Macule or mildly raised plaque

A lesion may be a relatively flat macule.

Others form slightly elevated plaques.

An uneven or “pebbly” surface may be observed.

Surface elevation alone does not establish malignancy.



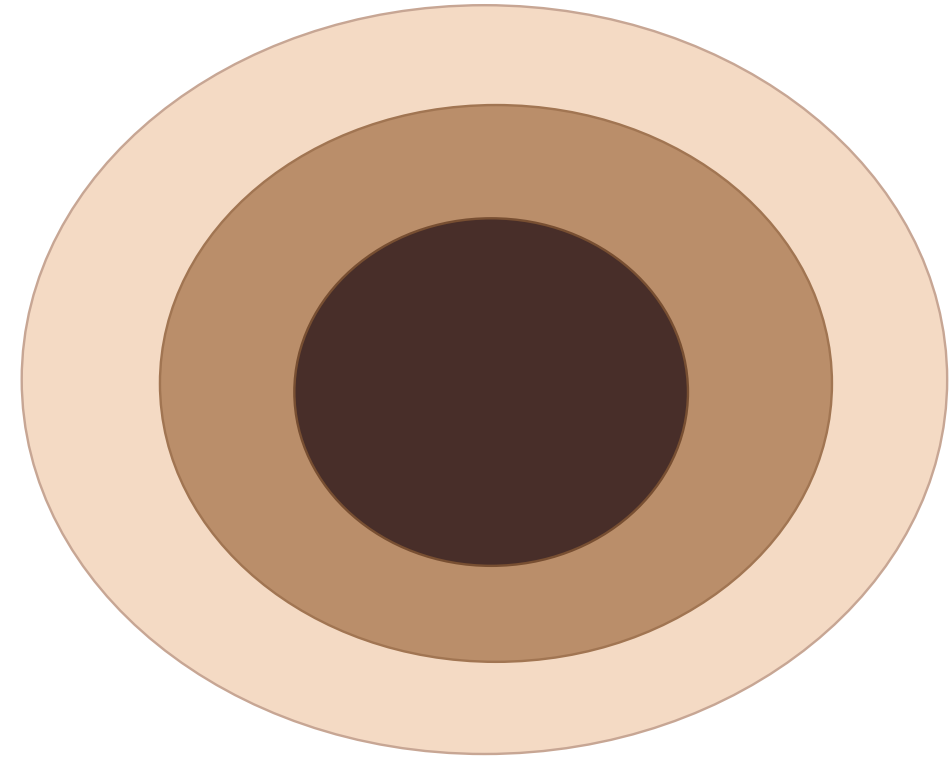
Schematic — not a clinical photograph

Target-like morphology: Darker center, flatter rim

A darker, raised central zone may coexist with an irregular, flat peripheral zone.

The peripheral macular extension may be less deeply pigmented.

Clinical heterogeneity mirrors a compound central portion and junctional extension in some lesions.



Schematic — not a clinical photograph

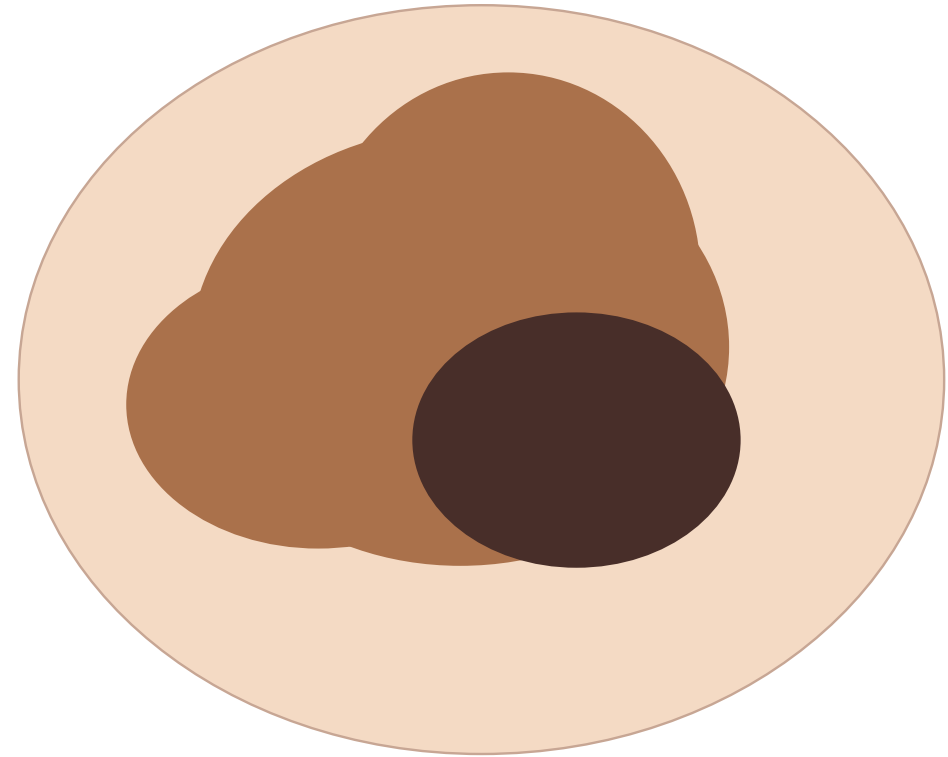
Border irregularity is a recognition feature

Dysplastic nevi may have uneven or irregularly outlined borders.

Compare with the smooth, rounded contours typical of ordinary nevi.

Irregularity is not specific: Melanoma also commonly has irregular borders.

Assessment requires the whole lesion and its clinical course.



Schematic — not a clinical photograph

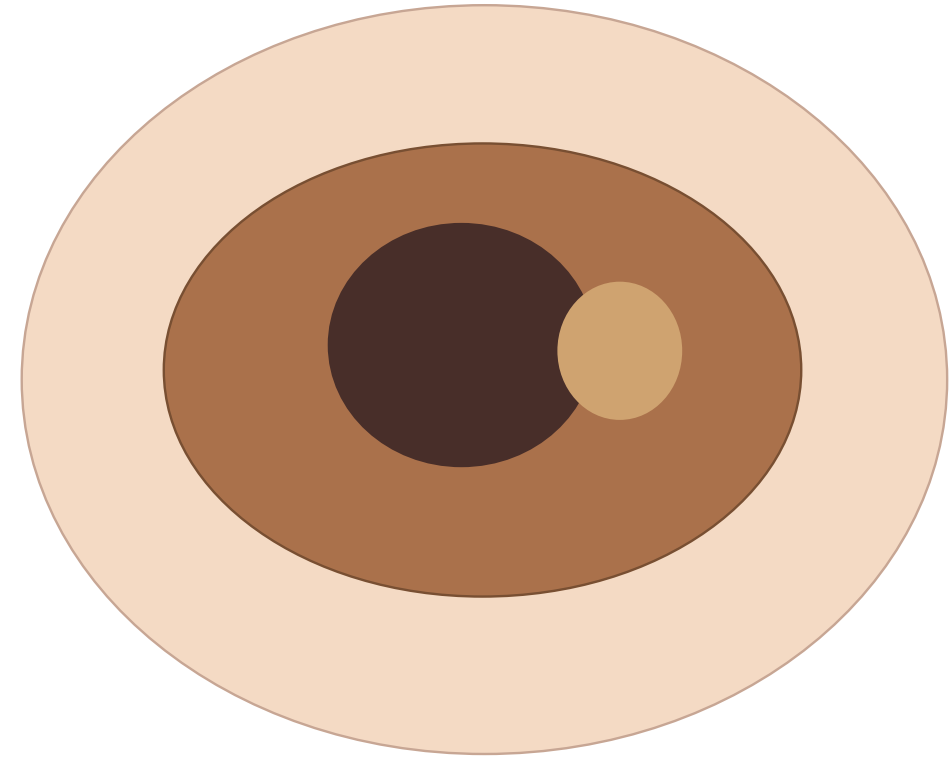
Variegated pigmentation signals internal heterogeneity

More than one shade of brown may occur in a dysplastic nevus.

A darker papular center may contrast with a lighter peripheral macule.

Melanoma may also be variegated, sometimes with colors beyond brown.

Pigment variation should be interpreted with other findings.



Schematic — not a clinical photograph

Anatomic distribution: Not restricted to sun exposure

Dysplastic nevi

May appear on sun-exposed skin.

May also appear on covered/protected skin.

Many lesions often occur in the familial syndrome.

Clinical interpretation

Do not exclude atypical nevi because of a protected site.

Total-body skin context can be important.

The distribution alone does not diagnose melanoma.

Lesion count changes the clinical interpretation

Patients with familial dysplastic nevus syndrome may have hundreds of clinically atypical nevi.

A single atypical mole may be sporadic and carry a very different risk interpretation.

The number of lesions should not be confused with a per-lesion malignant transformation rate.

Assessment should distinguish nevus burden from the behavior of a particular lesion.

Clinical warning signs: Dysplastic nevus versus melanoma

Observation	Dysplastic nevus	Melanoma concern
Asymmetry / border	May be atypical or irregular	May show pronounced irregularity
Pigment	Brown variegation may occur	Broad color heterogeneity can occur
Diameter	Often >5 mm	Size alone cannot confirm either diagnosis
Evolution	Many remain stable	Change over time is a major warning sign

Microscopic diagnosis requires an integrated pattern

Dysplastic nevi commonly involve both epidermis and dermis.

Architectural atypia and cytologic atypia are prominent diagnostic dimensions.

A stromal host response often provides corroborating clues.

No one isolated microscopic change is sufficient to establish the diagnosis.

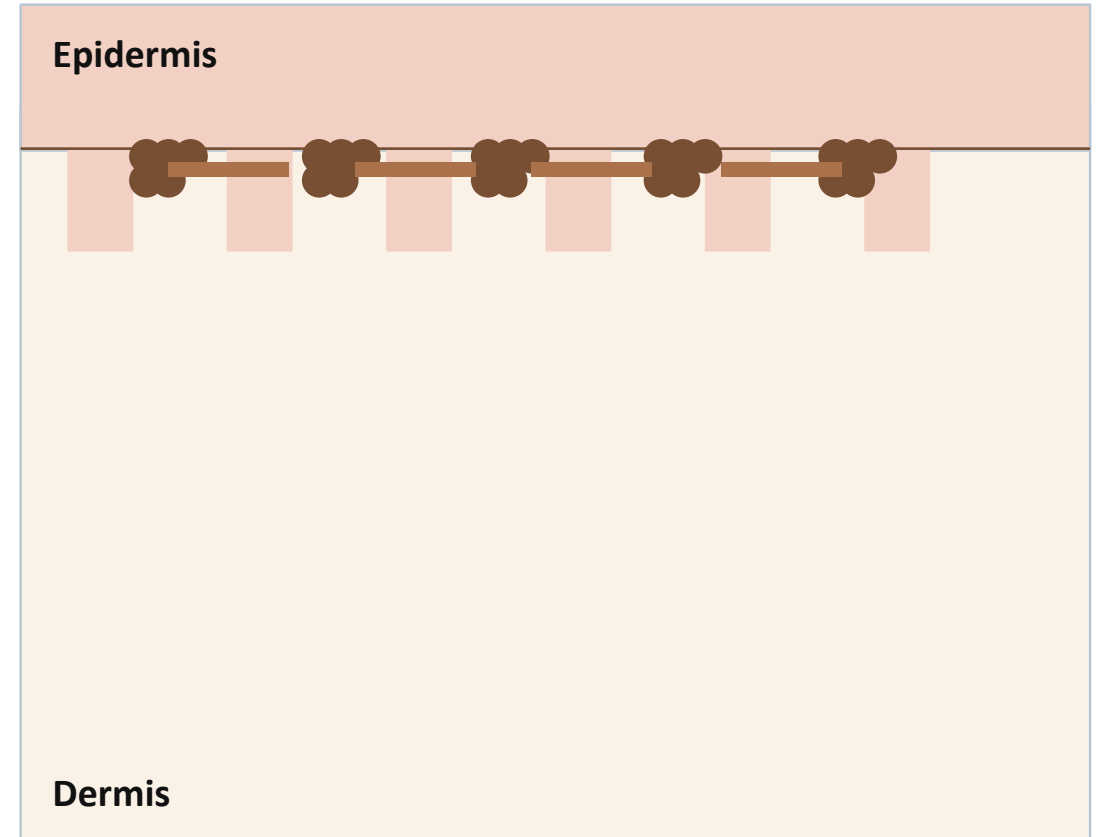
Architecture: Enlarged intraepidermal nevus nests

Histomorphologic interpretation

Junctional nests may exceed the size expected in a conventional nevus.

Nests may become irregularly arrayed across adjacent rete ridges.

Assess nest configuration together with melanocyte distribution and nuclear features.



Schematic — not a histologic specimen

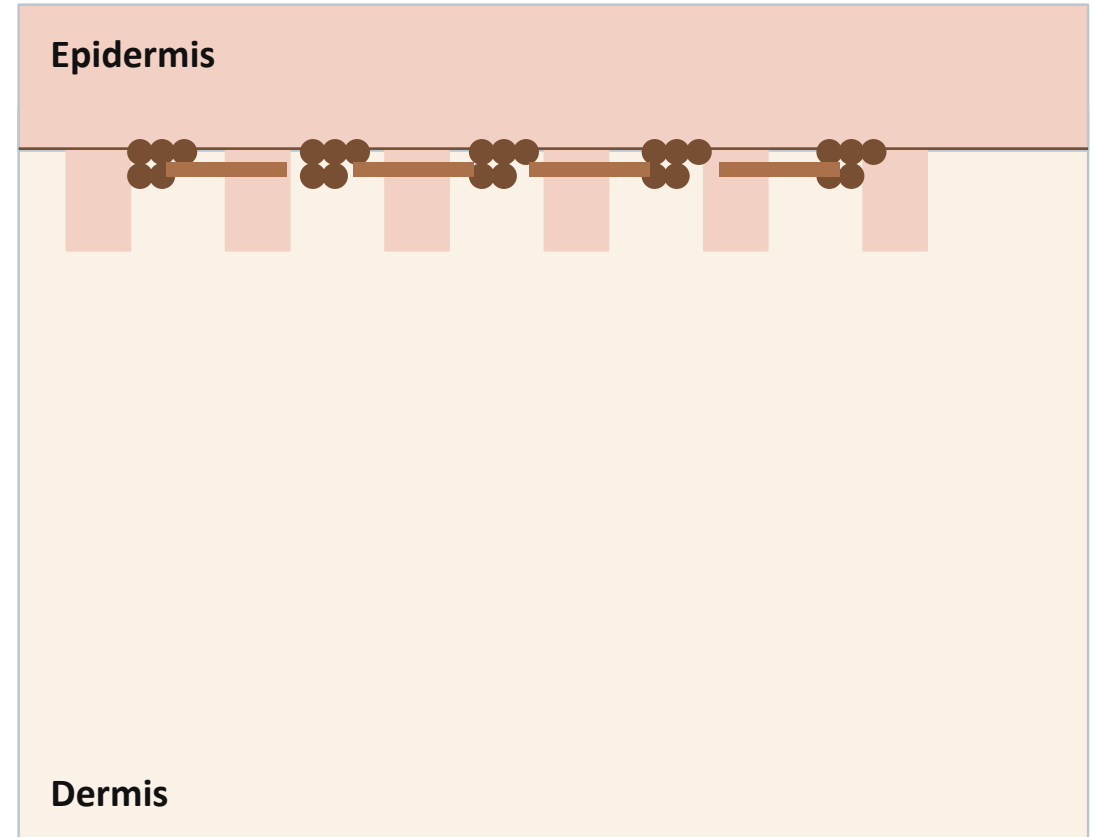
Architecture: Fusion and bridging of nests

Histomorphologic interpretation

Adjacent intraepidermal nests may fuse or coalesce.

Bridging disrupts the orderly pattern of discrete junctional nests.

Architecture is interpreted across the entire lesion, not in one field.



Schematic — not a histologic specimen

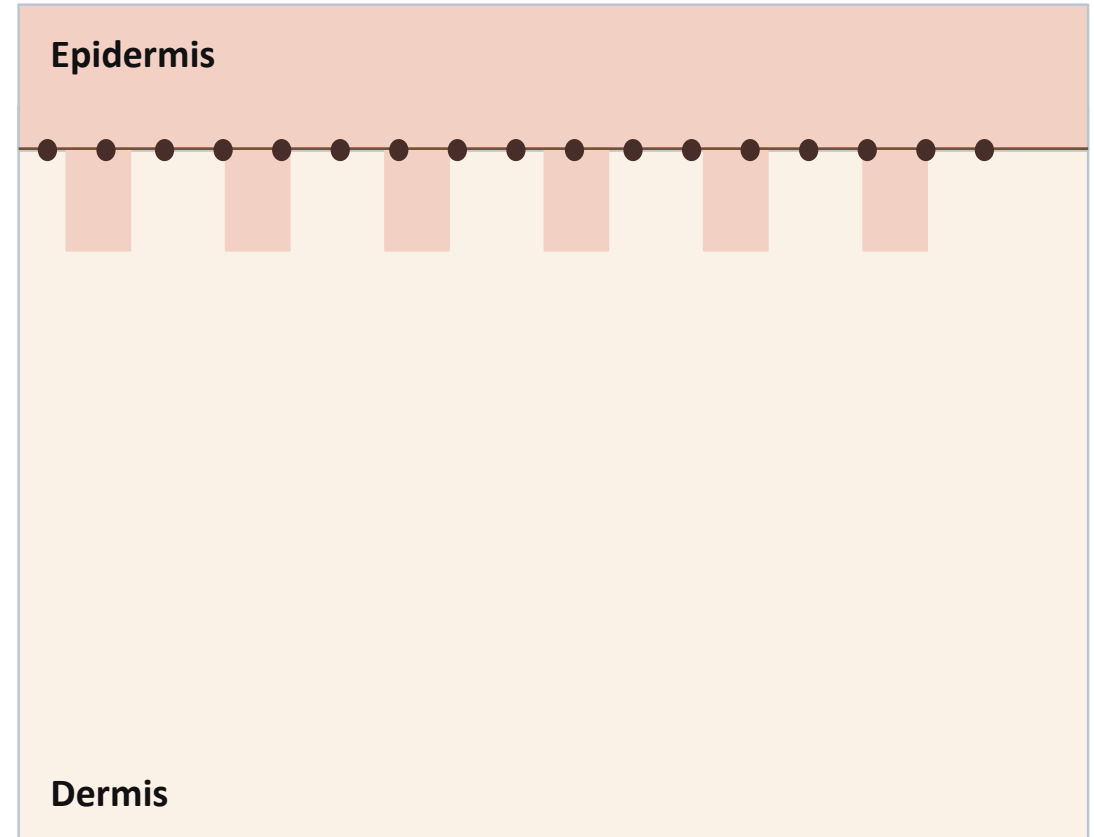
Lentiginous hyperplasia: Single cells along the basal layer

Histomorphologic interpretation

Single nevus cells increasingly populate the basal epidermal layer.

This creates a linear or lentiginous melanocytic proliferation.

The change accompanies, rather than replaces, other diagnostic clues.



Schematic — not a histologic specimen

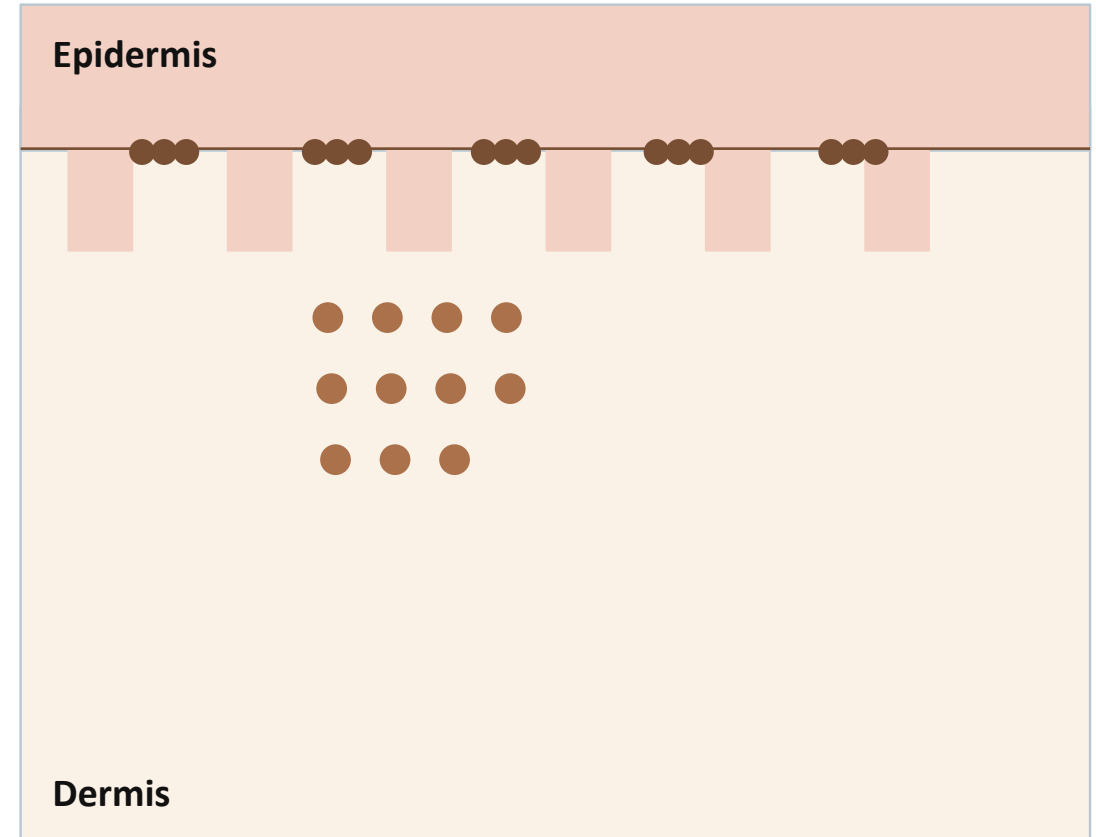
Epidermal plus dermal growth in dysplastic nevi

Histomorphologic interpretation

A junctional component is often combined with a dermal nevus component.

The architecture may be more irregular than in a conventional compound nevus.

Superficial atypia and dermal stromal reaction must be assessed together.



Schematic — not a histologic specimen

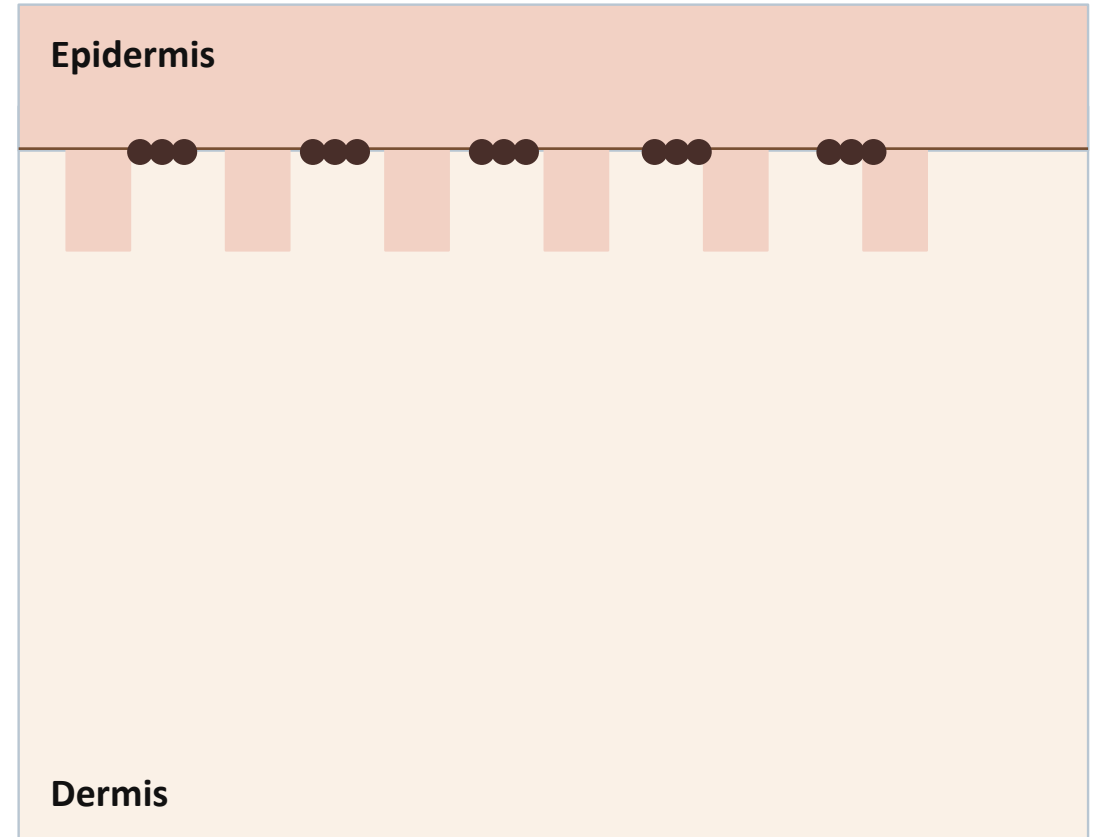
Cytology: Nuclear enlargement

Histomorphologic interpretation

Melanocytic nuclei may appear larger than their benign counterparts.

The relevant comparison is cell morphology in the context of architectural atypia.

Nuclear size alone is not sufficient to classify the lesion.



Schematic — not a histologic specimen

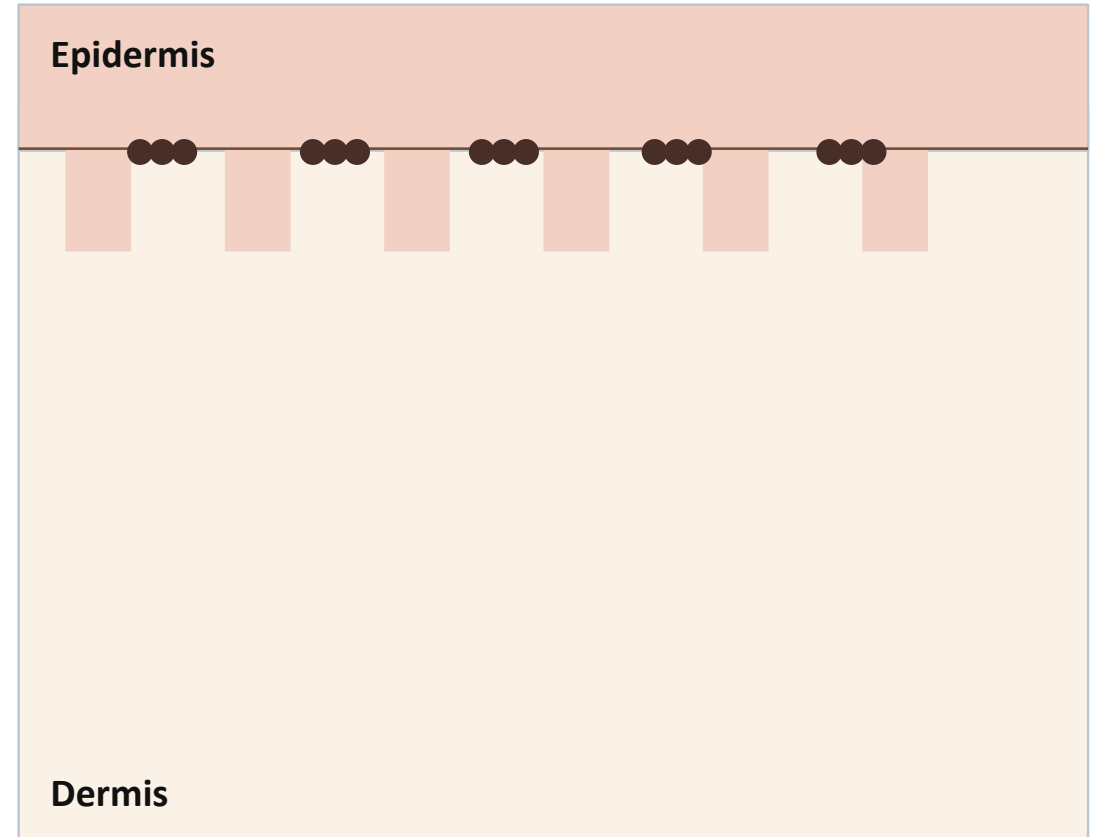
Cytology: Irregular or angulated nuclear contours

Histomorphologic interpretation

The nuclear outline may be uneven rather than smoothly rounded.

Some nuclei have angulated contours.

This distinction complements the presence of enlarged junctional nests.



Schematic — not a histologic specimen

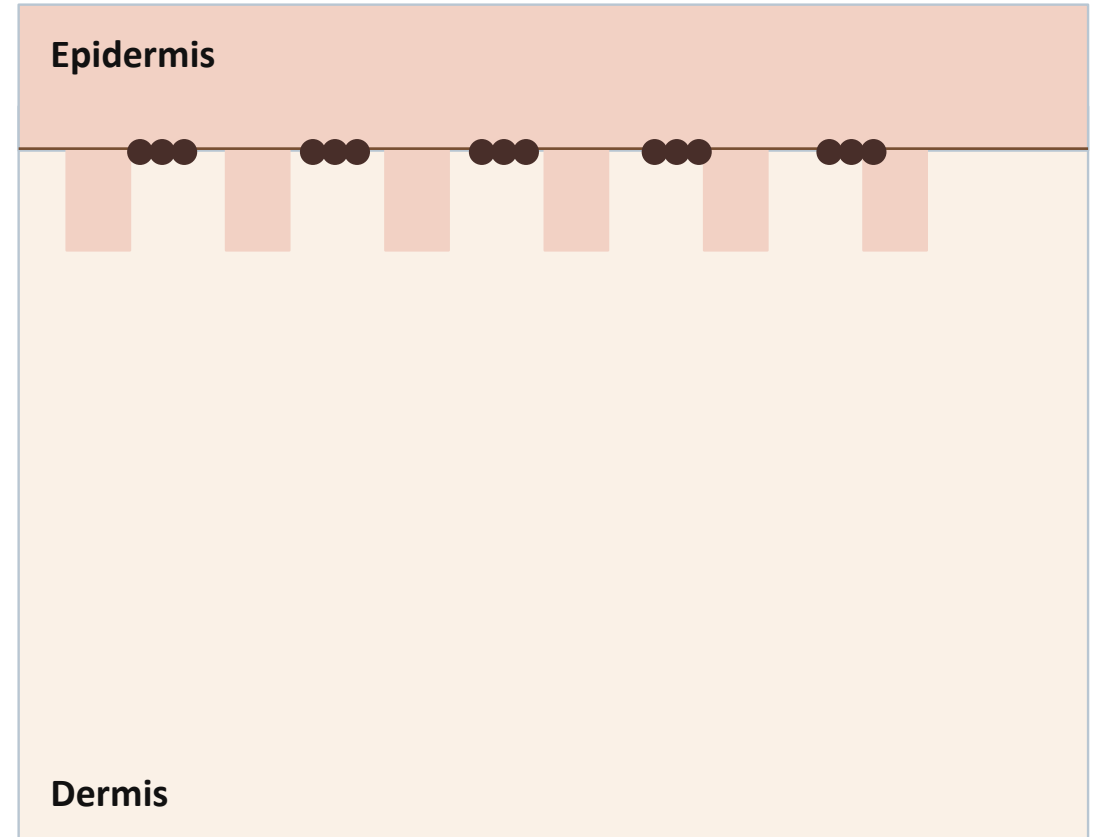
Cytology: Hyperchromasia

Histomorphologic interpretation

Affected nuclei may stain more darkly than typical nevus-cell nuclei.

Hyperchromasia is one component of the dysplastic cytologic pattern.

A diagnosis should not be made from chromasia alone.



Schematic — not a histologic specimen

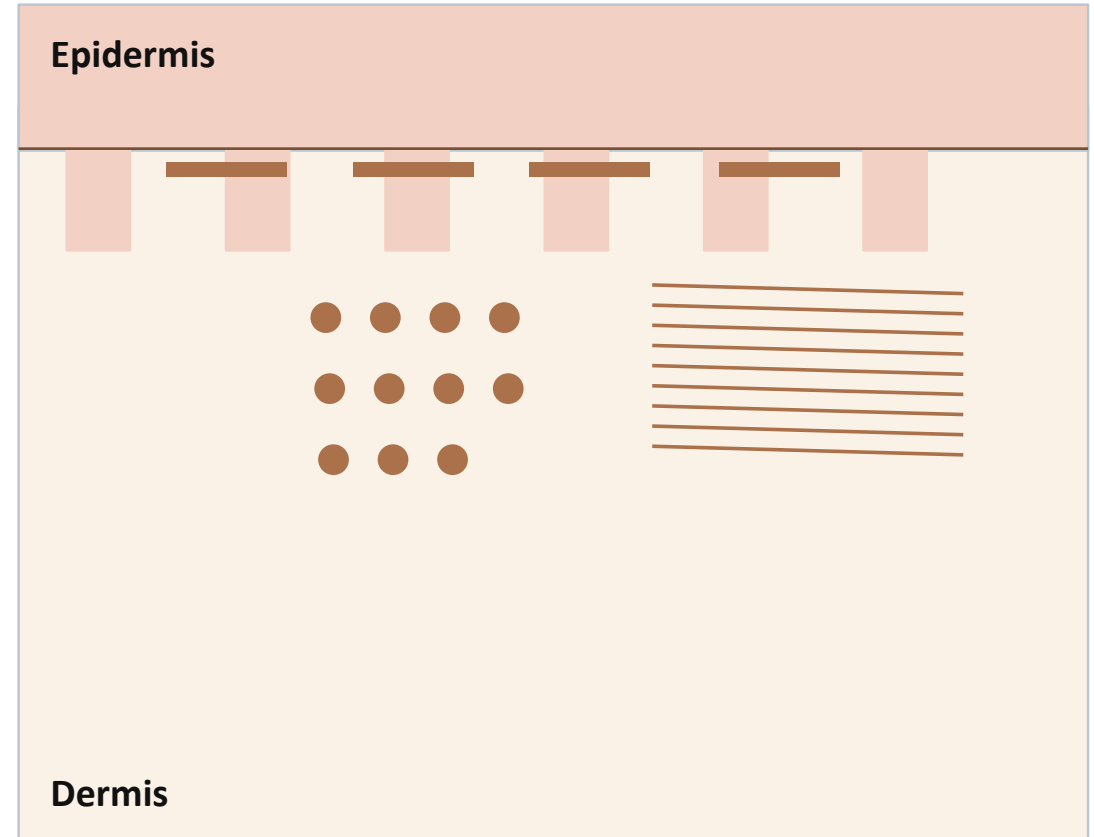
Dermal stromal response: Lamellar fibrosis

Histomorphologic interpretation

Linear or lamellar fibrous tissue may occur around involved rete ridges.

This distinctive superficial dermal response supports the overall pattern.

It is interpreted alongside architectural and cytologic atypia.



Schematic — not a histologic specimen

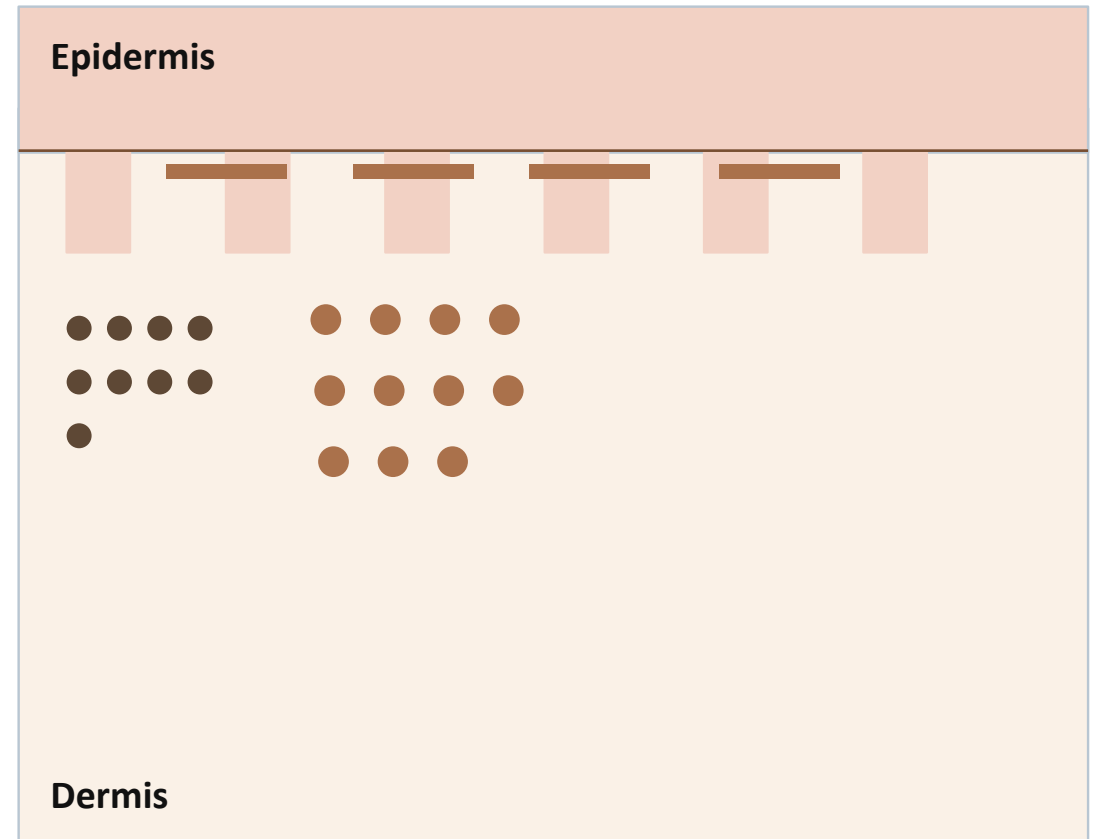
Melanin incontinence and melanophages

Histomorphologic interpretation

Pigment released from dead nevus cells may enter the dermis.

Dermal macrophages phagocytose the released melanin.

This stromal observation does not itself establish malignant progression.



Schematic — not a histologic specimen

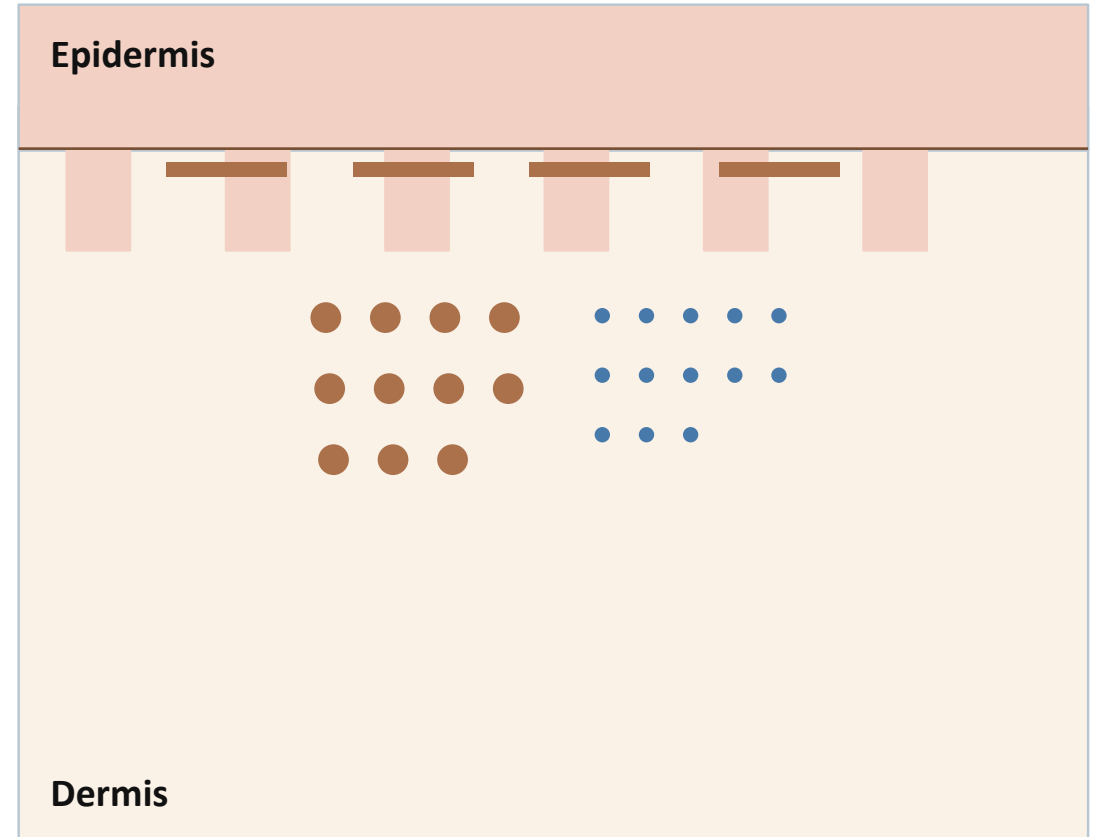
Sparse lymphocytes may accompany the lesion

Histomorphologic interpretation

A lymphocytic infiltrate may be present in the superficial dermis.

This infiltrate is usually sparse.

Inflammation is supportive context, not an obligatory or unique criterion.



Schematic — not a histologic specimen

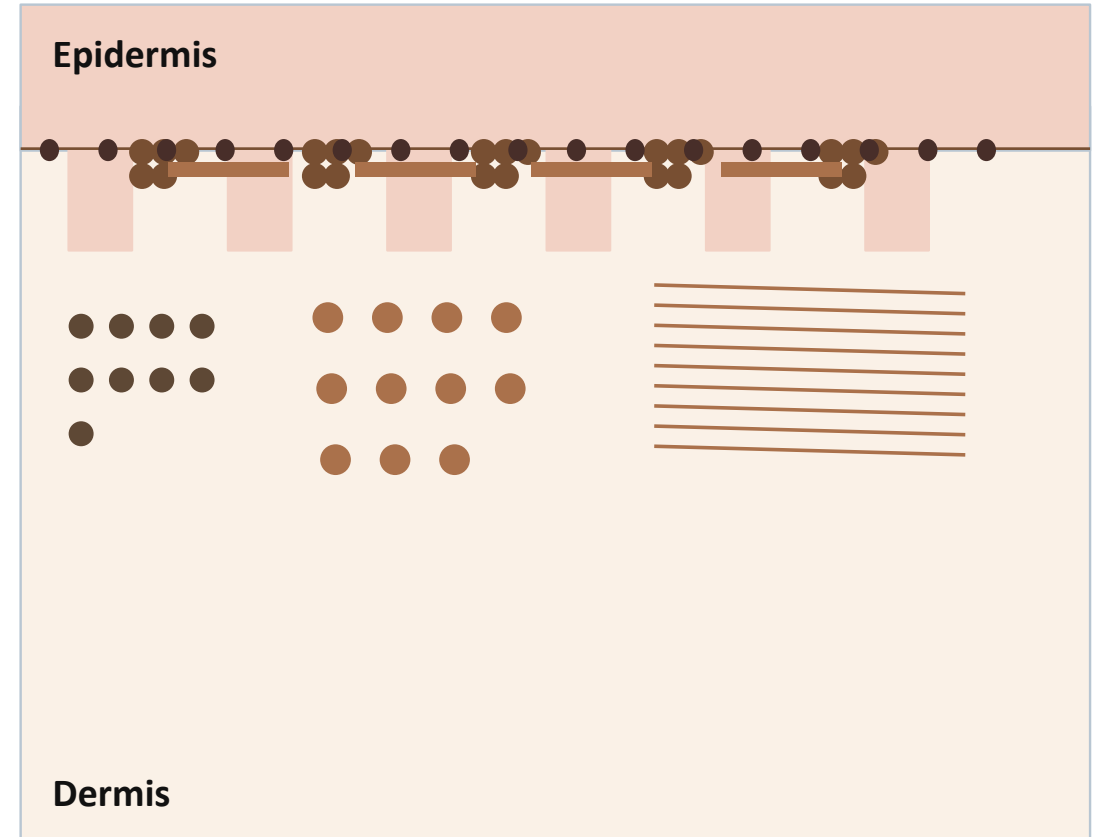
Integrated microscopic picture of a dysplastic nevus

Histomorphologic interpretation

Architectural disorder: Larger, confluent nests plus basal lentiginous cells.

Cytologic atypia: Enlarged, irregular, hyperchromatic nuclei.

Stromal clues: Lamellar fibrosis, melanophages, sparse lymphocytes.



Schematic — not a histologic specimen

A constellation of findings—not one “positive” sign

Atypical nests alone do not capture the full morphologic diagnosis.

Nuclear irregularity must be weighed against architecture and growth pattern.

Fibrosis, pigment incontinence, and inflammatory response may strengthen the interpretation.

The final assessment must integrate clinical presentation and the full section.

Histologic baseline: Ordinary versus dysplastic nevus

Parameter	Ordinary nevus	Dysplastic nevus
Junctional nests	Relatively rounded, discrete	Often enlarged / coalescent
Basal melanocytes	Nests predominate	Lentiginous single-cell growth
Nuclei	Bland and uniform	Enlarged, angulated, dark
Superficial dermis	Variable bland change	Lamellar fibrosis / melanophages
Whole-pattern reading	Symmetry + maturation	Architectural + cytologic atypia

Dysplastic nevus and melanoma: Critical distinctions

Dimension	Dysplastic nevus	Melanoma
Expected behavior	Usually stable	Malignant potential, including invasion
Interpretation of atypia	Architectural + cytologic, non-diagnostic of invasion	More pronounced atypia with malignant growth pattern
Growth pattern	May be junctional + dermal	Radial growth; vertical invasion in progression
Deep maturation	May be present in nevus component	Absent in invasive melanoma component

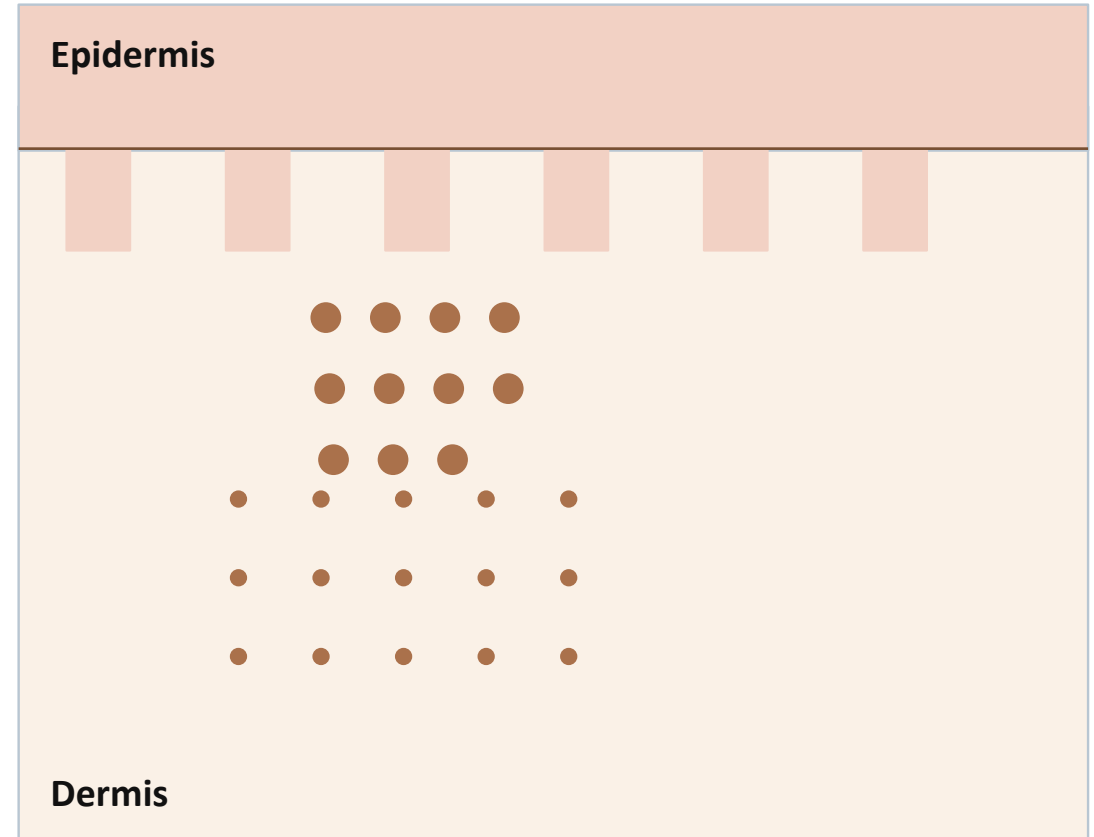
Deep maturation remains a major differential clue

Histomorphologic interpretation

In benign nevi, deep cells tend to become smaller and less pigmented.

The deepest portion can show neurotization.

This benign progression with melanoma, which lacks deep maturation.



Schematic — not a histologic specimen

Melanoma: Radial and vertical growth are not synonyms

Radial growth

Mainly horizontal spread in epidermis and superficial dermis.

Vertical growth

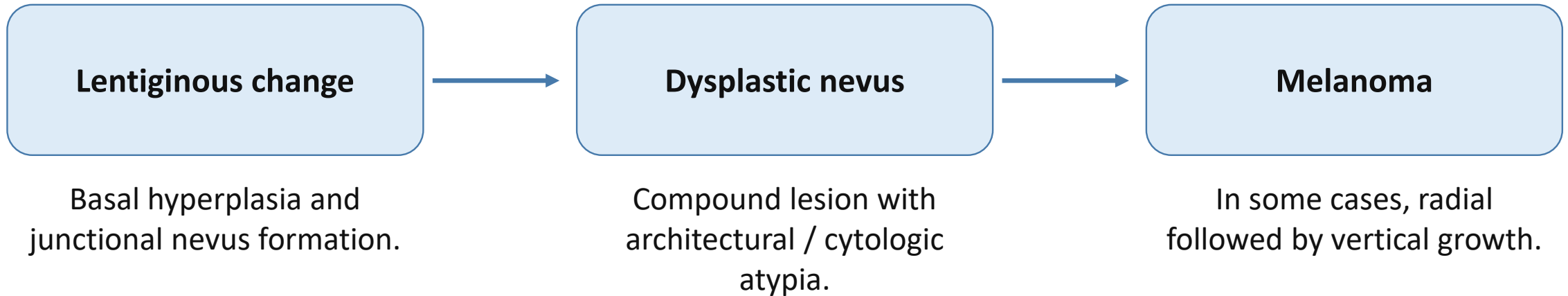
Expansile downward invasion into dermis.

Metastatic capability

Associated especially with the vertical growth component.

These are melanoma-specific concepts, not stages assigned to every dysplastic nevus.

A proposed—not inevitable—morphologic progression



Robbins Fig. 25.5 presents potential steps; Malignant conversion of any one dysplastic nevus is uncommon.

A key non-equivalence

Not all melanomas arise in dysplastic nevi

Even in dysplastic nevus syndrome, a melanoma may appear separately from a pre-existing dysplastic nevus.

Clinicopathologic discordance: Where errors arise

Clinical presentation

Size and border irregularity may resemble melanoma.

Pigmentation can be variegated in benign atypical nevi.

A stable nevus may still be atypical on histology.

Histopathologic interpretation

One striking nucleus alone is not a diagnosis.

The extent and pattern of growth must be evaluated.

Clinical context and histologic architecture are complementary.

Case 1: A solitary atypical nevus

A person with no family history notices a longstanding, slightly irregular, variegated pigmented lesion. Biopsy shows a dysplastic nevus.

Interpret the findings

Single lesion; No stated familial syndrome.

Histology demonstrates atypical nests and stromal fibrosis.

No evidence of melanoma is supplied.

Reasoned answer

A dysplastic nevus can arise sporadically. The risk of malignant conversion of this individual lesion is as very low; The diagnosis alone does not establish a high-risk pedigree.

Case 2: Multiple nevi in a melanoma-prone family

Several relatives have numerous clinically atypical nevi; Melanoma has occurred at multiple sites within the pedigree.

Interpret the findings

Multiplicity and a family history are salient.

The pattern may suggest familial dysplastic nevus syndrome.

Consider risk at the person/family level.

Reasoned answer

The key inference is elevated susceptibility to melanoma. Do not multiply an individual lesion's progression probability by the number of nevi or infer a genotype from phenotype alone.

Case 3: Assess the entire histologic pattern

A melanocytic lesion contains enlarged coalescent junctional nests, lentiginous melanocytes, irregular hyperchromatic nuclei, and lamellar fibrosis.

Interpret the findings

Architectural atypia is present.

Cytologic atypia is present.

A characteristic stromal response is present.

Reasoned answer

The constellation supports dysplastic nevus morphology. No single observation—bridging, hyperchromasia, or fibrosis—should be treated as sufficient alone.

Case 4: Molecular evidence is not a stand-alone diagnosis

A nevus contains an activating BRAF variant; The clinical lesion is small, evenly pigmented, and the cells show orderly maturation.

Interpret the findings

BRAF alterations occur in ordinary nevi.

Maturation is a hallmark of the conventional nevus.

No architectural/cytologic dysplasia is described.

Reasoned answer

Do not diagnose a dysplastic nevus or melanoma from BRAF activation alone. The acquired driver is compatible with a benign nevus with oncogene-induced senescence.

Four recurrent diagnostic reasoning errors

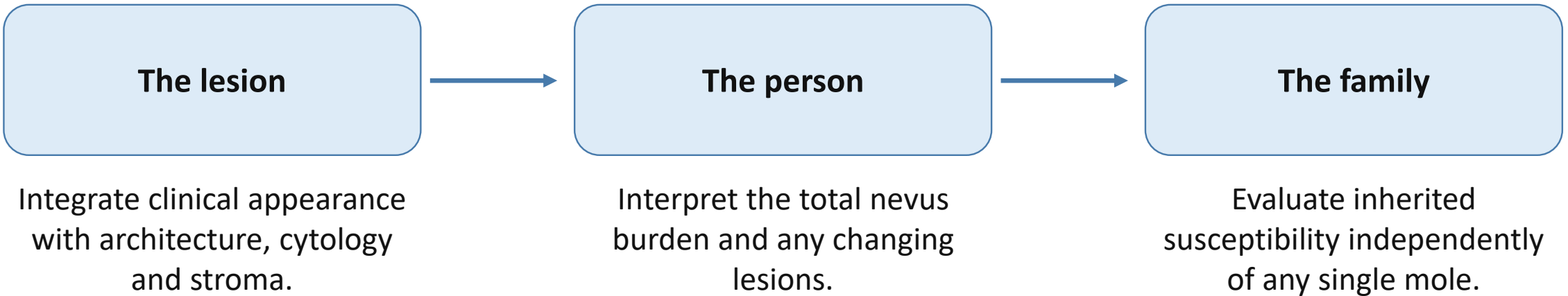
Equating every dysplastic nevus with a premalignant lesion destined to progress.

Applying a familial syndrome risk estimate to an isolated sporadic nevus.

Using one cytologic or architectural finding instead of the full pattern.

Treating a shared BRAF/NRAS driver as molecular proof of melanoma.

Conceptual synthesis: Lesion, patient, family



Different units of analysis lead to different risk statements.

Core conclusions for pathology teaching

Dysplastic nevi are atypical melanocytic neoplasms with architectural, cytologic, and stromal hallmarks.

Most remain stable; Rare cases may progress directly to melanoma.

Multiple dysplastic nevi may index substantially increased melanoma susceptibility, especially in the familial syndrome.

NRAS/BRAF activation overlaps with ordinary nevi; P16–CDK4/6 dysregulation helps explain inherited predisposition.

Diagnosis and risk interpretation require the full morphologic and clinical context.

References and teaching-source boundaries

Primary textbook

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 25: The Skin; “Dysplastic Nevi,” pp. 1031–1033.

Context: “Melanocytic Nevus,” p. 1031; “Melanoma,” pp. 1033–1035; Figs. 25.2–25.6 and Table 25.2.

Diagrams in this lecture are editable conceptual schematics, not clinical photographs or histologic evidence.