

Soft Tissue Tumors

Pathogenesis • Classification • Adipocytic and Fibroblastic Tumors

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Learning outcomes

- Define the soft tissue compartment and distinguish tumor behavior categories.
- Explain predisposition, putative origin, and the two broad cytogenetic patterns.
- Interpret representative sarcoma fusion events without confusing molecular alterations with malignancy.
- Compare lipoma, liposarcoma subtypes, and nodular fasciitis using clinicopathologic features.

Soft tissue: The pathology convention

**Included: Mesenchymal
soft tissues**



Excluded: Bone / joints



**Excluded: CNS / blood /
lymphoid**

Non-epithelial tissues outside skeleton and joints.

Central nervous system and hematopoietic/lymphoid tissues are excluded.

In this chapter, soft tissue pathology chiefly concerns neoplasms.

Why the soft tissue category is anatomically broad

Differentiation

Fat and fibroblastic lineages

Anatomic setting

Superficial, deep, extremity,
trunk, retroperitoneum

Behavior

Benign through malignant

The term designates a diagnostic compartment—not one unique cell type.

Most soft tissue neoplasms are benign

Approximately 100-fold more frequent

Benign soft tissue tumors versus sarcomas — skeletal muscle tumors excepted

- Benign tumors approximately 100-fold more frequently than sarcomas, excepting skeletal muscle neoplasms.
- A soft tissue mass is not automatically a sarcoma.
- Clinical context and tissue classification remain essential.

Soft tissue sarcoma: Uncommon, clinically consequential

Frequency	Clinical significance
Rare relative to all cancers	Can cause substantial morbidity and mortality
Most masses are benign	Aggressive sarcomas require precise diagnosis

Anatomic distribution has diagnostic value

Extremities predominate

Most soft tissue tumors arise in extremities.



Thigh: Frequent site

The thigh is a particularly frequent site.



Subtype location also matters

Location also helps narrow a specific subtype (e.g., deep thigh vs superficial trunk).

Sarcomas across the age spectrum

Childhood

Hereditary predisposition
deserves attention

Young adult

Some simple-karyotype tumors
predominate

Older adult

Many complex-karyotype
tumors occur

Most soft tissue sarcomas occur in adults, but childhood disease is important.

A typical sarcoma has no established precursor lesion

Carcinomas

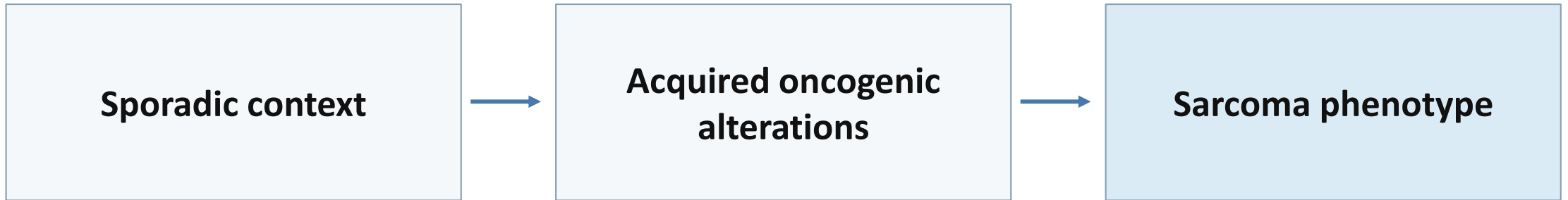
Sometimes recognizable precursor lesions

Sarcomas

Precursors generally undefined

Many carcinomas evolve through recognizable preinvasive lesions.

Most sarcomas are sporadic



In most cases, no specific predisposing cause is identified.

Somatic oncogenic changes drive neoplastic growth.

A smaller subset occurs with germline predisposition or identified exposures.

Inherited susceptibility syndromes

NF1

Neurofibromatosis type 1

Li–Fraumeni

Inherited tumor predisposition

Gardner

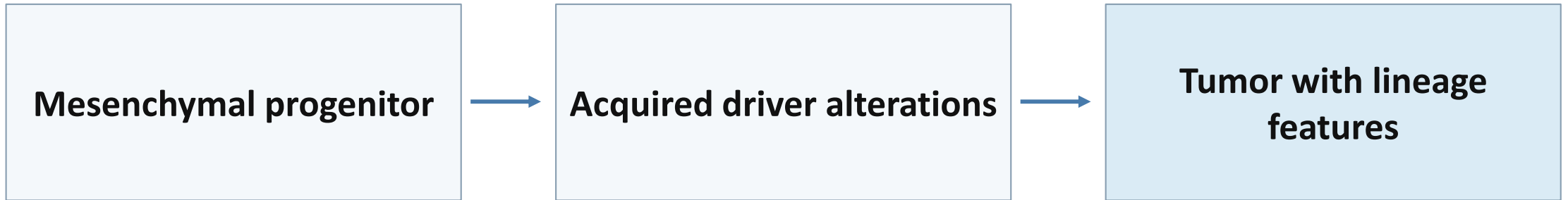
APC-associated context

NF1-associated predisposition, Li–Fraumeni syndrome, and Gardner syndrome among examples.

Environmental and acquired associations

- Recognized associations include radiation exposure.
- Burns, toxins, and chronic inflammation are also noted.
- These exposures account for a minority of sarcomas; Association is not a universal cause.

Mesenchymal stem cell: A proposed origin



Robbins frames sarcomas as arising from mesenchymal stem cells acquiring driver events.

Resulting neoplasms may express different differentiation programs.

This is a pathogenic model, not proof that each tumor derives from a fully mature tissue cell.

Differentiation does not prove the cell of origin

Where tumor arises

Anatomic soft tissue site

What tumor resembles

Mature or primitive mesenchymal lineage

Rhabdomyosarcoma can occur where mature skeletal muscle is sparse.

Molecular heterogeneity is a defining feature



Sarcoma genotypes range from recurrent specific rearrangements to highly complex copy-number changes.

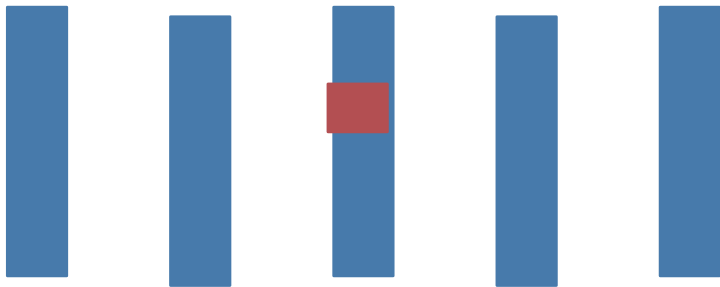
Different mechanisms may converge on malignant growth.

The genetic pattern can be diagnostically more informative than gross tumor appearance.

Two broad cytogenetic patterns

Simple karyotype

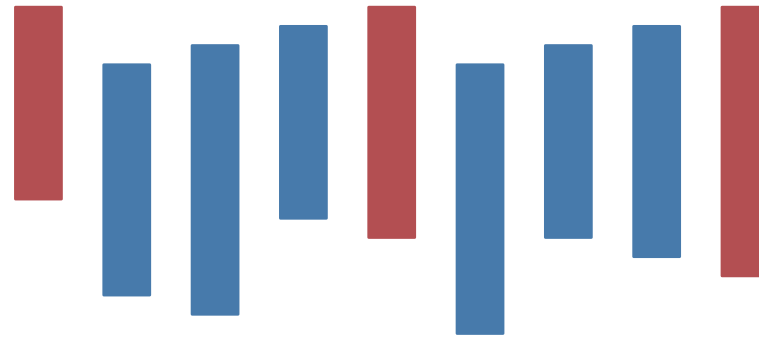
Few recurrent changes



One recurrent event

Complex karyotype

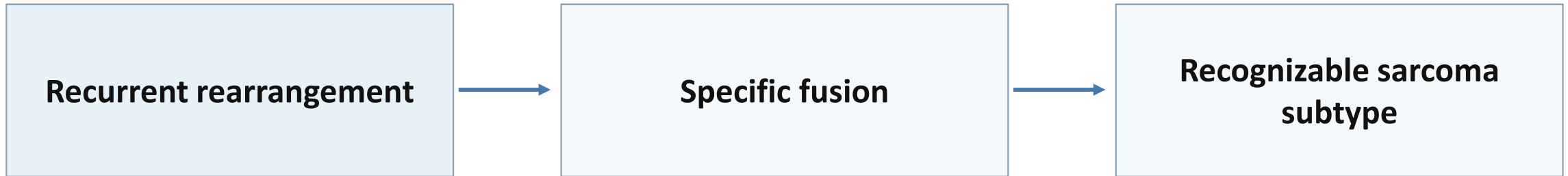
Numerous gains/losses



Multiple altered chromosomes

Schematic only (not patient cytogenetics)

Simple-karyotype sarcomas

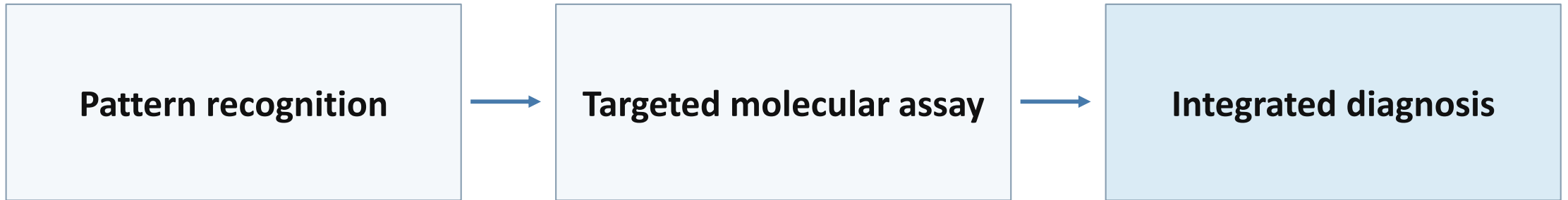


Often relatively limited chromosomal abnormalities, sometimes a defining rearrangement.

Many arise in younger individuals and have limited pleomorphism.

Diagnostic molecular markers can reflect early driving events.

Rearrangement-driven tumors and diagnosis

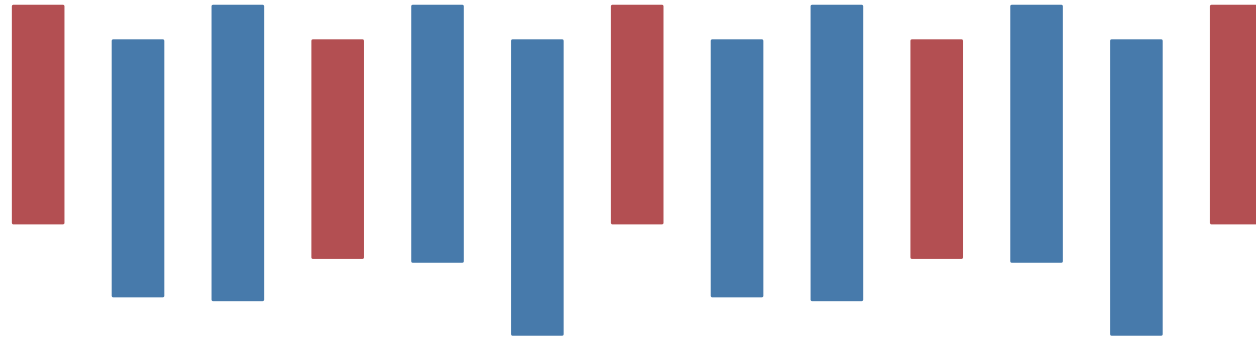


A recurrent fusion may be sufficiently specific to support entity assignment.

Detection can refine a differential suggested by age, site, and histology.

The genetic result must still be interpreted in clinicopathologic context.

Complex-karyotype sarcomas



Schematic genomic instability — not a measured karyogram

Schematic only (not patient cytogenetics)

Simple and complex karyotypes compared

Feature	Simple karyotype	Complex karyotype
Genomic pattern	Few recurrent changes	Multiple gains and losses
Usual morphology	Often limited pleomorphism	Often pleomorphic
Typical setting	Many younger patients	Often adults
Examples	Synovial sarcoma	Leiomyosarcoma; undifferentiated sarcoma

Gene fusions create more than one oncogenic mechanism

Transcription

EWSR1 family; PAX::FOXO1

Ligand signaling

COL1A1::PDGFB

Kinase signaling

ETV6::NTRK3

Some fusion proteins dysregulate transcription or chromatin remodeling.

Selected EWSR1-associated fusions

Tumor	Characteristic fusion	Interpretive role
Ewing sarcoma	EWSR1::FLI1 / EWSR1::ERG	Gene-regulatory fusion
Extraskeletal myxoid chondrosarcoma	EWSR1::NR4A3	Entity-associated rearrangement
Desmoplastic small round cell tumor	EWSR1::WT1	Entity-associated rearrangement
Clear-cell sarcoma	EWSR1::ATF1	Entity-associated rearrangement

FUS::DDIT3 blocks adipocytic differentiation

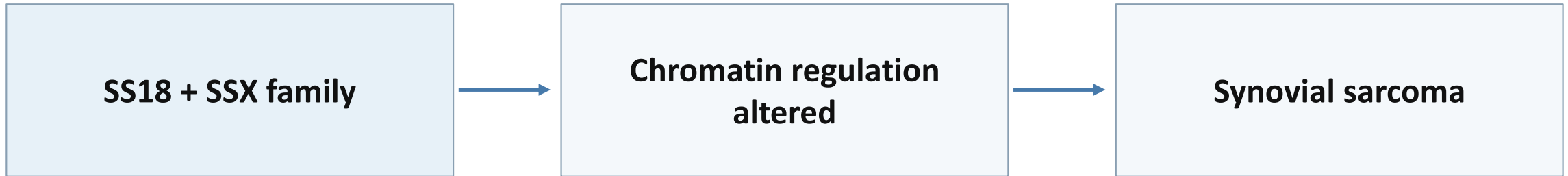


Myxoid liposarcoma commonly carries FUS::DDIT3 from t(12;16).

The chimeric protein interferes with normal adipocytic maturation.

Primitive adipocytic cells accumulate within a myxoid vascular matrix.

SS18::SSX affects chromatin-remodeling complexes



Synovial sarcoma is linked to t(X;18).

Reported fusion partners include SSX1, SSX2, and SSX4.

The resulting proteins dysregulate chromatin-remodeling complexes.

PAX::FOXO1 affects muscle differentiation

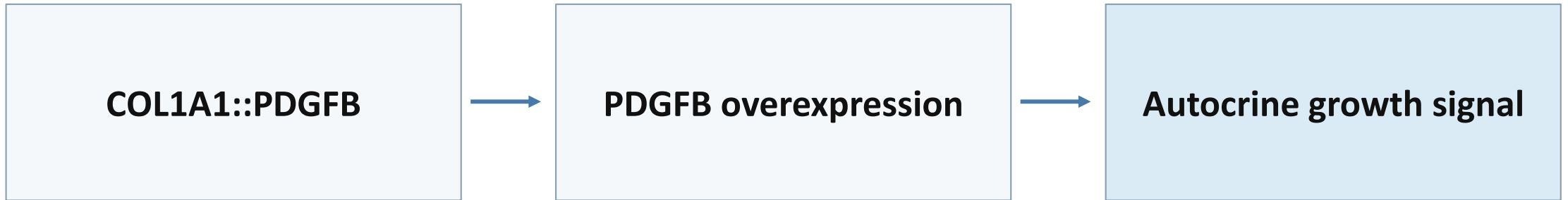


Alveolar rhabdomyosarcoma may contain PAX3::FOXO1 or PAX7::FOXO1.

These act as chimeric transcription factors.

They interfere with skeletal muscle differentiation programs.

COL1A1::PDGFB: Promoter-driven growth signaling

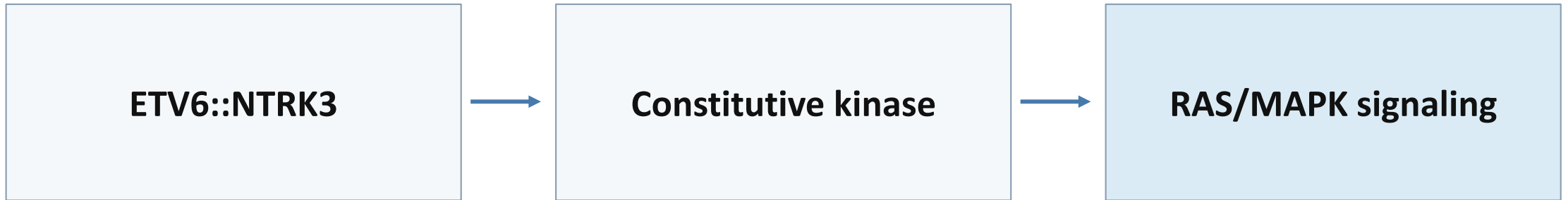


Dermatofibrosarcoma protuberans is associated with COL1A1::PDGFB.

The rearrangement promotes PDGFB overexpression.

PDGF signaling then supports autocrine proliferative stimulation.

ETV6::NTRK3: Constitutive kinase activation



Infantile fibrosarcoma is associated with ETV6::NTRK3.

The chimeric kinase is constitutively active.

Downstream RAS/MAPK pathway activation supports proliferation.

Fusion-positive does not equal malignant

Molecular feature

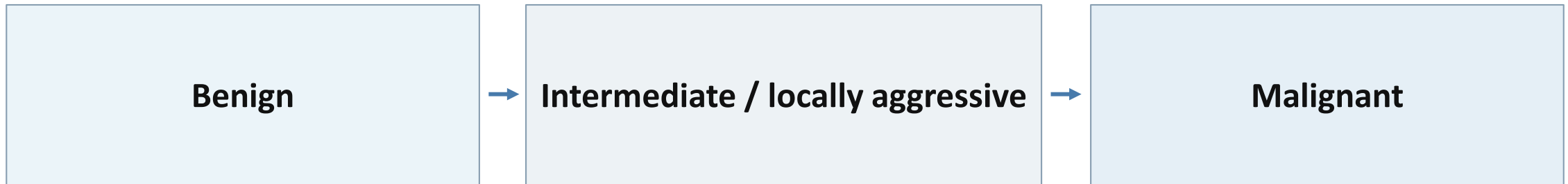
Clonal driver rearrangement

Biologic outcome

May be benign, intermediate, or malignant

Nodular fasciitis can harbor MYH9::USP6 but usually behaves in a self-limited fashion.

The behavioral continuum in soft tissue tumors



Benign lesions may require minimal treatment.

Intermediate/local-aggressive lesions can be infiltrative or recurrent without meaningful metastatic risk.

High-grade sarcomas may metastasize and cause death.

Benign is not synonymous with small

- Lipomas are generally soft, mobile, and painless.
- Occasional benign lipomas may be large or intramuscular.
- Size, depth, and margin are contextual findings rather than isolated proof of malignancy.

Locally aggressive tumors demand a separate category

Growth

Infiltrative locally

Clinical risk

Recurrence; Functional injury

Metastasis

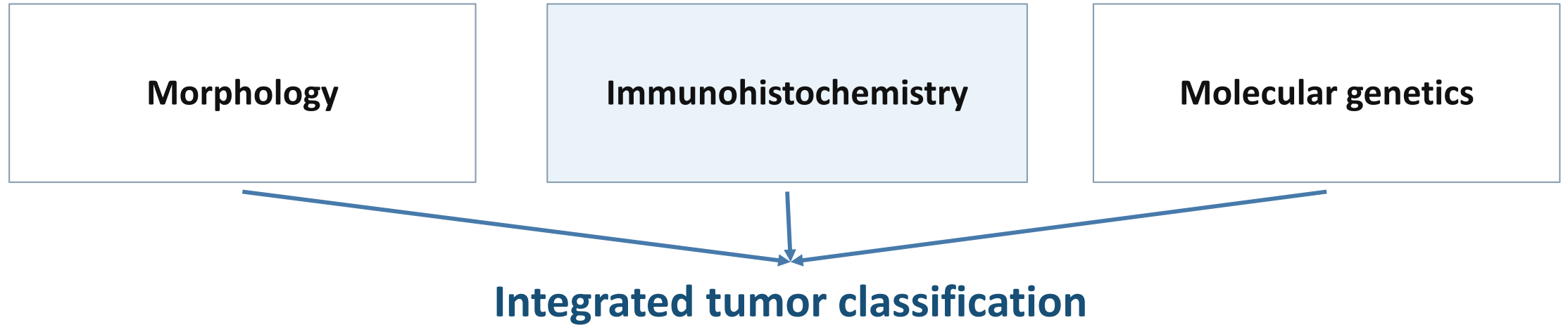
Not characteristic for desmoid tumor

Infiltrative growth creates morbidity through local tissue involvement.

A sarcoma diagnosis requires biologic specificity

- Aggressive soft tissue malignancies are classified as sarcomas.
- The term is not applied uniformly to every locally aggressive nonmetastasizing tumor.
- A precise tumor entity is more informative than the generic label “sarcoma.”

Integrated classification has three evidence domains



Morphology: Architecture, matrix, cytology, and differentiation.

Immunohistochemistry: Protein-expression evidence of lineage or state.

Molecular testing: Defining rearrangements or other genomic alterations.

Morphologic pattern guides the first differential

Adipocytic

Mature fat / atypia / lipoblasts

Spindle-cell

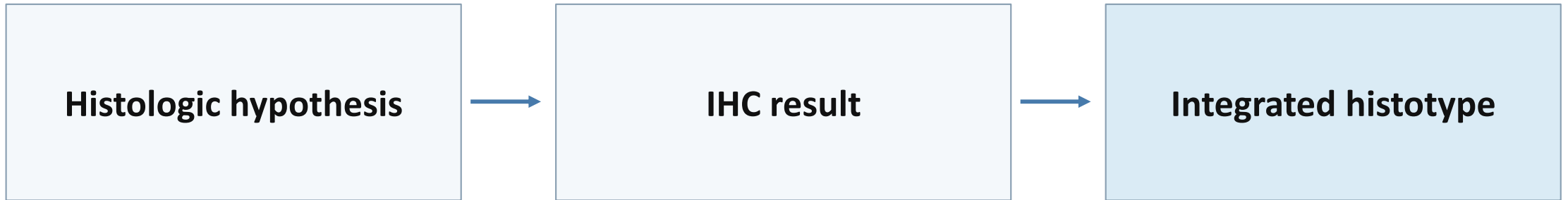
Fascicles, collagen, vascular pattern

Round / pleomorphic

Cell shape, atypia, necrosis

Mature adipocytes suggest an adipocytic tumor.

Immunohistochemistry refines lineage assignment

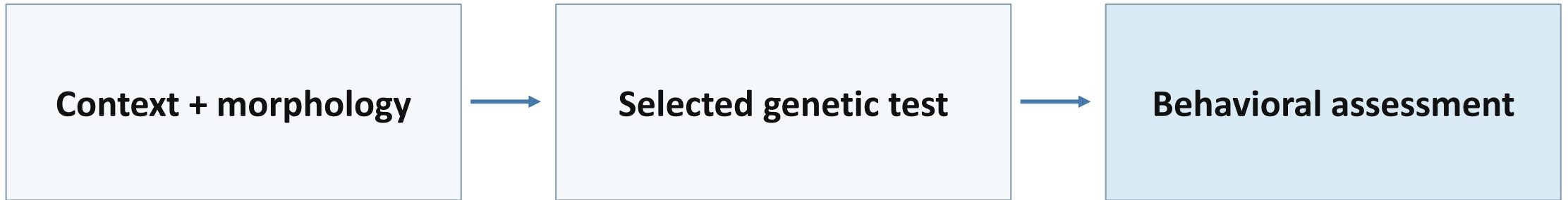


Marker patterns should answer a specific morphologic question.

A single stain rarely constitutes an entire diagnosis.

Combining immunophenotypic and molecular information with morphology.

Molecular testing serves the diagnostic differential



Recurrent fusions support recognition of selected entities.

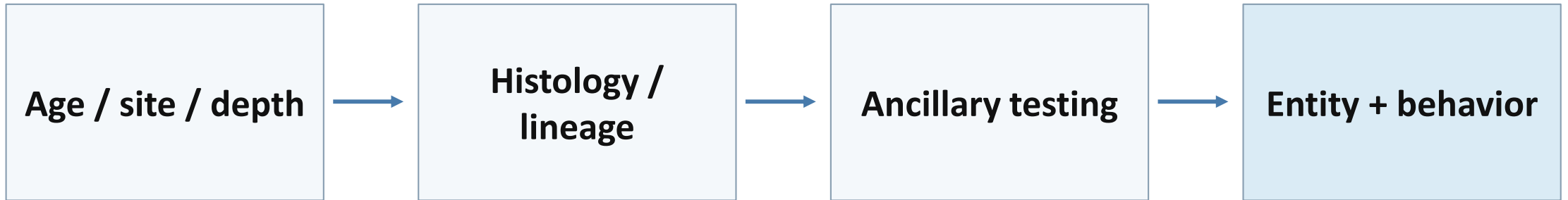
Results are strongest when predicted by clinical and morphologic features.

Genomic findings do not alone convey grade or stage.

Grade and stage answer different questions

Grade	Stage
Histologic tumor characteristics	Anatomic extent of disease
Biologic aggressiveness	Local and metastatic spread
Pathologic prognostic dimension	Clinical-anatomic prognostic dimension

A practical integrated diagnostic sequence

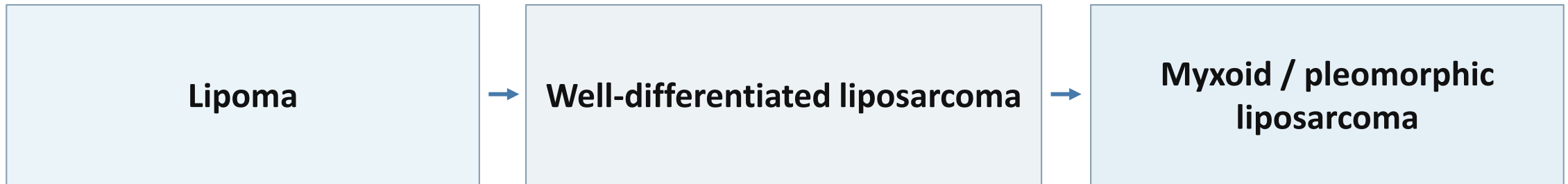


Establish clinical setting: Age, site, and superficial versus deep location.

Determine differentiation pattern and cytologic atypia in tissue.

Select ancillary tests only when they resolve a defined differential.

Adipocytic lesions illustrate the full spectrum



Lipoma is the most common benign adult soft tissue tumor.

Liposarcoma is as the commonest sarcoma in adulthood.

Subtype-level distinction matters because molecular pathways and outcomes differ.

Lipoma: Characteristic presentation

Patient

Middle adulthood

Site

Superficial trunk or proximal limb

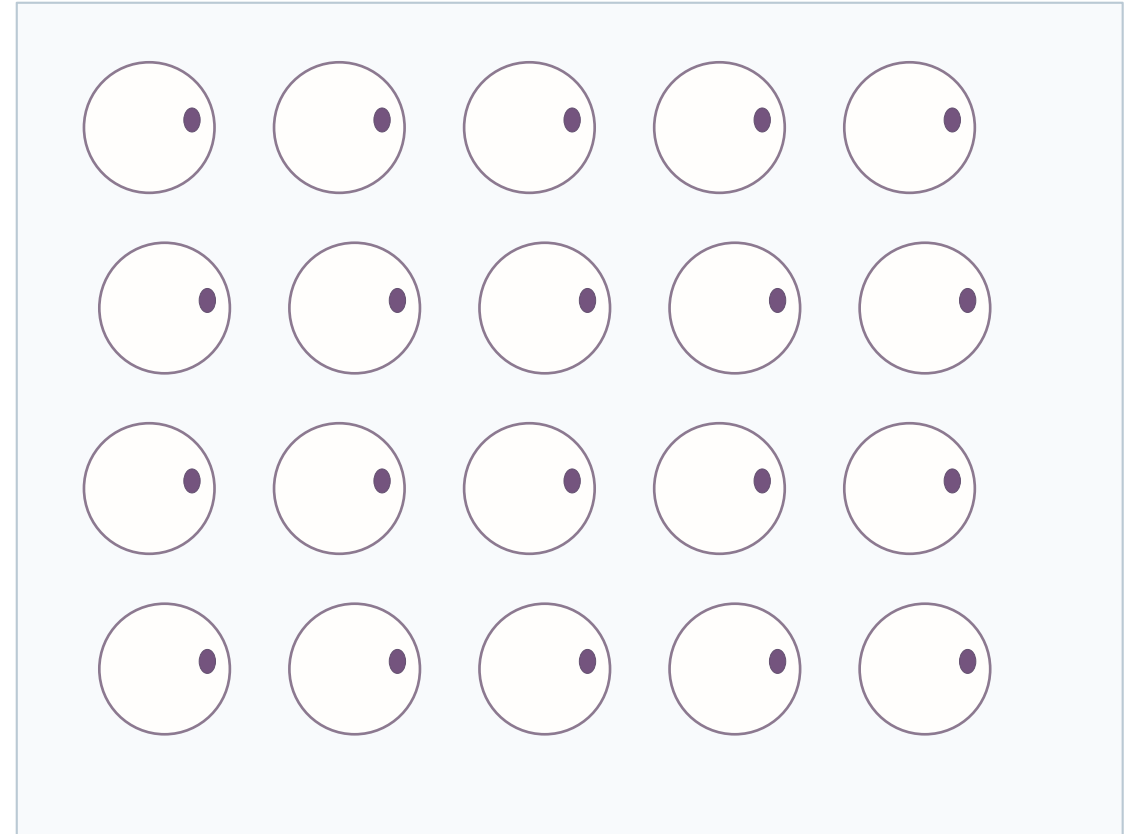
Clinical pattern

Soft, painless, mobile

Typically arises in middle adulthood.

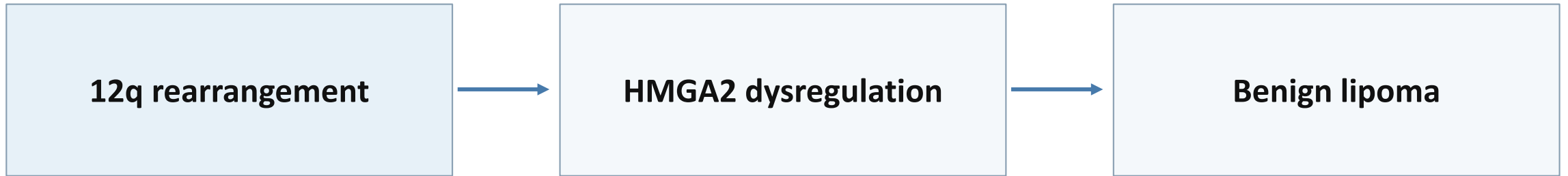
Conventional lipoma: Defining morphology

- Usually well encapsulated and composed of mature adipocytes.
- Adipocytic cells resemble normal fat at low and high power.
- Rare examples are intramuscular, large, or poorly circumscribed.



Original simplified schematic — not a histologic specimen

HMGA2 dysregulation in solitary lipoma



Chromosome 12q rearrangements are common in solitary lipomas.

They disrupt regulation of HMGA2, a chromatin-structure regulator.

A genomic alteration can occur in a lesion with benign clinical behavior.

Lipomatosis is distinct from a solitary lipoma

Solitary lipoma

Single localized fatty mass

Lipomatosis

Multiple lipomas in a limb

Lipomatosis denotes multifocal lipomas involving a limb.

Atypical adipocytic findings change the differential

- Scattered atypical hyperchromatic stromal cells are described in well-differentiated liposarcoma.
- Deep location can increase the clinical implications of an adipocytic lesion.
- Benign mature adipose tissue alone should not determine a deep tumor's final classification.

Liposarcoma: Adult sarcoma of adipocytic differentiation

Deep proximal extremity



Retroperitoneum



**Genetic subtype changes
prognosis**

Typically presents in deep soft tissue of proximal extremities or retroperitoneum.

The textbook places many patients in the fifth to sixth decades.

Different histologic subtypes have different genetics and behavior.

Three principal liposarcoma subtypes

Well differentiated

MDM2 amplification

Myxoid

FUS::DDIT3 fusion

Pleomorphic

Complex genotype

Well-differentiated: Mature adipocytes with scattered atypical spindle cells.

Well-differentiated liposarcoma: MDM2 amplification

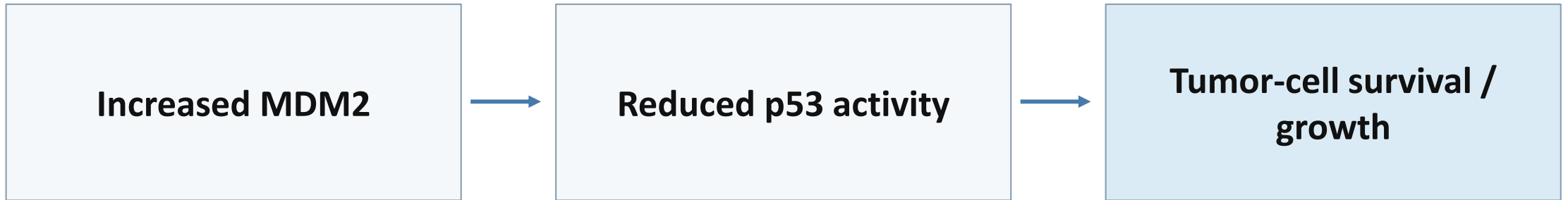


MDM2 at 12q13–q15 is amplified.

MDM2 promotes proteasomal degradation of p53.

The pathway weakens an important tumor-suppressor response.

MDM2 and p53: Pathogenetic direction



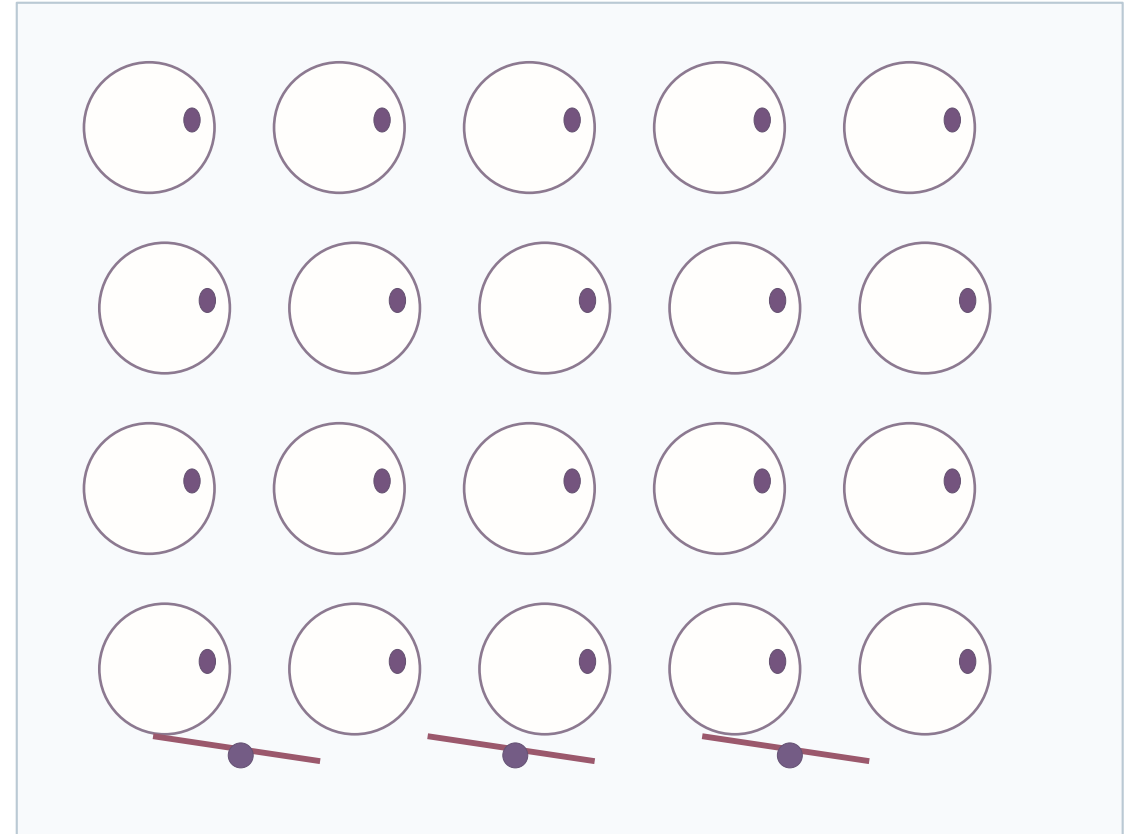
The MDM2 protein negatively regulates p53 stability.

MDM2 overexpression can reduce p53-mediated suppressive responses.

The oncogenic driver here is amplification, not a characteristic fusion.

Well-differentiated liposarcoma: Morphology

- Mature adipocytes remain a dominant component.
- Scattered stromal spindle cells show atypical, hyperchromatic nuclei.
- These atypical stromal cells distinguish the lesion from a straightforward lipoma.



Original simplified schematic — not a histologic specimen

ALT versus well-differentiated liposarcoma

Resectable extremity

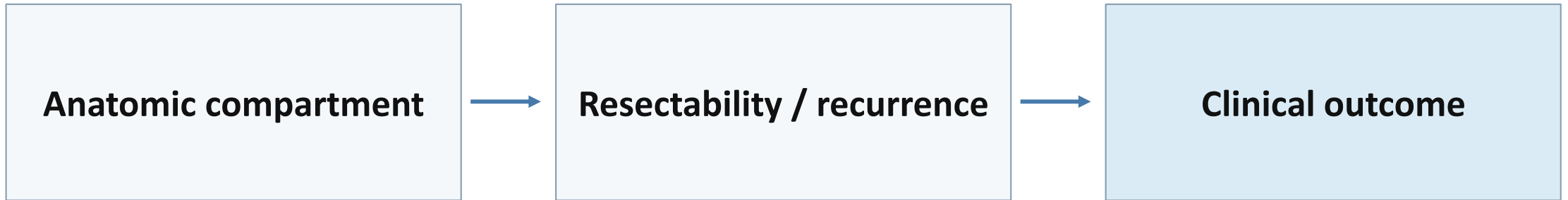
Atypical lipomatous tumor

Retroperitoneum

Well-differentiated liposarcoma

“atypical lipomatous tumor” for resectable extremity lesions.

Why site matters in well-differentiated adipocytic tumors

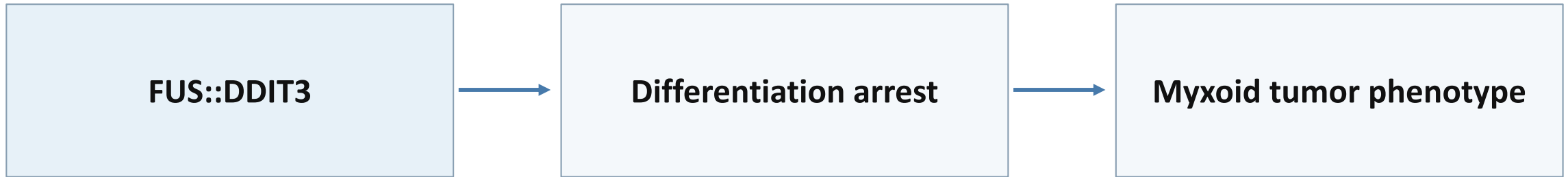


Extremity lesions may be completely removed and behave indolently.

Retroperitoneal lesions are more difficult to eradicate completely.

Repeated local recurrence can produce major morbidity even without high-grade morphology.

Myxoid liposarcoma: Fusion-driven disease



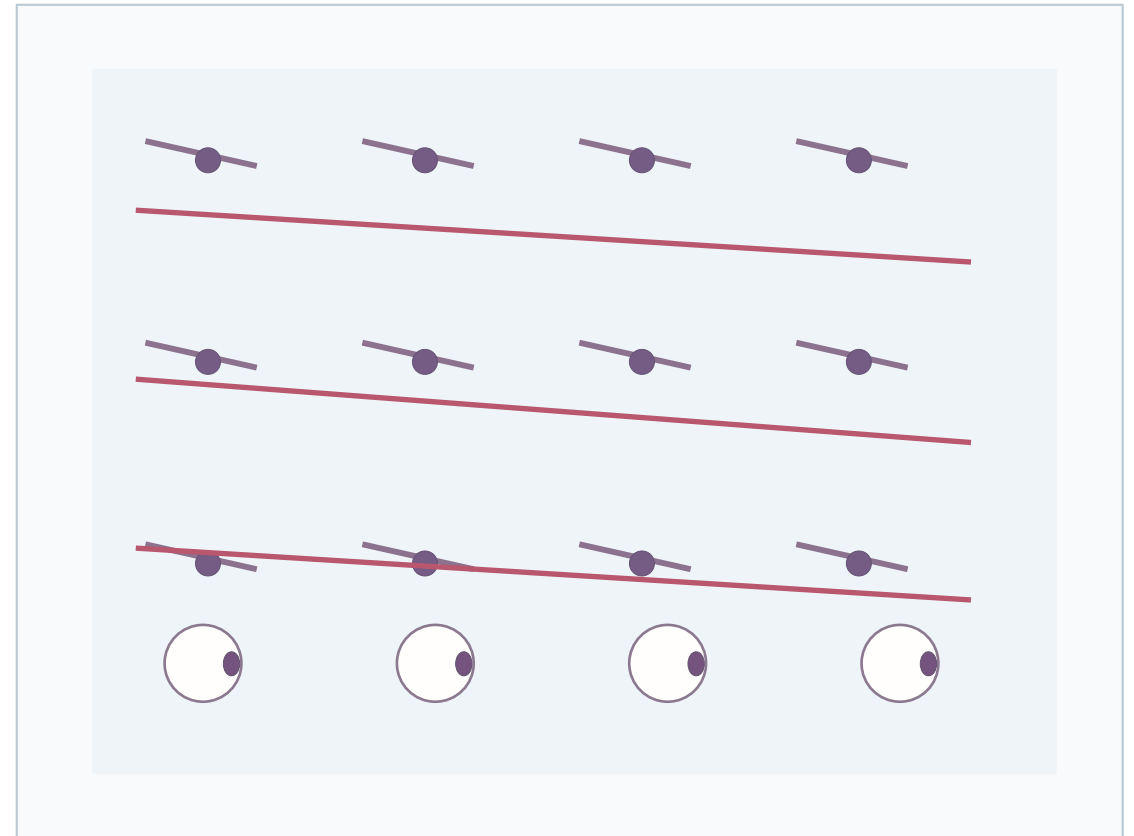
The t(12;16) rearrangement yields FUS::DDIT3.

A differentiation-arrest mechanism is proposed.

The characteristic tumor contains primitive adipocytic cells in a myxoid background.

Myxoid liposarcoma: Pattern recognition

- Abundant basophilic myxoid extracellular matrix.
- Delicate arborizing capillary network.
- Primitive round-to-stellate cells and immature adipocytes/lipoblasts.

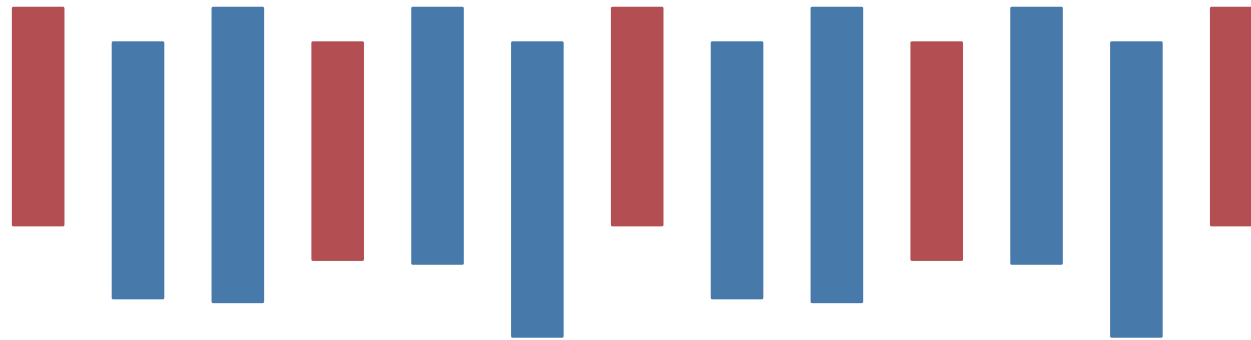


Original simplified schematic — not a histologic specimen

Myxoid liposarcoma: An unusual metastatic site

- Bone is a recognized metastatic destination in myxoid liposarcoma.
- This differs from the predominant metastatic patterns of many other soft tissue sarcomas.
- Histotype-specific patterns can influence clinical interpretation.

Pleomorphic liposarcoma: Genomically complex

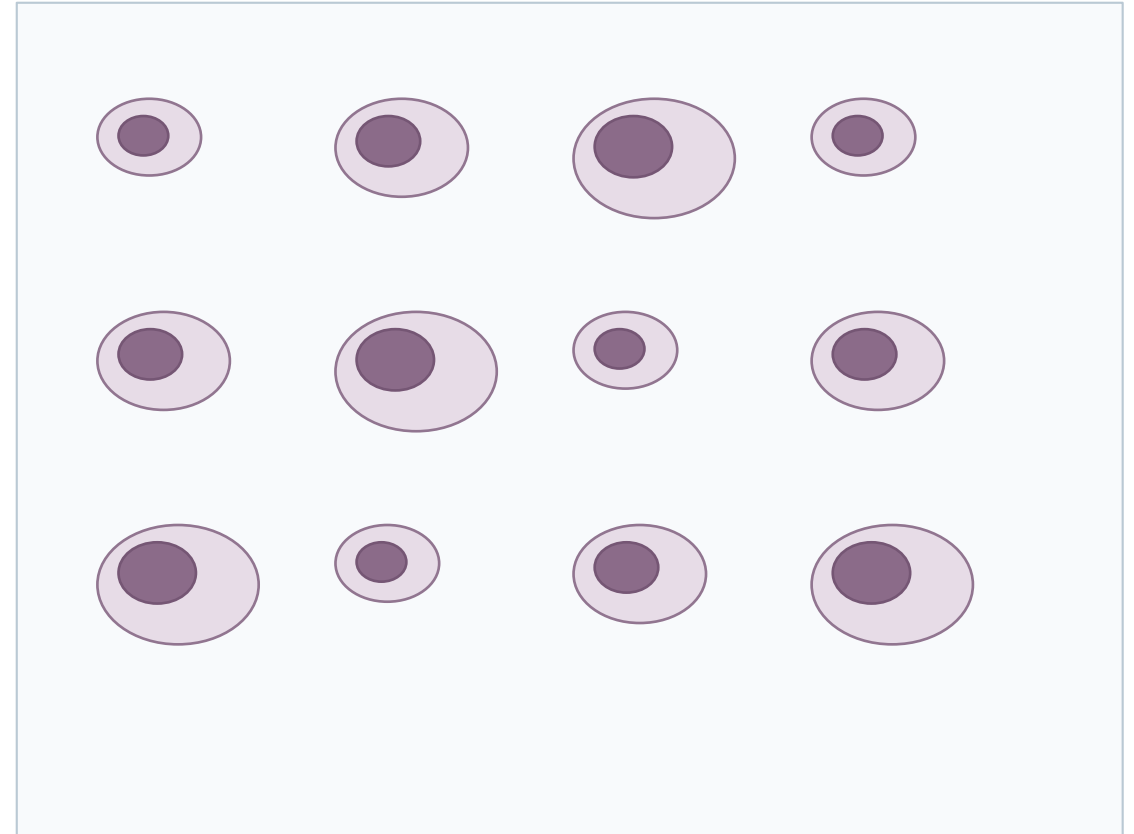


Schematic genomic instability — not a measured karyogram

Schematic only (not patient cytogenetics)

Pleomorphic liposarcoma: Morphology and behavior

- Sheets of anaplastic cells with bizarre nuclei.
- Variable numbers of immature adipocytes/lipoblasts.
- Aggressive behavior with frequent metastasis, unlike many well-differentiated lesions.



Original simplified schematic — not a histologic specimen

Major liposarcoma forms compared

Subtype	Molecular profile	Microscopic anchor
Well differentiated	MDM2 amplification	Mature fat + atypical spindle cells
Myxoid	FUS::DDIT3	Myxoid matrix + delicate vessels
Pleomorphic	Complex abnormalities	Anaplastic cells + lipoblasts

Liposarcoma classification is clinically consequential

- Morphology and molecular events classify the tumor; Site modifies consequences.
- A well-differentiated retroperitoneal tumor may be morbid through repeated local recurrence.
- Myxoid and pleomorphic subtypes carry metastatic potential, with the latter particularly aggressive.

Lipoma versus well-differentiated liposarcoma

Feature	Lipoma	WDLPS / ALT
Typical level	Often superficial	Often deep
Microscopic finding	Mature adipocytes	Mature fat + atypical spindle cells
Molecular association	HMGA2 rearrangement	MDM2 amplification
Behavior	Benign	Site-dependent local morbidity

Fibroblastic tumors: Different behavior with similar cells

Nodular fasciitis



Deep fibromatosis



Adult fibrosarcoma

The fibrous lineage spans self-limited proliferations, infiltrative fibromatoses, and malignant spindle tumors.

Spindle morphology does not uniquely imply malignancy.

Growth rate, nuclear atypia, mitotic character, and molecular data refine classification.

Nodular fasciitis: Rapid growth can still be benign

Site

Forearm, chest, back

Tempo

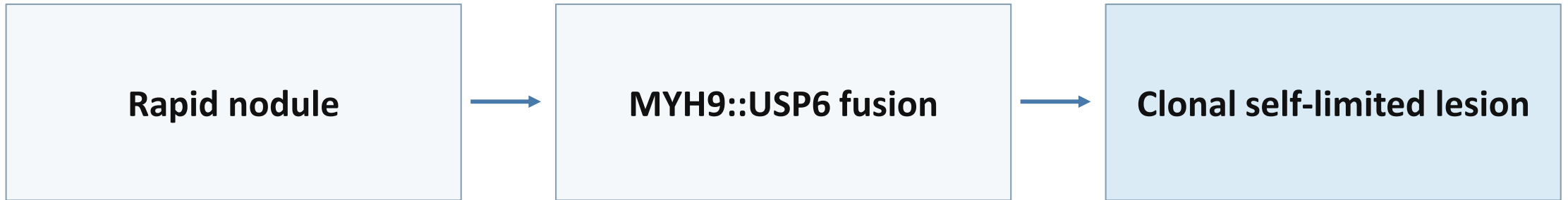
Rapid, weeks to months

Behavior

Usually self-limited

A self-limited fibroblastic/myofibroblastic proliferation.

Nodular fasciitis: Why reactive was reconsidered

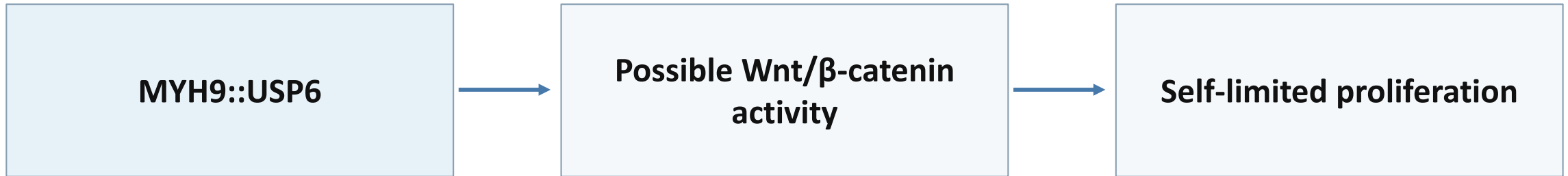


Regression and occasional preceding trauma led to a historical reactive interpretation.

Detection of a recurrent USP6 fusion demonstrated clonal proliferation.

Clonality and transient growth are biologically compatible.

MYH9::USP6: Molecular signature of nodular fasciitis



Robbins records a rearrangement involving MYH9 and USP6.

The fusion may augment Wnt/β-catenin signaling.

It provides molecular evidence against a purely nonspecific reactive process.

Nodular fasciitis: Tissue-culture-like histology

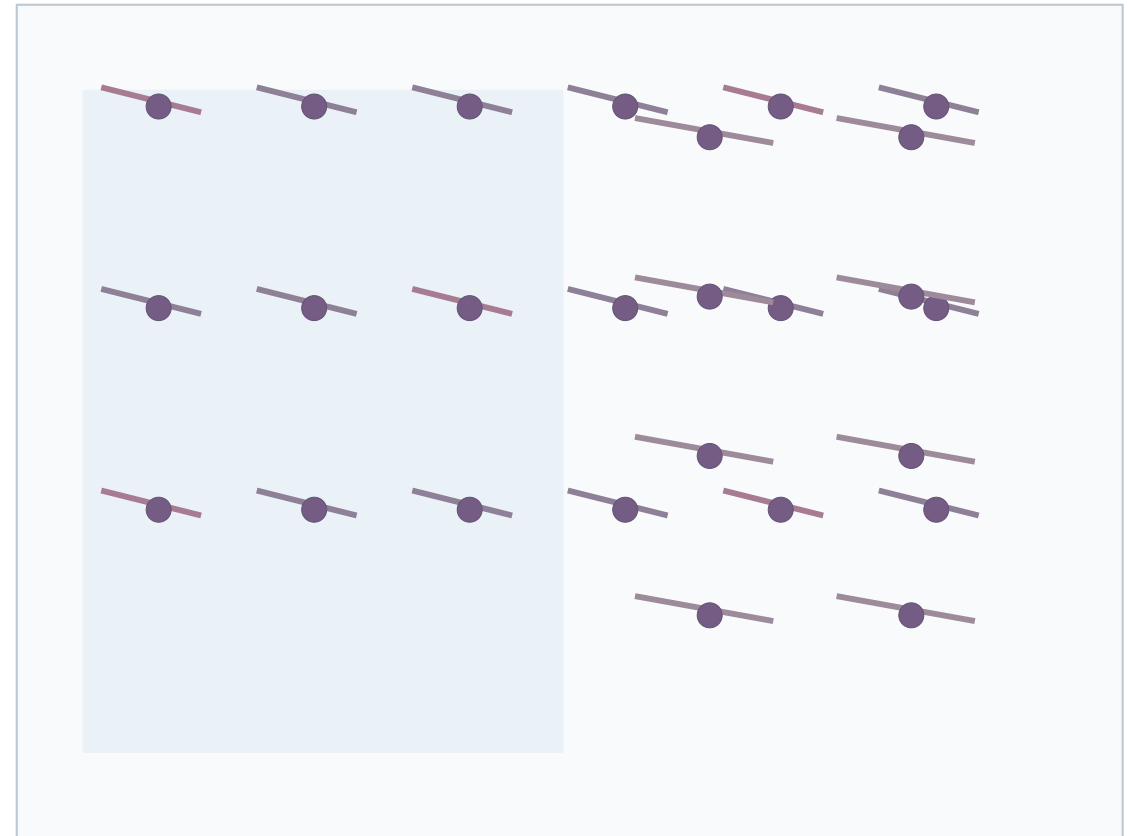
- Plump, immature-appearing fibroblasts and myofibroblasts.
- Loose, randomly oriented growth resembling cells in tissue culture.
- May involve subcutis, fascia, deep dermis, or muscle.



Original simplified schematic — not a histologic specimen

Nodular fasciitis: Maturation across the lesion

- Hypercellular myxoid and hypocellular fibrous zones may coexist.
- Extravasated erythrocytes, giant cells, and lymphocytes can occur.
- A zonation pattern helps recognize the entity.



Original simplified schematic — not a histologic specimen

Frequent mitoses do not always mean sarcoma

Nodular fasciitis

Mitoses may be frequent; Atypical forms absent

Malignancy concern

Assess atypia, architecture, necrosis and context

Nodular fasciitis can show conspicuous mitotic activity.

Nodular fasciitis versus malignant spindle-cell tumors

Criterion	Nodular fasciitis	Concern for sarcoma
Growth	Rapid but self-limited possible	May also grow rapidly
Cytology	Plump but relatively bland	May show marked atypia
Mitoses	Frequent; atypical absent	Atypical mitoses may occur
Molecular clue	MYH9::USP6	Depends on tumor subtype

Representative soft tissue tumor families

Lineage	Benign example	Malignant example
Adipocytic	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Vascular	Hemangioma	Angiosarcoma
Peripheral nerve sheath	Schwannoma / neurofibroma	Malignant peripheral nerve sheath tumor

Other diagnostic archetypes among sarcomas

Synovial sarcoma

Spindle $\pm$ pseudoglandular

Undifferentiated sarcoma

High-grade pleomorphic /
anaplastic

Fibrosarcoma

Monomorphic spindle fascicles

Synovial sarcoma: Uniform spindle fascicles and sometimes pseudoglandular structures.

Site and age can sharpen the differential

Superficial trunk

Lipoma context

Retroperitoneum

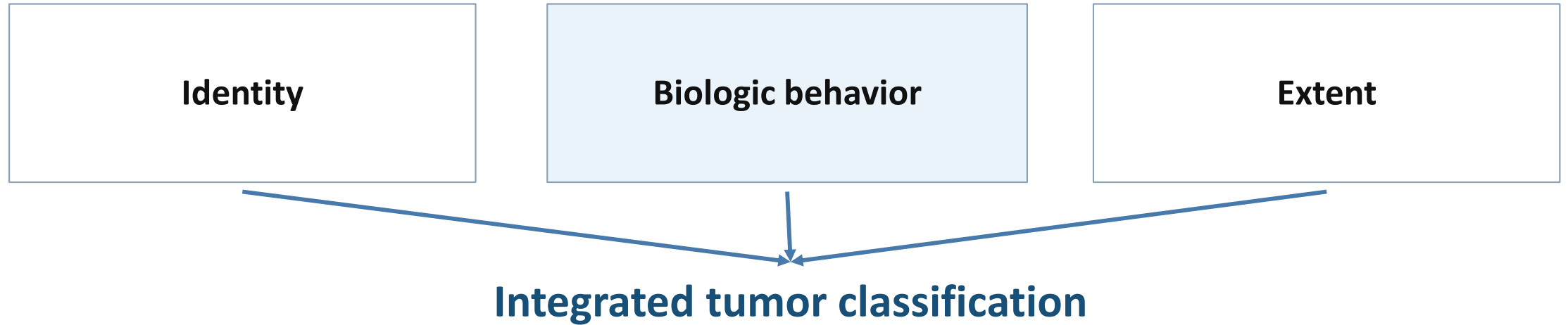
WDLPS context

Young adult forearm

Nodular fasciitis context

A superficial middle-aged patient with a mobile fatty mass fits common lipoma settings.

What molecular results can—and cannot—establish



A recurrent molecular alteration may strengthen tumor-entity assignment.

The same genomic testing does not replace assessment of local behavior or metastatic extent.

A benign self-limited proliferation may also harbor an oncogenic fusion.

Case 1: A mobile superficial fatty mass

Illustrative case — not a real patient

- A hypothetical middle-aged patient has a slow-growing painless, mobile subcutaneous mass over the proximal arm.
- Excision shows a well-circumscribed lesion of mature adipocytes.
- Question: Which diagnosis best fits, and what molecular pathway can be involved?

Case 1: Clinicopathologic resolution

Diagnostic reasoning

- Conventional lipoma best matches this presentation and morphology.
- A subset is associated with chromosome 12q rearrangements altering HMGA2.
- Absence of atypical stromal cells helps distinguish this pattern from well-differentiated liposarcoma.

Case 2: A deep adipocytic tumor

Illustrative case — not a real patient

- A hypothetical patient in their 50s has a large retroperitoneal fatty mass.
- Biopsy shows predominantly mature fat with scattered atypical hyperchromatic stromal cells.
- Question: How would tumor site and MDM2 status affect the classification?

Case 2: Diagnostic and behavioral resolution

Diagnostic reasoning

- The morphology supports well-differentiated liposarcoma rather than ordinary lipoma.
- MDM2 amplification fits the subtype.
- Retroperitoneal location makes complete removal harder and local recurrence clinically significant.

Case 3: A rapidly growing forearm nodule

Illustrative case — not a real patient

- A hypothetical young adult develops a subcutaneous forearm nodule enlarging over several weeks.
- Histology shows plump myofibroblasts in a loose matrix with numerous ordinary mitoses.
- Question: Does rapid growth mandate a sarcoma diagnosis?

Case 3: Recognizing a self-limited neoplasm

Diagnostic reasoning

- Nodular fasciitis is a leading consideration in the described setting.
- MYH9::USP6 can support a clonal lesion with self-limited behavior.
- Atypical mitotic figures and other malignant features must still be evaluated.

Integrated summary: Five governing principles

- Most soft tissue tumors are benign; The sarcomas are heterogeneous and consequential.
- Tumor entity is defined by integrating location, morphology, immunophenotype, and molecular findings.
- Simple fusion-driven and complex genomically unstable sarcomas differ in biology.
- A driver alteration does not, by itself, establish malignancy.
- Liposarcoma subtype and anatomic site materially shape behavior.

References and source notes

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Section: “Soft Tissue Tumors.”
- WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. WHO Classification of Tumours, 5th ed., vol. 3. IARC, 2020.
- Mechanism and morphology figures in this deck are original editable teaching schematics—not diagnostic specimen photographs.
- Molecular and behavioral examples emphasize the textbook account; WHO (2020) is included for classification context.