

Synovial Sarcoma

A translocation-associated malignant soft tissue tumor with variable epithelial differentiation

- Robbins-based pathology lecture | suitable for advanced undergraduate and pathology training

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Learning objectives

Define	Explain why the disease name does not establish synovial origin
Genetics	Interpret SS18::SSX fusion as a diagnostic and oncogenic event
Morphology	Discriminate monophasic and biphasic patterns
Diagnosis	Integrate morphology, immunohistochemistry, and molecular assays
Clinical	Relate extent, age, and metastatic pattern to outcomes

What makes synovial sarcoma distinct?

A sarcoma that may express epithelial markers despite arising in soft tissue

- Characteristic SS18::SSX fusion
- Monophasic or biphasic morphology

The term “synovial” is historical

Historical assumption

Early cases near the knee suggested a synovial origin

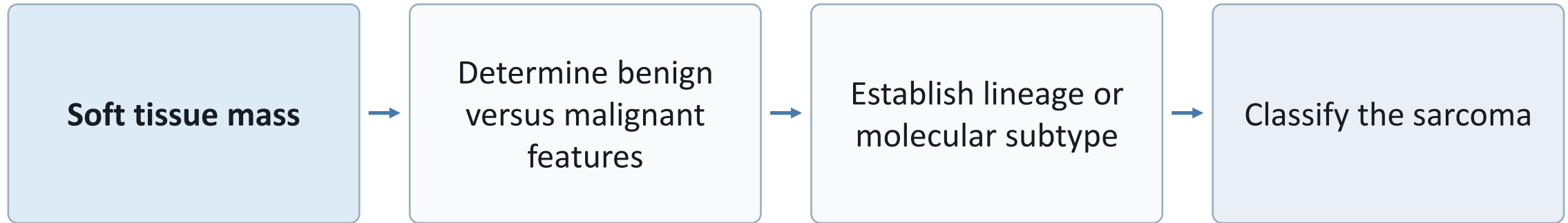
Anatomic proximity drove the original name

Current interpretation

Tumors may arise where synovium is absent

Epithelial differentiation does not establish synovial derivation

Position within soft tissue pathology



Synovial sarcoma is a molecularly defined soft tissue sarcoma.

Who develops synovial sarcoma?

- Typically affects adolescents and young adults
- Approximately 10% of soft tissue sarcomas
- Age helps define a clinical prior probability, not a diagnosis
- Occurrence outside the usual age range does not exclude it

Usual anatomical presentation

- Often a deep soft tissue mass of an extremity
- The thigh and leg are representative sites in the Robbins soft tissue table
- Joint-adjacent tumors are possible but not required
- Absence of synovial tissue is compatible with the diagnosis

A deceptively indolent history

A slowly recognized, persistent deep soft tissue mass may still be malignant

- Masses may have been present for several years
- Duration alone is not a reliable benign-versus-malignant discriminator

Clinical impression versus biological identity

Clinical impression

Slowly enlarging mass in a young individual

May initially resemble a less aggressive soft tissue lesion

Biological identity

Malignant, fusion-associated mesenchymal neoplasm

Can metastasize despite an extended prediagnostic history

Four anchors for recognition

Patient	Adolescent or young adult is typical
Site	Deep soft tissue, commonly in an extremity
Microscopy	Uniform spindle cells ± epithelial gland-like structures
Molecular	SS18::SSX rearrangement is the defining genetic hallmark

Simple fusion-driven versus complex-karyotype sarcomas

Synovial sarcoma

Recurrent t(X;18) creates SS18::SSX

Characteristic genetic event provides diagnostic leverage

Undifferentiated pleomorphic sarcoma

Typically complex and heterogeneous karyotype

Lacks a diagnostic lineage or specific rearrangement by definition

The defining t(X;18) event

Chromosome X

SSX1 / SSX2 / SSX4

Chromosome 18

SS18

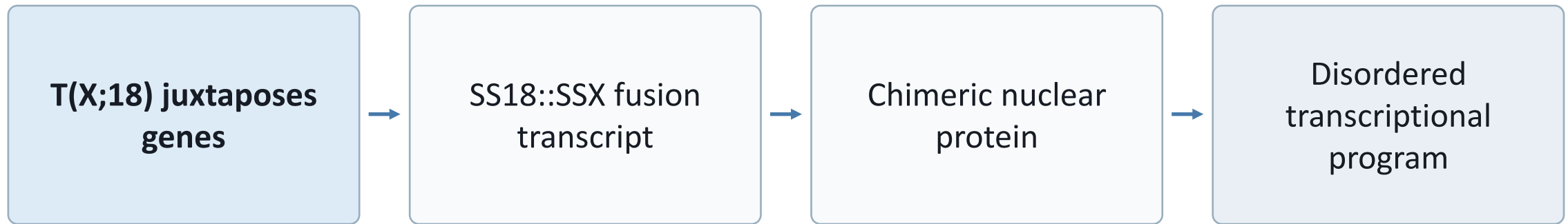
SS18::SSX

T(X;18)(p11;q11): Reciprocal chromosomal rearrangement

Fusion nomenclature matters

- The modern convention is SS18::SSX
- Common partners include SSX1 and SSX2; SSX4 is less frequent
- The shorthand t(X;18)(p11;q11) describes the chromosomal exchange
- Fusion protein, fusion transcript, and a break-apart signal are related but distinct assay targets

How a chromosomal fusion becomes oncogenic

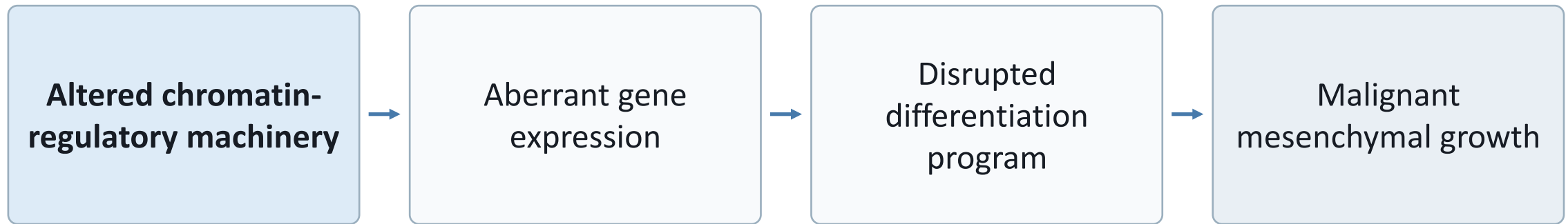


This is a mechanistic conceptual chain, not a quantitative signaling pathway.

Chromatin remodeling is the molecular target

- The fusion protein interferes with normal chromatin remodeling
- Dysregulated chromatin regulation changes gene expression
- Altered transcriptional programs contribute to oncogenic cell behavior
- Robbins does not assign a single linear downstream pathway

From fusion to tumor phenotype



Schematic causal model: Distal molecular details are simplified.

A fusion can be diagnostically specific

The value of SS18::SSX lies in identifying a particular tumor entity

- Anatomic site and histology alone are less specific
- Molecular testing adjudicates many ambiguous spindle-cell tumors

Fusion as driver and biomarker

Biological role

Oncogenic protein perturbs chromatin regulation

Mechanistic role: Altered transcriptional control

Diagnostic role

Specific genetic signature can confirm identity

Marker role: Differentiates from morphologic mimics

Do not confuse biomarker functions

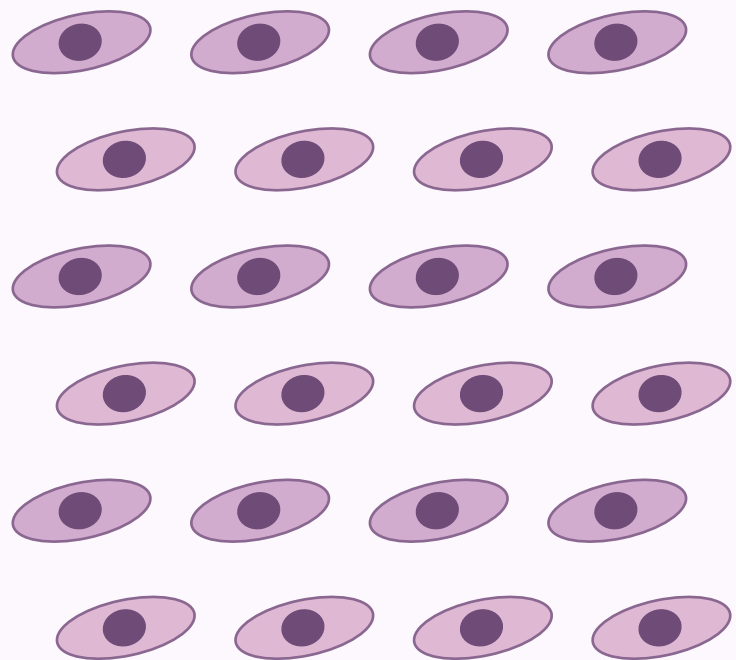
Diagnostic	SS18::SSX establishes tumor identity in an appropriate context
Prognostic	Stage, tumor extent, and age correlate with outcome
Predictive	MAGE-A4 and certain HLA types determine eligibility for a specific engineered T-cell therapy
Unproven	Do not assume SSX fusion partner alone dictates clinical benefit

Histologic heterogeneity is central

One disease can produce different architectural patterns

- Monophasic: Tightly packed spindle cells
- Biphasic: Spindle cells plus epithelial gland-like structures

Monophasic pattern: Architecture



Uniform spindle cells in compact fascicles

Schematic — original editable illustration; Not a histologic specimen

Monophasic tumor: Constituent cells

- Relatively uniform spindle-shaped tumor cells
- Scant cytoplasm
- Dense chromatin
- Short fascicles create an extremely cellular appearance

Why the monophasic pattern is challenging

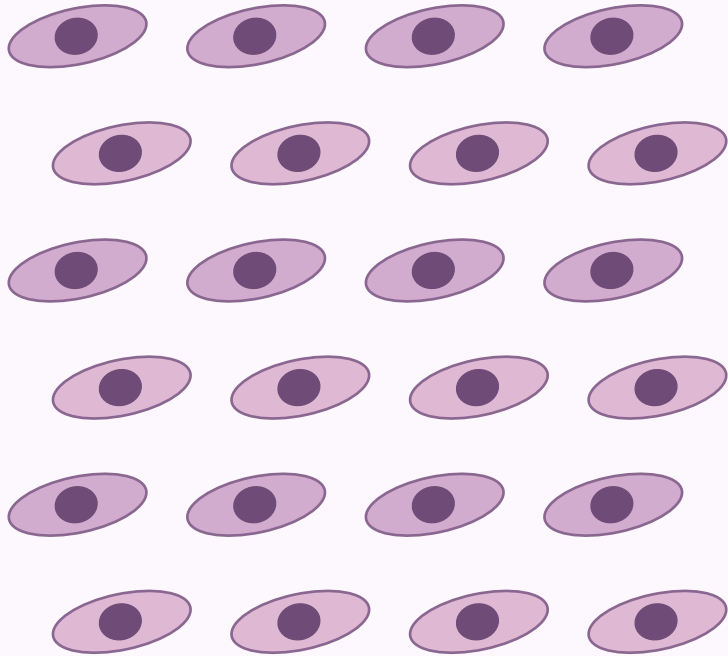
- A spindle-cell architecture is not exclusive to synovial sarcoma
- Uniformity can resemble other mesenchymal neoplasms
- The epithelial component may be inconspicuous or absent in a sampled section
- Molecular specificity becomes important when morphology overlaps

Monophasic does not mean molecularly different

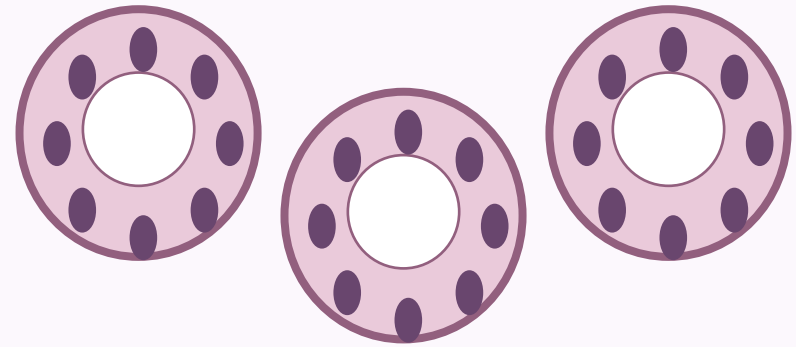
A purely spindle-cell appearance can still carry SS18::SSX

- Morphology describes differentiation patterns
- Molecular analysis identifies the disease-defining genetic event

Biphasic pattern: Two components



Uniform spindle cells in compact fascicles



Gland-like epithelial structures

Schematic — original editable illustration; Not a histologic specimen

Biphasic tumor: The epithelial element

- Gland-like structures accompany the spindle-cell component
- Epithelioid cells range from cuboidal to columnar
- These structures constitute epithelial differentiation within a sarcoma
- The epithelial element makes keratin expression biologically plausible

Monophasic versus biphasic pattern

Monophasic

Uniform spindle cells with scant cytoplasm

Dense chromatin; Short, tightly packed fascicles

Biphasic

Similar spindle component PLUS epithelioid cells

Cuboidal-to-columnar cells forming gland-like structures

Epithelial features are not the same as carcinoma

Synovial sarcoma can form gland-like structures and
express keratins

- A malignant soft tissue tumor can display divergent differentiation
- Location, morphology, and SS18::SSX clarify the lineage

Poorly differentiated morphology: Supplemental context

- NCI describes a poorly differentiated morphologic category
- Such tumors can resemble other high-grade round-cell or spindle-cell malignancies
- Reduced morphologic specificity increases dependence on immunophenotypic and molecular testing
- Do not infer exact genotype or prognosis from a small biopsy alone

Microscopic reporting checklist

Cell form	Spindle, epithelioid/glandular, or less differentiated
Architecture	Fascicular versus biphasic gland-forming areas
Cytology	Cellular uniformity, nuclear features, atypia
Sampling	Document component distribution and biopsy limitations
Ancillary tests	Record stains and fusion-directed results

What a biopsy can show—and miss

What may be present

Uniform spindle-cell fascicles

Focal keratin / EMA expression

A fusion-directed diagnostic signal

What may be missed

Gland-like component in limited tissue

Heterogeneity across the primary lesion

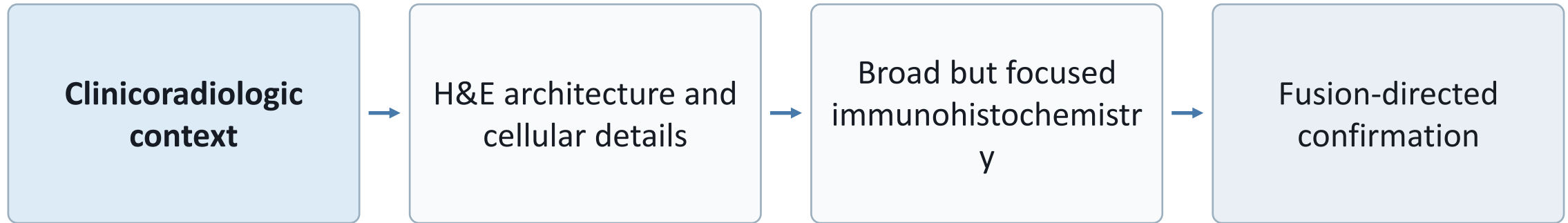
Features needed for comprehensive
resection assessment

The most informative morphologic question

Is there convincing spindle-to-epithelial differentiation within the same malignancy?

- If yes: Biphasic synovial sarcoma enters the differential
- If no: Monophasic synovial sarcoma remains plausible

Diagnostic reasoning in a spindle-cell mass



This is a teaching algorithm; Actual panels depend on morphology and site.

Major diagnostic confounders

MPNST	Can resemble a cellular spindle-cell sarcoma
Solitary fibrous tumor	May display monotonous spindle morphology
Other spindle-cell sarcomas	Overlap in fascicular architecture
Sarcomatoid carcinoma	Can express epithelial markers
Rhabdomyosarcoma	Muscle-specific differentiation separates the entity

Monophasic synovial sarcoma versus MPNST

Synovial sarcoma

Often relatively uniform spindle cell nuclei

Keratins/EMA may be detectable;
SS18::SSX is decisive

MPNST

May show wavy or buckled spindle nuclei

S100/SOX10 and H3K27me3 loss are
context-dependent clues

Synovial sarcoma versus solitary fibrous tumor

Synovial sarcoma

Tight fascicles, variable epithelioid differentiation

SS18::SSX drives diagnosis

Solitary fibrous tumor

Characteristic ectatic branching vasculature

STAT6 nuclear staining / NAB2::STAT6 support SFT

Synovial sarcoma versus sarcomatoid carcinoma

Synovial sarcoma

May show keratin-positive spindled cells

Deep tissue mass; SS18::SSX supports sarcoma identity

Sarcomatoid carcinoma

May also be spindle shaped and keratin positive

Look for epithelial primary or in situ component; Distinct molecular context

Synovial sarcoma versus rhabdomyosarcoma

Synovial sarcoma

SS18::SSX; Variable epithelial differentiation

Morphology ranges from spindled to biphasic

Rhabdomyosarcoma

True skeletal muscle differentiation

Myogenin and other myogenic regulators support lineage

Keratins: An unusual clue in a sarcoma

Epithelial antigens may be positive in synovial sarcoma

- Keratins, particularly with biphasic morphology
- A positive keratin stain is supportive—not independently diagnostic

Epithelial membrane antigen complements keratins

- EMA and cytokeratins support epithelial differentiation
- Staining may be focal, especially in monophasic tumors
- Lack of diffuse staining does not exclude the diagnosis
- Marker panels must be interpreted against H&E and fusion studies

TLE1 is supportive, not specific

TLE1 nuclear expression is frequent but occurs in mimics

- A TLE1-positive spindle-cell lesion is not automatically synovial sarcoma
- Prioritize lineage exclusion and fusion-directed confirmation

Fusion-specific SS18::SSX immunohistochemistry

- Detects a fusion-associated nuclear epitope
- Provides strong evidence of synovial sarcoma when validated staining is positive
- A negative result may be technical or reflect epitope variants
- Discordant cases merit molecular testing; Sensitivity is not absolute

Fusion-specific antibody versus TLE1

SS18::SSX fusion-specific IHC

Targets a fusion-dependent neoepitope

Generally high specificity; False negatives are possible

TLE1 nuclear IHC

Reflects a frequently expressed regulatory protein

Good screening context, but not sufficiently specific alone

Ancillary techniques answer different questions

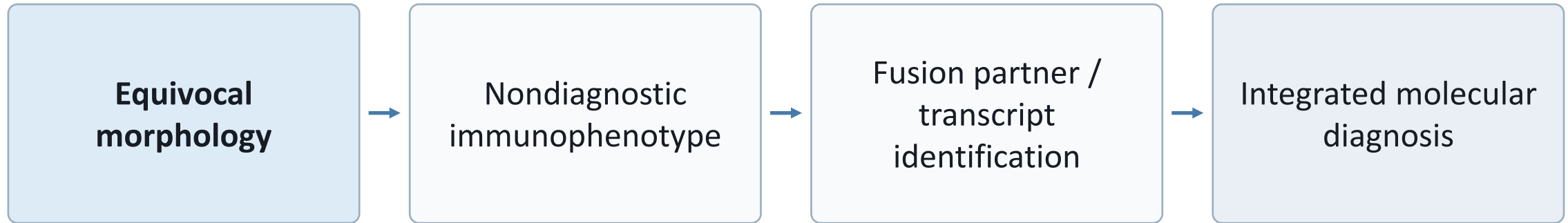
Keratins / EMA	Is epithelial differentiation detectable?
TLE1	Is there a supportive, nonspecific phenotype?
SS18::SSX IHC	Is the characteristic fusion neopeptide present?
SS18 break-apart FISH	Is SS18 rearranged?
RNA-based fusion testing	Which specific fusion transcript is present?

A break-apart FISH assay is not fusion sequencing

SS18 split signals indicate rearrangement at the locus

- They do not, by themselves, specify the partner transcript
- A positive assay supports the diagnosis when morphology is compatible

Where RNA-based fusion testing adds value



Interpret negative testing in light of RNA quality, assay coverage, and tumor fraction.

Positive and negative fusion-directed results

Positive result

Interpreted with a compatible tumor context

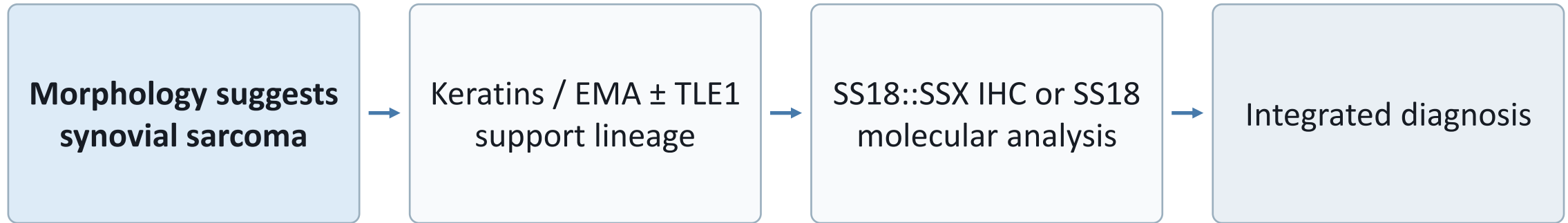
Usually resolves a broad spindle-cell differential

Negative or discordant result

Re-examine controls, specimen quality and test coverage

Consider additional IHC, FISH or sequencing before exclusion

Integrated diagnostic hierarchy



A single nonspecific positive stain never establishes the diagnosis.

Three avoidable diagnostic shortcuts

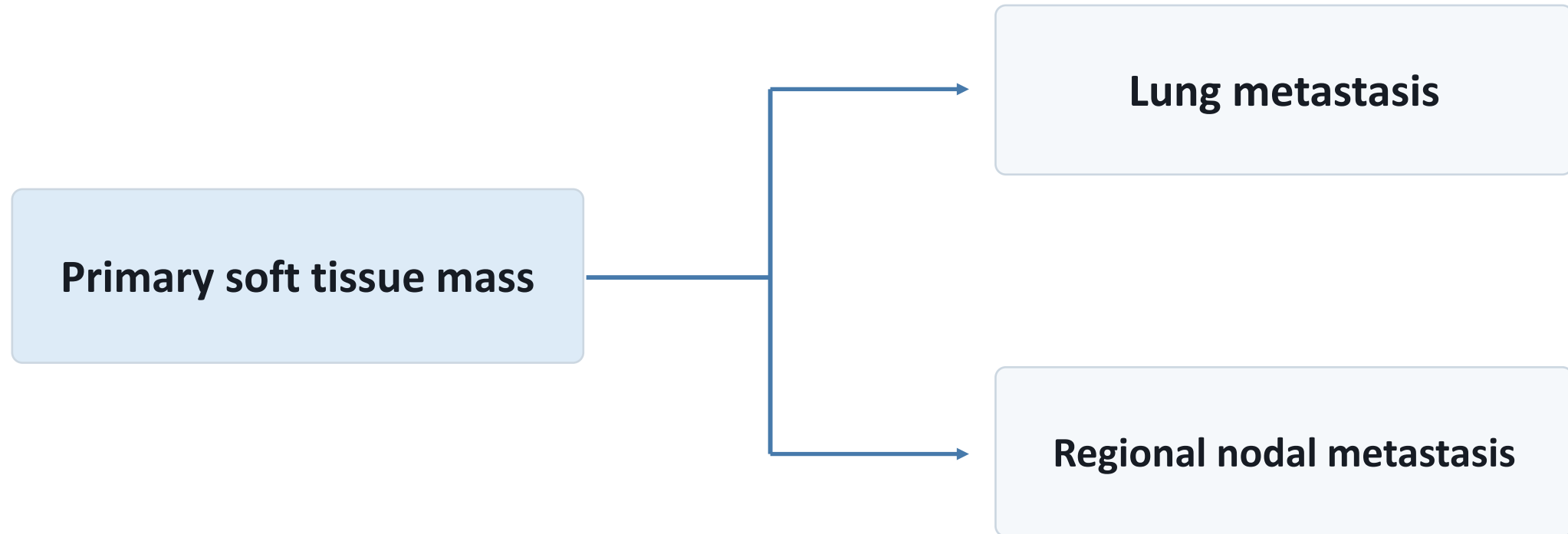
- Do not infer synovial origin from the tumor name
- Do not identify a sarcoma solely by keratin or TLE1 positivity
- Do not dismiss a case solely because glands are absent
- Do not treat a negative single fusion-directed assay as infallible

The signed-out diagnosis is an integration

Morphologic pattern + differential exclusions + validated
molecular evidence

- Ancillary assays confirm a biologic entity; They do not replace morphology and clinical context
- Record uncertainty rather than force a lineage label

Recognized metastatic destinations



Two potential routes from the primary tumor (not a sequential cascade)

Regional nodal spread deserves attention

Regional lymph nodes as a metastatic site

- Nodal involvement is unusual for sarcomas in general
- The possibility affects clinical staging and assessment

What drives clinical risk?

Tumor stage	Extent and dissemination are central prognostic variables
Patient age	Age with survival variation
Tumor size	Larger tumors are less favorable in NCI pediatric data
Local invasiveness	Important in pediatric risk descriptions
Site	Proximal or nonextremity presentations may alter outcome

Interpreting published survival ranges

Robbins gives 62%–83% five-year disease-specific survival

- This is a textbook-reported range, not a single modern pooled estimate
- Stage and age contribute to variability; Cohort definition matters

Localized and disseminated disease are different clinical problems

Localized disease

Aim for durable local control and prevention of spread

Surgery is central; Adjunctive treatment is risk-adapted

Metastatic disease

Systemic management and selective local measures

Biomarkers can determine eligibility for specialized treatment

Multidisciplinary assessment is essential

- Sarcoma-experienced pathology integrates tissue and fusion testing
- Imaging defines lesion extent and resectability
- Surgery, medical oncology, and radiation oncology consider local and systemic risk
- Do not plan treatment solely from a small-biopsy morphology label

Local treatment is typically limb sparing

Limb-sparing surgery

- Achieving appropriate local control requires anatomic planning
- Radiotherapy may be part of individualized management rather than an automatic rule

Chemotherapy: Textbook statement and practice nuance

Robbins overview

Mentions chemotherapy alongside limb-sparing surgery

This is not a universal instruction for every localized tumor

Risk-adapted practice

Use depends on disease extent, age, resectability and protocols

NCI pediatric guidance explicitly stratifies low-risk surgery-only patients

Treatment biomarkers: An important distinction

SS18::SSX	Disease-defining diagnostic rearrangement
MAGE-A4	Tumor antigen relevant to a specific engineered TCR-T therapy
HLA-A*02 variants	Host antigen-presentation eligibility for that therapy
Stage / resectability	Clinical variables defining the treatment setting

MAGE-A4-directed TCR-T therapy

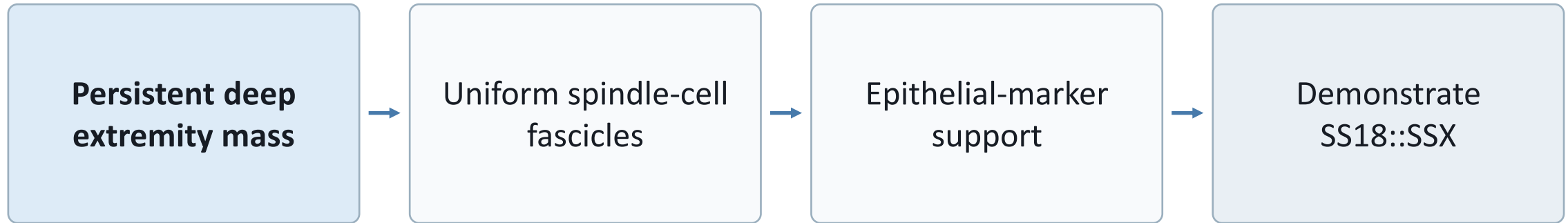
- Afamitresgene autoleucel: Autologous engineered T-cell receptor therapy
- U.S. Indication includes patients aged 12 years or older with unresectable or metastatic disease after chemotherapy
- Requires specified HLA-A*02 alleles AND MAGE-A4-positive tumor by an authorized companion diagnostic
- Cytokine release syndrome is a potentially serious treatment toxicity

Case 1: An indolent but deep mass

An otherwise healthy 22-year-old has a deep thigh mass present for two years. Biopsy shows uniform, tightly packed spindle cells and patchy keratin expression.

Question: Which molecular alteration would most strongly support synovial sarcoma?

Case 1: Diagnostic resolution



Extended symptom duration does not remove malignant potential.

Case 2: Dual differentiation

A resection contains compact spindle-cell sheets and distinct gland-like structures lined by cuboidal cells. Both components belong to a single malignancy.

Question: What morphologic subtype is most consistent with these findings?

Case 2: Biphasic synovial sarcoma

Two histologic components establish a biphasic pattern

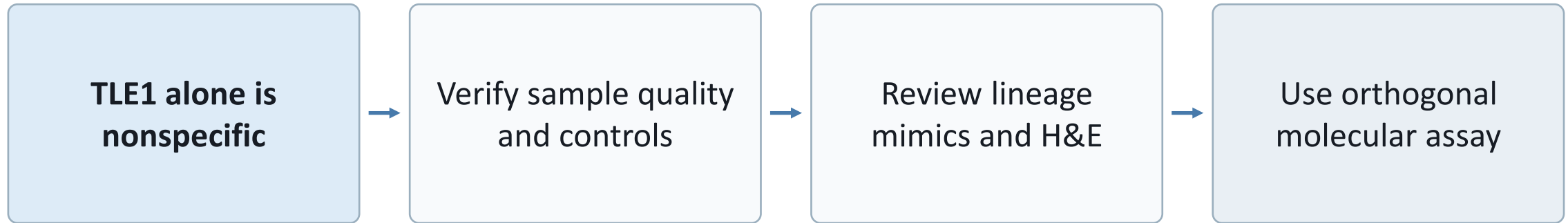
- Spindle + gland-forming epithelial differentiation
- Use a fusion-directed test when needed to exclude mimics

Case 3: An IHC pitfall

A spindle-cell tumor stains strongly for TLE1 but shows no convincing keratin staining. Fusion-specific immunostaining is negative on decalcified tissue.

Question: Is the diagnosis excluded, confirmed, or unresolved?

Case 3: Handle discordant evidence



Best classification may remain provisional until additional evidence is available.

Consolidated exam-level distinctions

Historical name	No requirement for synovial origin
Signature	T(X;18) → SS18::SSX
Monophasic	Uniform spindle-cell fascicles
Biphasic	Spindle cells + epithelial gland-like structures
Metastases	Lungs and regional lymph nodes are recognized

Final diagnostic safeguards

- Morphology identifies a pattern; The fusion helps identify the entity
- Keratins/EMA indicate differentiation, not an epithelial primary by themselves
- TLE1 is supportive and not disease defining
- Know the limits of every ancillary assay
- Report subtype, molecular evidence and clinically consequential uncertainty

Selected references and source boundaries

Primary textbook	Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Ch 26
Pediatric clinical detail	NCI Childhood Soft Tissue Sarcoma Treatment (PDQ), Synovial Sarcoma
IHC and molecular update	Molecular/pathology reviews and SS18::SSX antibody validation studies
Regulatory status	U.S. FDA TECELRA indication and updated prescribing letter