

Fibrous Tumors

Pediatric fibromatosis and infantile fibrosarcoma

Morphology · molecular pathogenesis · clinicopathologic reasoning

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Learning objectives

Distinguish fibromatosis from infantile fibrosarcoma.

Connect spindle-cell morphology to biologic behavior.

Explain ETV6::NTRK3–driven kinase signaling.

Integrate morphology, molecular findings, prognosis, and treatment relevance.

Fibrous lesions in childhood

Pediatric soft-tissue masses commonly arise from mesenchymal tissues.

Fibrous tumors are thought to derive from fibroblasts or myofibroblasts.

The category spans relatively hypocellular lesions and cellular sarcomatous tumors.

Tumor name, age, and biologic context modify morphologic interpretation.

Cell lineage and lesion spectrum



Cell lineage provides context; It is not sufficient for a specific diagnosis.

What do fibroblasts and myofibroblasts imply?

Fibroblast-associated features

Spindle-shaped stromal cells

Synthesis and organization of fibrous matrix

Collagen-rich lesions may appear hypocellular

Myofibroblast-associated features

Fibroblastic lineage with contractile phenotype

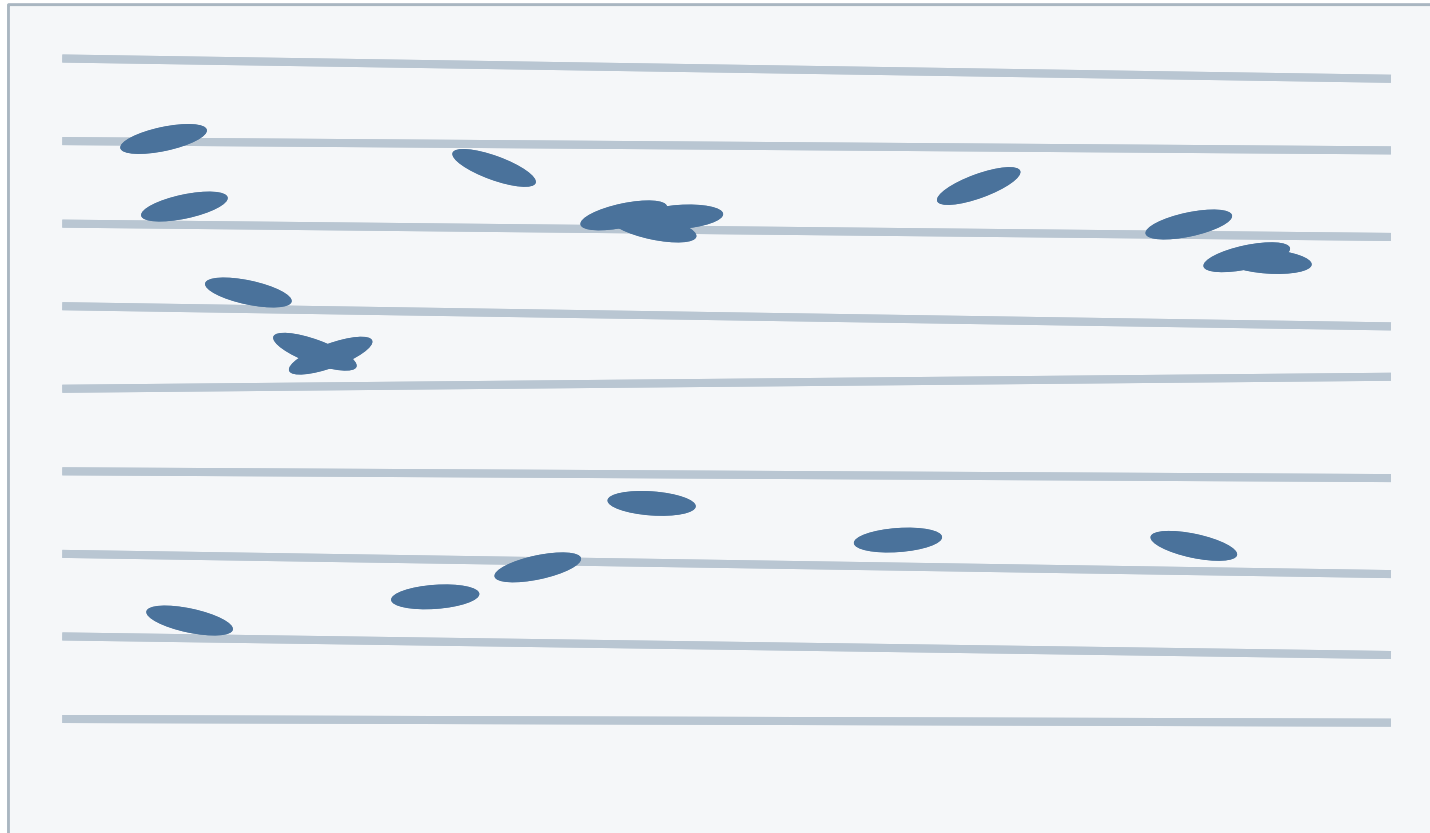
Contributes to tissue remodeling

Myofibroblastic proliferations may resemble scars

The pediatric fibrous tumor spectrum

Feature	Fibromatosis	Infantile fibrosarcoma
Cellularity	Relatively sparse	Relatively rich
Cell shape	Spindle shaped	Spindle shaped
Histology	Fibroblastic proliferation	Adult-fibrosarcoma-like
Interpretation	Context-dependent behavior	Often excellent prognosis despite appearance

Low cellularity: Conceptual architecture



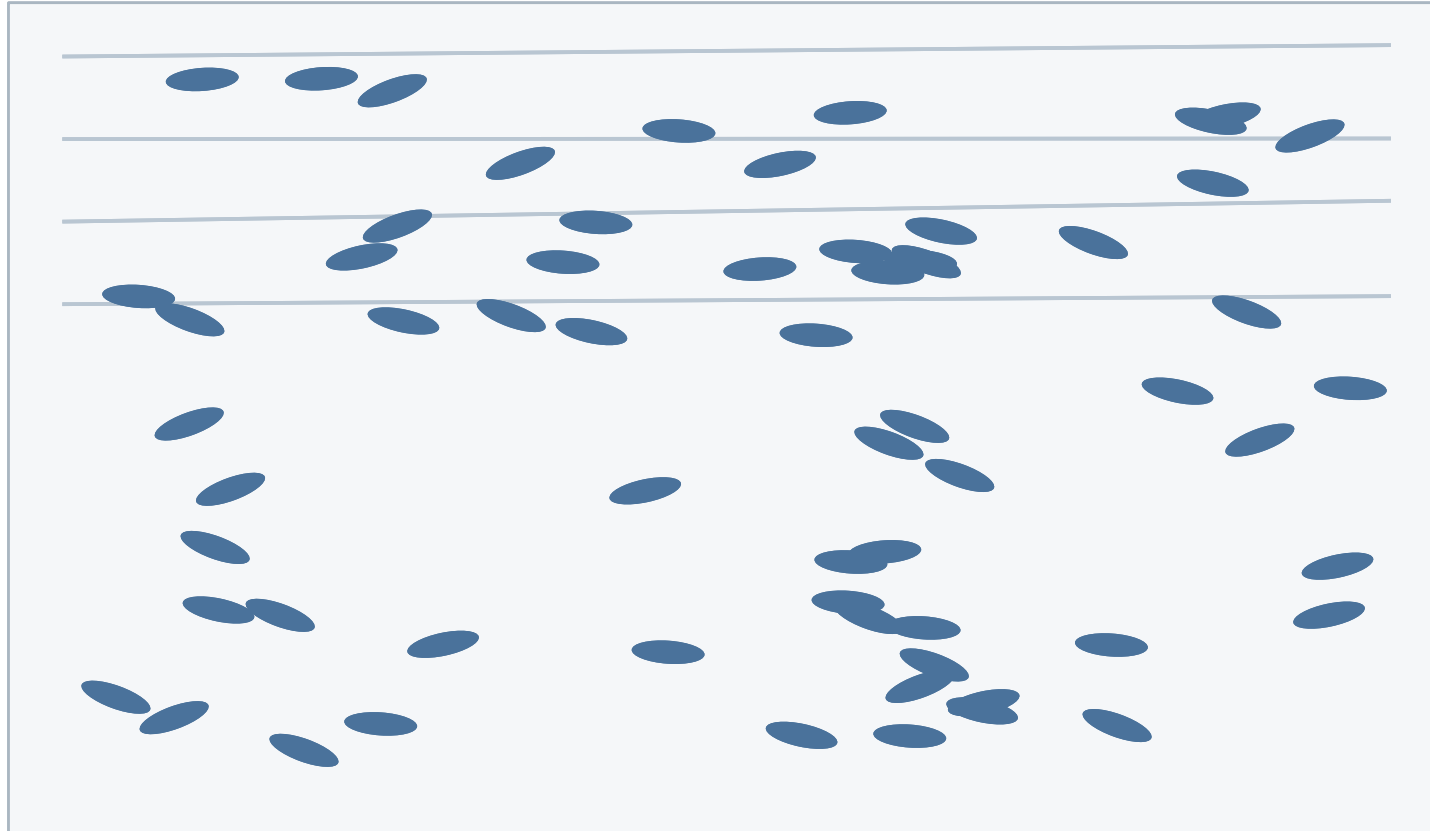
Schematic—not an H&E photomicrograph

Relatively few spindle cells

Prominent intervening fibrous
matrix

Illustrates low cellularity—not a
diagnostic image

High cellularity: Conceptual architecture



Schematic—not an H&E photomicrograph

Numerous spindle-shaped cells

Less matrix between
neighboring cells

Cellularity alone does not
establish clinical risk

Morphologic resemblance is not equivalence

Observed on a slide

Spindle-cell density

Fascicular arrangement

Amount of extracellular matrix

Beyond the slide

Patient age and anatomic site

Clinical course and growth behavior

Entity-defining molecular alterations

Why histology alone can mislead

A fibrous lesion in an infant appears strikingly cellular and resembles an adult fibrosarcoma. What can be concluded from the resemblance?

Morphologic similarity alone does not establish adult-type clinical prognosis.

Fibromatosis: Defining pattern

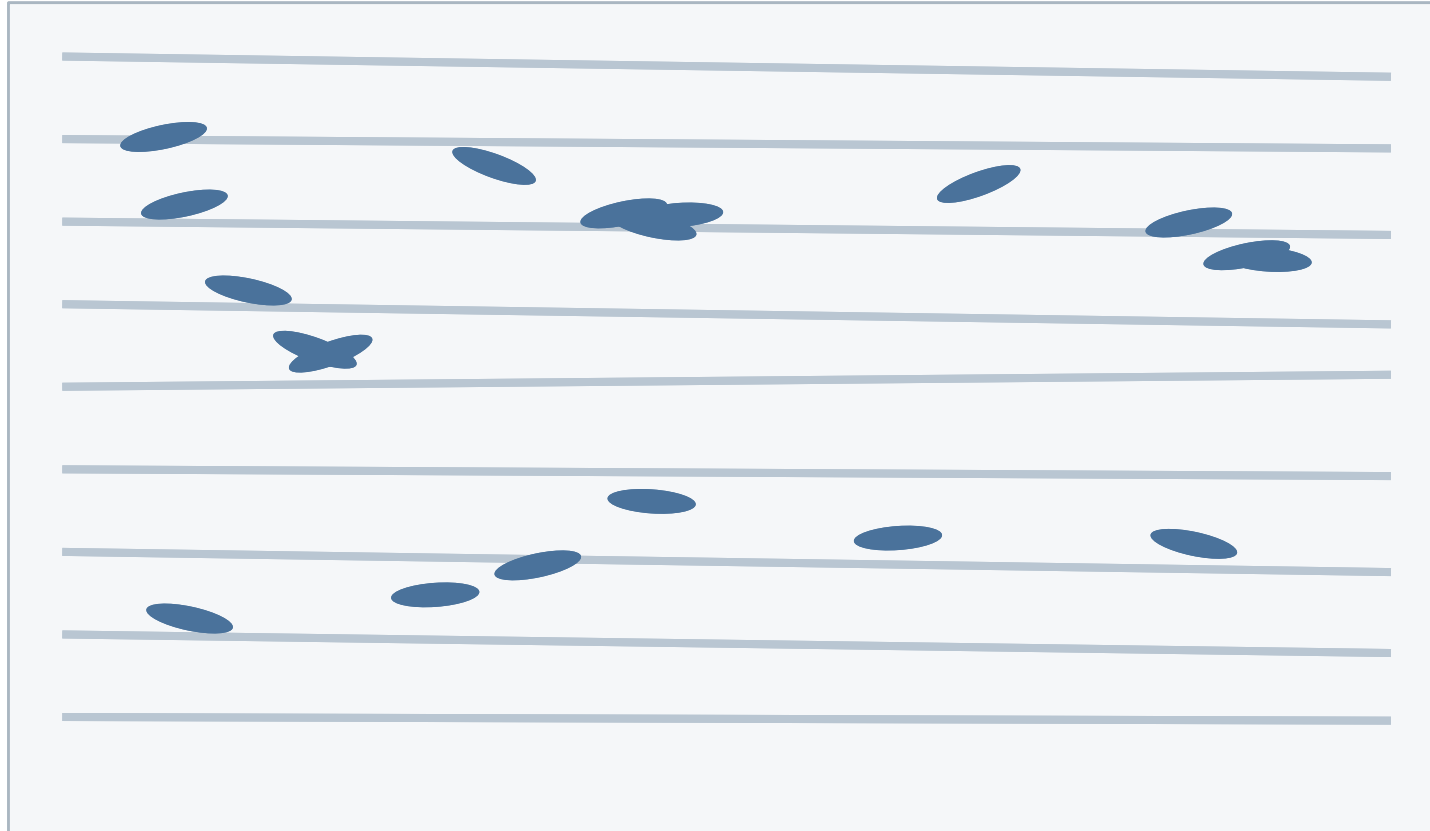
A sparsely cellular spindle-cell proliferation under the fibromatosis label.

The fibrous matrix forms a conspicuous component of the lesion.

Different anatomic and clinical forms of fibromatosis have distinct natural histories.

The term fibromatosis does not automatically mean a clinically insignificant lesion.

Fibromatosis: Spindle cells within matrix



Schematic—not an H&E photomicrograph

Relatively few spindle cells

Prominent intervening fibrous
matrix

Illustrates low cellularity—not a
diagnostic image

Why collagen matters to morphology

Fibroblastic proliferations may elaborate abundant dense collagen.

In collagen-rich lesions, the cell-to-matrix ratio is low.

A bland spindle-cell lesion may resemble a scar.

Tissue architecture and growth interface aid interpretation.

Fibromatosis: Anatomic and clinical forms

Form	Typical description	Clinical behavior
Superficial	Fascial / subcutaneous; collagenous	Usually indolent
Deep (desmoid)	Musculoaponeurotic or mesenteric	Infiltrative and locally recurrent

Superficial fibromatosis: Named syndromes

Name	Anatomic site	Key consequence
Dupuytren	Palmar fascia	Progressive flexion contracture
Ledderhose	Plantar fascia	Nodularity; typically no contracture
Peyronie	Penile fascia	Curvature or urethral narrowing

Palmar fibromatosis: Fascial contracture

Irregular or nodular thickening arises in palmar fascia.

Adherence to overlying skin may cause puckering or dimpling.

Progressive flexion contracture reflects tissue distortion.

This is contextual fibromatosis morphology, not a claim of pediatric predominance.

Plantar fibromatosis in younger patients

Ledderhose disease occurs from childhood into adolescence.

Robbins specifically describes boys younger than 10 years through adolescence.

Lesions are often unilateral and do not cause contractures.

Association with palmar or penile fibromatosis may occur.

Penile fibromatosis: Structure and effect

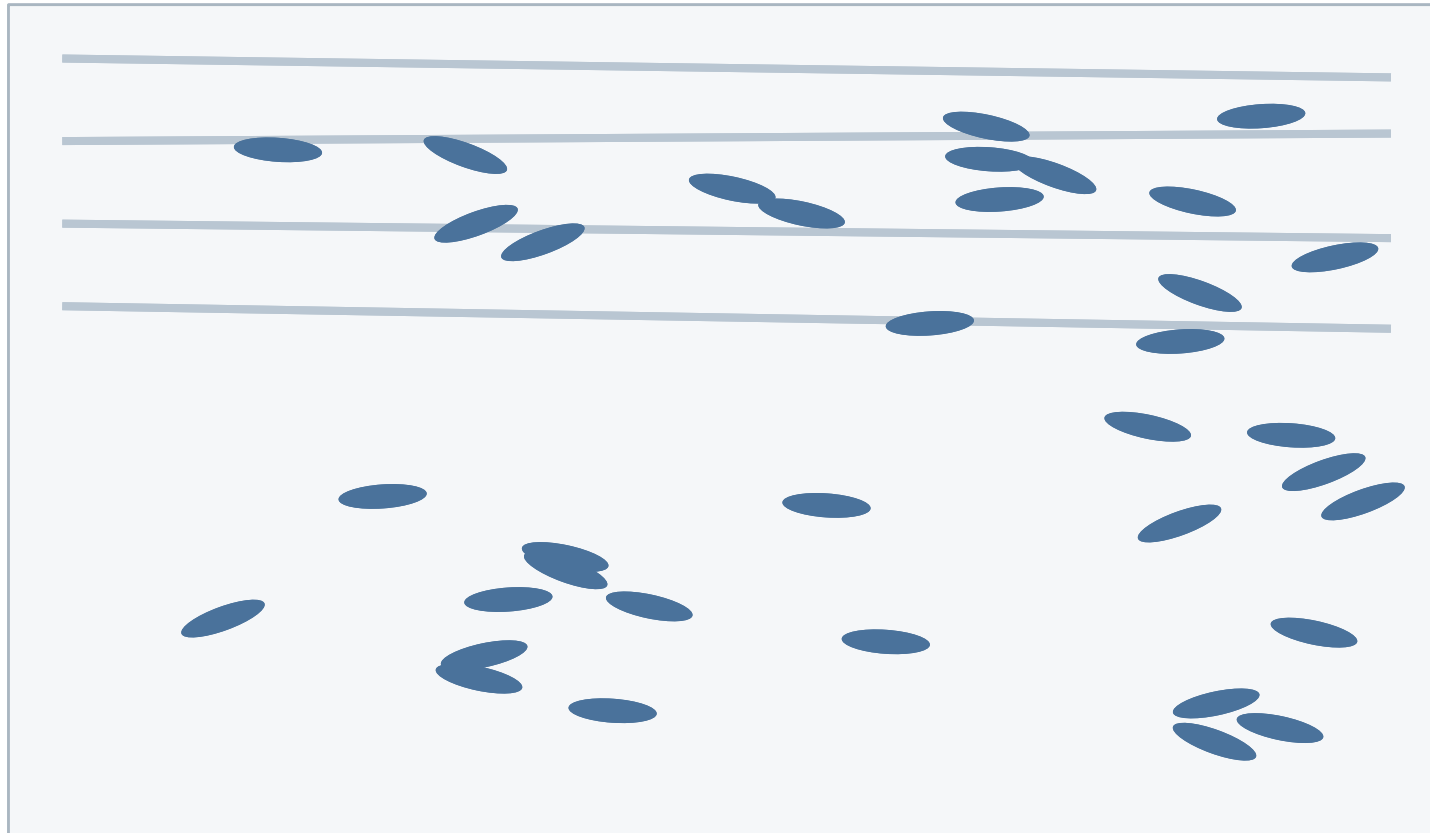
Peyronie disease produces palpable induration or a mass.

It affects the dorsolateral penile region.

Fibrosis may cause shaft curvature or urethral constriction.

The example illustrates structure–function consequences of collagenous proliferation.

Superficial fibromatosis: Sweeping fascicles



Schematic—not an H&E photomicrograph

Fascicular organization

Bland spindle-cell appearance

Architectural pattern requires
clinical context

Clinical course of superficial fibromatoses

Some palmar and plantar fibromatoses progressively enlarge.

Others stabilize or may regress spontaneously.

Anatomic location determines functional consequences.

Histologic blandness should not be confused with absence of morbidity.

Deep fibromatosis: Local aggression without metastasis



Desmoid-type fibromatosis can recur without acquiring metastatic potential.

Deep fibromatosis: Clinical context

Deep lesions arise in musculoaponeurotic structures.

Adolescents and young adults, particularly females.

Common locations include abdominal wall, limb girdles, and mesentery.

This entity broadens the fibromatosis differential beyond the infantile subset.

Deep fibromatosis: Macroscopic appearance

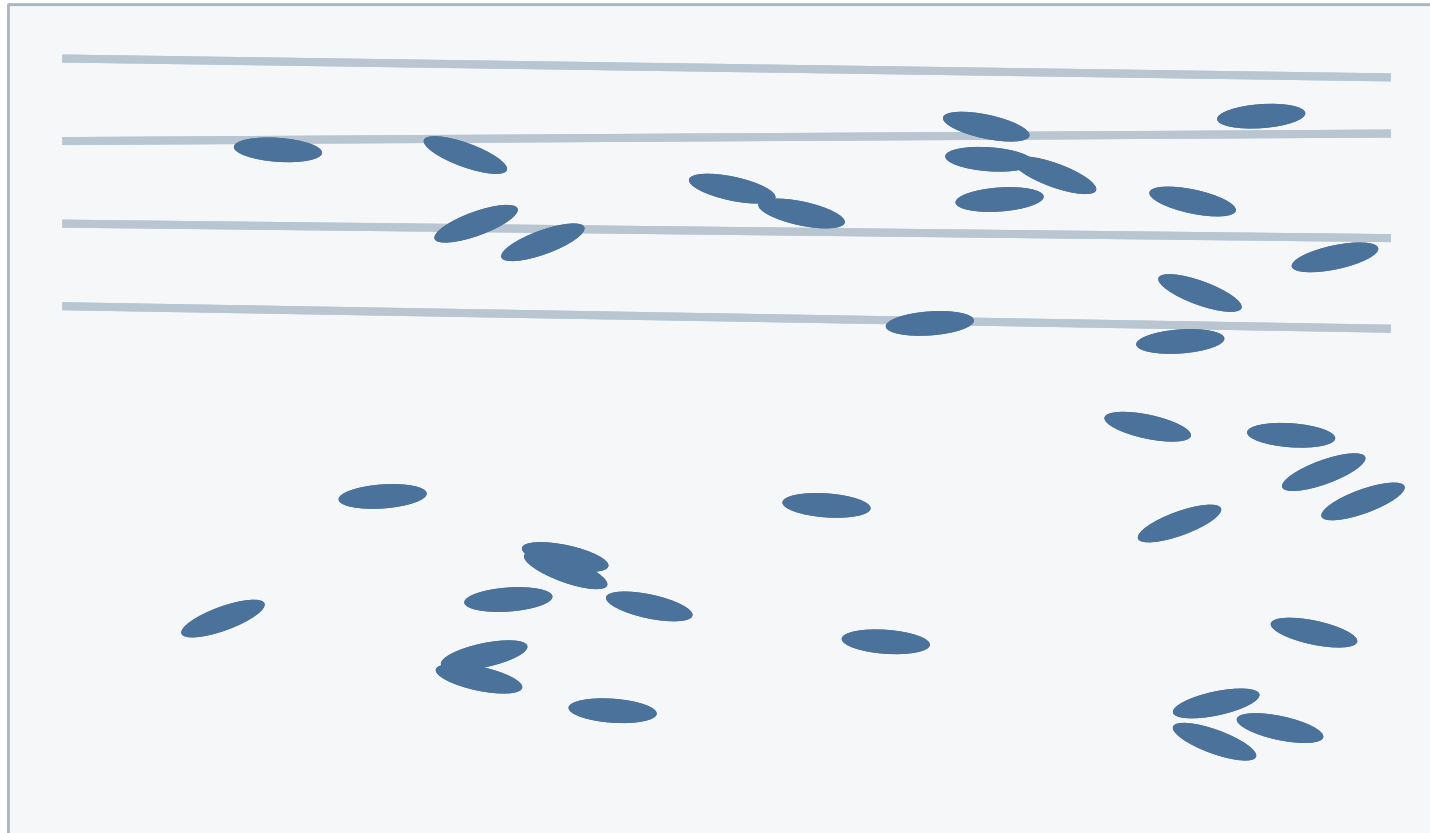
Firm, gray-white, collagen-rich mass.

Poorly demarcated margins suggest infiltration.

The lesion may involve skeletal muscle, fat, or nerve.

Gross appearance correlates with difficult complete excision.

Deep fibromatosis: Collagen and bland spindle cells



Schematic—not an H&E photomicrograph

Fascicular organization

Bland spindle-cell appearance

Architectural pattern requires
clinical context

Infiltration explains local recurrence

**Bland-appearing
spindle cells**



**Growth through
muscle and fat**



**Residual microscopic
disease may remain**

The key aggressive feature is local extension rather than distant spread.

Locally aggressive versus metastatic behavior

Feature	Desmoid-type fibromatosis	Metastatic sarcoma
Growth	Infiltrative	May infiltrate
Recurrence	Can recur after local treatment	May recur
Metastasis	Does not metastasize	May metastasize
Primary danger	Local morbidity	Local and distant disease

Deep fibromatosis: Wnt pathway context



Most deep fibromatoses are associated with sporadic CTNNB1 alterations.

CTNNB1 and APC: Genetic settings

Sporadic deep fibromatosis

CTNNB1 mutation described in most lesions

Increased Wnt signaling

Molecular context differs from infantile
fibrosarcoma

Hereditary predisposition

Germline APC variants underlie familial
adenomatous polyposis

Associated desmoid susceptibility

Gardner syndrome is the relevant
phenotype

Why a desmoid tumor is not simply a scar

A desmoid is a clonal fibroblastic neoplasm.

It may be poorly circumscribed and infiltrate adjacent structures.

Local recurrence is a clinically significant feature.

Its bland collagen-rich histology can overlap with scar-like tissue.

Scar, nodular fasciitis, and desmoid

Feature	Excessive scar	Nodular fasciitis	Desmoid
Process	Repair-related	Self-limited clonal proliferation	Infiltrative neoplasm
Architecture	Dense collagen	Loose / tissue-culture-like	Long fascicles; dense collagen
Course	May stabilize	Typically self-limited	Locally recurrent

Nodular fasciitis: Diagnostic comparator

A fibroblastic and myofibroblastic proliferation.

Often rapidly enlarges over weeks to months.

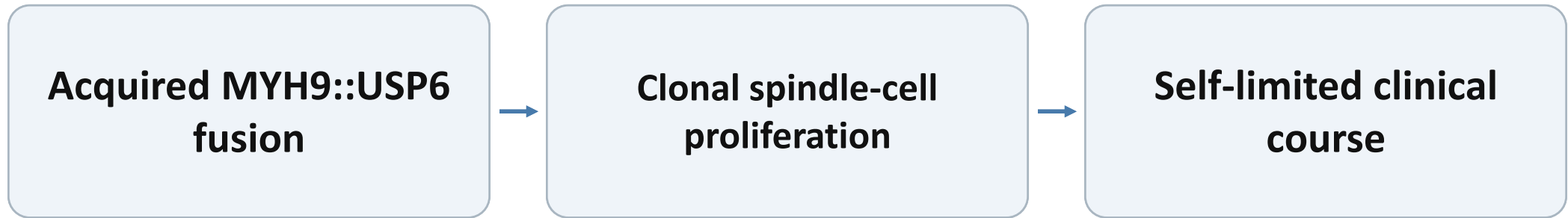
Generally self-limited despite brisk growth.

May be mistaken for a more aggressive spindle-cell neoplasm.

Nodular fasciitis: Microscopic cues

Feature	Reported appearance
Cells	Plump spindle-shaped fibroblasts / myofibroblasts
Pattern	Loose tissue-culture-like growth
Mitoses	Can be frequent, but atypical forms absent
Stroma	Myxoid regions with zonation to fibrous areas

MYH9::USP6 supports clonality



Clonality does not necessarily imply a highly aggressive clinical phenotype.

Three fibrous patterns to distinguish

Entity	Cellularity / matrix	Behavioral clue
Fibromatosis	Bland spindle cells, fibrous matrix	Superficial indolence or deep infiltration
Nodular fasciitis	Plump spindled cells, often myxoid	Rapidly growing yet self-limited
Infantile fibrosarcoma	Cell-rich spindle-cell lesion	Favorable pediatric outcome despite sarcomatous morphology

Infantile fibrosarcoma: Defining contrast

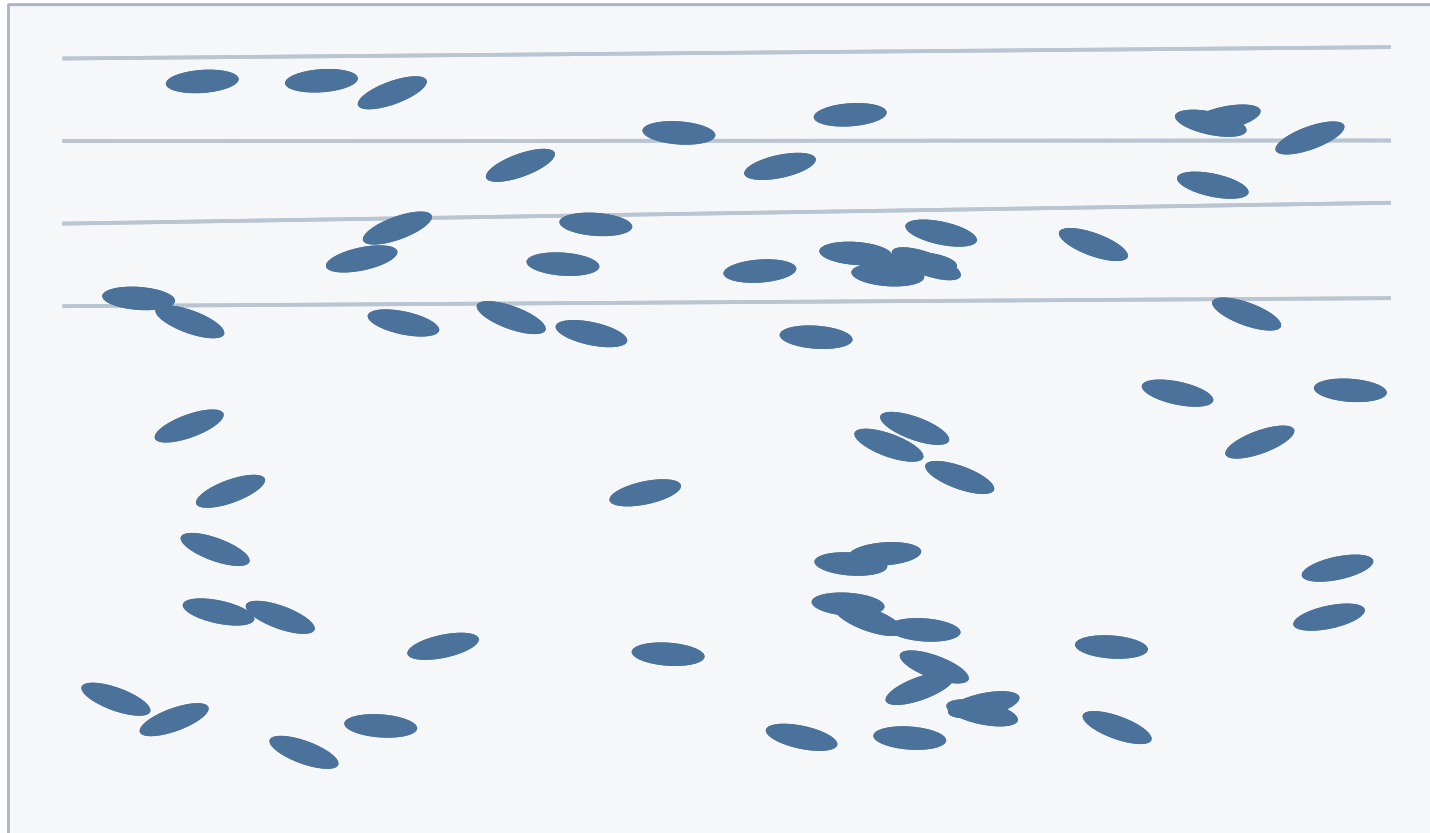
A richly cellular spindle-cell neoplasm of infancy and childhood.

Can be histologically indistinguishable from adult fibrosarcoma.

Nevertheless, it generally has an excellent prognosis.

The contrast exemplifies why age and molecular context matter.

Infantile fibrosarcoma: Cellular spindle cells



Schematic—not an H&E photomicrograph

Numerous spindle-shaped cells

Less matrix between
neighboring cells

Cellularity alone does not
establish clinical risk

Interpreting a cellular spindle-cell lesion

Identify elongated spindle-shaped tumor cells.

Assess cellularity relative to collagenous matrix.

Describe arrangement and cytologic features without overclaiming risk.

Integrate clinical and molecular evidence before final classification.

Adult-like appearance, different outcome

Histologic correspondence

Both may show densely cellular spindle-cell areas

Microscopy alone can appear similar

A malignant-looking pattern raises a diagnostic question

Biologic divergence

Infantile fibrosarcoma generally has a favorable prognosis

Clinical course cannot be extrapolated from adult histology

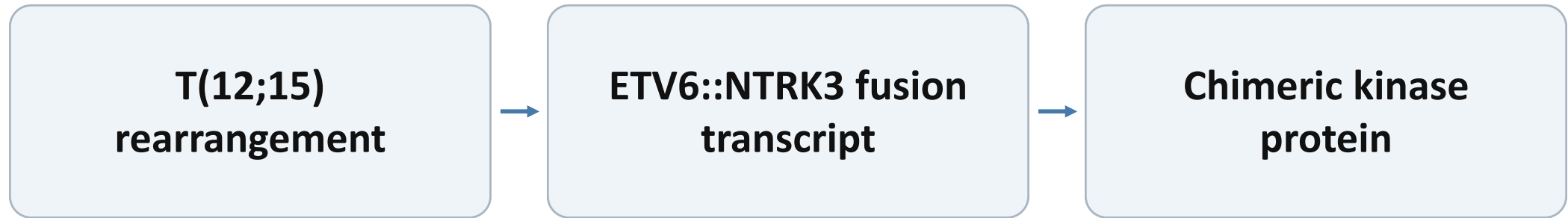
Fusion status provides entity-specific evidence

The diagnostic paradox

A pathologist sees a highly cellular fascicular tumor in an infant. Its microscopic appearance resembles adult fibrosarcoma. What additional evidence is particularly informative?

Evaluate the possibility of ETV6::NTRK3-driven infantile fibrosarcoma.

Chromosomal rearrangement creates a fusion



Fusion identity is the central diagnostic concept; Band-level notation is secondary.

ETV6: The transcription-factor partner

ETV6 normally encodes a transcription factor.

The chromosomal rearrangement brings ETV6 into a fusion transcript.

This alters the functional context of the partnered kinase.

The relevant oncogenic entity is the fusion, not ordinary ETV6 expression.

NTRK3: A tyrosine-kinase partner

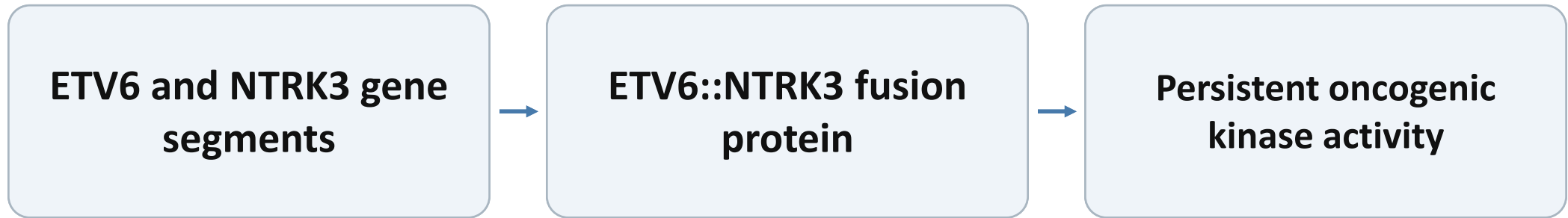
NTRK3 encodes the kinase also called TRKC.

Tyrosine-kinase signaling ordinarily depends on regulated activation.

The ETV6::NTRK3 fusion generates a constitutively active kinase.

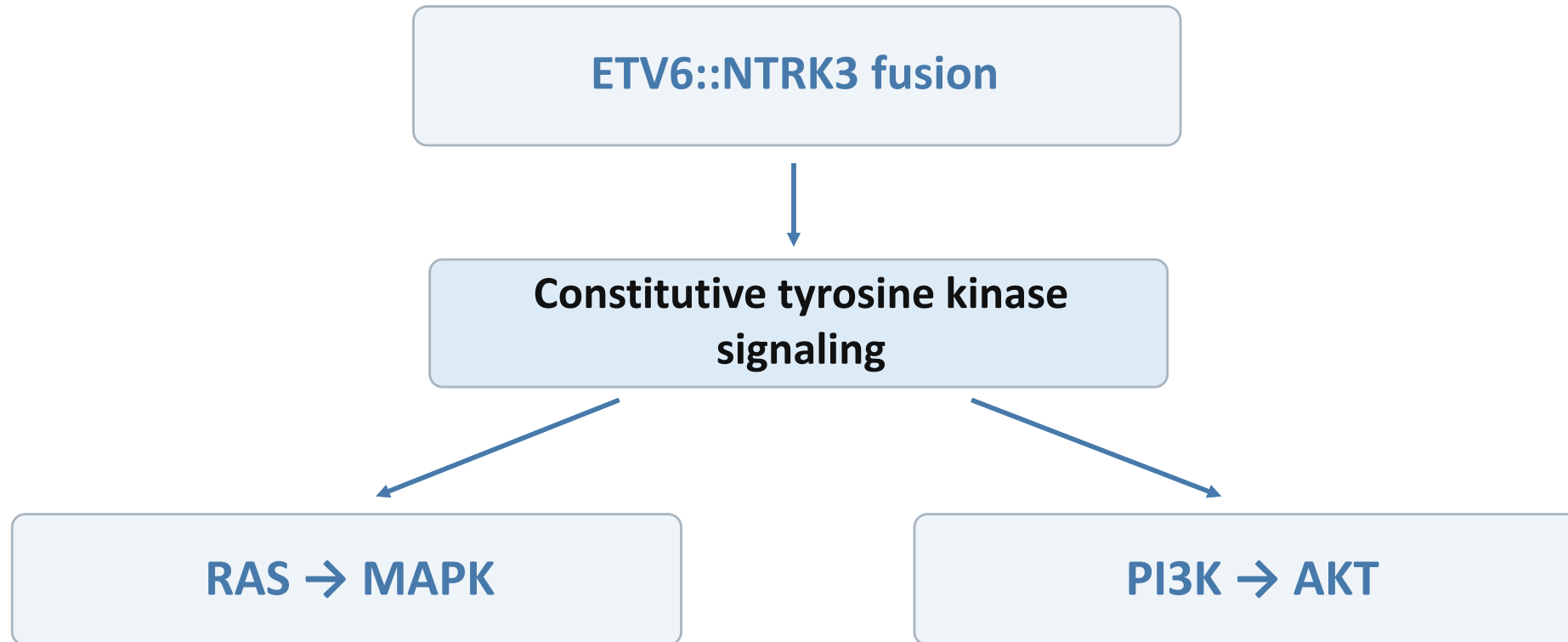
The kinase moiety supplies a pharmacologically targetable vulnerability.

From gene fusion to protein function



A fusion product acquires properties not conveyed by either normal gene name alone.

ETV6::NTRK3 activates two signaling branches



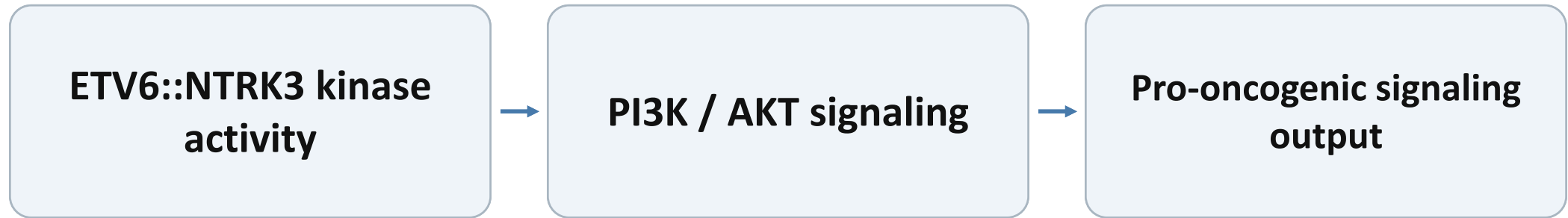
Both branches transmit oncogenic growth signals

RAS–MAPK branch of the fusion signal



This is a pathway-level schematic, not an exhaustive reaction mechanism.

PI3K–AKT branch of the fusion signal



The Robbins excerpt identifies pathway activation but not a complete molecular cascade.

Fusion biology: What is and is not established

Supported by the source

The fusion is a characteristic molecular event

The chimeric kinase is constitutively active

RAS–MAPK and PI3K/AKT pathways are stimulated

Do not infer without evidence

Every spindle-cell tumor carries this fusion

Morphology predicts targetable mutation status

A particular response percentage applies to all patients

Diagnostic value of ETV6::NTRK3

Finding	Interpretation
Compatible pediatric spindle-cell tumor	Raises suspicion for infantile fibrosarcoma
ETV6::NTRK3 identified	Strong molecular support in appropriate context
Cellularity without fusion information	Does not resolve the entity by itself
Fusion in an unexpected setting	Requires site-specific diagnostic correlation

Fusion testing: Evidence from an open case report

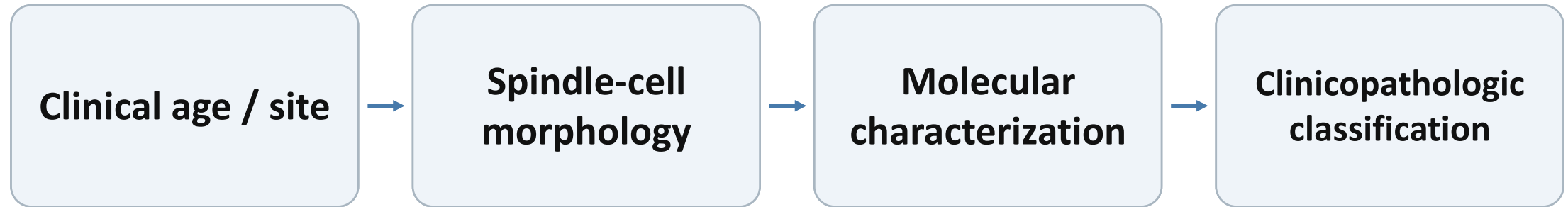
A published neonatal case used ETV6 break-apart FISH.

Fusion testing by sequencing demonstrated ETV6::NTRK3.

The molecular result was interpreted alongside biopsy morphology.

An ETV6 rearrangement is not identical to full fusion-partner identification.

Integrated interpretation of a pediatric mass



The sequence is conceptual; Local diagnostic workflows vary.

Fibromatosis versus infantile fibrosarcoma

Feature	Fibromatosis spectrum	Infantile fibrosarcoma
Dominant structure	Spindle cells + collagenous matrix	Densely cellular spindle cells
Risk inference	Depends on subtype and location	Adult-like histology may overstate risk
Molecular context	Wnt alterations in desmoid subset	Characteristic ETV6::NTRK3 fusion
Distinctive issue	Local infiltration in desmoid	Targetable kinase fusion

Prognosis requires pediatric context

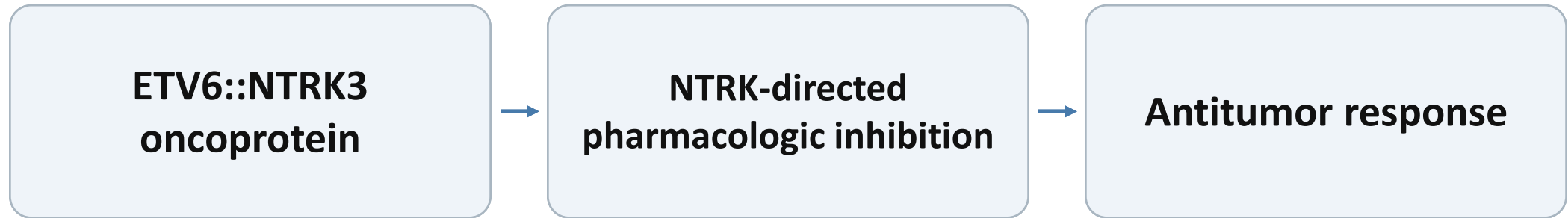
Infantile fibrosarcoma generally has an excellent prognosis.

Adult fibrosarcoma resemblance should not be used as a prognostic shortcut.

The diagnostic distinction has direct clinical implications.

A molecularly grounded diagnosis helps avoid misleading assumptions.

Kinase dependence suggests targeted treatment



Dramatic responses in previously unresectable ETV6::NTRK3-positive disease.

NTRK inhibitors: Disease-specific relevance

The oncogenic fusion encodes an active tyrosine kinase.

Selective NTRK inhibition targets this molecular mechanism.

Dramatic antitumor responses in selected unresectable cases.

A fusion-directed therapy illustrates the link from pathology to treatment.

Molecular finding changes clinical reasoning

Without fusion information

Histologic spindle-cell neoplasm may be ambiguous

Cellularity may suggest adult-type risk incorrectly

A therapeutic vulnerability may remain unrecognized

With ETV6::NTRK3 evidence

Supports an appropriate infantile fibrosarcoma diagnosis

Defines a kinase-driver mechanism

Provides a rationale for NTRK inhibitor consideration

Why unresectable disease matters

Mass location and local extension can limit surgical options.

Robbins specifically describes previously unresectable infantile fibrosarcoma.

Targeted treatment offers a biologically rational alternative in fusion-positive tumors.

Treatment selection requires multidisciplinary clinical assessment.

Treatment does not redefine morphology

An infantile fibrosarcoma responds dramatically to an NTRK inhibitor. Does treatment response mean that the original lesion was histologically benign?

No. Treatment response reflects the actionable oncogenic driver, not reclassification as a benign lesion.

Case exercise: Collagen-rich lesion

A patient has a firm, poorly demarcated lesion with bland spindle cells and abundant dense collagen infiltrating skeletal muscle. What biologic behavior is especially important?

Consider deep fibromatosis: Locally infiltrative behavior and risk of recurrence.

Case exercise: Rapidly growing spindle mass

A rapidly enlarging soft-tissue nodule has plump spindle cells, a loose myxoid background, frequent nonatypical mitoses, and zonation. Which comparator is important?

Nodular fasciitis; Correlate with clinical behavior and MYH9::USP6-related clonality.

Case exercise: Tumor in an infant

A neonatal mass has highly cellular spindle-cell morphology and molecular testing identifies ETV6::NTRK3. What entity best fits this combined profile?

Infantile fibrosarcoma, in the appropriate anatomic and clinicopathologic context.

Case exercise: Treatment linkage

A molecularly confirmed ETV6::NTRK3-positive infantile fibrosarcoma is not amenable to resection. What mechanism supplies a therapeutic rationale?

Constitutive NTRK kinase signaling creates a target for selective NTRK inhibition.

Final diagnostic synthesis

Observation	Key question	Useful evidence
Hypocellular / collagen-rich	Which fibromatosis subtype?	Site, margins, clinical behavior
Bland but infiltrative	Could this be desmoid?	Growth interface; CTNNB1/APC context
Rapidly growing myxoid	Could this be nodular fasciitis?	Zonation; MYH9::USP6 context
Cell-rich infantile tumor	Could this be infantile fibrosarcoma?	Age, histology, ETV6::NTRK3

Core distinctions for practice

Fibromatoses

Spindle-cell proliferations with variable collagen

Superficial lesions may remain indolent

Deep desmoids infiltrate and recur but do not metastasize

Infantile fibrosarcoma

Histologically resembles adult fibrosarcoma

Generally much better prognosis

ETV6::NTRK3 provides molecular support and an actionable target

Five clinical–pathologic checkpoints

Identify the patient's age and lesion site.

Describe spindle cells, cellularity, collagen, and tissue interface.

Distinguish locally aggressive growth from metastatic risk.

Use entity-specific molecular alterations for classification.

Link a verified kinase fusion to treatment relevance.

Selected references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026.

Source scope: pediatric soft-tissue neoplasms, fibromatosis, infantile fibrosarcoma, and related fibrous lesions.

Wang D, Zhang F, Feng W, Pan J, Yuan T. Front Oncol. 2023;13:1206833.
doi:10.3389/fonc.2023.1206833.

The lecture includes original schematic morphology diagrams; these are not authentic histopathology images.