Molecular Classification of Soft-Tissue and Bone Tumors

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Fellowship of Molecular Pathology and Cytogenetics

Soft-Tissue and Bone Tumors

Soft-tissue sarcomas are a heterogeneous group of malignant neoplasms.

Paediatric Tumours
WHO Classification of Tumours, 5th Edition, Volume 7

WHO Classification of Tumours Editorial Board

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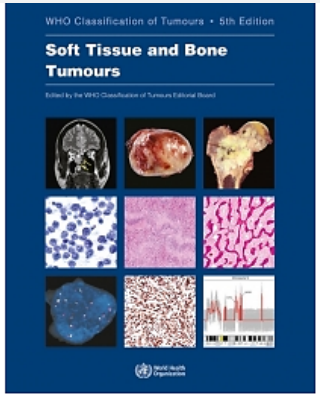

Soft Tissue and Bone Tumours
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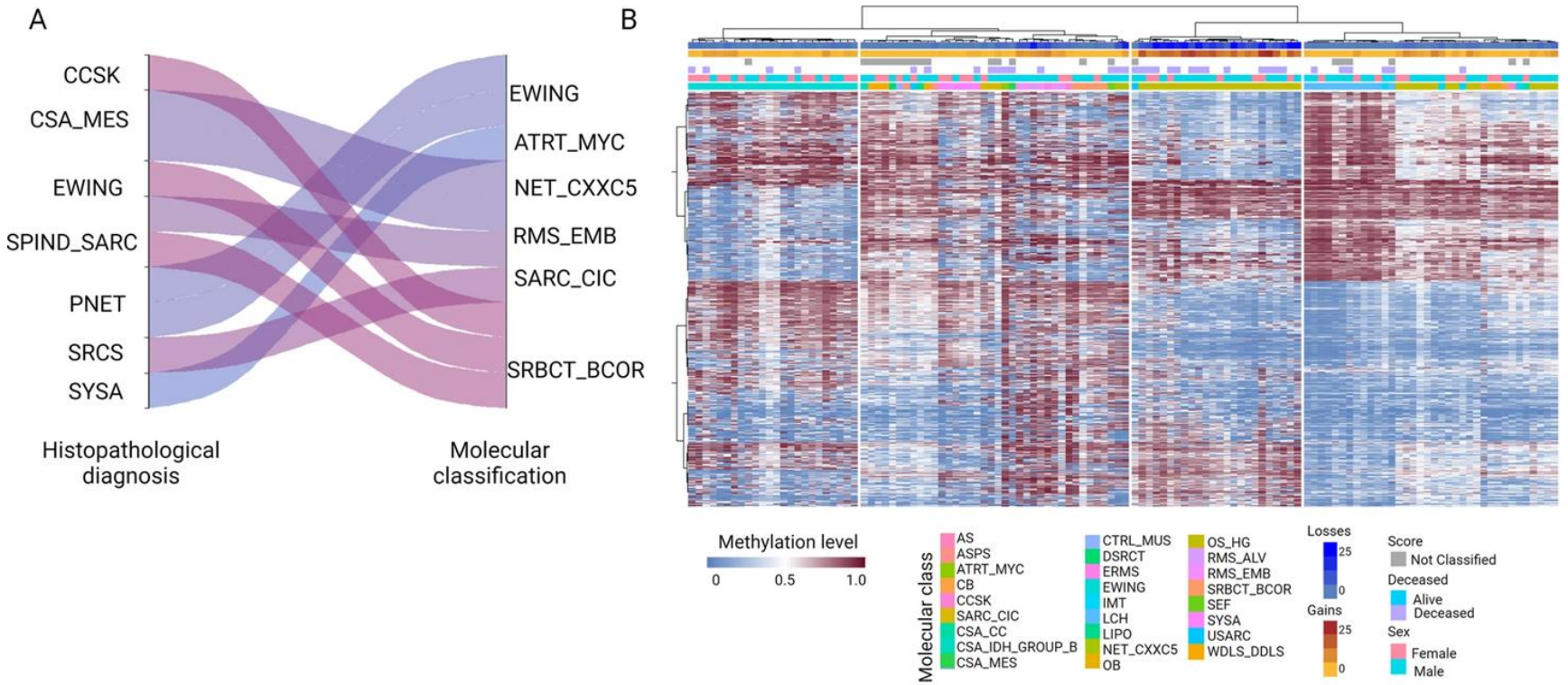
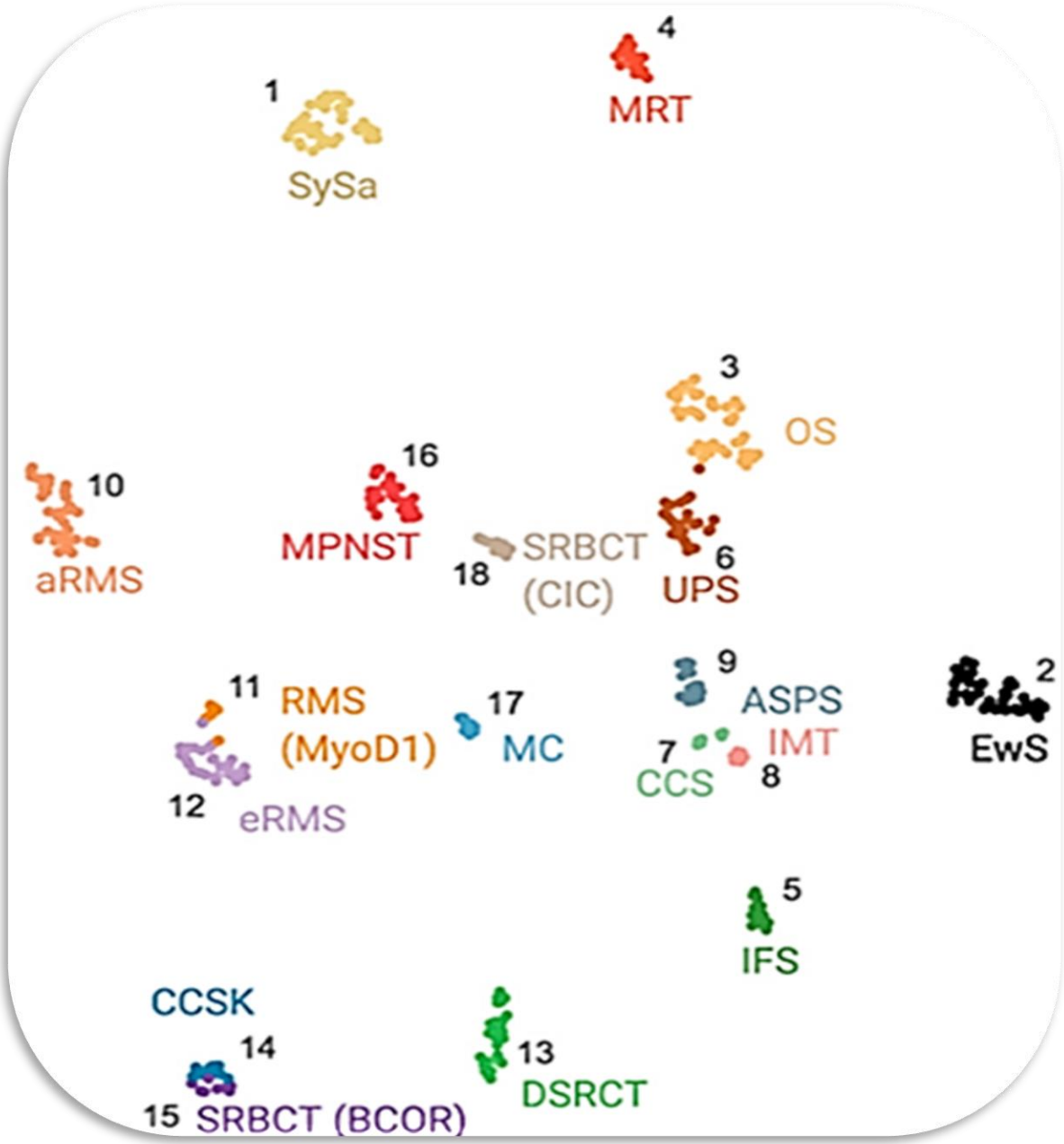


Classification of pediatric soft and bone sarcomas using DNA methylation-based profiling

Methylation profile predicted the classification of 88.5% of pediatric sarcomas

Silva et al. BMC Cancer (2024) 24:1428



Imle R, et al. J. Clin. Med. 2021

Imle R, et al. J. Clin. Med. 2021

Role of Biomarker	Example
Diagnostic	EWSR1 rearrangement in Ewing Sarcoma
Prognostic	Type of FOXO1 rearrangement in Alveolar Rhabdomyosarcoma
Predictive/Treatment	NTRK rearrangements in Infantile Fibrosarcoma
Genetic Predisposition to Cancer	TP53 mutations for Li–Fraumeni Syndrome

Molecular classification is not yet universally utilized.

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Prepared by the Association for Molecular Pathology Tr

Tissue Type	Tumor Type	Gene/Biomarker	
Adipocytic	Lipoblastoma	*PLAG1, HMGA2* (rare)	fusion
Skeletal Muscle	Alveolar Rhabdomyosarcoma	*PAX3::FOXO1, PAX7::FOXO1*	fusion
	Embryonal Rhabdomyosarcoma	*HRAS, KRAS, NRAS; FGFR4; NF1*	activat
	Spindle Cell / Sclerosing Rhabdomyosarcoma	*MYOD1*	sequen
		VGLL2, NCOA2	fusion
Myofibroblastic	Dermatofibrosarcoma Protuberans / Giant Cell Fibroblastoma	*COL1A1::PDGFB*	fusion
	Desmoid-Type Fibromatosis	*CTNNB1* (sporadic) *APC* (germline)	sequence
	Infantile Fibrosarcoma	*ETV6::NTRK3*, other *NTRK* fusions	fusion
	Inflammatory Myofibroblastic Tumor	*ALK, NTRK3, ROS1*	fusion
	Low-grade Fibromyxoid Sarcoma / Sclerosing Epithelioid Fibrosarcoma	*FUS::CREB3L2* *EWSR1::CREB3L1*	fusion
	Nodular Fasciitis, Cranial Fasciitis	*USP6*	fusion
Pericytic	Infantile Myofibroma / Myofibromatosis	*PDGFRB*	sequence va
Vascular	Pseudomyogenic Hemangioendothelioma	*FOSB*	fusion
	Epithelioid Hemangioendothelioma	*WWTR1::CAMTA1, YAP1::TFE3*	fusion
Bone	Aneurysmal Bone Cyst	*USP6*	fusion
	Giant Cell Tumor of Bone	*H3-3A (H3F3A)* p.G35W (p.G34W), p.G35L (p.G34L)	sequence vari
	Osteosarcoma	*TP53*	fusion, sequen deletion
Cartilage	Chondroblastoma	*H3-3B (H3F3B)* p.K37M (p.K36M)	sequence varia
	Mesenchymal Chondrosarcoma	*HEY1::NCOA2*	fusion
Miscellaneous	Ewing Sarcoma	*EWSR1::FLI1, EWSR1::ERG*, other FET-ETS fusions	fusion
	CIC-Rearranged Sarcoma	*CIC::DUX4*, other *CIC* fusions	fusion
	Sarcoma with *BCOR* Genetic Alterations	*BCOR::CCNB3, BCOR* internal tandem duplication (ITD)	fusion, internal ta duplication
	Alveolar Soft Part Sarcoma	*ASPSCR1::TFE3*	fusion
	Angiomatoid Fibrous Histiocytoma	*EWSR1::CREB1* (90%), *EWSR1::ATF1*	fusion
	Chordoma (Poorly Differentiated)	*SMARCB1* (*INI1*)	loss (usually partial
	Desmoplastic Small Round Cell Tumor	*EWSR1::WT1*	fusion

	RNA)
diagnosis, prognosis	FISH, RT-PCR, NGS (DNA, RNA)
diagnosis	NGS (DNA)
diagnosis, prognosis	NGS (DNA), ddPCR
diagnosis, prognosis	NGS (DNA, RNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis, familial cancer risk	NGS (DNA)
diagnosis, treatment	FISH, RT-PCR, NGS (DNA, RNA)
diagnosis, prognosis, treatment	IHC (ALK), FISH, NGS (DNA, RN
diagnosis	FISH, NGS (DNA, RNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis, treatment	NGS (DNA)
diagnosis	NGS (DNA, RNA)
diagnosis	FISH, RT-PCR, NGS (DNA, RNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis	IHC (H3.3 G34W), NGS (DNA)
diagnosis	NGS (DNA, RNA)
diagnosis	IHC (H3.3 K36M), NGS (DNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis	RT-PCR, FISH, NGS (DNA, RNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis	IHC (BCOR), NGS (DNA, RNA)
diagnosis	IHC (TFE3), RT-PCR, FISH, NGS (DNA, RNA)
diagnosis	FISH, NGS (DNA, RNA)
diagnosis, prognosis	IHC (INI1), CMA, NGS (DNA), MLPA
	RT-PCR, FISH, NGS (DNA, RNA)

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Table 1
Key features

	Age of Presentation	Typical Location	Morphology	Molecular	Methylation Pattern	Prognosis
Embryonal	<10 years	Head and neck & genitourinary tract	Round and spindle cells with variably dense cellularity	Variable RAS pathway	Fusion negative[a]	Variable
Alveolar	10–25 years	Extremities	Round	Majority with *FOXO1* fusion	Fusion positive[a]	Poor
Spindle Cell/ Sclerosing	Adolescent/ young adult (2–94 years)[27]	Head and neck & Paratesticular	Spindle/ sclerosing	*MyoD1* mutation	*MyoD1*	Poor
	<5 years	Chest wall		*VGLL2/NCOA2* fusion	Fusion negative	Favorable
	(11–86 years)[35]	Intraosseous craniofacial skeleton	Spindle and epithelioid	*TFCP2* fusion		Poor
	10–20 years	Not otherwise specified (NOS)	Spindled with embryonal-like areas	Unidentified		
Pleomorphic	50–60 years	Deep soft tissue of extremity	Large, atypical cells	Complex karyotype	Complex sarcomas	Poor

[a] Fusion positive and negative refers to *FOXO1* rearrangement.

Rhabdomyosarcoma Classification: Refining Our Understanding

Ashlie et al. Surgical Pathology 18 (2025) 301–311

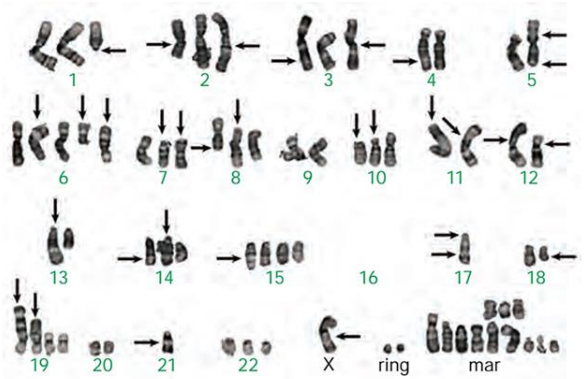
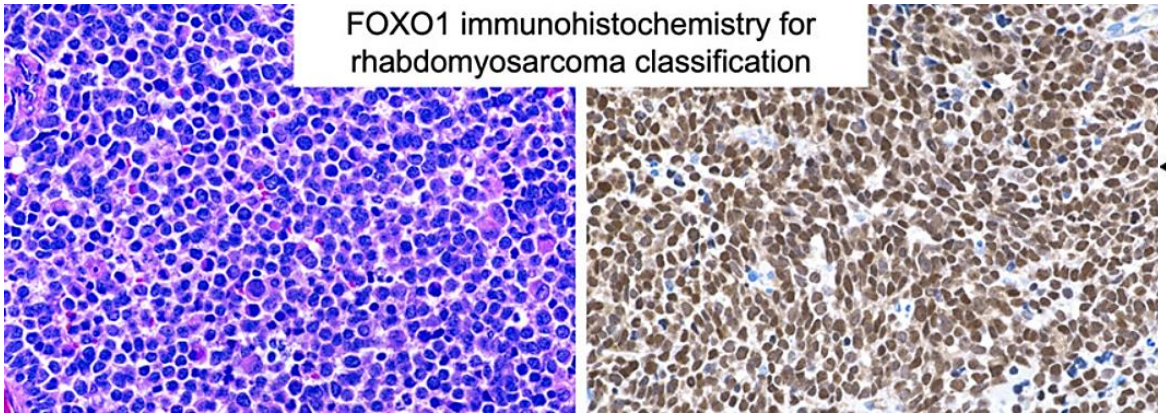
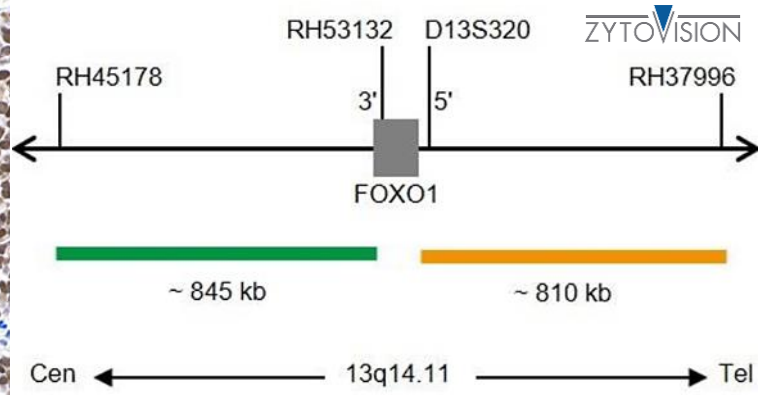
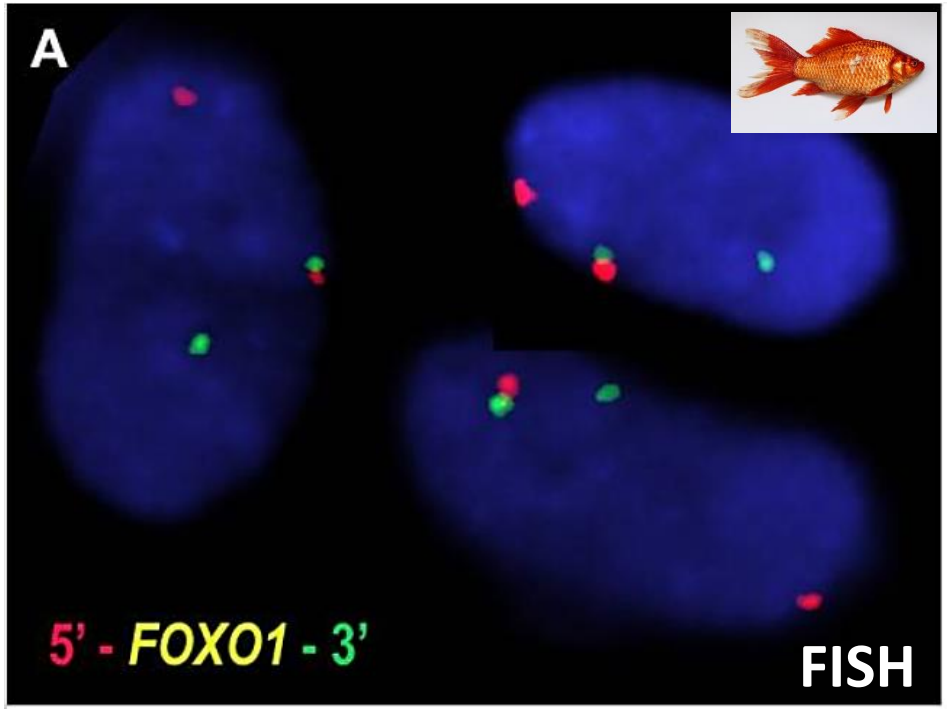
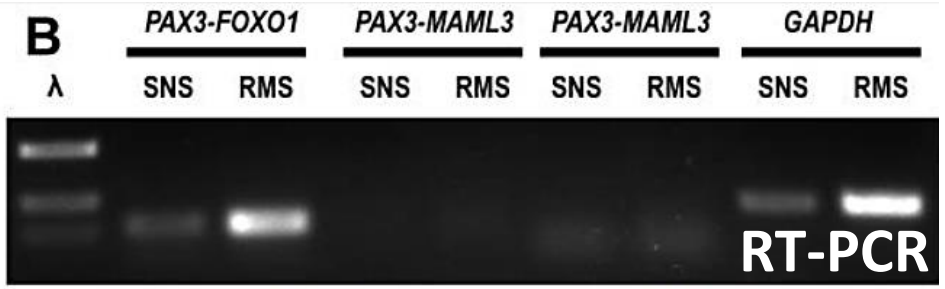


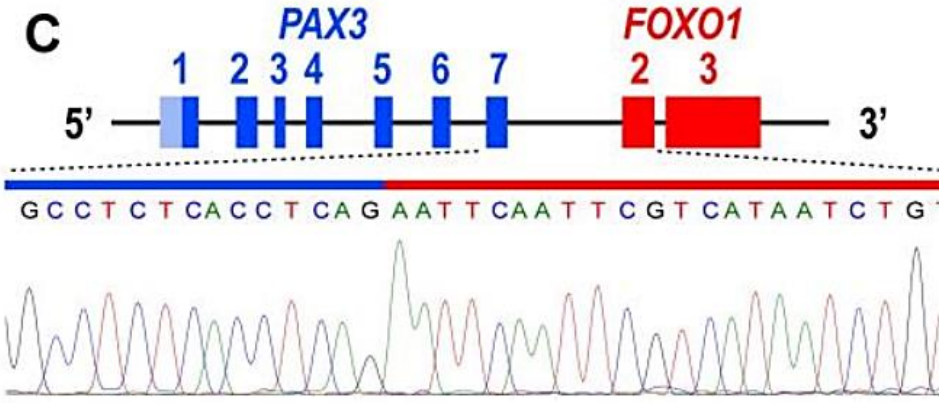
Figure 18.1 **Complex Karyotype.** This karyotype from an undifferentiated pleomorphic sarcoma shows numerous cytogenetic aberrations characteristic of sarcomas with complex cytogenetic features. (Courtesy Dr. Andre Oliveira, Mayo Clinic, Rochester, MN.)











Rutland et al. Histopathology. 2023 Jul;83(1):49-56
Wong et al. Genes Chromosomes Cancer. 2015 Sep 10;55(1):25–29

Undifferentiated sarcomas

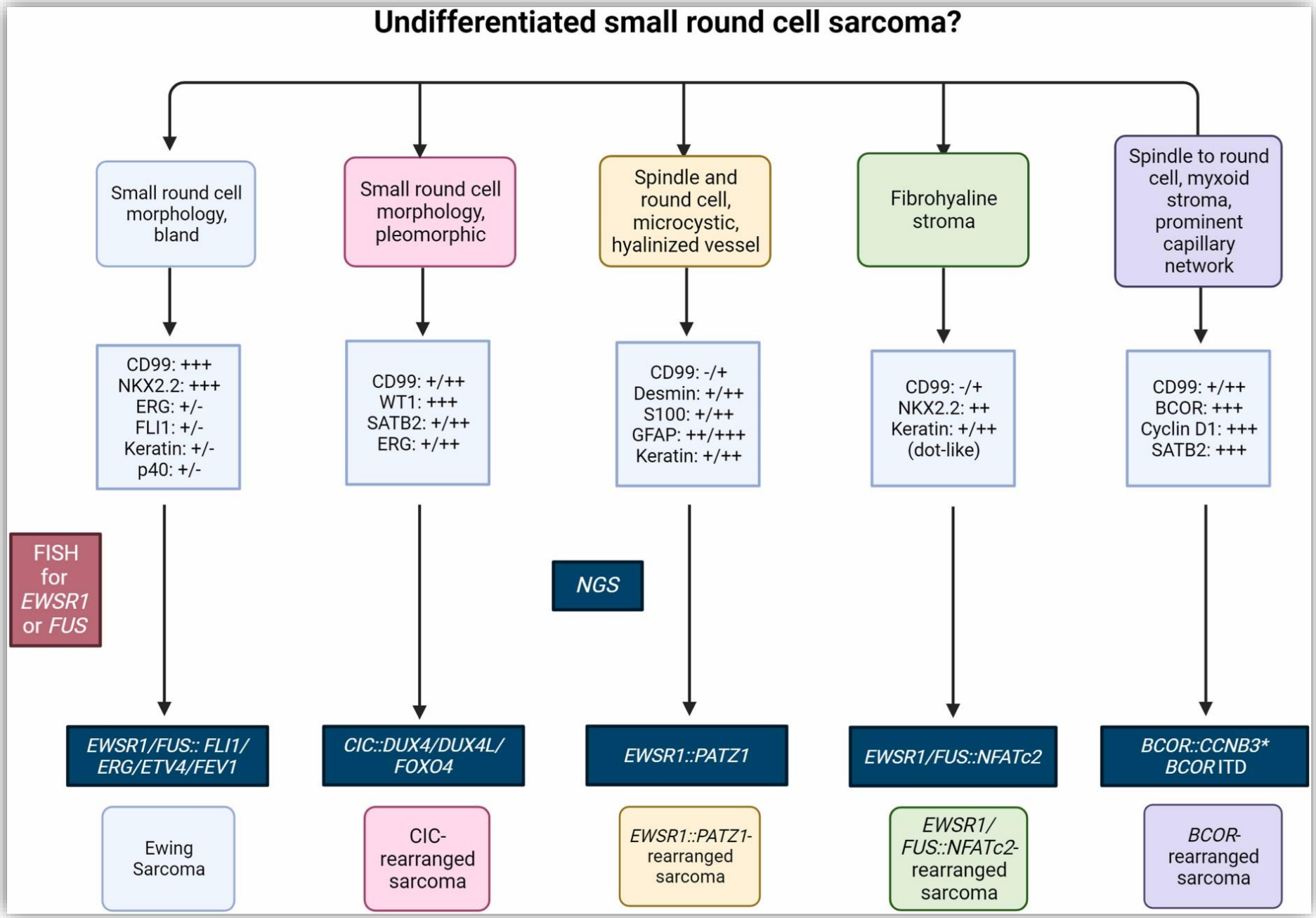
Undifferentiated small round cell sarcomas of soft tissue and bone

Ewing sarcoma

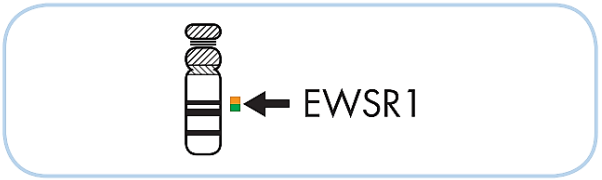
Round cell sarcoma with *EWSR1*::non-ETS fusions

CIC-rearranged sarcoma

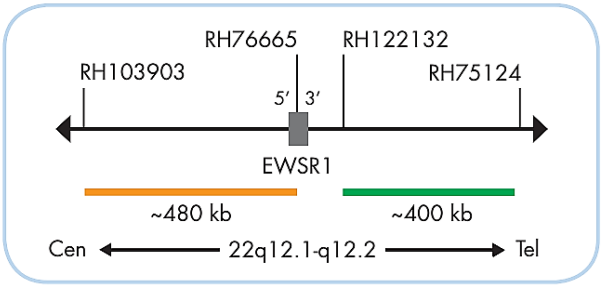
Sarcoma with *BCOR* genetic alterations



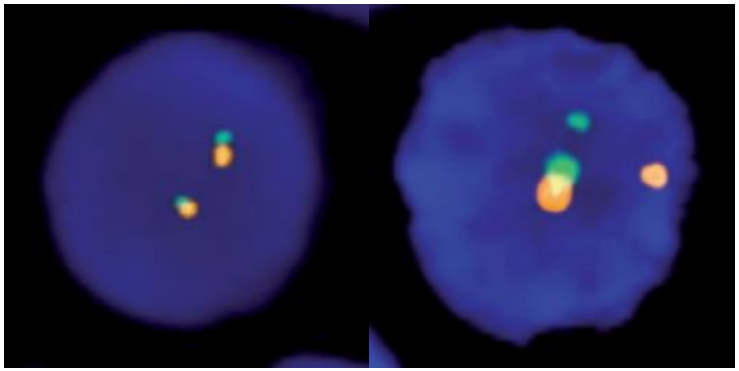
Updates on WHO classification for small round cell tumors: Ewing sarcoma vs. everything else
Dehner et al. Hum Pathol. 2024 May:147:101-113



Ideogram of chromosome 22 indicating the hybridization locations.



SPEC EWSR1 Probe map (not to scale).



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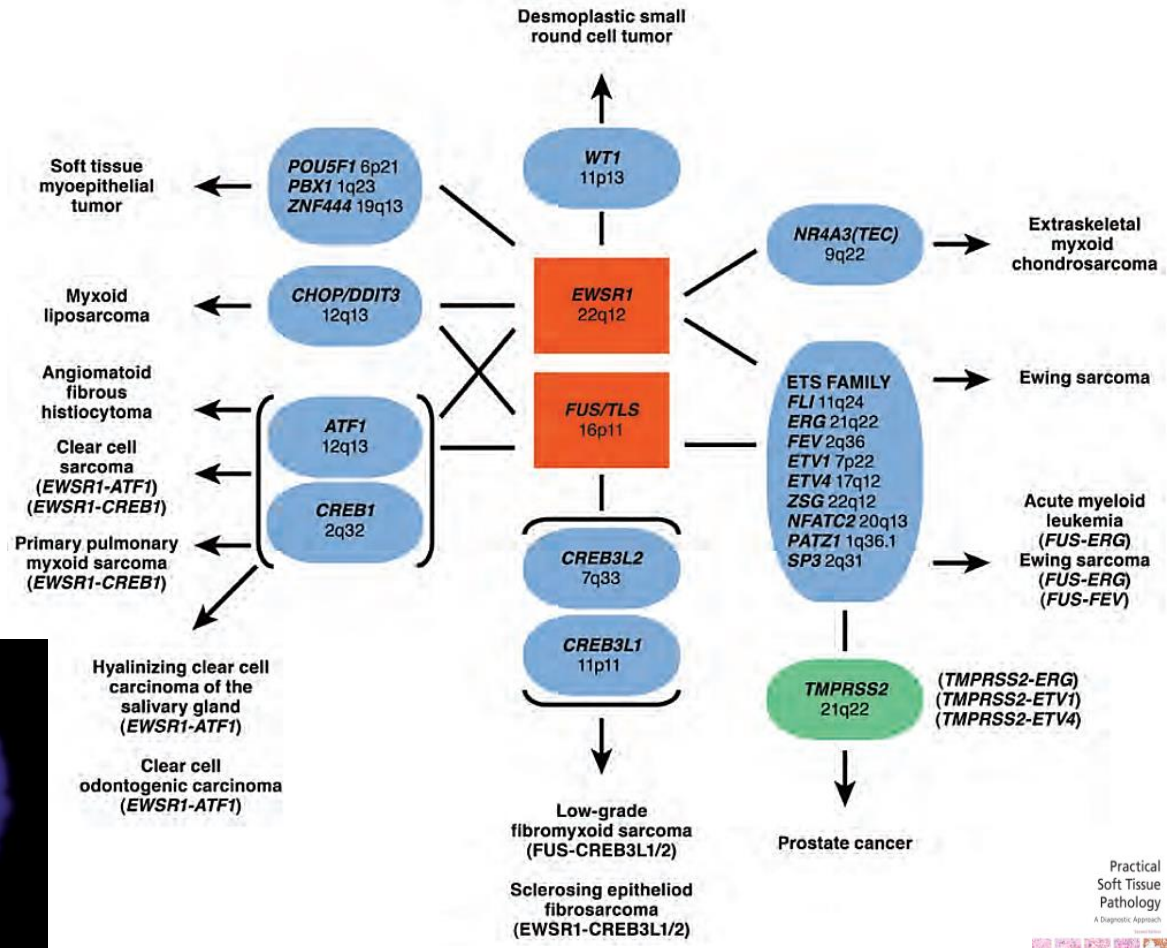
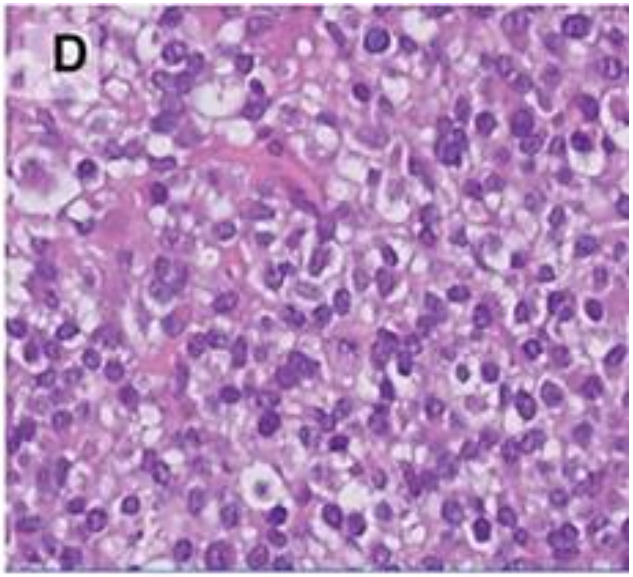
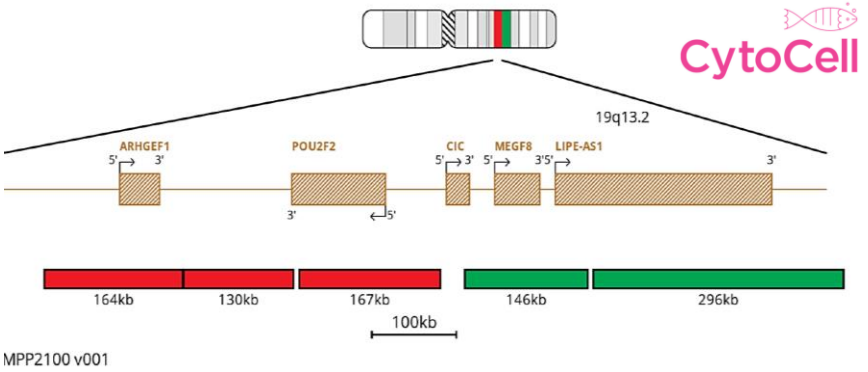
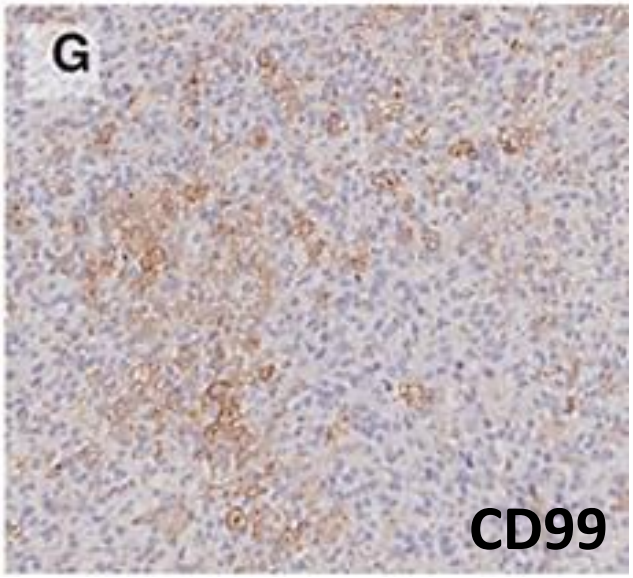
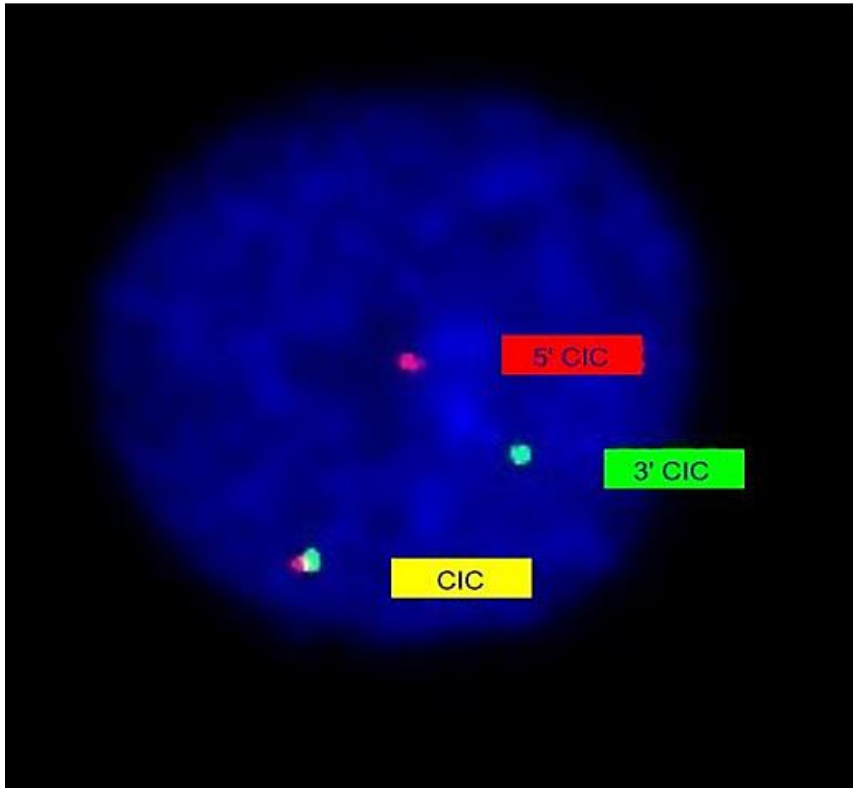


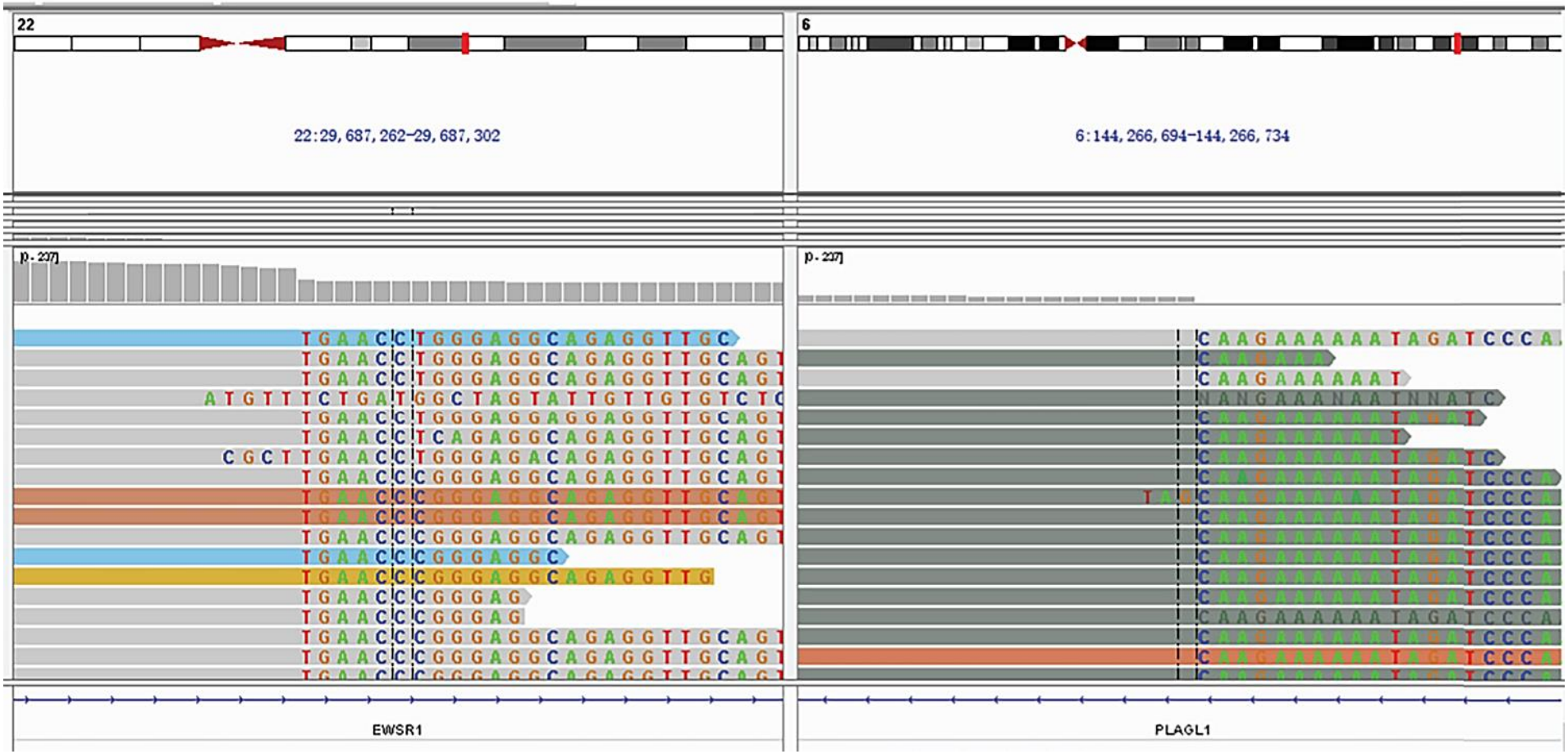


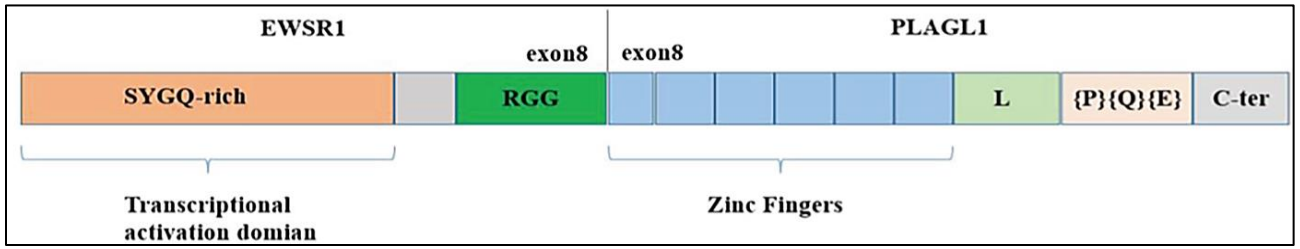




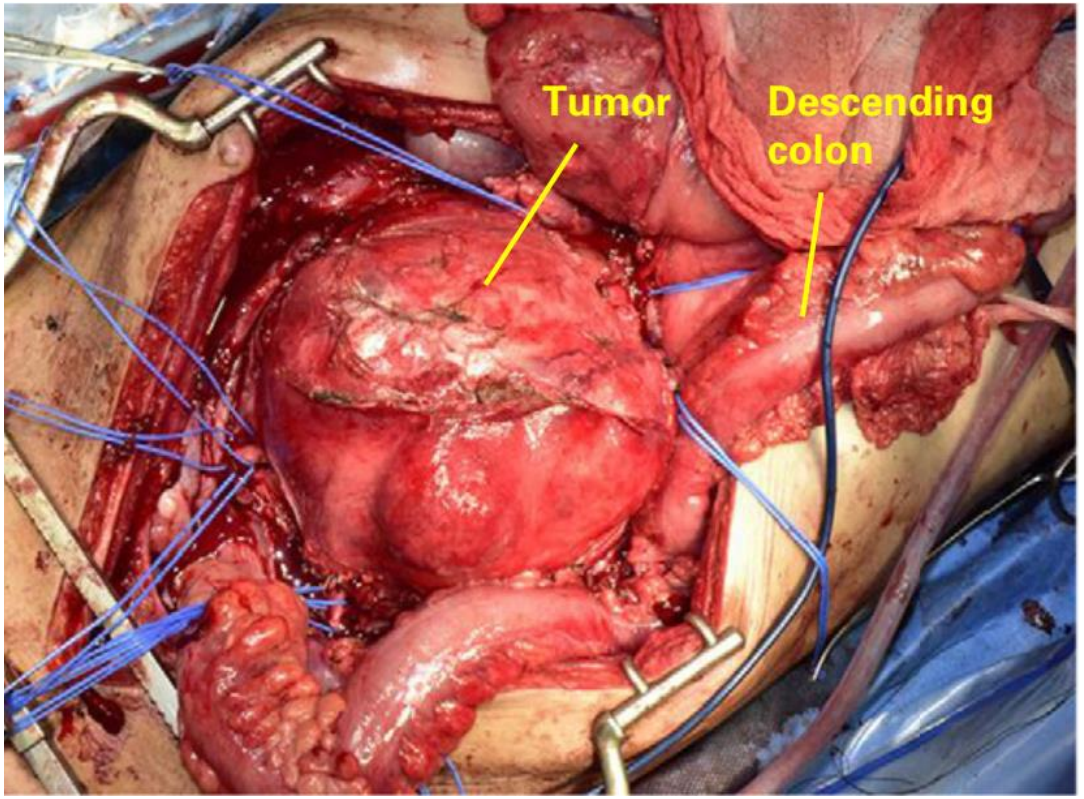


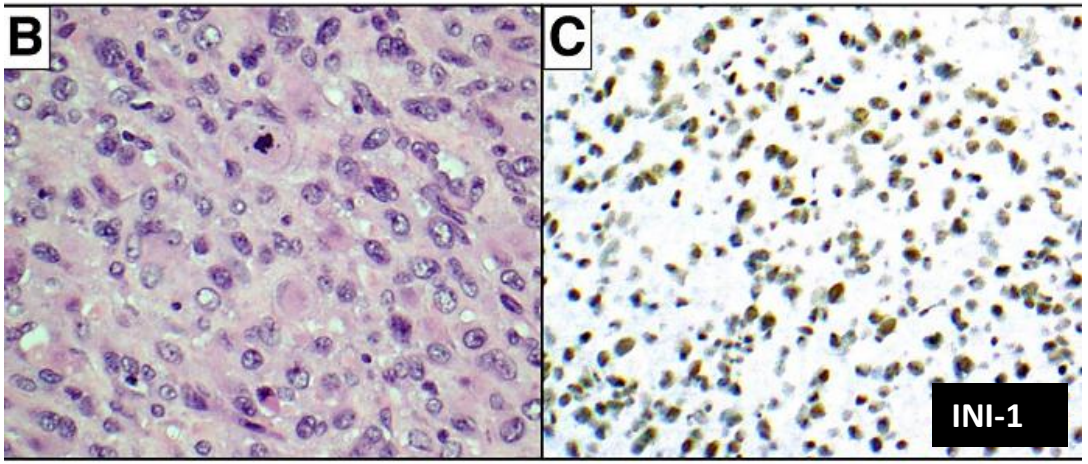
Pfister et al. Cancer Discov (2022) 12 (2): 331–355
Silva et al. BMC Cancer (2024) 24:1428





Xing et al. Front. Oncol. 12:938385





Wu, et al. ASCO. Precision Oncology. 2018

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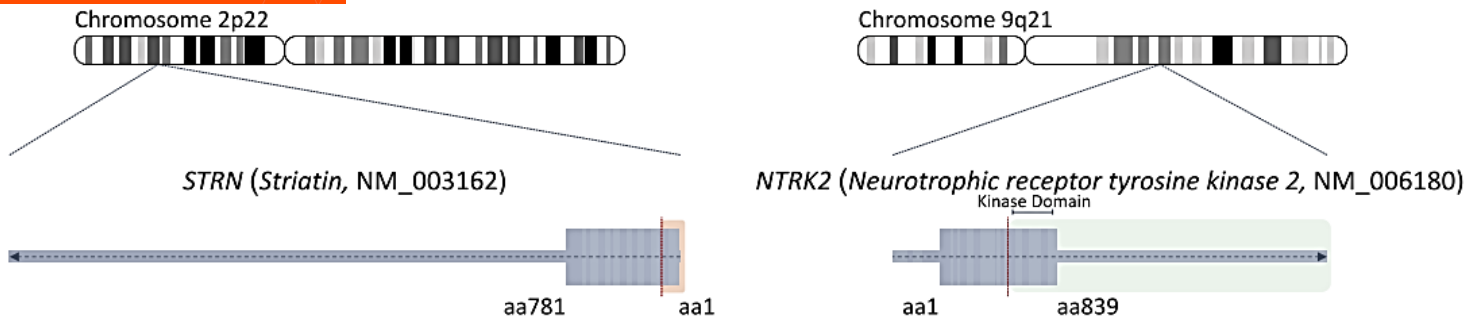
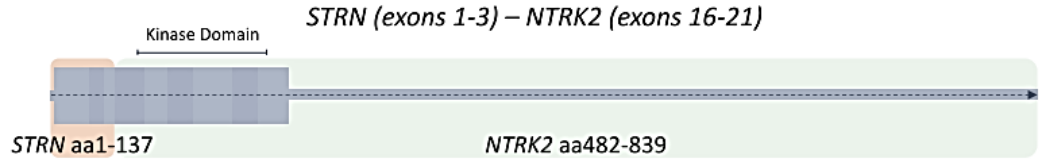
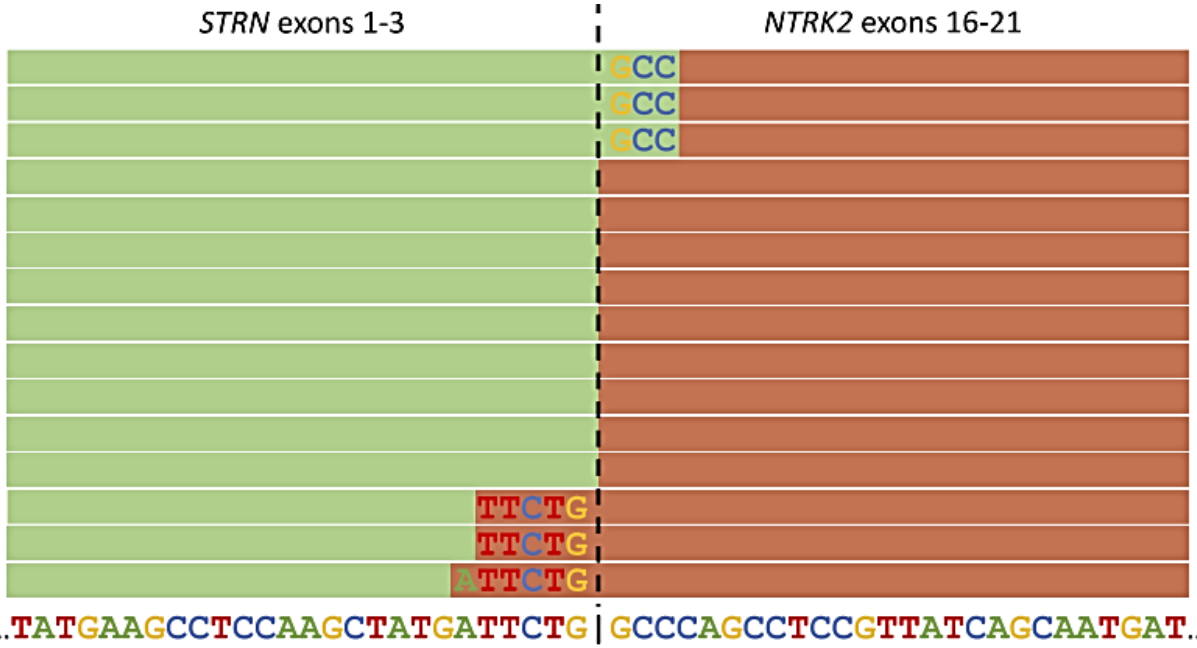
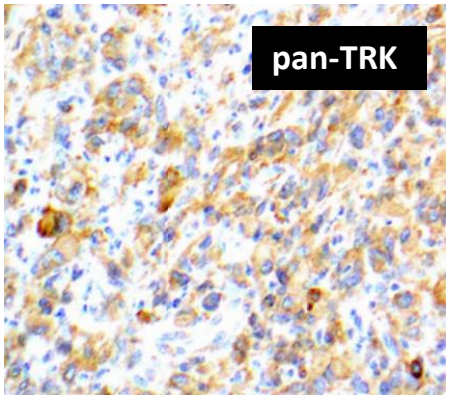


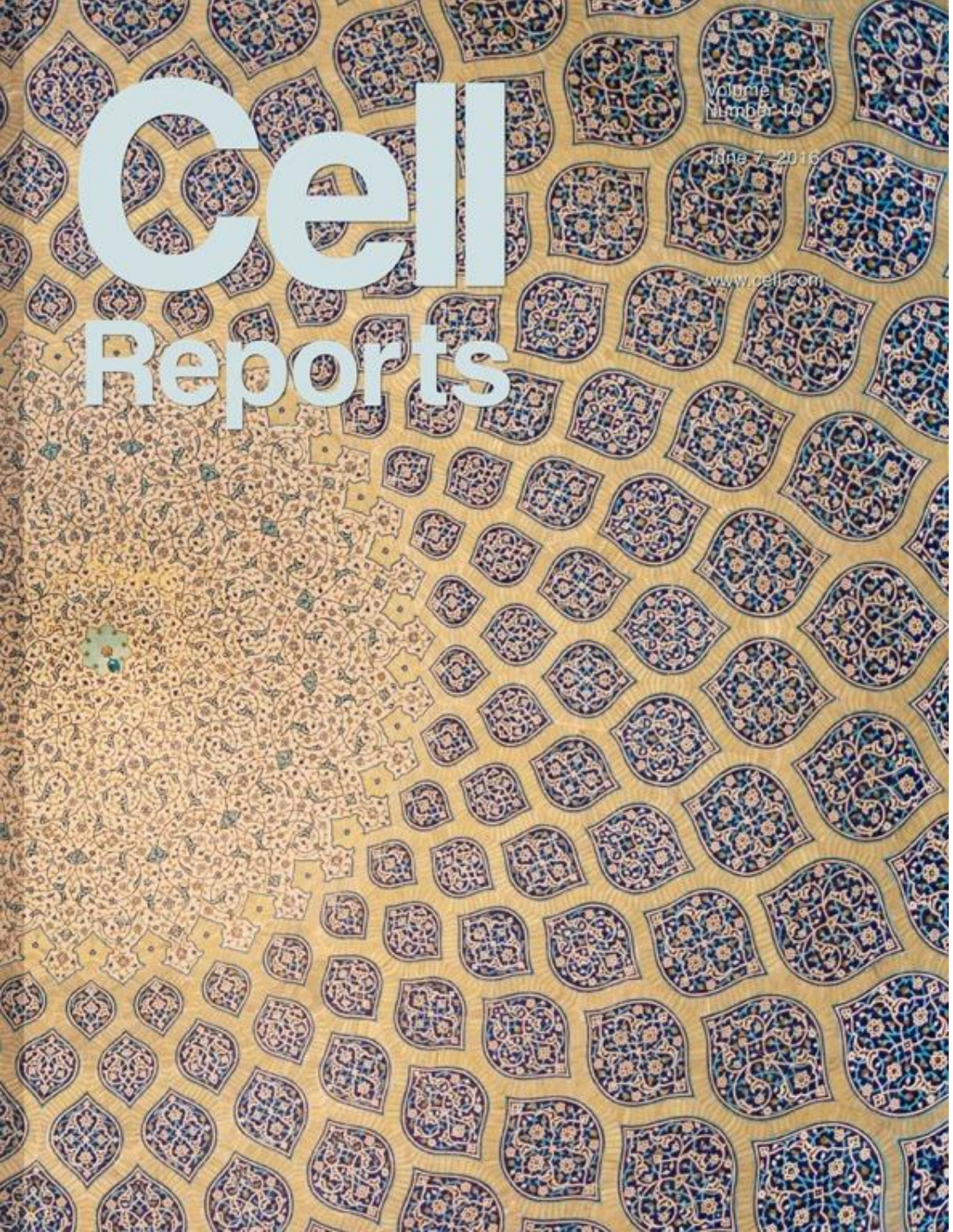






Durable Clinical Response to Larotrectinib in an Adolescent Patient With an Undifferentiated Sarcoma Harboring an *STRN-NTRK2* Fusion

Wu, et al. ASCO. Precision Oncology. 2018



On the cover: **Neighboring neurons can form non-overlapping dendrite arbors, a phenomenon known as dendrite tiling.** Yip and Heiman show that dendrite tiling could have evolved as the serendipitous byproduct of pre-existing mechanisms for dendrite patterning. **The photo shows the intricate tiling of the Sheikh Lotfollah Mosque in Isfahan, Iran.** Photo by Candice Yip.