Molecular In My Pocket™...

ONCOLOGY: *Diagnostic Biomarkers in Bone & Soft Tissue Tumors – Part I*

Differentiation	Entity	Gene(s)	Type	Assays	Notes
Adipocytic	Lipoma	*HMGA2, HMGA1*	Fusion	FISH, NGS	*HMGA2* rearrangements are not specific
	Angiolipoma	*PRKD2, PIK3CA*	Mutation (activating)	NGS, PCR	
	Spindle cell/pleomorphic lipoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Hibernoma	*MEN1, AIP*	Codeletion/Loss	FISH	11q13
	Lipoblastoma	*PLAG1* (70%), *HMGA2* (10%)	Fusion	FISH, NGS	Multiple different fusion partners
	Chondroid lipoma	*ZFTA::MRTFB*	Fusion	FISH, NGS, RT-PCR	
	Atypical lipomatous tumor Well-differentiated liposarcoma Dedifferentiated liposarcoma	*MDM2*	Amplification	IHC, FISH, NGS	*MDM2, CDK4, HMGA2, GLI1* (12q14-15) often coamplified
	Myxoid liposarcoma	*FUS::DDIT3*	Fusion	FISH, NGS, RT-PCR	*EWSR1::DDIT3* in <5%; *TERT* promoter mutations in 60%
Fibrohistiocytic	Tenosynovial giant cell tumor	*CSF1*	Fusion	FISH, NGS	Only rare neoplastic cells. CSF1R targeted therapy available (1)
	Deep benign fibrous histiocytoma	*PRKCB, PRKCD*	Fusion	FISH, NGS	
(Myo)Fibroblastic	Nodular fasciitis*	*USP6*	Fusion	FISH, NGS	*MYH9* most common partner
	Fibrous hamartoma of infancy	*EGFR*	Exon 20 insertion	NGS, PCR	
	Desmoplastic fibroblastoma	*FOSL1, FOS* (less common)	Fusion	IHC, FISH	IHC: Strong, diffuse nuclear FOSL1
	Myofibroblastoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Cellular angiofibroma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Superficial acral fibromyxoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Calcifying aponeurotic fibroma	*FN1::EGF*	Fusion	NGS, RT-PCR	
	EWSR1::SMAD3 fibroblastic tumor (emerging)	*EWSR1::SMAD3*	Fusion	FISH, NGS, RT-PCR	
	Superficial CD34+ fibroblastic tumor	*PRDM10*	Fusion	FISH, NGS	Emerging data; partners: *MED12, CITED2*
	Angiofibroma of soft tissue	*AHRR::NCOA2*	Fusion	NGS, RT-PCR	Less common: *AHRR::NCOA3*, other rare fusions
	Desmoid-type fibromatosis	*CTNNB1* (sporadic)	Mutation (activating)	NGS, IHC, PCR	IHC: Nuclear staining
		APC (FAP-related)	Mutation (LOF)	NGS	
	Lipofibromatosis	*EGF, EGFR, ROS1, RET, PDGFRB,* others	Fusion	NGS, FISH	Several fusions, including *EGFR* and EGFR ligands, receptor tyrosine kinases (*FN1::EGF* most common)
	Giant cell fibroblastoma	*COL1A1::PDGFB*	Fusion	FISH, NGS, RT-PCR	
	Dermatofibrosarcoma protuberans	*COL1A1::PDGFB*	Fusion	FISH, NGS, RT-PCR	>95%; *PDGFD* fusion in remaining cases. Tyrosine kinase inhibitor therapy available (1)
	Solitary fibrous tumor	*NAB2::STAT6*	Fusion	IHC, NGS, RT-PCR	
	Inflammatory myofibroblastic tumor	*ALK*	Fusion	FISH, IHC, NGS	~50-60%; 5-10% each *ROS1* or *NTRK3* fusion, rare cases with *RET*, *PDGFRB* fusion. ALK- and NTRK-targeted therapy available (1)
	Congenital/Infantile fibrosarcoma	*ETV6::NTRK3*	Fusion	FISH, NGS, RT-PCR	*BRAF, NTRK1, NTRK2, MET* fusions in minor subset. NTRK-targeted therapy available (1)
	Low-grade fibromyxoid sarcoma (LGFMS)**	*FUS::CREB3L2*	Fusion	FISH, IHC, NGS, RT-PCR	IHC: MUC4 positive Rare cases with *FUS::CREB3L1, EWSR1::CREB3L1*

Differentiation	Entity	Gene(s)	Type	Assays	Notes
(Myo)Fibroblastic (cont.)	Sclerosing epithelioid fibrosarcoma (SEF)**	*EWSR1::CREB3L1* (>60%) *FUS::CREB3L2*	Fusion	FISH, IHC, NGS, RT-PCR	IHC: MUC4 positive; *YAP1, KMT2A* fusions in a MUC4-negative subset showing overlap between LGFMS and SEF
Pericytic	Myopericytoma/myofibroma	*PDGFRB*	Mutation	NGS	
		SRF::RELA	Fusion	NGS, FISH, RT-PCR	Cellular/atypical myofibroma
	Glomus tumor	*NOTCH1/2/3*	Fusion	NGS	*CARMN::NOTCH1/2/3* (70-80%)
		BRAF, KRAS	Mutation	NGS, PCR	Small subset
Skeletal Muscle	Alveolar rhabdomyosarcoma	*PAX3::FOXO1* (70%) *PAX7::FOXO1* (20%)	Fusion	FISH, NGS, RT-PCR	
	Spindle cell/sclerosing rhabdomyosarcoma	*VGLL2, SRF, TEAD1, NCOA2, CITED2*	Fusion	FISH, NGS	Infantile cases (<1 year)
		MYOD1	Mutation (p.L122R)	NGS, PCR	Adolescents/young adults
		EWSR1::TFCP2, FUS::TFCP2, MEIS1::NCOA2	Fusion	FISH, NGS	Intraosseous spindle cell rhabdomyosarcoma
Vascular	Anastomosing hemangioma	*GNAQ, GNA14*	Mutation (activating)	NGS, PCR	
	Epithelioid hemangioma	*FOS, FOSB*	Fusion	FISH, NGS	
	Pseudomyogenic hemangioendothelioma	*FOSB*	Fusion	FISH, NGS	*SERPINE1* and *ACTB* are common partners
	Epithelioid hemangioendothelioma	*WWTR1::CAMTA1* (>90%) *YAP1::TFE3*	Fusion	FISH, IHC, NGS, RT-PCR	IHC: CAMTA1, TFE3 (depending on fusion)
GIST	Sporadic GIST	*KIT, PDGFRA*	Mutation (activating)	NGS, PCR	75% *KIT* mutant, 10% *PDGFRA* mutant. Tyrosine kinase inhibitor therapy available (2)
	Succinate dehydrogenase-deficient GIST	*SDHA, SDHB, SDHC, SDHD*	Mutation (LOF)	NGS, IHC	5-10% of cases, IHC: SDHB negative
Peripheral Nerve	Neurofibroma	*NF1*	Mutation (LOF)	NGS	Targeted kinase-inhibitor therapy available for patients with germline neurofibromatosis type I
	Schwannoma	*NF2*	Mutation (LOF)	NGS	50-75% of sporadic
		SH3PXD2A::HTRA1	Fusion	NGS	~10%
	Granular cell tumor	*ATP6AP1*	Mutation (LOF)	NGS	*ATP6AP2* in a subset
	Malignant peripheral nerve sheath tumor	*EED, SUZ12*	Mutation (LOF)	NGS, IHC	*80%; IHC: H3K27me3 negative (lost)*

**USP6* fusions with various partners have also been reported in proliferative fasciitis/myositis, cranial fasciitis, myositis ossificans, fibroma of tendon sheath, and fibro-osseous pseudotumor of digit; all are thought to be related entities.
** Some cases show morphologic overlap between low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma; these cases generally show *FUS::CREB3L2* fusions.

Note: Not all of the biomarkers above are diagnostically useful currently, and none (with rare exceptions) are completely specific.

Abbreviations: FISH: fluorescence *in situ* hybridization, GIST: gastrointestinal stromal tumor, IHC: immunohistochemistry, LOF: loss-of-function, NGS: next-generation sequencing, PCR: polymerase chain reaction, RT-PCR: reverse transcriptase polymerase chain reaction, RTK: receptor tyrosine kinase

***References*:**

1. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Soft Tissue Sarcoma Version 1.2024– April 26,2024 NCCN.org. *accessed 7/26/2024*
2. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Gastrointestinal Stromal Tumors Version 1.2024 — March 8, 2024, NCCN.org. *accessed 7/26/2024*.