Molecular In My Pocket™…

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

Differentiation	Entity	Gene(s)	Type	Assays	Notes
Peripheral Nerve	Neurofibroma	*NF1*	Mutations (LOF)	NGS	Targeted kinase-inhibitor therapy available for patients with germline Neurofibromatosis Type I.
	Schwannoma	*NF2*	Mutations (LOF)	NGS	
	Granular cell tumor	*ATP6AP1*	Mutations (LOF)	NGS	*ATP6AP2* in a subset
	Malignant peripheral nerve sheath tumor	*EED, SUZ12*	Mutations (LOF)	NGS, IHC	80%; IHC: H3K27me3 negative
Uncertain Differentiation	Intramuscular myxoma	*GNAS*	Mutations (activating)	NGS	>90%
	Deep angiomyxoma	*HMGA2*	Rearrangements	FISH, IHC, NGS	IHC: HMGA2 nuclear expression
	Angiomatoid fibrous histiocytoma	*EWSR1-CREB1*	Fusions	FISH, NGS, RT-PCR	*FUS-ATF1* or *EWSR1-ATF1* in <10%
	Ossifying fibromyxoid tumor	*PHF1*	Fusions	NGS, NGS	*EP400* is most common partner. Alternate fusions in *BCOR, BCORL1, WWTR1* have been reported
	Soft tissue myoepithelial tumor	*EWSR1*	Fusions	FISH, NGS	~50%; *POU5F1* is most common partner, but many others reported. *FUS* instead of *EWSR1* in 10-20%.
	Soft tissue mixed tumor	*PLAG1*	Fusions	FISH, NGS	
	Hemosiderotic fibrolipomatous tumor	*TGFBR3, OGA*	Rearrangements	FISH	85%; Leads to overexpression of *FGF4* and *NPM3*
	Phosphaturic mesenchymal tumor	*FN1-FGFR1*	Fusions	FISH, NGS	50-60%, *FN1-FGF1* in rare cases
	Synovial sarcoma	*SS18-SSX1*	Fusions	FISH, NGS, RT-PCR	*SS18-SSX2* also common, rarely *SS18-SSX4*
	Epithelioid sarcoma	*SMARCB1*	Loss	IHC, NGS	IHC: INI-1 loss. EZH2-inhibitor therapy available (1)
	Extrarenal rhabdoid tumor	*SMARCB1*	Loss	IHC, NGS	IHC: INI-1 loss
	Alveolar soft part sarcoma	*ASPSCR1-TFE3*	Fusions	FISH, IHC, NGS	IHC: Nuclear TFE3
Uncertain Differentiation	Clear cell sarcoma of soft tissue	*EWSR1-ATF1*	Fusions	FISH, NGS	*EWSR1-CREB1* in a subset
	Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	Fusions	FISH, NGS	*TAF15-NR4A3* in a subset
	Desmoplastic small round cell tumor	*EWSR1-WT1*	Fusions	FISH, IHC, NGS	IHC: C-terminal WT1 positive
	PEComa	*TSC2*	Mutations (LOF)	NGS	
		TFE3	Fusions	FISH, IHC, NGS	*SFPQ* is most common partner, but others reported
	Intimal sarcoma	*MDM2*	Amplification	FISH, NGS	
Undifferentiated Small Round Cell Sarcomas	Ewing sarcoma	*EWSR1-FLI1*	Fusions	FISH, NGS	*EWSR1-ERG* in ~10%, many other variant fusions reported
	Sarcoma with *EWSR1*-non-ETS fusions	*EWSR1-NFATC2*	Fusions	FISH, NGS	*FUS-NFATC2* in a subset
		EWSR1-PATZ1	Fusions	FISH, NGS	
	CIC-rearranged sarcoma	*CIC-DUX4*	Fusions	FISH, NGS	*CIC* with *FOXO4, LEUTX, NUTM1,* or *NUTM2A* rarely
	Sarcoma with *BCOR* alterations	*BCOR-CCNB3*	Fusions	FISH, IHC, NGS	IHC: CCNB3+
		BCOR	ITD	NGS, IHC	Infantile, rare cases with *YWHAE-NUTM2B*

Cartilage	Subungual exostosis	*IRS4*	Rearrangements		Possibly upregulates *IRS4* expression, breaks at *COL12A1* and *COL4A5*
	Enchondroma	*IDH1*	R132 mutations	NGS, PCR	*IDH2* R172 mutations less common
	Osteochondroma	*EXT1, EXT2*	Mutations (LOF)		Bilallelic inactivation
	Chondroblastoma	*H3F3B*	K36M	NGS, IHC	95%; IHC K36M-specific antibody
	Chondromyxoid fibroma	*GRM1*	Rearrangements		Highly upregulated expression often due to promoter swapping
	Synovial chondromatosis	*FN1-ACVR2A ACVR2A-FN1*	Fusions	FISH, NGS	
	Central chondrosarcoma	*IDH1*	R132 mutations	NGS, PCR	*IDH2* R172 mutations less common. IDH1-inhibitor therapy available (2)
	Mesenchymal chondrosarcoma	*HEY1-NCOA2*	Fusions	NGS, FISH	
Bone	Osteoid osteoma/osteoblastoma	*FOS*	Rearrangements	NGS, FISH	*FOSB* rearrangements less common
	Low-grade central osteosarcoma Parosteal osteosarcoma	*MDM2*	Amplification	FISH, IHC, NGS	
Other	Simple bone cyst	*EWSR1-NFATC2*	Fusions	NGS, FISH	Emerging data; also *FUS-NFATC2*
	Aneurysmal bone cyst	*CDH11-USP6*	Fusions	NGS, FISH	Many other partners reported
	Giant cell tumor of bone	*H3F3A*	G34W	NGS, IHC	90%, most of the rest have other G34 mutations
	Nonossifying fibroma	*KRAS, FGFR1*	Mutations (activating)	NGS	>80%
	Fibrous dysplasia	*GNAS*	R201 mutations	NGS	
Histiocytic	Langerhans cell histiocytosis	*BRAF*	V600E	NGS, PCR, IHC	Less commonly *MAP2K1*. Multiple targeted therapy options, dependent on alteration (3)
	Erdheim-Chester disease	*BRAF*	V600E	NGS, PCR, IHC	50-60%; also *KRAS, NRAS, ARAF, MAP2K1* in some. Multiple targeted therapy options, dependent on alteration (3)
	Rosai-Dorfman disease	MAPK pathway	Mutations (activating)	NGS, PCR, IHC	*BRAF, KRAS, NRAS, MAP2K1, ARAF*. Multiple targeted therapy options, dependent on alteration (3)
Emerging	Lipofibromatosis/lipofibromatosis-like neural tumor	*NTRK1, NTRK3*		FISH, IHC, NGS	Also reported: *RET, NTRK2, ROS1, ALK, MET, PDGFRB, BRAF*. NTRK-targeted therapy available
	S100+/CD34+ spindle cell neoplasms	*NTRK1, NTRK2, NTRK3*	Fusions	FISH, IHC, NGS	Similar *NTRK*-rearranged tumors are seen in the uterus as well as soft tissue. NTRK-targeted therapy available
	Round cell tumors with variable malignant potential and SMA expression	*ACTB-GLI1*	Fusions	FISH, NGS	Thought to be pericytomas originally
	ALK-positive histiocytosis	*KIF5B-ALK*	Fusions	FISH, IHC, NGS	

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, ITD: internal tandem duplication, LOF: loss-of-function, NGS: next-generation sequencing, PCR: polymerase chain reaction, RT-PCR: reverse transcriptase polymerase chain reaction, RTK: receptor tyrosine kinase

1. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Soft Tissue Sarcoma Version 2.2022 – May 17, 2022 NCCN.org. *accessed 6/27/2022*
2. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Bone Cancer Version 2.2022 – October 8, 2021 NCCN.org. *accessed 6/27/2022*
3. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Histiocytic Neoplasms Version 1.2022 – May 20, 2022 NCCN.org. *accessed 6/27/2022*