Molecular In My Pocket™...

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

Differentiation	Entity	Gene(s)	Type	Assays	Notes
Uncertain Differentiation	Intramuscular myxoma	*GNAS*	Mutation (activating)	NGS	>90%
	Deep angiomyxoma	*HMGA2*	Rearrangement	FISH, IHC, NGS	IHC: HMGA2 nuclear expression
	Angiomatoid fibrous histiocytoma	*EWSR1::CREB1*	Fusion	FISH, NGS, RT-PCR	*FUS::ATF1* or *EWSR1::ATF1* in <10%
	Ossifying fibromyxoid tumor	*PHF1*	Fusion	NGS	*EP400* is most common partner. Alternate fusions in *MEAF6, TFE3,* others have been reported
	Soft tissue myoepithelial tumor	*EWSR1*	Fusion	FISH, NGS	~50%; *POU5F1* and *PBX1* are most common partners. *FUS* instead of *EWSR1* in 10-20%
		PLAG1	Fusion	FISH, NGS	Mixed tumors with ductal differentiation
	Hemosiderotic fibrolipomatous tumor Pleomorphic hyalinizing angiectatic tumor	*TGFBR3, OGA*	Rearrangement	FISH	85%. Leads to overexpression of *FGF8* and *NPM3*
	Phosphaturic mesenchymal tumor	*FN1::FGFR1*	Fusion	FISH, NGS	50-60%; *FN1::FGF1* in rare cases
	NTRK-rearranged spindle cell neoplasm	*NTRK1, NTRK2, NTRK3*	Fusion	FISH, NGS	Most tumors harbor *NTRK1* fusions with a variety of partners
	Synovial sarcoma	*SS18::SSX1, SS18::SSX2*	Fusion	FISH, NGS, RT-PCR	Rarely *SS18::SSX4*
	Epithelioid sarcoma	*SMARCB1*	Loss	IHC, NGS	IHC: INI1 loss. EZH2-inhibitor therapy available (1)
	Extrarenal rhabdoid tumor	*SMARCB1*	Loss	IHC, NGS	IHC: INI1 loss
	Alveolar soft part sarcoma	*ASPSCR1::TFE3*	Fusion	FISH, IHC, NGS	IHC: Nuclear TFE3
	Clear cell sarcoma of soft tissue	*EWSR1::ATF1*	Fusion	FISH, NGS	70-90%; *EWSR1::CREB1* in a subset
	Extraskeletal myxoid chondrosarcoma	*EWSR1::NR4A3*	Fusion	FISH, NGS	*TAF15::NR4A3* in a subset
	Desmoplastic small round cell tumor	*EWSR1::WT1*	Fusion	FISH, IHC, NGS	IHC: C-terminal WT1 positive
	PEComa	*TSC2*	Mutation (LOF)	NGS	
		TFE3	Fusion	FISH, IHC, NGS	*SFPQ* is most common partner, but others reported
	Intimal sarcoma	*MDM2*	Amplification	FISH, NGS, IHC	IHC: MDM2 positive
	GLI1-altered mesenchymal tumor (emerging)	*GLI1*	Fusion	FISH, NGS	*ACTB* is typical fusion partner; Originally thought to be pericytomas
Undifferentiated Small Round Cell Sarcomas	Ewing sarcoma	*EWSR1::FLI1*	Fusions	FISH, NGS	~85%; *EWSR1::ERG* in ~10%, other variant fusions reported
	Sarcoma with *EWSR1*-non-ETS fusion	*EWSR1::NFATC2*	Fusion	FISH, NGS	*FUS::NFATC2* in a subset
		EWSR1::PATZ1	Fusion	FISH, NGS	
	CIC-rearranged sarcoma	*CIC::DUX4*	Fusion	FISH, NGS	95%; rarely *CIC* fused with *FOXO4, LEUTX, NUTM1,* or *NUTM2A*
	Sarcoma with *BCOR* alteration	*BCOR::CCNB3*	Fusion	FISH, IHC, NGS	IHC: BCOR, CCNB3 positive
		BCOR	ITD	NGS, IHC	Infants; rare cases with *YWHAE::NUTM2B*

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Cartilage	Subungual exostosis	*IRS4*	Rearrangement	FISH	Possibly upregulates *IRS4* expression; breakpoints in *COL12A1* and near *IRS4*
	Enchondroma	*IDH1*	Mutation (p.R132)	NGS, PCR	~50%; *IDH2* p.R172 mutations less common
	Osteochondroma	*EXT1, EXT2*	Mutation (LOF)	NGS	Bilallelic inactivation
	Chondroblastoma	*H3-3B*	Mutation (p.K37M)	NGS, IHC	95%; Also called p.K36M. IHC: K37M-specific antibody
	Chondromyxoid fibroma	*GRM1*	Fusion	NGS	Upregulated expression due to promoter swapping
	Synovial chondromatosis	*FN1::ACVR2A*	Fusion	FISH, NGS	~60%
	Central chondrosarcoma	*IDH1*	Mutation (p.R132)	NGS, PCR	~50%. Usually IDH1 p.R132C; *IDH2* p.R172 mutations less common. IDH1 inhibitor therapy available (2)
	Mesenchymal chondrosarcoma	*HEY1::NCOA2*	Fusion	NGS, FISH, RT-PCR	~100%
Bone	Osteoid osteoma Osteoblastoma	*FOS*	Fusion	NGS, FISH, IHC	IHC: N-terminal FOS positive; *FOSB* rearrangement less common
	Low-grade central osteosarcoma Parosteal osteosarcoma	*MDM2*	Amplification	FISH, IHC, NGS	IHC: MDM2 positive
Other Mesenchymal Tumors of Bone	Simple bone cyst	*EWSR1::NFATC2*	Fusion	NGS, FISH	>40%; Also *FUS::NFATC2*
	Aneurysmal bone cyst	*USP6*	Fusion	NGS, FISH	~70%; *CDH11* most common fusion partner
	Giant cell tumor of bone	*H3-3A*	Mutation (p.G35W)	NGS, IHC	~90%; Also called p.G34W
	Non-ossifying fibroma	*KRAS, FGFR1*	Mutation (activating)	NGS	>80% of sporadic cases
	Fibrous dysplasia	*GNAS*	Mutation (activating)	NGS	~60%, most commonly p.R201H and p.R201C
Histiocytic	Langerhans cell histiocytosis	*BRAF*	Mutation (p.V600E)	NGS, PCR, IHC	~50%; Less commonly *MAP2K1*. Multiple targeted therapy options, depending on alteration (3)
	Erdheim-Chester disease	*BRAF*	Mutation (p.V600E)	NGS, PCR, IHC	50-60%; also *KRAS, NRAS, ARAF, MAP2K1* in some. Multiple targeted therapy options, depending on alteration (3)
	Rosai-Dorfman disease	MAPK pathway	Mutation (activating)	NGS, PCR, IHC	~40%; most commonly *KRAS, MAP2K1, NRAS, ARAF*. Multiple targeted therapy options, depending on alteration (3)
	ALK-positive histiocytosis (emerging)	*KIF5B::ALK*	Fusion	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, 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

References:

1. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Soft Tissue Sarcoma Version 1.2024– April 26,2024 NCCN.org. *accessed 7/29/2024*
2. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Bone Cancer Version 2.2024 – March 12, 2024 NCCN.org. *accessed 7/29/2024*
3. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Histiocytic Neoplasms Version 2.2024 – July 19, 2024 NCCN.org. *accessed 7/29/2024*

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