Molecular In My Pocket…

Solid Tumors (Sporadic)

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

AMP	Anchored Multiplex PCR	ISH	*In Situ* Hybridization	MMR	Mismatch Repair	TKI	Tyrosine Kinase Inhibitor
CA	Carcinoma	FISH	Fluorescence ISH	MSI	Microsatellite Instability		
CGX	Cytogenetics	GI	Gastrointestinal	NGS	Next-Generation Sequencing		
IHC	Immunohistochemistry	LOF	Loss of Function	SGA	Single Gene Assay		

Tissue Type	Disease	Gene	Common Genomic Variant(s)	Significance	Primary Assays
Tissue-Agnostic (pan-cancer FDA approval)	All Solid Tumors	MSI testing *MLH1*, *MSH2*, *MSH6*, *PMS2*	MSI-High, Low, or Stable MMR deficiency	responsiveness to immunotherapy	MSI testing, NGS IHC
	All Solid Tumors	Tumor mutation burden (TMB)	TMB-High, Low	responsiveness to immunotherapy	NGS (large panel)
	All Solid Tumors	*NTRK*	*NTRK1/2/3* rearrangements	responsiveness to NTRK inhibitors	NGS, AMP, FISH
	All Solid Tumors	*BRAF*	V600E	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
Adrenal	Neuroblastoma	*MYCN*	amplification	prognosis	FISH
Bile Duct	Cholangiocarcinoma	*IDH1*	mutations	responsiveness to IDH1 inhibitors	SGAs, NGS
Brain	Glioma / Glioblastoma	*IDH1/IDH2*	*IDH1* R132, IDH2 R172, R140	diagnosis	IHC, SGAs, NGS
		MYCN	amplification	prognosis	FISH
		TERT	promoter mutations	prognosis	SGAs, NGS
		1p / 19q	codeletion	diagnostic of oligodendroglioma phenotype	FISH, CGX, NGS
		ATRX	LOF	prognosis	IHC, SGAs, NGS
		MGMT	promoter methylation	responsiveness to alkylating agents	Methylation assay
		EGFR	amplification; vIII transcript	diagnosis	FISH, CGX, SGAs, NGS
	Pediatric Glioma	*H3F3A, HIST1H3B*	K27 mutations	diagnosis	
	Medulloblastoma	*WNT* pathway genes	*CTNNB1* mutations	diagnostic of subtype	SGAs, NGS
		SHH pathway genes	*PTCH1* LOF	diagnostic of subtype	SGAs, NGS
Breast	Breast CA	Estrogen Receptor (ER or *ESR1*)	expression	responsiveness to anti-estrogen	IHC, SGAs, NGS
		Progesterone Receptor (PR or *PGR*)	expression	responsiveness to anti-estrogen	IHC, SGAs, NGS
		ERBB2 (HER2)	amplification / overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC
		PIK3CA	E542, E545, H1045	responsiveness to PI3K inhibitor	SGAs, NGS
		BRCA1 / *BRCA2*	LOF	responsiveness to PARP inhibitor	SGAs, NGS
	Breast CA (Lobular)	*CDH1* (E-Cadherin)	LOF	diagnosis	IHC, SGAs, NGS
Cervix	Squamous cell CA	High-risk HPV	high risk virus, type 16, 18, other	diagnosis	IHC (p16), ISH, viral typing
Endometrium	Endometrial CA	MSI testing	MSI-High, Low, or Stable	response to immunotherapy	MSI testing, NGS
		MLH1, *MSH2*, *MSH6*, *PMS2*	LOF	response to immunotherapy	IHC
		MLH1	LOF and promoter hypermethylation	somatic etiology (not Lynch Syndrome)	Promoter methylation
		ERBB2 (HER2)	amplification / overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC
	Uveal Melanoma	*GNAQ*, *GNA11*	*GNAQ* / *GNA11* Q209L	diagnosis	SGAs, NGS
GI Tract	Gastrointestinal Stromal Tumor (GIST)	*KIT* (CD117)	exon 9 variants	responsiveness to TKIs, associated with 1' resistance	SGAs, NGS ***IHC not a proxy****
			exon 11 in-frame indels; D820; less frequently exons 8, 17	responsiveness to TKIs	
			exon 14	resistance to first-line TKIs	
			exon 13	responsiveness to TKIs as 1' variant; as 2' variant confers resistance to TKIs	
		PDGFRA	exon 12, 14, 18 variants	responsiveness to TKIs	SGAs, NGS
			exon 18 D842V	resistance to TKIs	
		SDHA, SDHB, SDHC, SDHD	LOF	resistance to TKIs, risk of hereditary cancer	SGAs, NGS, IHC for SDHB
GI Tract (Lower)	Colorectal CA	*KRAS*, *NRAS*	G12; G13; Q61	decreased responsiveness to panitumumab or cetuximab	SGAs, NGS
		BRAF (therapeutic setting)	exon 15, V600E	decreased responsiveness to panitumumab or cetuximab responsiveness to encorafenib + cetuximab	SGAs, NGS
		MSI testing	MSI-High, Low, or Stable	risk of hereditary cancer; prognosis, responsiveness to immunotherapy	MSI testing
		MLH1, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	LOF	risk of hereditary cancer; prognosis, responsiveness to immunotherapy	MMR IHC, NGS
		ERBB2 (HER2)	Amplification / overexpression	responsiveness to HER2 targeted therapy	IHC, FISH, NGS
	Colorectal CA (to differ from Lynch Syndrome)	*MLH1*	promoter methylation	somatic etiology	Methylation studies
		BRAF	exon 15, V600E	somatic etiology when MLH1 deficient/MSI-High	IHC, SGAs, NGS
Kidney	Translocation-Associated Renal Cell CA	*TFE3* rearrangement	translocations involving Xp11	diagnosis	FISH, CGX

Liver	Hepatic Adenoma	*CTNNB1* (Beta-Catenin)	exon 3 mutations	diagnostic	IHC, SGAs, NGS
Lung	Non-Small Cell CA (NSCLC, adenocarcinoma)	*EGFR*	exons 18-21; particularly L858R and exon 19 deletion	responsiveness to TKIs	IHC, SGAs, NGS
			exon 20 insertion	resistance to traditional TKIs; responsiveness to mobocertinib and amivantamab-vmjw	SGAs, NGS
			T790M	resistance to first line therapy; responsiveness to osimertinib; de novo and acquired	SGAs, NGS
		KRAS	G12C	responsiveness to sotorasib	SGAs, NGS
		BRAF	V600E	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
		ERBB2 (HER2)	exon 20 insertion	responsiveness to fam-trastuzumab deruxtecan-nxki	SGAs, NGS
		ALK	rearrangements; *EML4::ALK* and multiple fusion partners; inv(2)	responsiveness to TKIs	FISH, IHC, SGAs, NGS, AMP
		ROS1	rearrangements; multiple fusion partners	responsiveness to TKIs	FISH, SGAs, NGS, AMP
		RET	rearrangements; multiple fusion partners	responsiveness to TKIs	FISH, SGAs, NGS, AMP
		MET	exon 14 skipping	responsiveness to TKIs	SGAs, NGS
Oropharynx	Squamous Cell CA	High-risk HPV	high risk virus, type 16, 18, other	prognosis	IHC (p16), ISH, viral typing
Ovary	Ovarian CA	*CTNNB1* (Beta-Catenin)	exon 3 mutations or intragenic deletion	diagnosis	IHC, SGAs, NGS
		PIK3CA	amplification	responsiveness to PI3K inhibitors	SGAs, NGS
	Small cell CA, hypercalcemic type	*SMARCA4* (BRG1)	LOF	diagnosis; risk of hereditary cancer	SGAs, NGS
	High-grade serous CA	*TP53*	SNVs, indels	diagnosis	IHC, SGAs, NGS
		BRCA1 / *BRCA2*	LOF	responsiveness to platinum-based chemotherapy & PARP inhibitor	SGAs, NGS
	Low-grade serous CA	*KRAS, BRAF*	SNVs	diagnostic, potential response to MEK-inhibitors	SGAs, NGS
Prostate	Prostate CA	*BRCA1*, *BRCA2*, *ATM*, and other genes involved in the HRR pathway	LOF	responsiveness to PARP inhibitor	SGAs, NGS
		AR	SNVs, amplification	diagnosis; prognosis; resistance to androgen deprivation	IHC, SGAs, NGS, FISH
		TMPRSS2 rearrangement	*TMPRSS2::ERG*; t(21;21)	diagnosis	FISH, NGS
Skin	Merkel Cell CA	Merkel Cell Polyoma Virus	Virus detection	diagnosis	ISH, Viral Test
	Melanoma	*BRAF*	V600E or V600K	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
		KIT (CD117)	exon 8, 9, 11, 13, 17 variants	responsiveness to TKIs	SGAs, NGS
		PDGFRA	exon 12, 14, 18 variants	responsiveness to TKIs	SGAs, NGS
		NRAS	G12; G13; Q61	diagnosis	SGAs, NGS
		NF1	LOF	diagnosis	SGAs, NGS
		TERT	promoter mutations	diagnosis	SGAs, NGS
Soft Tissue	Alveolar Rhabdomyosarcoma	*FOXO1* rearrangement	*PAX3::FOXO1*; t(2;13)	diagnosis	FISH, NGS, AMP
	Ewing Sarcoma	*EWSR1* rearrangement	*EWSR1::FLI1*; t(11;22) (most common)	diagnosis	FISH, NGS, AMP
	Infantile Fibrosarcoma	*ETV6* rearrangement	*ETV6::NTRK3*; t(12;15)	diagnosis; responsiveness to NTRK inhibitors	FISH, NGS, AMP
	Inflammatory Myofibroblastic Tumor	*ALK* rearrangement	*TPM3::ALK*; t(2;5)	responsiveness to TKIs	FISH, IHC, NGS, AMP
	Solitary Fibrous Tumor	*STAT6* rearrangement	*NAB2::STAT6*; inv(12)	diagnosis	IHC, SGAs, NGS, AMP
	Synovial Sarcoma	*SS18* rearrangement	*SS18::SSX1*; t(X;18)	diagnosis	FISH, NGS, AMP
	Dermatofibrosarcoma Protuberans	*COL1A1::PDGFRB* rearrangement	*COL1A1::PDGFRB*; t(17:22)	diagnosis, responsiveness to TKIs	FISH, NGS
	Epithelioid Sarcoma	*SMARCB1*	LOF	diagnosis, risk of hereditary cancer, responsiveness to tazemetostat	IHC, NGS
Stomach & Esophagus	Gastric and Esophageal Adenocarcinoma	*ERBB2* (HER2)	amplification / overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC; NGS, SGAs
Thymus	Thymic CA	*KIT* (CD117)	exon 11 variants; D820	responsiveness to TKIs	IHC, SGAs, NGS
Thyroid	Follicular Thyroid CA	*PAX8::PPARG* rearrangement	*PAX8::PPARγ*; t(2;3)	diagnosis	FISH
	Medullary Thyroid CA	*RET*	mutations	responsiveness to TKIs	SGAs, NGS
	Papillary Thyroid CA	*BRAF*	V600E	diagnosis; responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
		RET	rearrangements; *PTC1*, *PTC2*, *PTC3* common partners	diagnosis; responsiveness to TKIs	FISH, NGS, AMP
		TERT	promoter mutations	prognosis	SGAs, NGS
Urinary Tract	Urothelial CA	*FGFR3* rearrangement or mutation	*FGFR3::TACC3*; S249	responsiveness to FGFR inhibitors	NGS, AMP