

Molecular In My Pocket...

Solid Tumors (Sporadic)

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

AMP	Anchored Multiplex PCR	ISH	<i>In Situ</i> 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 <i>MLH1, MSH2, MSH6, PMS2</i>	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	<i>NTRK</i>	<i>NTRK1/2/3</i> rearrangements	responsiveness to NTRK inhibitors	NGS, AMP, FISH
	All Solid Tumors	<i>BRAF</i>	V600	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
Adrenal	Neuroblastoma	<i>MYCN</i>	amplification	prognosis	FISH
Bile Duct	Cholangiocarcinoma	<i>IDH1</i>	mutations	responsiveness to IDH1 inhibitors	SGAs, NGS
Brain	Glioma / Glioblastoma	<i>IDH1/IDH2</i>	<i>IDH1</i> R132, <i>IDH2</i> R172, R140	diagnosis	IHC, SGAs, NGS
		<i>MYCN</i>	amplification	prognosis	FISH
		<i>TERT</i>	promoter mutations	prognosis	SGAs, NGS
		1p / 19q	codeletion	diagnostic of oligodendroglioma phenotype	FISH, CGX, NGS
		<i>ATRX</i>	LOF	prognosis	IHC, SGAs, NGS
		<i>MGMT</i>	promoter methylation	responsiveness to alkylating agents	Methylation assay
	Pediatric Glioma	<i>EGFR</i>	amplification; vlll transcript	diagnosis	FISH, CGX, SGAs, NGS
Medulloblastoma	<i>H3F3A, HIST1H3B</i>	K27 mutations	diagnosis		
Breast	Breast CA	Estrogen Receptor (ER or <i>ESR1</i>)	expression	responsiveness to anti-estrogen	IHC, SGAs, NGS
		Progesterone Receptor (PR or <i>PGR</i>)	expression	responsiveness to anti-estrogen	IHC, SGAs, NGS
		<i>ERBB2</i> (HER2)	amplification / overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC
		<i>PIK3CA</i>	E542, E545, H1045	responsiveness to PI3K inhibitor	SGAs, NGS
	Breast CA (Lobular)	<i>BRCA1 / BRCA2</i>	LOF	responsiveness to PARP inhibitor	SGAs, NGS
Cervix	Squamous cell CA	<i>CDH1</i> (E-Cadherin)	LOF	diagnosis	IHC, SGAs, NGS
Endometrium	Endometrial CA	High-risk HPV	high risk virus, type 16, 18, other	diagnosis	IHC (p16), ISH, viral typing
		MSI testing	MSI-High, Low, or Stable	response to immunotherapy	MSI testing, NGS
	Uveal Melanoma	<i>MLH1, MSH2, MSH6, PMS2</i> <i>MLH1</i>	LOF LOF and promoter hypermethylation	response to immunotherapy somatic etiology (not Lynch Syndrome)	IHC Promoter methylation
GI Tract	Gastrointestinal Stromal Tumor (GIST)	<i>GNAQ, GNA11</i>	<i>GNAQ / GNA11</i> Q209L	diagnosis	SGAs, NGS
		<i>KIT</i> (CD117)	exon 9 variants	responsiveness to TKIs, associated with 1' resistance	
			exon 11 in-frame indels; D820; less frequently exons 8, 17	responsiveness to TKIs	SGAs, NGS
			exon 14	resistance to first-line TKIs	**IHC not a proxy**
		<i>PDGFRA</i>	exon 13	responsiveness to TKIs as 1' variant; as 2' variant confers resistance to TKIs	
			exon 12, 14, 18 variants	responsiveness to TKIs	SGAs, NGS
exon 18 D842V	resistance to TKIs				
GI Tract (Lower)	Colorectal CA	<i>SDHA, SDHB, SDHC, SDHD</i>	LOF	resistance to TKIs, risk of hereditary cancer	SGAs, NGS, IHC for SDHB
		<i>KRAS, NRAS</i>	G12; G13; Q61	decreased responsiveness to panitumumab or cetuximab	SGAs, NGS
		<i>BRAF</i> (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
		<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	LOF	risk of hereditary cancer; prognosis, responsiveness to immunotherapy	MMR IHC, NGS
		<i>ERBB2</i> (HER2)	Amplification / overexpression	responsiveness to HER2 targeted therapy	IHC, FISH, NGS
Colorectal CA (to differ from Lynch Syndrome)	<i>MLH1</i> <i>BRAF</i>	promoter methylation exon 15, V600E	somatic etiology somatic etiology when MLH1 deficient/MSI-High	Methylation studies IHC, SGAs, NGS	
Kidney	Translocation-Associated Renal Cell CA	<i>TFE3</i> rearrangement	translocations involving Xp11	diagnosis	FISH, CGX
Liver	Hepatic Adenoma	<i>CTNNB1</i> (Beta-Catenin)	exon 3 mutations	diagnostic	IHC, SGAs, NGS
			exons 18-21; particularly L858R and exon 19 deletion	responsiveness to TKIs	IHC, SGAs, NGS

Lung	Non-Small Cell CA (NSCLC, adenocarcinoma)	<i>EGFR</i>	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
		<i>KRAS</i>	G12C	responsiveness to sotorasib	SGAs, NGS
		<i>BRAF</i>	V600E	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
		<i>ERBB2 (HER2)</i>	exon 20 insertion	responsiveness to fam-trastuzumab deruxtecan-nxki	SGAs, NGS
		<i>ALK</i>	rearrangements; <i>EML4::ALK</i> and multiple fusion partners; inv(2)	responsiveness to TKIs	FISH, IHC, SGAs, NGS, AMP
		<i>ROS1</i>	rearrangements; multiple fusion partners	responsiveness to TKIs	FISH, SGAs, NGS, AMP
		<i>RET</i>	rearrangements; multiple fusion partners	responsiveness to TKIs	FISH, SGAs, NGS, AMP
	<i>MET</i>	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	<i>CTNNB1 (Beta-Catenin)</i>	exon 3 mutations or intragenic deletion	diagnosis	IHC, SGAs, NGS
		<i>PIK3CA</i>	amplification	responsiveness to PI3K inhibitors	SGAs, NGS
	Small cell CA, hypercalcemic type	<i>SMARCA4 (BRG1)</i>	LOF	diagnosis; risk of hereditary cancer	SGAs, NGS
	High-grade serous CA	<i>TP53</i>	SNVs, indels	diagnosis	IHC, SGAs, NGS
		<i>BRCA1 / BRCA2</i>	LOF	responsiveness to platinum-based chemotherapy & PARP inhibitor	SGAs, NGS
Low-grade serous CA	<i>KRAS, BRAF</i>	SNVs	diagnostic, potential response to MEK-inhibitors	SGAs, NGS	
Prostate	Prostate CA	<i>BRCA1, BRCA2, ATM</i> , and other genes involved in the HRR pathway	LOF	responsiveness to PARP inhibitor	SGAs, NGS
		<i>AR</i>	SNVs, amplification	diagnosis; prognosis; resistance to androgen deprivation	IHC, SGAs, NGS, FISH
		<i>TMPRSS2</i> rearrangement	<i>TMPRSS2::ERG</i> ; t(21;21)	diagnosis	FISH, NGS
Skin	Merkel Cell CA	Merkel Cell Polyoma Virus	Virus detection	diagnosis	ISH, Viral Test
	Melanoma	<i>BRAF</i>	V600E or V600K	responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
		<i>KIT (CD117)</i>	exon 8, 9, 11, 13, 17 variants	responsiveness to TKIs	SGAs, NGS
		<i>PDGFRA</i>	exon 12, 14, 18 variants	responsiveness to TKIs	SGAs, NGS
		<i>NRAS</i>	G12; G13; Q61	diagnosis	SGAs, NGS
		<i>NF1</i>	LOF	diagnosis	SGAs, NGS
<i>TERT</i>	promoter mutations	diagnosis	SGAs, NGS		
Soft Tissue	Alveolar Rhabdomyosarcoma	<i>FOXO1</i> rearrangement	<i>PAX3::FOXO1</i> ; t(2;13)	diagnosis	FISH, NGS, AMP
	Ewing Sarcoma	<i>EWSR1</i> rearrangement	<i>EWSR1::FLI1</i> ; t(11;22) (most common)	diagnosis	FISH, NGS, AMP
	Infantile Fibrosarcoma	<i>ETV6</i> rearrangement	<i>ETV6::NTRK3</i> ; t(12;15)	diagnosis; responsiveness to NTRK inhibitors	FISH, NGS, AMP
	Inflammatory Myofibroblastic Tumor	<i>ALK</i> rearrangement	<i>TPM3::ALK</i> ; t(2;5)	responsiveness to TKIs	FISH, IHC, NGS, AMP
	Solitary Fibrous Tumor	<i>STAT6</i> rearrangement	<i>NAB2::STAT6</i> ; inv(12)	diagnosis	IHC, SGAs, NGS, AMP
	Synovial Sarcoma	<i>SS18</i> rearrangement	<i>SS18::SSX1</i> ; t(X;18)	diagnosis	FISH, NGS, AMP
	Dermatofibrosarcoma Protuberans	<i>COL1A1::PDGFRB</i> rearrangement	<i>COL1A1::PDGFRB</i> ; t(17;22)	diagnosis, responsiveness to TKIs	FISH, NGS
	Epithelioid Sarcoma	<i>SMARCB1</i>	LOF	diagnosis, risk of hereditary cancer, responsiveness to tazemetostat	IHC, NGS
Stomach & Esophagus	Gastric and Esophageal Adenocarcinoma	<i>ERBB2 (HER2)</i>	amplification / overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC
Thymus	Thymic CA	<i>KIT (CD117)</i>	exon 11 variants; D820	responsiveness to TKIs	IHC, SGAs, NGS
Thyroid	Follicular Thyroid CA	<i>PAX8::PPARG</i> rearrangement	<i>PAX8::PPARG</i> ; t(2;3)	diagnosis	FISH
	Medullary Thyroid CA	<i>RET</i>	mutations	responsiveness to TKIs	SGAs, NGS
		<i>BRAF</i>	V600	diagnosis; responsiveness to dabrafenib-trametinib	IHC, SGAs, NGS
	Papillary Thyroid CA	<i>RET</i>	rearrangements; <i>PTC1, PTC2, PTC3</i> common partners	diagnosis; responsiveness to TKIs	FISH, NGS, AMP
		<i>TERT</i>	promoter mutations	prognosis	SGAs, NGS
Urinary Tract	Urothelial CA	<i>FGFR3</i> rearrangement or mutation	<i>FGFR3::TACC3</i> ; S249	responsiveness to FGFR inhibitors	NGS, AMP



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