Molecular In My Pocket…

Solid Tumors

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

AMP	Anchored Multiplex PCR	*ISH*	*In Situ* Hybridization	*MEN*	Multiple Endocrine Neoplasia	*NGS*	Next-Generation Sequencing
CA	Cancer	*FISH*	Fluorescence ISH	*LOF*	Loss of Function	*SGA*	Single Gene Assay
CGX	Cytogenetics	*GI*	Gastrointestinal	*MMR*	Mismatch Repair	*TKI*	Tyrosine Kinase Inhibitor
IHC	Immunohistochemistry	*HBOC*	Hereditary Breast and Ovarian CA Syndrome	*MSI*	Microsatellite Instability		

Tissue Type	Disease	Gene	Common Genomic Variant(s)	Significance	Primary Assays
Adrenal	Hereditary Paraganglioma / Pheochromocytoma	*SDHA, SDHB, SDHC, SDHD*	LOF	risk of hereditary cancer	IHC, SGAs, NGS
	Neuroblastoma	*MYCN*	Amplification	prognosis	FISH
Brain	Glioma / Glioblastoma	*IDH1 / IDH2*	*IDH1* R132, *IDH2* R172, R140	diagnostic	IHC, SGAs, NGS
		TERT	promoter mutations	prognosis	SGAs, NGS
		1p / 19q codeletion		oligodendroglioma phenotype	FISH, CGX, NGS
		ATRX	LOF	prognosis	IHC, SGAs, NGS
		MGMT	promoter methylation	response to alkylating agents	Methylation assay
		EGFR	amplification; vIII transcript	diagnostic	FISH, CGX, SGAs, NGS
	Pediatric Glioma	*H3F3A, HIST1H3B*	K27	diagnostic	
	Medulloblastoma	*WNT* pathway genes	*CTNNB1*	diagnostic subtype	SGAs, NGS
		SHH pathway genes	*PTCH1* LOF	diagnostic subtype	SGAs, NGS
Breast	Breast CA	*CTNNB1* (Beta-Catenin)	Exon 3 mutations	aberrant nuclear expression	IHC, SGAs, NGS
		Estrogen Receptor (ER or *ESR1*)		response to anti-estrogen	IHC, SGAs, NGS
		Progesterone Receptor (PR or *PGR*)		response to anti-estrogen	IHC, SGAs, NGS
		ERBB2 (HER2)	Amplification / Overexpression; S310; L755	responsiveness to trastuzumab	FISH, IHC
		PIK3CA	E542, E545, H1045	response to PI3K inhibitor	SGAs, NGS
	Breast CA (Lobular)	*CDH1* (E-Cadherin)	LOF	diagnostic	IHC, SGAs, NGS
	HBOC / Sporadic CA	*BRCA1 / BRCA2*	LOF	risk of hereditary cancer; response to PARP inhibitors	SGAs, NGS
Cervix	Squamous cell CA	High-risk HPV	high risk virus, type 16, 18, other	diagnostic	IHC (p16), ISH, Viral Typing
Endometrium	Endometrial CA (sporadic)	*MLH1*	LOF and promoter hypermethylation	somatic etiology (not Lynch Syndrome)	promoter methylation
	Lynch Syndrome	*MLH1, MSH2, MSH6, PMS2*	LOF	40-60% lifetime risk of endometrial cancer	IHC, SGAs, NGS, MSI
	Cowden Syndrome	*PTEN* (germline)	LOF	25% risk of endometrial cancer development	SGA, NGS
Eye	Retinoblastoma	*RB1*	LOF	risk of hereditary cancer	SGAs, NGS
	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	SGAs, NGS, IHC for SDHB
	Colorectal CA	*KRAS, NRAS*	G12; G13; Q61	decreased response to panitumumab or cetuximab	SGAs, NGS
		BRAF (therapeutic setting)	exon 15, V600E	decreased response to panitumumab or cetuximab	SGAs, NGS
		MSI testing	MSI-High, Low, or stable	risk of hereditary cancer; prognosis, response to immunotherapy	MSI testing
GI Tract (Lower)	Colorectal CA (Lynch Syndrome)	Most commonly *MLH1, MSH2, MSH6, PMS2, EPCAM*	LOF	risk of hereditary cancer; prognosis, response to immunotherapy	MMR IHC, NGS
		MLH1	promoter methylation	somatic etiology (not Lynch Syndrome)	methylation studies
		BRAF	exon 15, V600E	somatic etiology when MLH1 deficient/MSI-high	IHC, SGA, NGS
	Colorectal CA (FAP)	*APC*	LOF	risk of hereditary cancer	SGAs, NGS
	Hirschprung disease	*RET*	LOF	germline diagnosis	SGAs, NGS
Heart	Cardiomyopathy	*MYH7*		Both dilated and hypertrophic	SGAs, NGS
Kidney	Birt-Hogg-Dube syndrome	*FLCN*	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Clear Cell Renal CA	*VHL*	*3p deletion*	germline diagnosis; risk of hereditary cancer	CGX
	Polycystic Kidney Disease (Dominant / Recessive)	*PKD1 / PKHD1*	LOF	germline diagnosis	SGAs, NGS

Kidney (continued)	Hereditary leiomyomatosis and Renal Cell Carcinoma Syndrome	*FH*	LOF	adverse prognosis; risk of hereditary cancer	IHC, SGAs, NGS
	Renal CA; Von Hippel Lindau Syndrome	*VHL*	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Rhabdoid Sarcoma	*SMARCB1* (INI), *SMARCA4* (BRG1)	LOF	risk of hereditary cancer	IHC, NGS
	Translocation-Associated Renal CA	*TFE3* rearrangement	translocations involving Xp11	diagnostic	FISH, CGX
	Wilm's Tumor	*WT1*		germline diagnosis; risk of hereditary cancer	SGAs, NGS
Liver	Alagille Syndrome	*JAG1*	LOF	haploinsufficiency	SGAs, NGS
	Hepatic Adenoma	*CTNNB1* (Beta-Catenin)	Exon 3 mutations	aberrant nuclear expression	IHC, SGAs, NGS
	Hereditary Hemochromatosis	*HFE*	C282Y, H63D	germline diagnosis	SGAs, NGS
	Wilson Disease	*ATP7B*		germline diagnosis	SGAs
Lung	Non-Small Cell CA (NSCLC, adenocarcinoma)	*BRAF*	V600E	predicts response to BRAF inhibitors (dabrafenib-trametinib)	SGAs, NGS
		ROS1 rearrangement	Multiple fusion partners	responsiveness to TKIs	FISH, NGS, AMP
		ALK rearrangement	EML4-ALK; inv(2)	responsiveness to TKIs	FISH, IHC, NGS, AMP
		RET Rearrangement	Multiple fusion partners	responsiveness to TKIs	FISH, NGS, AMP
		EGFR	exons 18-21; L858R	responsiveness to TKIs	IHC, SGAs, NGS
			exon 20; T790M	resistance to first line therapy; de novo and acquired	SGA, NGS
Multi-System	α-1 antitrypsin deficiency	*SERPINA1*	PiMM / PiZZ alleles	germline diagnosis	SGAs
	Cowden Syndrome	*PTEN*	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Li-Fraumeni syndrome	*TP53*	LOF	risk of hereditary cancer	SGAs, NGS
	McCune Albright Syndrome	*GNAS*		germline diagnosis; risk of hereditary cancer	SGAs, NGS
	MEN Types 1 / 2A & 2B / 4	*MEN1* / *RET* / *CDKN1B*		germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Neurofibromatosis	*NF1* / *NF2*	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Peutz-Jeghers Syndrome	*STK11*	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Tuberous Sclerosis	*TSC1* / *TSC2*		germline diagnosis; risk of hereditary cancer	SGAs, NGS
Oropharynx	Squamous CA	High-risk HPV	high risk virus, type 16, 18, other	Improved prognosis	IHC (p16), ISH, Viral Typing
Ovary	Ovarian CA	*CTNNB1* (Beta-Catenin)	Exon 3 mutations or intragenic deletion	diagnostic	IHC, SGAs, NGS
		PIK3CA	Amplification	responsiveness to PI3K inhibitors	SGAs, NGS
		PTEN	LOF	germline diagnosis; risk of hereditary cancer	SGAs, NGS
	Small cell CA, hypercalcemic type	*SMARCA4* (BRG1)	LOF	diagnostic; risk of hereditary cancer	SGAs, NGS
	High grade serous carcinoma	*TP53*	SNVs, indels	diagnostic	IHC, SGAs, NGS
		BRCA1 / *BRCA2*, germline and somatic		response to Platinum-based chemotherapy & PARPi	SGA, NGS
	Low-grade serous carcinoma	*KRAS, BRAF*	SNVs	diagnostic, potential response to MEK-inhibitors	
	HBOC / Sporadic	*BRCA1* / *BRCA2*	LOF	response to PARP inhibitors	SGAs, NGS
Prostate	Prostate CA	*AR*	SNVs, Amplification	diagnostic, prognosis, resistance to androgen deprivation	IHC, SGAs, NGS, FISH
		TMPRSS2 rearrangement	*TMPRSS2-ERG*; t(21;21)	diagnostic,	FISH, NGS
Skin	Merkel Cell Carcinoma	Merkel Cell Polyoma Virus	Virus	diagnostic	ISH, Viral Test
	Melanoma	*BRAF*	V600	responsiveness to vemurafenib, dabrafenib	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	diagnostic	SGAs, NGS
		NF1	LOF	diagnostic	SGAs, NGS
		TERT	promoter mutations	diagnostic	SGAs, NGS
Soft Tissue	Alveolar Rhabdomyosarcoma	*FOXO1* rearrangement	*PAX3-FOXO1*; t(2;13)	diagnostic	FISH, NGS, AMP
	Ewing sarcoma	*EWSR1* rearrangement	*EWSR1-FLI1*; t(11;22) (most common)	diagnostic	FISH, NGS, AMP
	Fibrosarcoma	*ETV6* rearrangements	*ETV6-NTRK3*; t(12;15)	diagnostic, response 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)	diagnostic	IHC, SGAs, NGS,AMP
	Synovial Sarcoma	*SS18* rearrangement	SS18-SSX1; t(X;18)	diagnostic	FISH, NGS, AMP
Stomach	Gastric CA	*ERBB2* (HER2)	Amplification / Overexpression; S310; L755	responsiveness to Trastuzumab	FISH, IHC
	Hereditary Diffuse Gastric CA	*CDH1* (E-Cadherin)	LOF	risk of hereditary cancer	SGAs, NGS
Thymus	Thymic carcinoma	*KIT* (CD117)	exon 11 variants; D820	responsiveness to TKIs	IHC, SGAs, NGS
Thyroid	Follicular Thyroid CA	*PAX8-PPARG* rearrangement	*PAX8-PPARγ*; t(2;3)	diagnostic	FISH
	Papillary Thyroid CA	*BRAF*	V600	diagnostic; responsiveness to vemurafenib, dabrafenib	IHC, SGAs, NGS
		RET rearrangement	*PTC1*, *PTC2*, *PTC3* common partners	diagnostic; responsive to targeted RET inhibition	FISH, NGS, AMP
		TERT	promoter mutations	prognosis	SGAs, NGS
Urinary Tract	Urothelial carcinomas	*FGFR3* rearrangement or mutation	FGFR3-TACC3; S249	response to FGFR inhibitors	NGS, AMP

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