

Molecular In My Pocket™ ...

ONCOLOGY: Molecular Biomarkers of Ovarian Cancer

Samples to Test: Formalin-fixed paraffin-embedded tissue (FFPE); fresh, frozen, or alcohol-fixed tissue; any type of cytology specimen with adequate cellularity and appropriate validation

EPITHELIAL TUMORS

Biomarker	Alteration	Indications	Result Interpretation/Significance	Assay Techniques
ARID1A	LOF mutations	Diagnostic	Found in endometrioid and clear cell carcinomas	NGS
BRAF	Activating mutations	Diagnostic	Associated with early stage low-grade serous carcinoma	NGS, IHC
BRCA1/2	LOF mutations	Therapeutic	Predicts response to platinum-based chemotherapy and PARP-inhibitors	NGS, Sanger sequencing, aCGH, MLPA
		Germline screening	BRCA1/2-associated hereditary breast and ovarian cancer	
Non-BRCA HRD genes*	LOF mutations	Therapeutic	Predicts response to PARP-inhibitors	NGS
CCNE1	Copy number gain/amplification	Prognostic	Treatment resistance and poor outcome in high-grade serous carcinoma	NGS
CDKN2A/B	Copy number loss	Therapeutic	Potential for response to CDK4/6 inhibitors (experimental)	FISH, NGS, aCGH
CTNNB1	Activating mutations	Prognostic	Increased risk of recurrence in uterine endometrioid adenocarcinomas, ovarian data accumulating	NGS
ERBB2 (HER2)	Amplification	Therapeutic	Predicts response to HER2-targeted therapy (i.e. trastuzumab, not FDA approved)	FISH, IHC, NGS, aCGH
KRAS	Activating mutations	Diagnostic	Associated with low-grade serous carcinoma; also seen in clear cell and mucinous carcinomas	NGS
MSI/MMR	LOF mutations in <i>MLH1</i> , <i>PMS2</i> , <i>MSH2</i> , or <i>MSH6</i> , methylation of <i>MLH1</i> promoter	Prognostic	Part of molecular categorization for endometrioid adenocarcinomas**	IHC, PCR-based assays, aCGH, NGS
		Therapeutic	Predicts response to pembrolizumab	
		Germline screening	Lynch syndrome screening	
NRAS	Activating mutations	Diagnostic	Associated with low-grade serous carcinoma	NGS
NTRK	Fusions with <i>NTRK1</i> , <i>NTRK2</i> , <i>NTRK3</i>	Therapeutic	Rare, predicts response to tumor-agnostic TRK inhibitors larotrectinib and entrectinib	FISH, IHC, RT-PCR, NGS including RNA-Seq, anchored multiplex PCR
PIK3CA	Activating mutations	Therapeutic	Potential for PIK3CA inhibitor therapy (FDA-approved only for breast cancer)	NGS
POLE	Mutations resulting in ultra-mutated phenotype	Prognostic	Part of molecular categorization for endometrioid adenocarcinomas**	NGS, PCR-based assays, SNP genotyping, Sanger sequencing
PTEN	LOF mutations	Diagnostic	Found in endometrioid carcinomas and at lower frequency in other carcinomas	NGS
SMARCB1	LOF mutations	Diagnostic	Found in small cell carcinoma hypercalcaemic type, and undifferentiated carcinoma	NGS, IHC (INI1)
SMARCA4	LOF mutations and copy number	Diagnostic	Diagnostic of small cell carcinoma, hypercalcaemic type	NGS, IHC (BRG1)
TMB	Tumor mutational burden	Therapeutic	TMB ≥ 10 mutations/Mb eligible for pembrolizumab (advanced/progressive and unresectable tumors)	NGS
TP53	LOF mutations	Diagnostic	High frequency in high-grade serous carcinoma, also seen in clear cell, mucinous, and endometrioid adenocarcinomas	NGS, PCR-based assays, Sanger sequencing
		Prognostic	Part of molecular categorization for endometrioid adenocarcinomas**; poor prognosis in clear cell and mucinous carcinomas	

*ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, MRE11A, NBN, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L, etc. Clinical guidelines recommend BRCA1/2 germline/somatic analysis followed by HRD assessment if former is negative. HRD is currently tested by commercial assays analyzing a combination of mutations of genomic scars (genomic loss of heterozygosity, large-scale genomic transitions, telomeric allelic imbalance).

**The molecular classification of endometrioid adenocarcinomas of the uterus and ovaries includes four groups: POLE-mutated/ultramutated, MMR-deficient/MSI-high, TP53-mutated/copy number high, and no specific molecular profile (NSMP). There is emerging evidence this classification can be applicable to clear cell carcinomas as well.

GERM CELL TUMORS

Biomarker	Alteration	Indications	Result Interpretation/Significance	Assay Techniques
KIT	Activating mutations	Diagnostic	Predominantly found in dysgerminomas	NGS
KRAS	Activating mutations	Diagnostic	Reported in yolk sac tumors	NGS
12p gain	Chromosomal gain	Diagnostic	High frequency in dysgerminomas, also found in yolk sac tumors	FISH, aCGH

SEX CORD-STROMAL TUMORS

Tumor Type	Biomarker	Alteration	Significance	Assay Techniques
Fibroma	SUFU, PTCH1	Germline LOF mutation	Gorlin Syndrome	Sequencing (DNA)
	PTCH1	Germline LOF mutation	Gorlin Syndrome	Sequencing (DNA)
	IDH1	Somatic mutation	Ollier Disease	Sequencing (DNA)
	Imbalances of chromosomes 4, 9, 12, and 19	Copy number alterations	Diagnostic	CGX, aCGH, NGS (DNA)
Thecoma	FOXL2	Somatic p.C134W	Controversial: May represent adult granulosa cell tumor with thecoma-like foci	Sequencing (DNA)
Sclerosing stromal tumor	GLI2	Fusions (<i>FHL2</i> most common partner)	Diagnostic	Sequencing (RNA/DNA)
Signet-ring stromal tumor	CTNNB1	Somatic missense (typically exon 3) mutation	Controversial: May represent microcystic stromal tumor	Sequencing (DNA)
Microcystic stromal tumor	CTNNB1	Somatic missense (typically exon 3) mutation	Diagnostic	Sequencing (DNA)
	APC	Germline LOF mutation	Familial adenomatous polyposis	Sequencing (DNA)
Adult granulosa cell tumor	FOXL2	Somatic p.C134W	Diagnostic, Monitoring	Sequencing (DNA)
	KMT2D	Somatic inactivating mutation	Prognostic (enriched in recurrent cases)	Sequencing (DNA)
	TERT	Somatic promoter mutation	Prognostic (enriched in recurrent cases)	Sequencing (DNA)
	TP53	Somatic LOF mutation	Diagnostic and prognostic (cases with high- grade transformation)	Sequencing (DNA)
Juvenile granulosa cell tumor	AKT1	Somatic activating mutation	Diagnostic	Sequencing (DNA)
	GNAS	Somatic activating mutation	Diagnostic	Sequencing (DNA)
	DICER1	Somatic hotspot mutation, germline LOF mutation	Diagnostic, DICER1 syndrome when germline	Sequencing (DNA)
	KMT2C	Somatic inactivating mutations	Diagnostic	Sequencing (DNA)
	IDH1	Somatic mutation	Ollier Disease, Maffucci Syndrome	Sequencing (DNA)
Sertoli-Leydig cell tumor	DICER1	Somatic hotspot mutation, germline LOF mutation	Diagnostic, DICER1 syndrome when germline	Sequencing (DNA)
	FOXL2	Somatic p.C134W	Diagnostic	Sequencing (DNA)
Sex-cord tumor with annular tubules	STK11	Germline LOF	Peutz-Jeghers Syndrome	Sequencing (DNA)

Abbreviations: HRD Homologous Recombination Deficiency, MSI Microsatellite Instability, dMMR Mismatch Repair Deficiency, TMB Tumor Mutational Burden, LOF Loss of Function, NGS Next-Generation Sequencing, IHC Immunohistochemistry, aCGH Array Comparative Genomic Hybridization, FISH Fluorescence *In Situ* Hybridization, MLPA Multiplex Ligation-Dependent Probe Amplification, PCR Polymerase Chain Reaction, RT-PCR Reverse Transcription PCR, SNP Single Nucleotide Polymorphism, DNA Deoxyribonucleic Acid, RNA Ribonucleic Acid

Where to Test: Testing should be performed in the laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA88) as qualified to perform high complexity (molecular pathology) testing.

References:

1. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Ovarian Cancer. Version 5.2022 – September 16, 2022; NCCN.org. accessed 9/19/2022



Prepared by the Association for Molecular Pathology Training and Education Committee For more educational resources, see: www.amp.org/AMPEducation