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Laboratory Bulletin

DATE:	29 May 2023
TO:	All Pathologists, Oncologists, Gynecologic Oncologists, and Medical Geneticists
FROM:	Molecular Pathology Program, Alberta Precision Laboratories
RE:	**New Comprehensive Molecular Testing for Solid Tumors**

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Key Message

- As of June 5, 2023, a new solid tumor molecular test (Cancer Biomarker Comprehensive DNA Panel, Tumor) will be available in APL for all pathologists and oncologists to assist in tumor DNA profiling for cancer diagnosis, cancer risk stratification, and selection of targeted therapies for the treatment and management of patients with solid tumors. Testing is available for pan-provincial cases that meet specific clinical and/or pathological indications (see **Appendix A**).

Background

- Comprehensive genomic profiling is a next-generation sequencing (NGS) approach that uses a single assay to assess hundreds of genes including relevant cancer biomarkers and molecular signatures, as established in guidelines and clinical trials, for diagnostic and therapy guidance.
- The Cancer Biomarker Comprehensive DNA Panel, Tumor is a new APL-developed NGS assay that is validated to detect single nucleotide variants (SNVs), insertion or deletions of one or multiple nucleotides (small indels), copy number alterations (full gene amplification, homozygous full gene deletion, and homozygous partial gene deletion) in the following 130 genes: *ACVR1, AKT1, AKT3, ALK, APC, AR, ARAF, ARHGAP35, ARID1A, ATM, ATRX, BAP1, BARD1, BCOR, BRAF, BRCA1, BRCA2, BRIP1, CCND1, CCNE1, CDC42, CDH1, CDK12, CDK4, CDK6, CDKN2A, CDKN2B, CHEK2, CIC, CTNNB1, DICER1, EGFR, EIF1AX, ELOC, EPCAM, ERBB2, ERBB3, ERBB4, ESR1, EZH1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FOXL2, FUBP1, GNA11, GNAQ, GNAS, H3F3A, H3F3B, HIST1H3B, HIST1H3C, HNF1A, HOXB13, HRAS, IDH1, IDH2, KEAP1, KLF4, KIT, KRAS, MAP2K1, MAP2K2, MAP2K4, MAPK1, MDM2, MDM4, MEN1, MET, MLH1, MSH2, MSH6, MTOR, MYC, MYCN, MYD88, MYOD1, NBN, NF1, NF2, NRAS, NTRK1, NTRK2, NTRK3, PALB2, PBRM1, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PIK3R1, PLEKHS1, PMS2, POLE, POLR2A, PPP2R1A, PRKCA, PRKD1, PTEN, RAD51C, RAD51D, RAC1, RAF1, RB1, RET, ROS1, SDHA, SDHB, SDHC, SDHD, SETD2, SMAD4, SMARCA4, SMARCB1, SMO, SPOP, STK11, TERT, TFEB, TP53, TRAF7, TSC1, TSC2, TSHR, and VHL*.
- Loss-of-heterozygosity (LOH) with corresponding copy number status (gain, loss, or copy-neutral) is assessed in all chromosome arms and reported when clinically valuable.
- Microsatellite instability (MSI-High) status is assessed in selected 76 microsatellite loci and reported based on a validated instability score and/or the presence of mutations in the mismatch repair genes.
- This assay may be used as a screening test for tumors with high tumor mutational burden (TMB-High) where the TMB score is expected to be equal or superior to 10 mutations per megabase (mut/Mb); however, confirmation of the TMB-High status by an orthogonal method is encouraged if clinically indicated.
- This panel uses tumor DNA sequencing and does not detect fusions or RNA oncogenic isoforms which are assessed by separate APL panels (Pan-Solid Tumor Fusion RNA panel, Kinase Fusion RNA panel).

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How this will impact you

- This panel provides a molecular diagnostics tool for solid tumors in diverse organ systems. The utility depends on the clinicopathologic context, and good stewardship entails rationing the use of this panel to clinically relevant settings. This test should be ordered by a subspecialty pathologist if a diagnostic consensus cannot be achieved among peers using morphology and other ancillary testing.
- This panel provides a companion diagnostic tool for targeted therapies covered by AHS-Pharmacy and AHS-approved clinical indications.
- Please see **Appendix A** for APL-approved indications and guideline recommendations for the Cancer Biomarker Comprehensive DNA Panel testing (updated as of **May 2023**).
- The test is available to all Alberta pathologists, oncologists, and medical geneticists.
- The target turnaround time of the Cancer Biomarker Comprehensive DNA Panel, Tumor is 15 working days from tissue receipt in the Molecular Pathology laboratory. Molecular test results will be reported in ConnectCare (EPIC) and Netcare.

Action Required

- **Pathologists**: To order this test, please choose task protocol “MP – Cancer Biomarker Comprehensive DNA Panel, Tumor (E)” in Case Builder on the appropriate block. The pathologists who are not enrolled in ConnectCare (EPIC) should order the test by hand-labeling the Molecular Pathology paper requisition and faxing the request to the respective Molecular Pathology lab (North or South). Look for results in EPIC or Netcare under the accession number generated by Molecular Pathology.
- **Oncologists and Medical Geneticists:** To order this test, please open task procedure “Request for additional testing pathology” in EPIC, select “Cancer Biomarker Comprehensive DNA Panel, Tumor” in the Requested Test field, write the surgical case number, and add a comment to specify the clinical indication. The oncologists who are not enrolled in ConnectCare (EPIC) should order the test by hand-labeling the Molecular Pathology paper requisition and faxing the request to the respective Molecular Pathology lab (Edmonton or Calgary). Look for results in EPIC or Netcare under the accession number generated by Molecular Pathology.
- If individual case questions occur, please contact Molecular Pathology program (North lab: 780-407-6648; South lab: 403-220-4240).

Effective **June 5, 2023**

Questions/Concerns

- Soufiane El Hallani, Molecular Pathology North soufiane.elhallani@albertaprecisionlabs.ca
- Cheryl Mather, Molecular Pathology North cheryl.mather@albertaprecisionlabs.ca

Approved by

- Adrian Box, Provincial Medical Lead, Molecular Pathology Program, Alberta Precision Laboratories

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Appendix A: APL-approved indications for the Cancer Biomarker Comprehensive DNA Panel testing

* The report will include any molecular alterations in the other biomarkers included in the panel, if detected.

Solid Tumor Type	Testing Indication	Utility	Principal Biomarkers*	Ordering
Central Nervous System	Gliomas (all grades, adult and pediatric)	Diagnosis	IDH1, IDH2, TP53, ATRX, TERT, CDKN2A, CDKN2B, H3F3A, H3F3B, HIST1H3B, HIST1H3C, BRAF, FGFR1, FGFR2, FGFR3, MYCN, chromosomes 1p19q co-deletion, chromosome 7 gain, chromosome 10 loss	**Reflex testing ordered by the pathologist**
	Meningiomas grade 2 and 3	Diagnosis	CDKN2A, CDKN2B, TERT, NF2, chromosomes 1p and 22q loss	**Reflex testing ordered by the pathologist**
Ovary	High-grade serous carcinomas	Predictive and Germline screening	BRCA1, BRCA2, ATM, BRIP1, CHEK2, NBN, PALB2, RAD51C, RAD51D, TP53	**Reflex testing ordered by the pathologist**
	Granulosa cell tumors	Diagnosis	FOXL2, AKT1	Ordered by the pathologist if no diagnostic consensus
	Poorly differentiated Sertoli tumors	Diagnosis	DICER1	Ordered by the pathologist if no diagnostic consensus
	Small cell carcinoma - hypercalcemic type	Diagnosis	SMARCA4	Ordered by the pathologist if no diagnostic consensus
	Serous carcinomas with equivocal p53 IHC	Diagnosis	TP53	Ordered by the pathologist if no diagnostic consensus
	High-grade carcinomas with ambiguous morphology	Diagnosis	POLE, TP53, PTEN, ARID1A, SMARCB1, SMARCA4, MLH1, MSH2, MSH6, PMS2, EPCAM, microsatellite instability	Ordered by the pathologist if no diagnostic consensus

Fallopian Tube	High-grade serous carcinomas	Predictive and Germline screening	BRCA1, BRCA2, ATM, BRIP1, CHEK2, NBN, PALB2, RAD51C, RAD51D, TP53	**Reflex testing ordered by the pathologist**
Endometrium	1. Stage IA endometrioid + high grade + LVSI negative or focal 2. Stage IB endometrioid + low grade + LVSI negative or focal 3. Stage IA/IB endometrioid + substantial LVSI 4. Stage IB endometrioid + high grade 5. Stage II	Prognosis	POLE, TP53, MLH1, MSH2, MSH6, PMS2, EPCAM, microsatellite instability	**Reflex testing ordered by the pathologist**
	High-grade carcinomas with ambiguous morphology	Diagnosis	POLE, TP53, PTEN, ARID1A, SMARCB1, SMARCA4, MLH1, MSH2, MSH6, PMS2, EPCAM, microsatellite instability	Ordered by the pathologist if no diagnostic consensus
	Negative germline testing in patient with MMR-deficient endometrioid carcinoma and clinical suspicion of Lynch syndrome	Germline screening	MLH1, MSH2, MSH6, PMS2, EPCAM, microsatellite instability	Ordereded by medical genetics
Mesothelium	Malignant mesotheliomas	Diagnosis	CDKN2A, CDKN2B, BAP1, NF2, TRAF7, CDC42	Ordered by the pathologist if no diagnostic consensus
Prostate	Metastatic prostate carcinomas	Predictive and germline screening	ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, TP53, BARD1, BRIP1, CDK12, RAD51C, RAD51D	Ordered by the oncologist
Kidney	Unclassifiable renal tumors	Diagnosis	VHL, BAP1, TSC1, TSC2, FH, FLCN, ELOC, SDHA, SDHB, SDHC, SDHD, SETD2, NF2, MET, MTOR, SMARCB1, TERT, TFEB, chromosomal copy number alterations	Ordered by the pathologist if no diagnostic consensus
Testes	Germ cell tumors	Diagnosis	Chromosome 12p gain	Ordered by the pathologist if no diagnostic consensus
Thyroid	Metastatic and radio-iodine refractory thyroid carcinomas	Predictive	BRAF, NRAS, HRAS, KRAS, MAP2K1, MAP2K2, MAP2K4, MAPK1	Ordered by the oncologist

Lymphoma	Lymphoplasmacytic Lymphoma	Diagnosis	MYD88	Ordered by the pathologist if no diagnostic consensus
Skin	Dysplastic nevus	Diagnosis	Chromosomal copy number alterations	Ordered by the pathologist if no diagnostic consensus
Soft Tissue	Atypical Lipomatous Tumors; Dedifferentiated Liposarcoma	Diagnosis	MDM2, CDK4 amplification	Ordered by the pathologist if no diagnostic consensus
	Gastro-Intestinal Stromal Tumors	Predictive and Diagnosis	KIT, PDGFRA, BRAF, NF1, SDHA, SDHB, SDHC, SDHD	Ordered by the oncologist
	Desmoid Fibromatosis; Fibrous Dysplasia; Myxoma; Giant Cell Tumor of Bone, Chondroblastoma, Aneurysmal Bone Cyst	Diagnosis	APC, CTNNB1, GNAS, IDH1, IDH2, H3F3A, H3F3B	Ordered by the pathologist if no diagnostic consensus
	Neuroblastoma	Prognosis and Predictive	MYCN amplification, ALK mutations	Ordered by the oncologist
	Perivascular epithelioid cell neoplasms (PEComa)	Diagnosis	TSC1, TSC2	Ordered by the pathologist if no diagnostic consensus
Salivary Gland	Polymorphous Low-Grade Adenocarcinoma	Diagnosis	PRKD1	Ordered by the pathologist if no diagnostic consensus
Colorectal Carcinoma	Negative germline testing in patient with MMR-deficient colon carcinona and clinical suspicion of Lynch syndrome	Germline screening	MLH1, MSH2, MSH6, PMS2, EPCAM, microsatellite instability	Ordereded by medical genetics