Solid Tumor Mutation Panel (v.1)

A panel of tests interrogates selected regions of 26 cancer –related genes using amplicon next generation sequencing to help confirm tumor classification, to identify tumor markers, and to guide selection of standard or experimental therapy in cancer patients.

Rationale for testing:
Somatic gene mutation is thought to promote uncontrolled cell division underlying tumor growth. Presence of certain gene variants helps diagnose neoplasia and classify tumor type in a manner that facilitates clinical decisions. Gene variants that commonly confer susceptibility or resistance to therapy are compiled into this test panel that promotes efficient use of laboratory resources to identify tumor markers that can improve clinical decision-making. Primary or metastatic tumor tissue is evaluated to identify actionable mutations.

Clinical Indications for Solid Tumor Mutation Panel:
1) Patient with colorectal adenocarcinoma, gastrointestinal stromal tumor, melanoma, or non-small cell lung carcinoma in whom knowledge of pertinent gene variants would facilitate patient care*
2) Cancer patient in whom knowledge of pertinent gene variants could assist in clinical trial enrollment (for example, *PIK3CA* mutation in endometrial carcinoma)

Specimen Requirements:
This assay sequences segments of genomic DNA extracted from paraffin-embedded tumor tissue or from a fine needle aspirate slide. Ten unstained sections from formalin-fixed, paraffin-embedded (FFPE) tumor tissue on plain, uncoated glass slides (5 uM thick) are required. For fine needle aspirates, a diff-quick-stained slide (typically the first pass) is photographed to document cytomorphology before it is submitted for testing. An H&E or diff-quick stained slide must be evaluated by a pathologist to circle areas for testing having >20% malignant cells. A copy of the surgical pathology or cytopathology report is requested.

Method: Reagents in the TruSight Tumor kit (Illumina) are used to generate amplicons that are then sequenced on an Illumina Miseq and interpreted by a pathologist. When necessary, confirmatory tests are done.

Gene regions tested:

AKT1 exon 2	FOXL2 exon 1	MET exon 13	PIK3CA exon 7
ALK exon 23	GNAQ exons 4-6	MET exon 15	PIK3CA exon 9
APC exon 15	GNAS exon 6	MET exon 16	PIK3CA exon 20
BRAF exon 11	GNAS exon 8	MET exon17	PTEN exons 1-7
BRAF exon 15	KIT exon 9	MET exon 18	PTEN exon 9
CDH1 exon 8	KIT exon 11	MET exon 20	SMAD4 exon 8
CDH1 exon 9	KIT exon 13	MSH6 exon 5	SMAD4 exon 11
CDH1 exon 12	KIT exon 17	NRAS exons 1-4	SRC exon 10
CTNNB1 exon 2	KIT exon 18	PDGFRA exon 11	STK11 exon 1
EGFR exons 18-21	KRAS exons 1-4	PDGFRA exon 13	STK11 exon 4
ERBB2 exon 20	MAP2K exon 2	PDGFRA exon 17	STK11 exon 6
FBXW7 exons 7-11	MET exon 1	PIK3CA exon 1	STK11 exon 8
FGFR2 exon 6	MET exon 4	PIK3CA exon 2	TP53 exons 2-11

Limitations:
Gene amplifications, translocations, and insertions or deletions over 25 bases in length are not detectable by this assay. Variants predicted to be non-deleterious (such as synonymous coding changes and common population variants) are not reported. Normal tissue is not tested to prove whether a gene variant is somatic (acquired) or germline (heritable). If the patient has evidence of a heritable cancer syndrome (e.g. different tumor types, early age of onset, family history), genetic counseling is recommended.

***Valid clinical uses:**

***EGFR* mutation-** Detect *EGFR* mutation in non-small cell lung cancer to predict response to anti-EGFR therapy.

***KRAS* mutation-** Detect *KRAS* mutation in colorectal adenocarcinoma to predict resistance to anti-EGFR therapy. Subclassify non-small cell lung cancer.

***BRAF* mutation-** Detect *BRAF* mutation to 1) predict resistance to anti-EGFR therapy in colorectal adenocarcinoma; 2) predict response to BRAF inhibitors in melanoma; 3) help rule out Lynch syndrome; and 4) add value beyond traditional histopathologic methods to diagnose and classify neoplasia (e.g. hairy cell leukemia, Langerhans cell histiocytosis, papillary thyroid carcinoma).

***KIT* mutation-** In melanoma or gastrointestinal stromal tumor, detect mutant *KIT* predicting responsiveness to tyrosine kinase inhibitor therapy.

***PDGFRA* mutation-** In gastrointestinal stromal tumor, detect mutant *PDGFRA* predicting responsiveness to tyrosine kinase inhibitor therapy.

***PIK3CA* mutation-** Detect *PIK3CA* mutation and other defective genes in the PI3K signaling pathway (*AKT1, STK11* or *PTEN*) to evaluate options for clinical trial enrollment in a wide range of solid tumors.

***NRAS* mutation-** Detect *NRAS* mutation in metastatic melanoma to explore options for clinical trial enrollment.

***PIK3CA* mutation-** Detect *PIK3CA* mutation for prognosis and to predict drug response in colon cancer. Detect mutation in PI3K signaling pathway (*PIK3CA, AKT1, STK11* or *PTEN*) to evaluate options for clinical trial enrollment in a wide range of solid tumors.

***ERBB2 (Her2)* mutation -** Detect *ERBB2* kinase domain (exon 20) mutation in breast cancer or gastric cancer to evaluate options for clinical trial enrollment.

***NRAS* mutation-** Detect *NRAS* mutation in colon cancer to predict resistance to anti-EGFR therapy, or in metastatic melanoma to explore options for clinical trial enrollment.

References:

1. Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. Gastroenterology. 2015 Oct;149:1177-1190. PMID: 26216840
2. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing **guideline** for selection of **lung** cancer patients for **EGFR** and ALK tyrosine kinase inhibitors: **guideline** from the College of American Pathologists, International Association for the Study of **Lung** Cancer, and Association for Molecular Pathology. J Mol Diagn. 2013, PMID: 23562183
5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, at www.nccn.org.

To consult a pathologist about indications for testing or the significance of a result, call the Molecular Genetics Lab at (984) 974-1825 or Dr. Patel at (984) 974-1454. E-mail: nirali_patel@med.unc.edu

For other genomic test options for myeloid neoplasia, gastric cancer, or heritable cancer risk, visit the lab website, http://www.uncmedicalcenter.org/uncmc/professional-education-services/mclendon-clinical-laboratories/directory/molecular-pathology-and-genetics