PrimBio Cancer Hotspot Panel - Targeted Mutation Detection by Next Generation Sequencing

Test Information: Cancer is caused by acquired accumulation of genetic changes. These genetic changes result in abnormal cell proliferation and invasive behaviors which can lead to neoplastic growth or cancer. The genetic molecular changes in cancer can be categorized into two major groups: chromosomal genetic changes and nucleotide sequence changes. Most common nucleotide sequence changes in cancer involve single-nucleotide variants (missense and nonsense) and small insertions or deletions (some of which may result in frameshift mutations). This assay tests for individual genetic changes in 50 genes associated with most human cancers.

The genes tested in this panel are common tumor suppressor genes and oncogenes. All of the tested genes are "driver" genes, in that deleterious mutations in these genes can be involved in the initiation, progression or metastasis of cancer. This test can be utilized to test solid tumors or hematological cancers. The variants tested in this assay are associated with almost all known cancers including breast, ovarian, lung, colorectal, liver, skin, brain and blood. In addition there are approximately 120 therapy options (FDA approved and in clinical trials) associated with the variants tested.

This panel is used to determine the genetic information (somatic mutations) of a specific cancer or tumor so that a physician, genetic counselor, or other health provider can offer the optimal treatment plan for a cancer patient. The primary cause of chemotherapy treatment failure of most cancers is due to acquired resistance to therapy, which occurs approximately 90% of the time. This test can determine which therapies will be effective for a specific cancer or which cancers will be resistant to a specific therapy. In addition the health provider can determine alternate therapies associated with a specific variant that are FDA approved for a different condition or are in clinical trials.

The ordering physician or genetic counselor will receive a comprehensive clinical report along with the sequencing information that will list all pathogenic variants, as defined by strict regulatory guidelines. In addition the report will contain, but will not be limited to: the clinical significance of the variant, the biological function of the variant, FDA approved therapies for the condition and the variant, therapies that are in clinical trials for the condition, therapies that are in clinical trials for a particular variant in an alternate condition and all available therapies. In addition the report will contain information on which variants will be resistant to specific therapies. Below is an example of the first pages of the comprehensive clinical report:

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Advancing Personalized Medicine Using Genomic Innovation

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Patient	**Sample 390_LC_CHP**	Sample ID	**Sample 390_LC_CHP**	Test	**PrimBio Cancer Hotspot Panel**
Gender	**Male**	Specimen Type	**FFPE Block**	Type	**Full Report**
Age	**54 Years**	Block ID		Sample Collected	**07-Feb-2018**
MRN		Tumor Content	**56%**	Sample Received	**08-Feb-2018**
Clinician	**Dr. John Smith**	Specimen Site		Report Generated	**13-Feb-2018**
Hospital	**Prim Bio**				

Clinical Indications

Non-small cell lung carcinoma (NSCLC)

Note

Mutations were detected in PTEN and TP53 genes and their implications on therapeutic response are summarized below.

Summary for Standard Drugs

Drugs NOT INDICATED Based on FDA Mandated/ Guideline Recommended Markers (see page 4 for details).

Therapy	*Tested Marker(s)*	*Relevant Marker(s)*
Dabrafenib	*BRAF*	None
Trametinib	*BRAF*	None
Vemurafenib	*BRAF*	None
Afatinib	*EGFR*	None
Erlotinib	*EGFR*	None
Gefitinib	*EGFR*	None
Osimertinib	*EGFR*	None
Trastuzumab	*ERBB2*	None

Enhanced Response - Better than standard population response due to the presence or absence of specific markers.
Limited - Enhanced Response - Better than standard population response mitigated by the presence of conflicting markers.
Standard Response - Expected response similar to the typical population response for the specific therapy.
Reduced Response - Likely reduced response compared to the standard population response due to the presence of specific markers.
Poor Response - Likely poorer than the standard population response due to the presence of specific markers.

Markers for **Alectinib, Atezolizumab, Pembrolizumab, Ceritinib, Vinorelbine, Carboplatin, Paclitaxel, Docetaxel, Cisplatin, Cabozantinib, Pemetrexed, Gemcitabine, Nivolumab, Crizotinib, Brigatinib** are not part of this test

No well-established markers with sufficient clinical evidence in this tissue exist for **Bevacizumab, Etoposide, Irinotecan, Ramucirumab, Necitumumab, Vinblastine**

Summary for In-Trial/ Off-Label Drugs

Therapy	Relevant Markers	Approved Indications	Trials
Everolimus	PTEN ^{G293fs}	Pancreatic Neuroendocrine Tumor, Gastrointestinal Neuroendocrine Tumor, Lung Neuroendocrine Tumor, Kidney Cancer, Astrocytoma, Hormone receptor-positive HER2-negative Breast Cancer	NCT02890069, NCT02029001, NCT01061788, NCT01624766, NCT01582191
Temsirolimus	PTEN ^{G293fs}	Kidney Cancer	NCT01529593, NCT01552434, NCT02389309
Niraparib	PTEN ^{G293fs}	Ovarian Epithelial Cancer	NCT03209401, NCT03307785
Olaparib	PTEN ^{G293fs}	Ovarian Epithelial Cancer, Ovarian Cancer	NCT02498613, NCT01562210, NCT02576444, NCT03057145
Rucaparib Phosphate	PTEN ^{G293fs}	Ovarian Cancer	NCT02986100
Copanlisib	PTEN ^{G293fs}	Haematological Cancers	NCT02253420
Akt Inhibitor MK2206	PTEN ^{G293fs}	None	NCT01306045
Akt inhibitor AZD5363	PTEN ^{G293fs}	None	NCT01226316, NCT02664935, NCT02576444, NCT02117167
PARP Inhibitor BGB-290	PTEN ^{G293fs}	None	NCT02660034, NCT02361723
PARP Inhibitor BMN-673	PTEN ^{G293fs}	None	NCT03330405, NCT02286687, NCT02997163, NCT02921919
Veliparib	PTEN ^{G293fs}	None	NCT02944396, NCT02106546, NCT02412371, NCT02264990
Dual PI3 Kinase/mTOR Inhibitor PKI-587	PTEN ^{G293fs}	None	NCT03065062, NCT01920061, NCT02069158
mTOR Kinase Inhibitor AZD2014	PTEN ^{G293fs}	None	NCT02664935, NCT02583542, NCT02576444, NCT02117167
Prexasertib	TP53 ^{R213L}	None	NCT02124148, NCT03057145

Test Details

Special Notes:	This PrimBio Cancer Hotspot Gene Panel, performed by next generation sequencing (NGS), uses the Ion Ampliseq Cancer Hotspot Panel v2 primer set, which is designed to target 2855 mutations in the following 50 key cancer genes: *ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAS, GNAQ, HNF1A, HRAS, IDH1, JAK2, JAK3, IDH2, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, and VHL*. This mutation panel is designed to detect targeted mutations only. The 50 genes are not sequenced in their entirety. Mutations outside the targeted regions will not be detected. The limit of detection is 3.5% at 500X coverage and 5% at 200X coverage. This technology cannot reliable detect mutations at coverage below 200X. Confirmation of questionable mutations should be performed by Sanger sequencing or any other CLIA validated procedure.

Technical Information

Methodology:	Multiplex PCR followed by Next Generation Sequencing
Test Type:	Sequence Analysis

Sample & Shipping Information

PrimBio currently accepts extracted DNA samples, frozen fresh tissues, blood samples and FFPE slides for gene panel testing.