Genomic Testing Cooperative, LCA, 175 Technology Drive, Suite 100, Irvine, CA 92618
Tel: 1-866-484-8870 www.genomictestingcooperative.com
CLIA #: 05D2111917 CAP #: 9441547

Solid Tumor Profile Plus

Patient Name:		Ordering Physician:	
Date of Birth:		Physician ID:	
Gender (M/F):		Accession #:	
Client:		Specimen Type:	
Case #:		Specimen ID:	
Body Site:	COLON		

MRN:		Tumor Type:	
Collected Date:			
Received Date:			
Reported Date:			

Detected Genomic Alterations				
Level 1 (FDA-Approved)	Level 2 (Standard of Care)	Level 3 (Clinical Evidence)	Level 4 (Biological Evidence)	Other
-BRAF (V600E) -Microsatellite instability: positive-high (MSI-H) -Tumor Mutation Burden High: 59 Mut/Mb	Homologous recombination deficiency (HRD): Positive-High	ASXL1, RNF43, NBN, TOP2A, RB1, AXIN2 (2 mutations), MAP2K4, MLH1, GRIN2A, RARA	STAT6, TNFRSF1A, KMT2D (2 mutations), EPAS1, BCORL1, CTC1, PIK3C2B, QKI, CTCF, MSH6, GABRA6, FAT1, IL7R, KMT2B (2 mutations), ZMYM2, PPP1R13L	-HPV viral RNA : Detected at low level (type 82) -Chromosomal structural analysis shows 1q+, +6, 8p+, 9q+ (distal), 12q+, 13q+ and others

Results Summary

- **-Mutations in ASXL1, RNF43, BRAF (V600E), STAT6, NBN, TNFRSF1A, KMT2D (2 mutations), EPAS1, BCORL1, TOP2A, RB1, CTC1, AXIN2 (2 mutations), PIK3C2B, QKI, CTCF, MSH6, MAP2K4, GABRA6, MLH1, FAT1, IL7R, GRIN2A, KMT2B (2 mutations), RARA, ZMYM2, and PPP1R13L genes**
  -Microsatellite instability: positive-high (MSI-H)
  -Tumor Mutation Burden High: 59 Mut/Mb
  -Homologous recombination deficiency (HRD): Positive-High
  -Increased PD-L1 mRNA
  -EBV viral RNA: Not detected
  -HPV viral RNA: Detected at low level (type 82)
  -TTV viral RNA: Not detected
  -HLA Genotyping:
  -HLA-A: A*02:07-A*02:11
  -HLA-B: B*46:01-B*07:06
  -HLA-C: C*01:02-C*07:02

  -MSI-High and high TMB suggest response to Immune Checkpoint Inhibitors.

-BRAF mutation in colorectal tumors suggests response to treatment with triple therapy: BRAF inhibitor, anti-EGFR, and MEK inhibitor (Encorafenib, Cetuximab, and Binimetinib).

-Positive homologous recombination deficiency (HRD) suggests response to platinum-based chemotherapy and PARP inhibitors.

-RNF43 mutations suggests possible response to porcupine inhibitors.

-NBN and TOP2A mutation suggests response to PARP inhibitors.

-RB1 mutation suggests possible response to aurora A kinase inhibitors or BCL2 inhibitors as well as cisplatin-based therapy.

-AXIN2 mutation suggests possible response to WNT inhibitors.

-MAP2K4 mutation suggests possible response to MEK inhibitors.

-FAT1 abnormality can be targeted by Verteporfin to suppress metastasis.

Additional mutations detected: MAP3K14 (p.Glu601Gly, 46.11%), RARA (p.Pro38Thr, 44.46%), NOTCH1 (p.Arg2179Gln, 21.03%), ELANE (p.Arg96Trp, 19.76%), PPP2R1A (p.Glu510Gln, 17.49%), KMT2D (p.Ala5047Val, 17.41%), NOTCH2 (p.Met600Thr, 13.36%), FLT4 (p.Arg1145Cys, 12.86%), POLE (p.Thr26Ser, 12.84%), LRP1B (p.Ala225Val, 12.76%), FLCN (p.Pro228Ser, 12.45%), MVK (p.Arg325Cys, 12.28%), SF3B1 (p.Thr1187Met, 12.07%), GRIN2A (p.Val1090Met, 11.57%), ARID2 (p.Arg1787Cys, 11.54%), PIK3CG (p.Val67Met, 11.17%), PIK3CB (p.Pro220His, 10.84%), NTRK1 (p.Pro35His, 10.58%), EPHA5 (p.Glu600Lys, 10.32%), CHEK2 (p.Arg361Cys, 9.84%), NF1 (p.Arg2349His, 9.83%), EPHB1 (p.Arg84His, 9.73%), CTNNA1 (p.Val390Ile, 9.72%), ARID2 (p.Ala530Thr, 9.71%), IDH2 (p.Phe148Leu, 9.32%), KMT2D (p.Glu1658Lys, 9.05%), NOTCH1 (p.Ala105Thr, 9.05%), CREBBP (p.Gln2199Leu, 8.96%), GLI2 (p.Arg550His, 8.85%), DOT1L (p.Met1523Thr, 8.71%), NLRP3 (p.His784Asn, 8.67%), TSC1 (p.Tyr761Phe, 8.57%), ABRAXAS1 (p.Lys201Asn, 8.44%), FOXP1 (p.Thr240Ile, 8.4%), SMC3 (c.3583-2A>G, 8.22%), KMT2C (p.Ala4642Ser, 8.14%), IKBKE (p.Arg162Trp, 8.04%), PTCH1 (p.Tyr452Cys, 7.91%), SMAD4 (p.Ala425Asp, 7.89%), STAT4 (p.Asn392Ser, 7.68%), PRKAR1A (p.Arg13His, 7.56%), SMARCA4 (p.Arg1477Gln, 7.38%), GNA13 (p.Ile70Asn, 7.34%), IKZF3 (p.Arg223Cys, 7.21%), FANCB (p.Met1Val, 7.2%), SMARCA4 (p.Ala598Val, 6.86%), ARFRP1 (p.Asp153Asn, 6.76%), RTEL1 (p.Ala76Val, 6.67%), GALNT12 (p.Arg297Gln, 6.67%), SFTA3 (p.Ala189Val, 6.58%), NF1 (p.Asp100Asn, 6.52%), GNAS (p.Gly468Arg, 6.31%), PTCH1 (p.Leu39CysfsTer41, 6.12%), PTCH1 (p.Leu39AlafsTer51, 6.02%), RIT1 (p.Phe177Leu, 5.94%), U2AF2 (p.Glu425Lys, 5.93%), KDM6A (p.Ala212Thr, 5.92%), FANCC (p.Thr420ArgfsTer27, 5.84%), NOTCH3 (p.Ala2070Val, 5.36%), SUZ12 (p.Leu385ProfsTer10, 5.18%), DOT1L (p.Ala935GlnfsTer133, 5.04%), IRF4 (p.Ala16Val, 4.96%), FAT1 (p.Asp2309Asn, 4.82%), ATRX (p.Lys1169del, 4.73%), FLT3 (p.Glu204LysfsTer26, 4.58%), KMT2D (p.Gly5041Arg, 4.03%), FANCM (p.Lys1663GlufsTer10, 3.72%), ROS1 (p.Glu2120Gly, 3.69%), B2M (p.Tyr46Ser, 3.61%), SMARCA4 (p.Tyr552Ter, 3.37%), ATM (p.Arg2849Ter, 3.33%), AMER1 (p.Phe173LeufsTer36, 3.29%), JAK2 (p.Glu386Asp, 3.25%), TCIRG1 (p.Ala684Thr, 3.16%), KMT2B (p.Leu1071Gln, 3.02%), PIK3CA (p.His1047Arg, 2.38%), NBN (p.Arg551GlyfsTer8, 1.41%), B2M (p.Leu15PhefsTer41, 1.02%)

Tumor Heterogeneity

There is an abnormal clone with ASXL1, RNF43, BRAF (V600E), STAT6, NBN, TNFRSF1A, KMT2D (2 mutations), EPAS1, BCORL1, TOP2A, RB1, CTC1, AXIN2 (2 mutations), PIK3C2B, QKI, CTCF, MSH6, MAP2K4, GABRA6, MLH1, FAT1, IL7R, GRIN2A, KMT2B (2 mutations), RARA, ZMYM2, and PPP1R13L mutations.

Expression

Increased PD-L1 mRNA

Diagnostic Implications

ASXL1, RNF43, BRAF (V600E), STAT6, NBN, TNFRSF1A, KMT2D (2 mutations), EPAS1, BCORL1, TOP2A, RB1, CTC1, AXIN2 (2 mutations), PIK3C2B, QKI, CTCF, MSH6, MAP2K4, GABRA6, MLH1, FAT1, IL7R, GRIN2A, KMT2B (2 mutations), RARA, ZMYM2, PPP1R13L	These findings are consistent with colorectal cancer primary

FDA-Approved Therapeutics

BRAF (V600E)	Encorafenib + Cetuximab..
MSI-High	Ipilimumab, Ipilimumab + Nivolumab.. Pembrolizumab.

FDA-Approved Therapeutics in Other Tumor Types

HRD Positive	Niraparib + platinum-based chemotherapy

Relevant Alteration Associated with Resistance

BRAF mutation may suggest resistance to targeted anti-EGFR therapy

Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence)

ASXL1	Bromodomain and Extra-Terminal motif (BET) inhibitors & DNA methyltransferase inhibitors
RNF43	Porcupine inhibitors
NBN	PARP inhibitors
TOP2A	TOP2A inhibitors
RB1	Aurora A kinase inhibitors or BCL2 inhibitors as well as cisplatin-based therapy

AXIN2	WNT inhibitors
MAP2K4	MEK inhibitors
MLH1	Possible response to immunotherapy
GRIN2A	GRIN2A inhibitors
RARA	ATRA (with combined cytotoxic chemotherapy or arsenic trioxide (ATO)
TMB-High	Immunotherapy with checkpoint inhibitor

Relevant Genes with NO Alteration		
-No evidence of mutation in KRAS, NRAS, EGFR, TP53, or BRCA 1/2 -No specific mutation in DPYD gene, associated with enzymatic deficiency	No evidence of fusion mRNA involving ALK, RET, ROS1, or NTRK	-No evidence of MET14 deletion or EGFR Viii -No evidence of ERBB2 (HER2) amplification

Test Description:

This is a comprehensive molecular profile which uses next generation sequencing (NGS) to identify molecular abnormalities, including single nucleotide variants (SNVs), insertions/deletions (indels), copy number variants (CNVs), fusions, tumor mutational burden (TMB), microsatellite instability (MSI), homologous recombination deficiency (HRD), B- and T-cell clonality, and viruses (HPV, EBV, and TTV), in DNA of 434 genes and RNA in greater than 1600 genes implicated in solid tumors. Whenever possible, clinical relevance and implications of detected abnormalities are described below.

Biological relevance of detected Alterations

- ASXL1. This gene is similar to the Drosophila additional sex combs gene, which encodes a chromatin-binding protein required for normal determination of segment identity in the developing embryo. The protein is a member of the Polycomb group of proteins, which are necessary for the maintenance of stable repression of homeotic and other loci. The protein is thought to disrupt chromatin in localized areas, enhancing transcription of certain genes while repressing the transcription of other genes. The protein encoded by this gene functions as a ligand-dependent co-activator for retinoic acid receptor in cooperation with nuclear receptor coactivator 1. Mutations in this gene are associated with myelodysplastic syndromes and chronic myelomonocytic leukemia. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Sep 2009]

- RNF43. The protein encoded by this gene is a RING-type E3 ubiquitin ligase and is predicted to contain a transmembrane domain, a protease-associated domain, an ectodomain, and a cytoplasmic RING domain. This protein is thought to negatively regulate Wnt signaling, and expression of this gene results in an increase in ubiquitination of frizzled receptors, an alteration in their subcellular distribution, resulting in reduced surface levels of these receptors. Mutations in this gene have been reported in multiple tumor cells, including colorectal and endometrial cancers. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Mar 2015]

- BRAF. This gene encodes a protein belonging to the RAF family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion. Mutations in this gene, most commonly the V600E mutation, are the most frequently identified cancer-causing mutations in melanoma, and have been identified in various other cancers as well, including non-Hodgkin lymphoma, colorectal cancer, thyroid carcinoma, non-small cell lung carcinoma, hairy cell leukemia and adenocarcinoma of lung. Mutations in this gene are also associated with cardiofaciocutaneous, Noonan, and Costello syndromes, which exhibit overlapping phenotypes. A pseudogene of this gene has been identified on the X chromosome. [provided by RefSeq, Aug 2017]

- STAT6. The protein encoded by this gene is a member of the STAT family of transcription factors. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators. This protein plays a central role in exerting IL4 mediated biological responses. It is found to induce the expression of BCL2L1/BCL-X(L), which is responsible for the anti-apoptotic activity of IL4. Knockout studies in mice suggested the roles of this gene in differentiation of T helper 2 (Th2) cells, expression of cell surface markers, and class switch of immunoglobulins. Alternative splicing results in multiple transcript variants.[provided by RefSeq, May 2010]

- NBN. Mutations in this gene are associated with Nijmegen breakage syndrome, an autosomal recessive chromosomal instability syndrome characterized by microcephaly, growth retardation, immunodeficiency, and cancer predisposition. The encoded protein is a member of the

MRE11/RAD50 double-strand break repair complex which consists of 5 proteins. This gene product is thought to be involved in DNA double-strand break repair and DNA damage-induced checkpoint activation. [provided by RefSeq, Jul 2008]

- TNFRSF1A. This gene encodes a member of the TNF receptor superfamily of proteins. The encoded receptor is found in membrane-bound and soluble forms that interact with membrane-bound and soluble forms, respectively, of its ligand, tumor necrosis factor alpha. Binding of membrane-bound tumor necrosis factor alpha to the membrane-bound receptor induces receptor trimerization and activation, which plays a role in cell survival, apoptosis, and inflammation. Proteolytic processing of the encoded receptor results in release of the soluble form of the receptor, which can interact with free tumor necrosis factor alpha to inhibit inflammation. Mutations in this gene underlie tumor necrosis factor receptor-associated periodic syndrome (TRAPS), characterized by fever, abdominal pain and other features. Mutations in this gene may also be associated with multiple sclerosis in human patients. [provided by RefSeq, Sep 2016]

- KMT2D. The protein encoded by this gene is a histone methyltransferase that methylates the Lys-4 position of histone H3. The encoded proteir is part of a large protein complex called ASCOM, which has been shown to be a transcriptional regulator of the beta-globin and estrogen receptor genes. Mutations in this gene have been shown to be a cause of Kabuki syndrome. [provided by RefSeq, Oct 2010]

- EPAS1. This gene encodes a transcription factor involved in the induction of genes regulated by oxygen, which is induced as oxygen levels fall. The encoded protein contains a basic-helix-loop-helix domain protein dimerization domain as well as a domain found in proteins in signal transduction pathways which respond to oxygen levels. Mutations in this gene are associated with erythrocytosis familial type 4. [provided by RefSeq, Nov 2009]

- BCORL1. The protein encoded by this gene is a transcriptional corepressor that is found tethered to promoter regions by DNA-binding proteins. The encoded protein can interact with several different class II histone deacetylases to repress transcription. Two transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, May 2010]

- TOP2A. This gene encodes a DNA topoisomerase, an enzyme that controls and alters the topologic states of DNA during transcription. This nuclear enzyme is involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. It catalyzes the transient breaking and rejoining of two strands of duplex DNA which allows the strands to pass through one another, thus altering the topology of DNA. Two forms of this enzyme exist as likely products of a gene duplication event. The gene encoding this form, alpha, is localized to chromosome 17 and the beta gene is localized to chromosome 3. The gene encoding this enzyme functions as the target for several anticancer agents and a variety of mutations in this gene have been associated with the development of drug resistance. Reduced activity of this enzyme may also play a role in ataxia-telangiectasia. [provided by RefSeq, Jul 2010]

- RB1. The protein encoded by this gene is a negative regulator of the cell cycle and was the first tumor suppressor gene found. The encoded protein also stabilizes constitutive heterochromatin to maintain the overall chromatin structure. The active, hypophosphorylated form of the protein binds transcription factor E2F1. Defects in this gene are a cause of childhood cancer retinoblastoma (RB), bladder cancer, and osteogenic sarcoma. [provided by RefSeq, Jul 2008]

- CTC1. This gene encodes a component of the CST complex. This complex plays an essential role in protecting telomeres from degradation. This protein also forms a heterodimer with the CST complex subunit STN1 to form the enzyme alpha accessory factor. This enzyme regulates DNA replication. Mutations in this gene are the cause of cerebroretinal microangiopathy with calcifications and cysts. Alternate splicing results in both coding and non-coding variants. [provided by RefSeq, Mar 2012]

- AXIN2. The Axin-related protein, Axin2, presumably plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway, like its rodent homologs, mouse conductin/rat axil. In mouse, conductin organizes a multiprotein complex of APC (adenomatous polyposis of the colon), beta-catenin, glycogen synthase kinase 3-beta, and conductin, which leads to the degradation of beta-catenin. Apparently, the deregulation of beta-catenin is an important event in the genesis of a number of malignancies. The AXIN2 gene has been mapped to 17q23-q24, a region that shows frequent loss of heterozygosity in breast cancer, neuroblastoma, and other tumors. Mutations in this gene have been associated with colorectal cancer with defective mismatch repair. [provided by RefSeq, Jul 2008]

- PIK3C2B. The protein encoded by this gene belongs to the phosphoinositide 3-kinase (PI3K) family. PI3-kinases play roles in signaling pathways involved in cell proliferation, oncogenic transformation, cell survival, cell migration, and intracellular protein trafficking. This protein contains a lipid kinase catalytic domain as well as a C-terminal C2 domain, a characteristic of class II PI3-kinases. C2 domains act as calcium-dependent phospholipid binding motifs that mediate translocation of proteins to membranes, and may also mediate protein-protein interactions. The PI3-kinase activity of this protein is sensitive to low nanomolar levels of the inhibitor wortmanin. The C2 domain of this protein was shown to bind phospholipids but not Ca2+, which suggests that this enzyme may function in a calcium-independent manner. [provided by RefSeq, Jul 2008]

- QKI. The protein encoded by this gene is an RNA-binding protein that regulates pre-mRNA splicing, export of mRNAs from the nucleus, protein translation, and mRNA stability. The encoded protein is involved in myelinization and oligodendrocyte differentiation and may play a role in schizophrenia. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2014]

- CTCF. This gene is a member of the BORIS + CTCF gene family and encodes a transcriptional regulator protein with 11 highly conserved zinc finger (ZF) domains. This nuclear protein is able to use different combinations of the ZF domains to bind different DNA target sequences and proteins. Depending upon the context of the site, the protein can bind a histone acetyltransferase (HAT)-containing complex and function as a transcriptional activator or bind a histone deacetylase (HDAC)-containing complex and function as a transcriptional repressor. If the protein is bound to a transcriptional insulator element, it can block communication between enhancers and upstream promoters, thereby regulating imprinted expression. Mutations in this gene have been associated with invasive breast cancers, prostate cancers, and Wilms' tumors.

Alternatively spliced transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2010]

- MSH6. This gene encodes a member of the DNA mismatch repair MutS family. In E. coli, the MutS protein helps in the recognition of mismatched nucleotides prior to their repair. A highly conserved region of approximately 150 aa, called the Walker-A adenine nucleotide binding motif, exists in MutS homologs. The encoded protein heterodimerizes with MSH2 to form a mismatch recognition complex that functions as a bidirectional molecular switch that exchanges ADP and ATP as DNA mismatches are bound and dissociated. Mutations in this gene may be associated with hereditary nonpolyposis colon cancer, colorectal cancer, and endometrial cancer. Transcripts variants encoding different isoforms have been described. [provided by RefSeq, Jul 2013]

- MAP2K4. This gene encodes a member of the mitogen-activated protein kinase (MAPK) family. Members of this family act as an integration point for multiple biochemical signals and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation, and development. They form a three-tiered signaling module composed of MAPKKKs, MAPKKs, and MAPKs. This protein is phosphorylated at serine and threonine residues by MAPKKKs and subsequently phosphorylates downstream MAPK targets at threonine and tyrosine residues. A similar protein in mouse has been reported to play a role in liver organogenesis. A pseudogene of this gene is located on the long arm of chromosome X. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2013]

- GABRA6. GABA is the major inhibitory neurotransmitter in the mammalian brain where it acts at GABA-A receptors, which are ligand-gated chloride channels. Chloride conductance of these channels can be modulated by agents such as benzodiazepines that bind to the GABA-A receptor. At least 16 distinct subunits of GABA-A receptors have been identified. [provided by RefSeq, Jul 2008]

- MLH1. MLH1 is a tumor suppressor gene involved in DNA mismatch repair. Germline mutations in this gene are known to cause Lynch syndrome. The most common malignancies in Lynch syndrome are colorectal and endometrial carcinomas. In addition to germline mutations, somatic mutations in this gene have been described in colorectal and endometrial cancers.The protein encoded by this gene can heterodimerize with mismatch repair endonuclease PMS2 to form MutL alpha, part of the DNA mismatch repair system. When MutL alpha is bound by MutS beta and some accessory proteins, the PMS2 subunit of MutL alpha introduces a single-strand break near DNA mismatches, providing an entry point for exonuclease degradation. The encoded protein is also involved in DNA damage signaling and can heterodimerize with DNA mismatch repair protein MLH3 to form MutL gamma, which is involved in meiosis. This gene was identified as a locus frequently mutated in hereditary nonpolyposis colon cancer (HNPCC). [provided by RefSeq, Aug 2017]

- FAT1. This gene is an ortholog of the Drosophila fat gene, which encodes a tumor suppressor essential for controlling cell proliferation during Drosophila development. The gene product is a member of the cadherin superfamily, a group of integral membrane proteins characterized by the presence of cadherin-type repeats. In addition to containing 34 tandem cadherin-type repeats, the gene product has five epidermal growth factor (EGF)-like repeats and one laminin A-G domain. This gene is expressed at high levels in a number of fetal epithelia. Its product probably functions as an adhesion molecule and/or signaling receptor, and is likely to be important in developmental processes and cell communication. Transcript variants derived from alternative splicing and/or alternative promoter usage exist, but they have not been fully described. [provided by RefSeq, Jul 2008]

- IL7R. The protein encoded by this gene is a receptor for interleukin 7 (IL7). The function of this receptor requires the interleukin 2 receptor, gamma chain (IL2RG), which is a common gamma chain shared by the receptors of various cytokines, including interleukins 2, 4, 7, 9, and 15. This protein has been shown to play a critical role in V(D)J recombination during lymphocyte development. Defects in this gene may be associated with severe combined immunodeficiency (SCID). Alternatively spliced transcript variants have been found. [provided by RefSeq, Dec 2015]

- GRIN2A. This gene encodes a member of the glutamate-gated ion channel protein family. The encoded protein is an N-methyl-D-aspartate (NMDA) receptor subunit. NMDA receptors are both ligand-gated and voltage-dependent, and are involved in long-term potentiation, an activity-dependent increase in the efficiency of synaptic transmission thought to underlie certain kinds of memory and learning. These receptors are permeable to calcium ions, and activation results in a calcium influx into post-synaptic cells, which results in the activation of several signaling cascades. Disruption of this gene is associated with focal epilepsy and speech disorder with or without cognitive disability. Alternative splicing results in multiple transcript variants. [provided by RefSeq, May 2014]

- KMT2B. This gene encodes a protein which contains multiple domains including a CXXC zinc finger, three PHD zinc fingers, two FY-rich domains, and a SET (suppressor of variegation, enhancer of zeste, and trithorax) domain. The SET domain is a conserved C-terminal domain that characterizes proteins of the MLL (mixed-lineage leukemia) family. This gene is ubiquitously expressed in adult tissues. It is also amplified in solid tumor cell lines, and may be involved in human cancer. Two alternatively spliced transcript variants encoding distinct isoforms have been reported for this gene, however, the full length nature of the shorter transcript is not known. [provided by RefSeq, Jul 2008]

- RARA. This gene represents a nuclear retinoic acid receptor. The encoded protein, retinoic acid receptor alpha, regulates transcription in a ligand-dependent manner. This gene has been implicated in regulation of development, differentiation, apoptosis, granulopoeisis, and transcription of clock genes. Translocations between this locus and several other loci have been associated with acute promyelocytic leukemia. Alternatively spliced transcript variants have been found for this locus.[provided by RefSeq, Sep 2010]

- ZMYM2. The protein encoded by this gene is a zinc finger protein that may act as a transcription factor. The encoded protein may be part of a BHC histone deacetylase complex. Translocation of this gene with the fibroblast growth factor receptor-1 gene (FGFR1) results in a fusion gene, which may be a cause of stem cell leukemia lymphoma syndrome (SCLL). Several transcript variants encoding the same protein have been found for this gene. [provided by RefSeq, Jul 2010]

- PPP1R13L. IASPP is one of the most evolutionarily conserved inhibitors of p53 (TP53; MIM 191170), whereas ASPP1 (MIM 606455) and ASPP2 (MIM 602143) are activators of p53.[supplied by OMIM, Mar 2008]

Drug Information

Pembrolizumab

Pembrolizumab is a highly selective IgG4-kappa humanized monoclonal antibody against PD-1 receptor. It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype with the containing a stabilizing S228P Fc mutation.

Talazoparib

Talazoparib is a poly(ADP-ribose) Polymerase 1, 2 (PARP 1;2 inhibitor).

Talazoparib was approved by the FDA for use in germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancer on October 16, 2018 under the trade name Talzenna. Talazoparib prevents PARP-mediated repair of DNA damage in cancer cells, allowing accumulation of damage and PARP-DNA complexes. Repair related errors by error prone secondary repair pathways may also contribute to the cytotoxicity of Talazoparib. Talazoparib is indicated for the treatment of deleterious or suspected deleterious germline BRCA mutated, HER2 negative locally advanced or metastatic breast cancer in adults.

Niraparib

Niraparib (ZEJULA) is an inhibitor of poly (ADP-ribose) polymerase (PARP) with potential antineoplastic activity. PARP Inhibitor MK4827 inhibits PARP activity, enhancing the accumulation of DNA strand breaks and promoting genomic instability and apoptosis. The PARP family of proteins detect and repair single strand DNA breaks by the base-excision repair (BER) pathway. The specific PARP family member target for PARP inhibitor MK4827 is unknown. (NCI Thesaurus)

ZEJULA is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Olaparib

Olaparib (Lynparza) is an antineoplastic agent, Poly(ADP-ribose) Polymerase 1;2;3 inhibitor. (PARP 1;2;3 inhibitor).

Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Rucaparib

Rucaparib is a potent mammalian poly(ADP-ribose) polymerase 1, 2 and 3 inhibitor with anticancer properties (PARP 1;2;3 inhibitor).

PPAR is an enzyme that plays an essential role in DNA repair by activating response pathways and facilitating repair, and defects in these repair mechanisms have been demonstrated in various malignancies, including cancer. Regulation of repair pathways is critical in promoting necessary cell death. BRCA genes are tumor suppressor genes mediate several cellular processes including DNA replication, transcription regulation, cell cycle checkpoints, apoptosis, chromatin structuring and homologous recombination (HR). Homologous recombination deficiency (HRD), along with PPAR inhibition, is a vulnerability that enhances the cell death pathway when the single mutations alone would permit viability. Ovarian cancer commonly possesses defects in DNA repair pathways such as HRD due to BRCA mutations or otherwise. Rucaparib has shown to induce cytotoxicity in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Of all the BRCA1/2 mutations in ovarian cancer, most are due to germline mutations (18%), and approximately 7% represent somatic mutations acquired within the tumor.

Rucaparib is an inhibitor of PARP-1, PARP-2, and PARP-3. Via an inhibitory effect on the PARP enzymatic activity, rucaparib decreases the formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. It is proposed that PARP inhibition specifically targets tumor cells with preexisting HRD, such as those cells possessing mutations in the BRCA1 or BRCA2 genes.

Nivolumab

Nivolumab is a fully human IgG4 antibody targeting the immune checkpoint programmed death receptor-1 (PD-1). This molecule was produced entirely on mice and grafted onto human kappa and IgG4 Fc region with the mutation S228P for additional stability and reduced variability.

Ipilimumab

Ipilimumab is a monoclonal antibody to the cytotoxic T lymphocyte antigen-4 (CTLA-4) which activates antitumor immunity by inhibiting this major checkpoint.
After T-cell activation, pilimumab interrupts the stimulatory signal which in order blunts T-cell proliferation response. The action of ipilimumab produces an exacerbated autoimmunity. This is explained as the absence or presence of CTLA-4 can augment or suppress the immune system's T-cell response in fighting disease. Ipilimumab is designed to block the activity of CTLA-4, thereby sustaining a potent T-cell response against tumor

cells.

Ipilimumab was FDA approved for the treatment of melanoma and for the combination of low dose ipilimumab and nivolumab for the treatment of previously treated microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) metastatic colorectal cancer.

Dabrafenib

Dabrafenib mesylate (Tafinlar) is a reversible ATP-competitive kinase inhibitor and targets the MAPK pathway.

Dabrafenib is an orally bioavailable inhibitor of B-raf (BRAF) protein with antineoplastic activity. Dabrafenib selectively binds to and inhibits the activity of B-raf, which may inhibit the proliferation of tumor cells which contain a mutated BRAF gene.

Dabrafenib causes an inhibition of phosphorylated extracellular signal-regulated kinase (ERK). This indicates a decrease in cell proliferation. Furthermore, within 24 hours of administration, downstream mediators of the MAPK pathway are inhibited. BRAF belongs to the raf/mil family of serine/threonine protein kinases and plays a role in regulating the MAP kinase/Extracellular Signal-regulated Kinases signaling pathway, which may be constitutively activated due to BRAF gene mutations.

Vemurafenib

Vemurafenib is a competitive kinase inhibitor with activity against BRAF kinase with mutations like V600E. Vemurafenib blocks downstream processes to inhibit tumour growth and eventually trigger apoptosis. Vemurafenib does not have antitumour effects against melanoma cell lines with the wild-type BRAF mutation. It exerts its function by binding to the ATP-binding domain of the mutant BRAF. Vemurafenib was co-developed by Roche and Plexxikon and it obtained its FDA approval on August 17, 2011, under the company Hoffmann La Roche. BRAF activation results in cell growth, proliferation, and metastasis. BRAF is an intermediary molecule in MAPK whose activation depends on ERK activation, elevation of cyclin D1 and cellular proliferation. The mutation V600E produces a constitutively form of BRAF. Vemurafenib has been shown to reduce all activation markers related to BRAF; in clinical trials, vemurafenib treatment showed a reduction of cytoplasmic phosphorylated ERK and a cell proliferation driven by Ki-67. Studies also reported decrease in MAPK-related metabolic activity. All the different reports indicate thet Vemurafenib generates an almost complete inhibition of the MAPK pathway.

Trametinib

Trametinib is an orally bioavailable inhibitor of mitogen-activated protein kinase kinase (MEK MAPK/ERK kinase) with potential antineoplastic activity. Trametinib specifically binds to and inhibits MEK 1 and 2, resulting in an inhibition of growth factor-mediated cell signaling and cellular proliferation in various cancers. MEK 1 and 2, dual specificity threonine/tyrosine kinases often upregulated in various cancer cell types, play a key role in the activation of the RAS/RAF/MEK/ERK signaling pathway that regulates cell growth.

Palbociclib

Palbociclib is an investigational selective, small-molecule inhibitor of CDK4 and CDK6. CDK4 and CDK6 along with their regulatory partner cyclin D1 play a key role in regulating the G1- to S-phase cell-cycle transition via regulation of phosphorylation of the retinoblastoma (Rb) protein. Inhibition of these proteins leads to reduced phosphorylation of Rb, inhibition of downstream signalling, and increased tumor growth arrest.

Palbociclib is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Ribociclib

Ribociclib inhibits both CDK4 and CDK6. An orally available cyclin-dependent kinase (CDK) inhibitor targeting cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway, with potential antineoplastic activity. CDK4/6 inhibitor LEE011 specifically inhibits CDK4 and 6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Inhibition of Rb phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth. Overexpression of CDK4/6, as seen in certain types of cancer, causes cell cycle deregulation.

Trametinib

Trametinib is an orally bioavailable inhibitor of mitogen-activated protein kinase kinase (MEK MAPK/ERK kinase) with potential antineoplastic activity. Trametinib specifically binds to and inhibits MEK 1 and 2, resulting in an inhibition of growth factor-mediated cell signaling and cellular proliferation in various cancers. MEK 1 and 2, dual specificity threonine/tyrosine kinases often upregulated in various cancer cell types, play a key role in the activation of the RAS/RAF/MEK/ERK signaling pathway that regulates cell growth.

Binimetinib

Binimetinib is an orally available inhibitor of mitogen-activated protein kinase kinase 1 and 2 (MEK1/2) with potential antineoplastic activity. Binimetinib, noncompetitive with ATP, binds to and inhibits the activity of MEK1/2. Inhibition of MEK1/2 prevents the activation of MEK1/2-dependent effector proteins and transcription factors, which may result in the inhibition of growth factor-mediated cell signaling. This may eventually lead to an inhibition of tumor cell proliferation and an inhibition in production of various inflammatory cytokines including interleukin-1, -6

and tumor necrosis factor. MEK1/2 are dual-specificity threonine/tyrosine kinases that play key roles in the activation of the RAS/RAF/MEK/ERK pathway and are often upregulated in a variety of tumor cell types.

Cobimetinib

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase 1 (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK inhibitor Cobimetinib specifically binds to and inhibits the catalytic activity of MEK1, resulting in inhibition of extracellular signal-related kinase 2 (ERK2) phosphorylation and activation and decreased tumor cell proliferation. Cobimetinib targets kinase activity in the RAS/RAF/MEK/ERK pathway.

Selumetinib

Selumetinib is a MEK inhibitor that targets PDGFR, KIT, VEGFR, FLT3, RET, CSF1R. It is an orally bioavailable small molecule with potential antineoplastic activity. Selumetinib inhibits mitogenactivated protein kinase kinases (MEK or MAPK/ERK kinases) 1 and 2, which may prevent the activation of MEK1/2-dependent effector proteins and transcription factors, and so may inhibit cellular proliferation in MEK-overexpressing tumor cells. MEK 1 and 2 are dual-specificity kinases that are essential mediators in the activation of the RAS/RAF/MEK/ERK pathway, are often upregulated in various tumor cell types, and are drivers of diverse cellular activities, including cellular proliferation.

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
https://classic.clinicaltrials.gov/show/NCT05425940	Recruiting	Study of XL092 + Atezolizumab vs Regorafenib in Subjects With Metastatic Colorectal Cancer	Colorectal Cancer	XL092 Atezolizumab Regorafenib	Exelixis Clinical Site #65, Jonesboro, Alabama, United States Exelixis Clinical Site #30, Phoenix, Arizona, United States Exelixis Clinical Site #70, Tucson, Arizona, United States
https://classic.clinicaltrials.gov/show/NCT03668431	Recruiting	Dabrafenib + Trametinib + PDR001 In Colorectal Cancer	Colorectal Cancer	Dabrafenib Trametinib PDR001	Massachusetts General Hosital Cancer Center, Boston, Massachusetts, United States Dana Farber Cancer Institite, Boston, Massachusetts, United States
https://classic.clinicaltrials.gov/show/NCT05319314	Recruiting	GCC19CART for Patients With Metastatic Colorectal Cancer	Colorectal Cancer	GCC19CART	City of Hope Comprehensive Cancer Center, Duarte, California, United States University of California San Francisco Medical Center, San Francisco, California, United States University of Colorado Hospital - Anschutz Cancer Pavilion, Aurora, Colorado, United States

https://classic.clinicaltrials.gov/show/NCT04907539	Recruiting	A Study to Assess Efficacy of RXC004 +/- Nivolumab in Ring Finger Protein 43 (RNF43) or R-spondin (RSPO) Aberrated, Metastatic, Microsatellite Stable, Colorectal Cancer After Progression on Standard of Care (SOC)	Colorectal Cancer	RXC004 Nivolumab Denosumab	Community Health Network Cancer Center North - Community Hospital Network, Indianapolis, Indiana, United States UT MD Anderson Cancer Center, Houston, Texas, United States Lumi Research, Kingswood, Texas, United States

Detailed Results

Single Nucleotide Variant (SNV) and Insertions-Deletions (INDELS)

Gene name	Hgvsp	Hgvsc	Aminoacids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
ASXL1	NP_056153.2:p.Gly645ValfsTer58	NM_015338.5:c.1934delG	G/X	Ggg/gg	frameshift_variant	32.38	698	0
RNF43	NP_060233.3:p.Gly659ValfsTer41	NM_017763.4:c.1976delG	G/X	gGt/gt	frameshift_variant	27.92	573	0
BRAF	NP_004324.2:p.Val600Glu	NM_004333.4:c.1799T>A	V/E	gTg/gAg	missense_variant	27.33	1321	deleterious (0)
STAT6	NP_003144.3:p.Gln281ArgfsTer3	NM_003153.4:c.841delC	Q/X	Cag/ag	frameshift_variant	19.33	781	0
NBN	NP_002476.2:p.Arg466GlyfsTer18	NM_002485.4:c.1396delA	R/X	Agg/gg	"frameshift_variant, splice_region_variant"	18.83	563	0
TNFRSF1A	NP_001056.1:p.Ala321LeufsTer31	NM_001065.3:c.961delG	A/X	Gct/ct	frameshift_variant	17.61	914	0
KMT2D	NP_003473.3:p.Gln773ProfsTer3	NM_003482.3:c.2317dupC	Q/PX	cag/cCag	frameshift_variant	14.53	743	0
KMT2D	NP_003473.3:p.Val3089TrpfsTer30	NM_003482.3:c.9265delG	V/X	Gtg/tg	frameshift_variant	14.05	605	0
EPAS1	NP_001421.2:p.Gln561SerfsTer7	NM_001430.4:c.1681delC	T/X	aCc/ac	frameshift_variant	13.0	554	0
BCORL1	NP_068765.3:p.Pro1681GlnfsTer20	NM_021946.4:c.5042delC	S/X	tCc/tc	frameshift_variant	12.28	920	0
TOP2A	NP_001058.2:p.Thr1205HisfsTer19	NM_001067.3:c.3613delA	T/X	Aca/ca	frameshift_variant	11.97	685	0
RB1	NP_000312.2:p.Asn290MetfsTer11	NM_000321.2:c.869delA	K/X	Aaa/aa	frameshift_variant	10.57	331	0
CTC1	NP_079375.3:p.Ala825LeufsTer59	NM_025099.5:c.2472delC	P/X	ccC/cc	frameshift_variant	10.55	1592	0
AXIN2	NP_004646.3:p.Gly270Ter	NM_004655.3:c.808G>T	G/*	Gga/Tga	stop_gained	10.43	278	0

PIK3C2B	NP_002637.3:p.Pro798LeufsTer53	NM_002646.3:c.2393delC	P/X	cCt/ct	frameshift_variant	9.3	774	0
QKI	NP_006766.1:p.Lys134ArgfsTer14	NM_006775.2:c.401delA	K/X	Aaa/aa	frameshift_variant	8.89	1328	0
CTCF	NP_006556.1:p.Arg342His	NM_006565.3:c.1025G>A	R/H	cGt/cAt	missense_variant	8.69	1393	deleterious (0.01)
AXIN2	NP_004646.3:p.Glu405GlyfsTer56	NM_004655.3:c.1214_1215delAG	E/X	gAG/g	frameshift_variant	8.46	910	0
MSH6	NP_000170.1:p.Lys247AsnfsTer32	NM_000179.2:c.741delA	I/X	atA/at	frameshift_variant	8.3	1795	0
MAP2K4	NP_001268364.1:p.Gln137Ter	NM_001281435.1:c.409C>T	Q/*	Caa/Taa	stop_gained	8.23	1288	0
GABRA6	NP_000802.2:p.Arg84ProfsTer6	NM_000811.2:c.248dupT	V/VX	gtt/gTtt	frameshift_variant	8.08	767	0
MLH1	NP_000240.1:p.Lys134AsnfsTer2	NM_000249.3:c.402delA	G/X	ggA/gg	frameshift_variant	7.96	691	0
FAT1	NP_005236.2:p.Pro1877LeufsTer20	NM_005245.3:c.5630delC	P/X	cCt/ct	frameshift_variant	7.91	1365	0
IL7R	NP_002176.2:p.Arg267GlyfsTer28	NM_002185.3:c.799delA	K/X	Aaa/aa	frameshift_variant	7.02	983	0
GRIN2A	NP_000824.1:p.Ser1341LysfsTer25	NM_000833.3:c.4021dupA	S/KX	agc/aAgc	frameshift_variant	6.96	1308	0
KMT2B	NP_055542.1:p.Trp1314Ter	NM_014727.1:c.3941G>A	W/*	tGg/tAg	stop_gained	6.9	536	0
KMT2B	NP_055542.1:p.Arg2057AlafsTer34	NM_014727.1:c.6169delC	A/X	gCc/gc	frameshift_variant	6.37	1068	0
RARA	NP_000955.1:p.Pro30LeufsTer12	NM_000964.3:c.89delC	F/X	ttC/tt	frameshift_variant	6.3	381	0
ZMYM2 (RNA)	NP_003444.1:p.Lys1044ArgfsTer33	NM_003453.3:c.3131delA	K/X	Aaa/aa	frameshift_variant	21.82	385	0
PPP1R13L (RNA)	NP_001135974.1:p.Arg519GlyfsTer118	NM_001142502.1:c.1555delC	R/X	Cgg/gg	frameshift_variant	19.56	317	0

Methodology and Test Background

This is a next generation sequencing (NGS) test that analyzes DNA for abnormalities in 434 genes and RNA of >1600 genes that are reported to be altered in various types of solid tumors. The assay also detects several viruses that are important in oncology, including EBV, HPV and TTV. TTV (torque teno virus) was first discovered in a patient with non-A-E hepatitis and is now regarded as a part of the human virome. In general, TTV does not cause pathology in immunocompetent individuals. TTV is considered as a marker of immune competence in patients with immunological impairment and inflammatory disorders. High TTV load is associated with increased risk of infection. In patients with organ transplant, low TTV load is associated with an increased risk of rejection.

Nucleic acid is isolated from paraffin-embedded tissue. For optimal results neoplastic cells should be greater than 30% of the analyzed cells. H&E-sections are reviewed by a pathologist and tumor-enrichment is performed by macrodissection when possible. Testing is performed using massive parallel sequencing of the coding DNA of the listed genes. This includes sequencing of all the exons as well as approximately 50 nucleotides at the 5’ and 3’ ends of each coding exon to detect splice site abnormalities. The TERT promoter region, including the hotspots at -124 and

-146 bp, is also covered. Our DNA sequencing method has a sensitivity of 3% for detecting hotspot mutations and 5% for detecting single nucleotide variants (SNVs) and small (<60 bp) insertions/ deletions (indels). MSI status is inferred by interrogating all available genomic microsatellites covered. Tumor mutational burden (TMB) is measured by counting all nonsynonymous variants and filter settings as follows: (A) Pass all filters; (B) inside genes; (C) had a mutant allele frequency >5%; (D) not found in the dbSNP (to exclude germline variations). The median for TMB is 10 mutations/Mb based on lung carcinoma analysis. The cut off for other types of tumors is not well-established at this time. Significant gene amplification and deletion (copy number variants) are also reported. Targeted RNA NGS is performed by hybrid capture and duplicates are excluded for levels measurements. The Universal Human Reference (UHR) RNA is used as control. All detected fusion transcripts are reported. While the major focus of the RNA analysis is the detection of fusion mRNA, mutations in the expressed RNA of the analyzed genes, HLA class I genotyping, and Epstein-Barr virus (EBV), human papillomavirus (HPV) and torque teno virus (TTV) viral RNA are also analyzed and reported. B- and T-cell clonality will be reported, if clonal or clinically relevant. The sensitivity of this assay in detecting fusion mRNA is between 5% and 10%. This test specifically covers translocations that lead to the expression of fusion RNA. Translocations that lead to deregulation of expression can be addressed by this test if compared to the expression proper normal control. Since the clinical relevance of the RNA expression level of most of the genes is not characterized at this time, only a few specific genes will be commented on when abnormalities are detected. CD274 (PD-L1) mRNA levels are reported when they are significantly elevated. This assay is not designed to detect minimal residual disease and should be used for diagnosis. Performance of the assay may vary dependent on the quantity and quality of nucleic acid, sample preparation and sample age. Decalcified specimens have not been validated. Decalcification with strong acids is not recommended and may lead to poor nucleic acid quality and suboptimal results.

This test specifically covers translocations that lead to the expression of fusion RNA. Translocations that lead to deregulation of expression can be addressed by this test if compared to the expression proper normal control. Since the clinical relevance of the RNA expression level of most of the genes is not characterized at this time, only a few specific genes will be commented on when abnormalities are detected. CD274 (PD-L1) mRNA levels are reported when they are significantly elevated.

Based on our validation study, the following exonic regions of the genes listed below are not covered appropriately <100X coverage and sequencing by NGS may not be reliable in these regions. This poor coverage is mainly due to high GC content and inherent problem in obtaining adequate coverage. ASXL1 NM_001164603 20:30946620- 30946635, ATM NM_000051 11:108186550-108186638, BAP1 NM_004656 3:52443858-52443894, BCR NM_004327 22:23652510 -23652620, BRD4 NM_058243 19:15353808-15354193,5355041-15355411, CCNE1 NM_001238 19:30303463-30303485, CD274 NM_001267706 9:5456109-5456165, CD79A NM_001783 19:42384736-42384805, CSF3R NM_000760 1:36937667-36937740, DDX11 NM_001257144 12:31240872-31240917, ERBB3 NM_001982 12:56492284 -56492359, FANCI NM_001113378 15:89835919-89836052, FLT3 NM_004119 13:28674605-28674652, FLT4 NM_002020 5:180035281-180035284, GEN1 NM_001130009 2:17954486-17954525, H3-3A NM_002107 1:226259140-226259180, IRS2 NM_003749 13:110437126-110437363, 110437805-110437899, 110438359- 110438400, JAK1 NM_002227 1:65309747-65309771, MAGI2 NM_012301 7:77648719-77649044, MITF NM_000248 3:70005606-70005681, MYCL NM_001033081 1:40367518-40367565, NF1 NM_000267 17:29664837-29664898, NOTCH2 NM_001200001 1:120572528-120572610, PBRM1 NM_018313 3:52677264-52677322, PIK3R2 NM_005027 19:18272089-18272305, PMS2 NM_000535 7:6013024-6013173, RANBP2 NM_006267 2:109363166-109363254, 109367779-109367838, 109367984-109368069, 109369453-109369497, 109378578-109378651, .RHEB NM_005614 7:151216546-151216597, SUFU NM_001178133 10:104263911-104264039, TNFRSF14 NM_003820 1:2494304-2494335.

The table below contains a partial list of the tested DNA genes. For a complete list, please go to: https://genomictestingcooperative.com/genomic-tests/solid-tumor-profile-plus/ *(click the DNA tab)*

The table below contains a partial list of the tested RNA genes (Fusions/Expression). For a complete list, please go to: https://genomictestingcooperative.com/genomic-tests/solid-tumor-profile-plus/ *(click the RNA tab)*

Tested genes

Genes Tested for Abnormalities in Coding Sequence																
ABCB7	AURKB	C15ORF41	CEBPA	DNMT3A	FANCC	FLT3	GRIN2A	IRF2	LMO1	MSH6	NTRK2	POT1	RARA	SF3B1	STAT6	TSHR
ABL1	AURKC	CALR	CHD2	DOT1L	FANCD2	FLT4	GRM3	IRF4	LPIN2	MTOR	NTRK3	PPM1D	RB1	SLIT2	STK11	U2AF1
ABL2	AXIN1	CARD11	CHD4	EED	FANCE	FOXL2	GSK3B	IRS2	LRP1B	MUTYH	NUP93	PPP2R1A	RBBP6	SLX4	SUFU	U2AF2
ACD	AXIN2	CBFB	CHEK1	EGFR	FANCF	FOXP1	GSKIP	JAGN1	LYN	MVK	PAK3	PRDM1	RBM10	SMAD2	SUZ12	VEGFA
ACVR1B	AXL	CBL	CHEK2	EGLN1	FANCG	FRS2	H3F3A	JAK1	LYST	MYC	PALB2	PREX2	RBM8A	SMAD3	SYK	VHL
ADA	B2M	CBLB	CIC	ELANE	FANCI	FUBP1	HAX1	JAK2	LZTR1	MYCL	PARK2	PRKAR1A	RET	SMAD4	TAF1	WAS
AK2	BAP1	CBLC	CREBBP	EP300	FANCL	G6PC3	HGF	JAK3	MAGI2	MYCN	PAX5	PRKCI	RHEB	SMAD9	TAL1	WHSC1
AKT1	BARD1	CCND1	CRKL	EPAS1	FANCM	GABRA6	HIST1H3B	JUN	MAP2K1	MYD88	PBRM1	PRKDC	RHOA	SMAD9L	TBX3	WISP3
AKT2	BCL2	CCND2	CRLF2	EPCAM	FAS	GALNT12	HNF1A	KAT6A	MAP2K2	NBN	PDCD1LG2	PRSS1	RICTOR	SMARCA4	TCF3	WT1
AKT3	BCL2L1	CCND3	CSF1R	EPHA3	FAT1	GATA1	HOXA11	KDM5A	MAP2K4	NF1	PDGFRA	PRSS8	RIT1	SMARCB1	TCIRG1	XPO1
ALK	BCL2L2	CCNE1	CSF3R	EPHA5	FBXW7	GATA2	HOXB13	KDM5C	MAP3K1	NF2	PDGFRB	PSTPIP1	RNF168	SMC1A	TERC	XRCC2
AMER1	BCL6	CD274	CTC1	EPHA7	FGF10	GATA3	HRAS	KDM6A	MAP3K14	NFE2L2	PDK1	PTCH1	RNF43	SMC3	TERF1	XRCC3
ANKRD26	BCOR	CD79A	CTCF	EPHB1	FGF14	GATA4	HSD3B1	KDR	MAPK1	NFKBIA	PHF6	PTEN	ROS1	SMO	TERF2	ZBTB2
APC	BCORL1	CD79B	CTNNA1	ERBB2	FGF19	GATA6	HSP90AA1	KEAP1	MCL1	NHP2	PIK3C2B	PTPN11	RPTOR	SNCAIP	TERF2IP	ZNF217
AR	BCR	CDAN1	CTNNB1	ERBB3	FGF23	GEN1	ID3	KEL	MDM2	NKX2-1	PIK3CA	QKI	RTEL1	SOCS1	TERT	ZNF703
ARAF	BIRC3	CDC73	CUL3	ERBB4	FGF3	GFI1	IDH1	KIF23	MDM4	NLRP3	PIK3CB	RAB27A	RUNX1	SOX10	TET2	ZRSR2
ARFRP1	BLM	CDH1	CUX1	ERCC4	FGF4	GFI1B	IDH2	KIT	MED12	NME1	PIK3CG	RAC1	RUNX1T1	SOX2	TGFBR2	-
ARID1A	BMPR1A	CDK12	CXCR4	ERG	FGF6	GID4	IGF1R	KLF1	MEF2B	NOP10	PIK3R1	RAD21	SBDS	SOX9	TNFAIP3	-
ARID1B	BRAF	CDK4	CYLD	ERRFI1	FGFR1	GLI1	IGF2	KLHL6	MEFV	NOTCH1	PIK3R2	RAD50	SBF2	SPEN	TNFRSF14	-
ARID2	BRCA1	CDK6	DAXX	ESR1	FGFR2	GLI2	IKBKE	KLLN	MEN1	NOTCH2	PIM1	RAD51	SDHA	SPOP	TNFRSF1A	-
ASXL1	BRCA2	CDK8	DDR2	ETV6	FGFR3	GNA11	IKZF1	KMT2A	MET	NOTCH3	PLCG1	RAD51B	SDHB	SPTA1	TOP1	-
ATG2B	BRD4	CDKN1A	DDX11	EXO1	FGFR4	GNA13	IKZF3	KMT2B	MITF	NPM1	PLCG2	RAD51C	SDHC	SRC	TOP2A	-
ATM	BRIP1	CDKN1B	DDX41	EZH2	FH	GNAQ	IL2RG	KMT2C	MLH1	NRAS	PMS1	RAD51D	SDHD	SRSF2	TP53	-
ATR	BTG1	CDKN2A	DICER1	FAM175A	FLCN	GNAS	IL7R	KMT2D	MPL	NROB1	PMS2	RAD54L	SEC23B	STAG2	TRAF3	-
ATRX	BTK	CDKN2B	DKC1	FAM46C	FLI1	GPR124	INHBA	KRAS	MRE11A	NSD1	POLD1	RAF1	SETBP1	STAT3	TSC1	-
AURKA	C11orf40	CDKN2C	DNM2	FANCA	FLT1	GREM1	INPP4B	LIG4	MSH2	NTRK1	POLE	RANBP2	SETD2	STAT4	TSC2	-

RNA Fusions/Expression

Fusion/Expression													
ABL1	BCL2	CBFB	ERG	FGFR2	FOXO1	IKZF3	MAP3K1	NTRK1	NUP98	PICALM	RHOA	SS18	TCF3
AKT3	BCL6	CIC	ETV6	FGFR3	FUS	JAK2	MECOM	NTRK2	PDGFRA	PML	ROS2	STAT6	TFG
ALK	BRAF	CREBBP	EWSR1	FIP1L1	GLI1	KIAA1549	MYC	NTRK3	PDGFRB	RARA	RUNX1	TAFG	YWHAE
BCL1	CAMTA1	EGFR	FGFR1	FLAG1	HMGA2	KMT2A	NOTCH1	NUP214	PD-L1	RET	RUNX1T1	TAL1	

Reference

1. Treatment sequencing in metastatic colorectal cancer. Modest DP, Pant S, Sartore-Bianchi A. Modest DP, et al. Eur J Cancer. 2019 Mar;109:70-83. doi: 10.1016/j.ejca.2018.12.019. Epub 2019 Jan 25. Eur J Cancer. 2019. PMID: 30690295

2. Colorectal Cancer Immunotherapy: Options and Strategies. Johdi NA, Sukor NF. Johdi NA, et al. Front Immunol. 2020 Sep 18;11:1624. doi: 10.3389/fimmu.2020.01624. eCollection 2020. Front Immunol. 2020. PMID: 33042104

3. Immunotherapy in colorectal cancer: rationale, challenges and potential. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, Segal NH, Diaz LA Jr. Ganesh K, et al. Nat Rev Gastroenterol Hepatol. 2019 Jun;16(6):361-375. doi: 10.1038/s41575-019-0126-x. Nat Rev Gastroenterol Hepatol. 2019. PMID: 30886395

4. Management of pain in colorectal cancer patients. Zieli?ska A, W?odarczyk M, Makaro A, Sa?aga M, Fichna J. Zieli?ska A, et al. Crit Rev Oncol Hematol. 2021 Jan;157:103122. doi: 10.1016/j.critrevonc.2020.103122. Epub 2020 Oct 19. Crit Rev Oncol Hematol. 2021. PMID: 33171427

5. Systemic treatment for metastatic colorectal cancer in the era of precision medicine. Sandhu J, Lavingia V, Fakih M. Sandhu J, et al. J Surg Oncol. 2019 Apr;119(5):564-582. doi: 10.1002/jso.25421. Epub 2019 Feb 25. J Surg Oncol. 2019. PMID: 30802315

Electronic Signature

Ahmad Charifa, M.D.

The test (sample processing, sequencing and data generation) was performed at Genomic Testing Cooperative, LCA, Genomic Testing Cooperative, LCA, 175 Technology Drive, Suite 100, Irvine, CA 92618. Medical Director Maher Albitar, M.D. Analysis of the data was performed by Genomic Testing Cooperative, LCA, 175 Technology Drive, Suite 100, Irvine, CA 92618. Medical Director: Maher Albitar, M.D.

The test was developed and its performance characteristics have been determined by Genomic Testing Cooperative, LCA. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.