GENOMIC TESTING COOPERATIVE

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CLIA #: 05D2111917 CAP #: 9441547

Solid Tumor Profile Plus

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

MRN:		Indication for Testing:	
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: 62 Mut/Mb -Homologous recombination deficiency (HRD): Positive - Intermediate	RNF43, CREBBP (2 mutations), PREX2, APC, PIK3CG, CDKN1B, PPM1D, GLI1, ESR1, GNAS, HRAS, TSC1, TP53, DOT1L, RPTOR, PDGFRB, MED12, FANCA	ABCB7, HOXB13, FAM175A, PBRM1, MSH6, TAL1, FANCM, GRM3, GFI1B, KIF23	Autosomal chromosomal structural analysis shows 4q-, 5q-, 8p-(distal), 8q+, 16p-
PD-L1 testing by immunohistochemistry (IHC) Clone SP263: Tumor cells: <1; Immune cells: 5; Combined Positive Score (CPS): 5				

Results Summary

- **-Mutations in RNF43, CREBBP (2 mutations), PREX2, APC, PIK3CG, ABCB7, CDKN1B, PPM1D, GLI1, ESR1, HOXB13, FAM175A, GNAS, PBRM1, BRAF (V600E), MSH6, HRAS, TAL1, TSC1, TP53, FANCM, DOT1L, RPTOR, GRM3, PDGFRB, GFI1B, KIF23, MED12, and FANCA genes**
  -Microsatellite instability: Positive-High (MSI-H)
  -Tumor Mutation Burden High: 62 Mut/Mb
  -Increased MYC mRNA
  -Autosomal chromosomal structural analysis shows 4q-, 5q-, 8p- (distal), 8q+, 16p-
  -Homologous recombination deficiency (HRD): Positive - Intermediate
  -No evidence of fusion mRNA involving ALK, RET, ROS1, or NTRK
  -EBV viral RNA: Not detected
  -HPV viral RNA: Not detected
  -TTV viral RNA: Not detected

-HLA Genotyping:
-HLA-A: A*03:01-A*02:01
-HLA-B: B*07:06-B*35:01
-HLA-C: C*04:01-C*15:05

-High TMB and MSI-High 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).

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

-RNF43 mutations suggests possible response to porcupine inhibitors.

-PREX2 mutation suggests response to PARP inhibitors.

-APC mutation activates beta-catenin and WNT signaling pathway and suggests possible response to WNT and COX-2 inhibitors.

-PIK3CG abnormality suggests response to PI3K inhibitors duvelisib (Copiktra).

-GLI1 mutation suggests possible response to hedgehog inhibitors (vismodegib and Erismodegib).

-GNAS mutation suggests possible response to MEK inhibitors.

-HRAS mutation suggets response to MEK/MAPK inhibitors. (trametinib, binimetinib, cobimetinib).

-TSC1 mutation suggests possible response to PI3K/AKT/MTOR inhibitors.

-TP53 mutation suggests possible response to eprenetapopt (APR-246), Aurora kinase A and Wee1 inhibitors.

-DOT1L mutation suggests response to DOT1L inhibitors (Pinometostat).

-RPTOR mutation suggests response to mTOR and PI3K/AKT inhibitors.

-Mutations in FANCA gene suggest possible response to PARP inhibitors.

-Additional mutations detected: DNMT3A (p.Arg899Cys, 35.15%), MAP2K4 (p.Gly276Cys, 34.73%), SETD2 (p.Arg1407GlyfsTer5, 34.65%), ATRX (p.Asn1726MetfsTer10, 34.41%), PRKDC (p.Lys3608AsnfsTer?, 34.38%), TCIRG1 (p.Arg662Cys, 34.32%), GRM3 (p.Cys804Arg, 34.21%), CUX1 (p.Arg1462AlafsTer34, 33.95%), CBL (p.Ala672Val, 33.94%), NF1 (p.Arg2812Gln, 33.84%), TP53 (p.Pro153AlafsTer28, 33.41%), INPP4B (p.Arg818GlufsTer4, 33.21%), MED12 (p.Pro1869His, 32.84%), LRP1B (p.Arg2856Trp, 32.75%), PTCH1 (p.Leu758TrpfsTer14, 32.03%), PRKDC (p.Leu3809Val, 31.85%), CDKN2A (p.Pro48Leu, 25.39%), RUNX1T1 (p.Ala635LeufsTer24, 24.37%), PREX2 (p.Ser662Gly, 23.97%), MSH6 (p.Thr1284Met, 23.56%), FAT1 (p.Gly2679Glu, 23.01%), ABL1 (p.Arg171His, 22.47%), ATM (p.Arg447Ter, 22.38%), MDM4 (p.Ile366Thr, 22.19%), ARID1A (p.Lys1094SerfsTer67, 20.74%), MYCN (p.Arg357His, 19.91%), PLCG2 (p.Thr596Ala, 19.07%), EPHA3 (p.Tyr310Ter, 15.93%), FBXW7 (p.Gln229Ter, 15.83%), KMT2B (p.Arg2565His, 15.33%), BRCA2 (p.Thr2515HisfsTer9, 13.05%), RET

(p.Glu251GlyfsTer102, 6.39%), ZNF217 (p.Pro21Thr, 5.22%), NKX2-1 (p.Gly271AlafsTer24, 3.75%), GALNT12 (p.Cys229Ter, 3.6%), CTCF (p.Glu478Ter, 3.57%), TET2 (p.Ala1882Val, 4.25%), PCLO (RNA, p.Lys2442SerfsTer2, 74.42%), IRF2BP2 (RNA, p.Ser438GlnfsTer18, 44.61%), MECOM (RNA, p.Asn794ThrfsTer38, 42.08%), PRPF40B (RNA, p.Met46Ter, 40.77%), ZFP64 (RNA, p.Gln601HisfsTer12, 38.77%), CASP8 (RNA, p.Lys532AsnfsTer73, 38.27%), ROBO2 (RNA, p.Pro47ArgfsTer20, 35.94%), PCSK7 (RNA, p.Pro52ArgfsTer33, 35.47%), WNT11 (RNA, p.Thr181AsnfsTer7, 35%), JARID2 (RNA, p.Ala396GlyfsTer25, 34.83%), EPHA2 (RNA, p.Ser330ProfsTer63, 34.6%), ROBO2 (RNA, p.Val1095SerfsTer22, 33.33%), RLTPR (RNA, p.Trp392MetfsTer139, 32.88%), NGF (RNA, p.Val232AlafsTer39, 32.2%), TEAD2 (RNA, p.His299MetfsTer12, 31.9%), KCNB1 (RNA, p.Arg736GlyfsTer9, 30.77%), NCOR2 (RNA, p.Arg1060ValfsTer3, 30.58%), SPN (RNA, p.Gly395GlufsTer10, 29.52%), IRS4 (RNA, p.Gly591AlafsTer20, 28.66%), RTEL1-TNFRSF6B (RNA, p.Gly156ArgfsTer35, 28.46%), NCOR2 (RNA, p.Pro997GlnfsTer66, 28.22%), TEAD2 (RNA, p.Glu3AsnfsTer66, 27.48%), ALDH2 (RNA, p.Lys289ArgfsTer122, 27.14%), CNTRL (RNA, p.Lys1409AsnfsTer10, 25.67%), MKI67 (RNA, p.Glu1665GlnfsTer10, 24.63%), RHBDF2 (RNA, p.Pro311HisfsTer26, 24.63%), CRTC1 (RNA, p.Ser588AlafsTer6, 24.32%), DAB2IP (RNA, p.His997ThrfsTer5, 22.4%), DDX10 (RNA, p.Thr80HisfsTer2, 21.55%), WDR70 (RNA, p.Glu523AspfsTer18, 21.48%), MEAF6 (RNA, p.Arg171Ter, 21.13%), DGKZ (RNA, p.Pro1037GlnfsTer38, 20.85%), ACE (RNA, p.Pro485LeufsTer40, 20.39%), JAG2 (RNA, p.Gly741ArgfsTer66, 19.83%), AKAP12 (RNA, p.Asn1461MetfsTer26, 19.61%), NIN (RNA, p.Asn435MetfsTer19, 18.76%), BAX (RNA, p.Arg89GlufsTer44, 18.63%), MAF (RNA, p.Lys34ArgfsTer27, 12.75%), PIWIL1 (RNA, p.Ala750CysfsTer17, 10.24%)

Tumor Heterogeneity

There are abnormal clones with RNF43, CREBBP (2 mutations), PREX2, APC, PIK3CG, ABCB7, CDKN1B, PPM1D, GLI1, ESR1, HOXB13, FAM175A, GNAS, PBRM1, BRAF (V600E), MSH6, HRAS, TAL1, TSC1, TP53, FANCM, DOT1L, RPTOR, GRM3, PDGFRB, GFI1B, KIF23, MED12, and FANCA mutations.

Expression

Increase MYC mRNA

Diagnostic Implications

RNF43, CREBBP (2 mutations), PREX2, APC, PIK3CG, ABCB7, CDKN1B, PPM1D, GLI1, ESR1, HOXB13, FAM175A, GNAS, PBRM1, BRAF, MSH6, HRAS, TAL1, TSC1, TP53, FANCM, DOT1L, RPTOR, GRM3, PDGFRB, GFI1B, KIF23, MED12, FANCA	These findings are consistent with aggressive neoplasm.

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

FDA-Approved Therapeutics in Other Tumor Types	
ESR1	Elacestrant
TSC1	Everolimus..
TMB-High	Pembrolizumab

Relevant Alteration Associated with Resistance
PPM1D mutations may confer resistance to chemotherapy
ESR1 mutations may confer acquired resistance to estrogen deprivation therapies
BRAF mutation may suggest resistance to targeted anti-EGFR therapy
HRAS mutation may suggest resistance to therapy with anti-EGFR therapy
TP53 mutation is associated with resistance to therapy.
MED12 mutations may predict resistance to targeted therapies

Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence)	
RNF43	Porcupine inhibitors
CREBBP	Bromodomain and Extra-Terminal motif (BET) inhibitors
PREX2	PARP inhibitors
APC	WNT, beta-catenin, and COX-2 inhibitors
PIK3CG	PI3K, AKT, MTOR inhibitors
CDKN1B	CDK inhibitors
PPM1D	PPM1D inhibitors
GLI1	hedgehog inhibitors
ESR1	ESR1 mutations may confer acquired resistance to estrogen deprivation therapies
GNAS	MEK inhibitors
HRAS	MEK/MAPK inhibitors
TSC1	MTOR inhibitors
TP53	Aurora kinase A inhibitors, Wee1 inhibitors, Chk1 inhibitors, kevetrin, APR-246, nutlins, gene therapy
DOT1L	DOT1L inhibitors
RPTOR	mTOR and PI3K/AKT inhibitors
FANCA	DNA cross-linking agents such as diepoxybutane (DEB) and mitomycin C (MMC)
MSI-High	Immunotherapy with checkpoint inhibitor
TMB-High	Immunotherapy with checkpoint inhibitor

HRD Positive - Intermediate	PARP Inhibitors & Platinum based chemotherapy

Relevant Genes with NO Alteration		
-No evidence of mutation in KRAS, NRAS, EGFR, 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 METex14 skipping or EGFRvIII -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

- 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]

- CREBBP. This gene is ubiquitously expressed and is involved in the transcriptional coactivation of many different transcription factors. First isolated as a nuclear protein that binds to cAMP-response element binding protein (CREB), this gene is now known to play critical roles in embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition. The protein encoded by this gene has intrinsic histone acetyltransferase activity and also acts as a scaffold to stabilize additional protein interactions with the transcription complex. This protein acetylates both histone and non-histone proteins. This protein shares regions of very high sequence similarity with protein p300 in its bromodomain, cysteine-histidine-rich regions, and histone acetyltransferase domain. Mutations in this gene cause Rubinstein-Taybi syndrome (RTS). Chromosomal translocations involving this gene have been associated with acute myeloid leukemia. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Feb 2009]

- PREX2. The protein encoded by this gene belongs to the phosphatidylinositol 3,4,5-trisphosphate (PIP3)-dependent Rac exchanger (PREX) family, which are Dbl-type guanine-nucleotide exchange factors for Rac family small G proteins. Structural domains of this protein include the catalytic diffuse B-cell lymphoma homology and pleckstrin homology (DHPH) domain, two disheveled, EGL-10, and pleckstrin homology (DEP) domains, two PDZ domains, and a C-terminal inositol polyphosphate-4 phosphatase (IP4P) domain that is found in one of the isoforms. This protein facilitates the exchange of GDP for GTP on Rac1, allowing the GTP-bound Rac1 to activate downstream effectors. Studies also show that the pleckstrin homology domain of this protein interacts with the phosphatase and tensin homolog (PTEN) gene product to inhibit PTEN phosphatase activity, thus activating the phosphoinositide-3 kinase (PI3K) signaling pathway. Conversely, the PTEN gene product has also been shown to inhibit the GEF activity of this protein. This gene plays a role in insulin-signaling pathways, and either mutations or overexpression of this gene have been observed in some cancers. [provided by RefSeq, Apr 2016]

- APC. This gene encodes a tumor suppressor protein that acts as an antagonist of the Wnt signaling pathway. It is also involved in other processes including cell migration and adhesion, transcriptional activation, and apoptosis. Defects in this gene cause familial adenomatous polyposis (FAP), an autosomal dominant pre-malignant disease that usually progresses to malignancy. Mutations in the APC gene have been found to occur in most colorectal cancers. Disease-associated mutations tend to be clustered in a small region designated the mutation cluster region (MCR) and result in a truncated protein product. [provided by RefSeq, Dec 2019]

- PIK3CG. Phosphoinositide 3-kinases (PI3Ks) phosphorylate inositol lipids and are involved in the immune response. The protein encoded by this gene is a class I catalytic subunit of PI3K. Like other class I catalytic subunits (p110-alpha p110-beta, and p110-delta), the encoded protein binds a p85 regulatory subunit to form PI3K. This gene is located in a commonly deleted segment of chromosome 7 previously identified in myeloid leukemias. Several transcript variants encoding the same protein have been found for this gene. [provided by RefSeq, Jun 2015]

- ABCB7. The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in multidrug resistance as well as antigen presentation. This gene encodes a half-transporter involved in the transport of heme from the mitochondria to the cytosol. With iron/sulfur cluster precursors as its substrates, this protein may play a role in metal homeostasis. Mutations in this gene have been associated with mitochondrial iron accumulation and isodicentric (X)(q13) and sideroblastic anemia. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Nov 2012]

- CDKN1B. This gene encodes a cyclin-dependent kinase inhibitor, which shares a limited similarity with CDK inhibitor CDKN1A/p21. The encoded protein binds to and prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controls the cell cycle progression at G1. The degradation of this protein, which is triggered by its CDK dependent phosphorylation and subsequent ubiquitination by SCF complexes, is required for the cellular transition from quiescence to the proliferative state. Mutations in this gene are associated with multiple endocrine neoplasia type IV (MEN4). [provided by RefSeq, Apr 2014]

- PPM1D. The protein encoded by this gene is a member of the PP2C family of Ser/Thr protein phosphatases. PP2C family members are known to be negative regulators of cell stress response pathways. The expression of this gene is induced in a p53-dependent manner in response to various environmental stresses. While being induced by tumor suppressor protein TP53/p53, this phosphatase negatively regulates the activity of p38 MAP kinase, MAPK/p38, through which it reduces the phosphorylation of p53, and in turn suppresses p53-mediated transcription and apoptosis. This phosphatase thus mediates a feedback regulation of p38-p53 signaling that contributes to growth inhibition and the suppression of stress induced apoptosis. This gene is located in a chromosomal region known to be amplified in breast cancer. The amplification of this gene has been detected in both breast cancer cell line and primary breast tumors, which suggests a role of this gene in cancer development. [provided by RefSeq, Jul 2008]

- GLI1. This gene encodes a member of the Kruppel family of zinc finger proteins. The encoded transcription factor is activated by the sonic hedgehog signal transduction cascade and regulates stem cell proliferation. The activity and nuclear localization of this protein is negatively regulated by p53 in an inhibitory loop. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, May 2009]

- ESR1. This gene encodes an estrogen receptor and ligand-activated transcription factor. The canonical protein contains an N-terminal ligand-independent transactivation domain, a central DNA binding domain, a hinge domain, and a C-terminal ligand-dependent transactivation domain. The protein localizes to the nucleus where it may form either a homodimer or a heterodimer with estrogen receptor 2. The protein encoded by this gene regulates the transcription of many estrogen-inducible genes that play a role in growth, metabolism, sexual development, gestation, and other reproductive functions and is expressed in many non-reproductive tissues. The receptor encoded by this gene plays a key role in breast cancer, endometrial cancer, and osteoporosis. This gene is reported to have dozens of transcript variants due to the use of alternate promoters and alternative splicing, however, the full-length nature of many of these variants remain uncertain. [provided by RefSeq, Jul 2020]

- HOXB13. This gene encodes a transcription factor that belongs to the homeobox gene family. Genes of this family are highly conserved among vertebrates and essential for vertebrate embryonic development. This gene has been implicated to play a role in fetal skin development and cutaneous regeneration. In mice, a similar gene was shown to exhibit temporal and spatial colinearity in the main body axis of the embryo, but was not expressed in the secondary axes, which suggests functions in body patterning along the axis. This gene and other HOXB genes form a gene cluster at chromosome the 17q21-22 region. [provided by RefSeq, Jul 2008]

- ABRAXAS1. This gene encodes a protein that binds to the C-terminal repeats of breast cancer 1 (BRCA1) through a phospho-SXXF motif. The encoded protein recruits ubiquitin interaction motif containing 1 protein to BRCA1 protein and is required for DNA damage resistance, DNA repair, and cell cycle checkpoint control. Pseudogenes of this gene are found on chromosomes 3 and 8. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Sep 2016]

- GNAS. This locus has a highly complex imprinted expression pattern. It gives rise to maternally, paternally, and biallelically expressed transcripts that are derived from four alternative promoters and 5' exons. Some transcripts contain a differentially methylated region (DMR) at their 5' exons, and this DMR is commonly found in imprinted genes and correlates with transcript expression. An antisense transcript is produced from an overlapping locus on the opposite strand. One of the transcripts produced from this locus, and the antisense transcript, are paternally expressed noncoding RNAs, and may regulate imprinting in this region. In addition, one of the transcripts contains a second overlapping ORF, which encodes a structurally unrelated protein - Alex. Alternative splicing of downstream exons is also observed, which results in different forms of the stimulatory G-protein alpha subunit, a key element of the classical signal transduction pathway linking receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular reponses. Multiple transcript variants encoding different isoforms have been found for this gene. Mutations in this gene result in pseudohypoparathyroidism type 1a, pseudohypoparathyroidism type 1b, Albright hereditary osteodystrophy, pseudopseudohypoparathyroidism, McCune-Albright syndrome, progressive osseus heteroplasia, polyostotic fibrous dysplasia of bone, and some pituitary tumors. [provided by RefSeq, Aug 2012]

- PBRM1. This locus encodes a subunit of ATP-dependent chromatin-remodeling complexes. The encoded protein has been identified as in integral component of complexes necessary for ligand-dependent transcriptional activation by nuclear hormone receptors. Mutations at this locus have been associated with primary clear cell renal cell carcinoma. [provided by RefSeq, Feb 2012]

- 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]

- 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]

- HRAS. This gene belongs to the Ras oncogene family, whose members are related to the transforming genes of mammalian sarcoma retroviruses. The products encoded by these genes function in signal transduction pathways. These proteins can bind GTP and GDP, and they have intrinsic GTPase activity. This protein undergoes a continuous cycle of de- and re-palmitoylation, which regulates its rapid exchange between the plasma membrane and the Golgi apparatus. Mutations in this gene cause Costello syndrome, a disease characterized by increased growth at the prenatal stage, growth deficiency at the postnatal stage, predisposition to tumor formation, cognitive disability, skin and musculoskeletal abnormalities, distinctive facial appearance and cardiovascular abnormalities. Defects in this gene are implicated in a variety of cancers, including bladder cancer, follicular thyroid cancer, and oral squamous cell carcinoma. Multiple transcript variants, which encode different isoforms, have been identified for this gene. [provided by RefSeq, Jul 2008]

- TAL1. Enables several functions, including DNA-binding transcription factor activity; E-box binding activity; and histone deacetylase binding activity. Involved in several processes, including myeloid cell differentiation; positive regulation of cellular component organization; and positive regulation of erythrocyte differentiation. Located in chromatin and nucleoplasm. Part of transcription regulator complex. Implicated in acute lymphoblastic leukemia. [provided by Alliance of Genome Resources, Apr 2022]

- TSC1. This gene is a tumor suppressor gene that encodes the growth inhibitory protein hamartin. The encoded protein interacts with and stabilizes the GTPase activating protein tuberin. This hamartin-tuberin complex negatively regulates mammalian target of rapamycin complex 1 (mTORC1) signalling which is a major regulator of anabolic cell growth. This protein also functions as a co-chaperone for Hsp90 that inhibits its ATPase activity. This protein functions as a facilitator of Hsp90-mediated folding of kinase and non-kinase clients, including Tsc2 and thereby preventing their ubiquitination and proteasomal degradation. Mutations in this gene have been associated with tuberous sclerosis. [provided by RefSeq, Apr 2018]

- TP53. This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome. Alternative splicing of this gene and the use of alternate promoters result in multiple transcript variants and isoforms. Additional isoforms have also been shown to result from the use of alternate translation initiation codons from identical transcript variants (PMIDs: 12032546, 20937277). [provided by RefSeq, Dec 2016]

- FANCM. The Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2 FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2). The previously defined group FANCH is the same as FANCA. Fanconi anemia is a genetically heterogeneous recessive disorder characterized by cytogenetic instability, hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair. The members of the Fanconi anemia complementation group do not share sequence similarity; they are related by their assembly into a common nuclear protein complex. This gene encodes the protein for complementation group M. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Apr 2015]

- DOT1L. The protein encoded by this gene is a histone methyltransferase that methylates lysine-79 of histone H3. It is inactive against free core histones, but shows significant histone methyltransferase activity against nucleosomes. [provided by RefSeq, Aug 2011]

- RPTOR. This gene encodes a component of a signaling pathway that regulates cell growth in response to nutrient and insulin levels. The encoded protein forms a stoichiometric complex with the mTOR kinase, and also associates with eukaryotic initiation factor 4E-binding protein-1 and ribosomal protein S6 kinase. The protein positively regulates the downstream effector ribosomal protein S6 kinase, and negatively regulates the mTOR kinase. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2009]

- GRM3. L-glutamate is the major excitatory neurotransmitter in the central nervous system and activates both ionotropic and metabotropic glutamate receptors. Glutamatergic neurotransmission is involved in most aspects of normal brain function and can be perturbed in many neuropathologic conditions. The metabotropic glutamate receptors are a family of G protein-coupled receptors, that have been divided into 3 groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group I includes GRM1 and GRM5 and these receptors have been shown to activate phospholipase C. Group II includes GRM2 and GRM3 while Group III includes GRM4, GRM6, GRM7 and GRM8. Group II and III receptors are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities. [provided by RefSeq, Jul 2008]

- PDGFRB. The protein encoded by this gene is a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin. The identity of the growth factor bound to a receptor monomer determines whether the functional receptor is a homodimer (PDGFB or PDGFD) or a heterodimer (PDGFA and PDGFB). This gene is essential for normal development of the cardiovascular system and aids in rearrangement of the actin cytoskeleton. This gene is flanked on

chromosome 5 by the genes for granulocyte-macrophage colony-stimulating factor and macrophage-colony stimulating factor receptor; all three genes may be implicated in the 5-q syndrome. A translocation between chromosomes 5 and 12, that fuses this gene to that of the ETV6 gene, results in chronic myeloproliferative disorder with eosinophilia. [provided by RefSeq, Aug 2017]

- GFI1B. This gene encodes a zinc-finger containing transcriptional regulator that is primarily expressed in cells of hematopoietic lineage. The encoded protein complexes with numerous other transcriptional regulatory proteins including GATA-1, runt-related transcription factor 1 and histone deacetylases to control expression of genes involved in the development and maturation of erythrocytes and megakaryocytes. Mutations in this gene are the cause of the autosomal dominant platelet disorder, platelet-type bleeding disorder-17. Alternate splicing results in multiple transcript variants. [provided by RefSeq, Aug 2014]

- KIF23. The protein encoded by this gene is a member of kinesin-like protein family. This family includes microtubule-dependent molecular motors that transport organelles within cells and move chromosomes during cell division. This protein has been shown to cross-bridge antiparallel microtubules and drive microtubule movement in vitro. Alternate splicing of this gene results in multiple transcript variants. [provided by RefSeq, Jul 2013]

- MED12. The initiation of transcription is controlled in part by a large protein assembly known as the preinitiation complex. A component of this preinitiation complex is a 1.2 MDa protein aggregate called Mediator. This Mediator component binds with a CDK8 subcomplex which contains the protein encoded by this gene, mediator complex subunit 12 (MED12), along with MED13, CDK8 kinase, and cyclin C. The CDK8 subcomplex modulates Mediator-polymerase II interactions and thereby regulates transcription initiation and reinitation rates. The MED12 protein is essential for activating CDK8 kinase. Defects in this gene cause X-linked Opitz-Kaveggia syndrome, also known as FG syndrome, and Lujan-Fryns syndrome. [provided by RefSeq, Aug 2009]

- FANCA. The Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2 FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2). The previously defined group FANCH is the same as FANCA. Fanconi anemia is a genetically heterogeneous recessive disorder characterized by cytogenetic instability, hypersensitivity to DNA crosslinking agents, increased chromosomal breakage, and defective DNA repair. The members of the Fanconi anemia complementation group do not share sequence similarity; they are related by their assembly into a common nuclear protein complex. This gene encodes the protein for complementation group A. Alternative splicing results in multiple transcript variants encoding different isoforms. Mutations in this gene are the most common cause of Fanconi anemia. [provided by RefSeq, Jul 2008]

Drug Information

Pembrolizumab

Pembrolizumab: A humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation and plays a key role in in tumor evasion from host immunity.

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.

Niraparib

Niraparib 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.

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

Olaparib

Olaparib (LYNPARZA) is an antineoplastic agent, Poly(ADP-ribose) Polymerase1;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(gBRCAm) 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. (1.1, 2.2)

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.

Birabresib

Birabresib (OTX015 or MK-8628) is a potent BET bromodomian inhibitor, which targets the BET bromodomain proteins 2, 3, and 4 (BRD2/3/4). BRDs 2, 3, and 4 are considered potential cancer targets because of their pivotal role in regulating the transcription of growth-promoting genes and cell cycle regulators. OTX015 is the first BRD2/3/4 inhibitor to enter clinical trials. Upon administration, birabresib binds to the acetylated lysine recognition motifs on the bromodomain of BET proteins, thereby preventing the interaction between the BET proteins and acetylated histone peptides. This disrupts chromatin remodeling and gene expression.

Sulindac

Sulindac is a COX-1/COX-2 inhibitor. It is being evaluated as a potential cancer chemo-preventive and therapeutic drug in clinical trials for a variety of malignancies.

Celecoxib

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is a nonsteroidal anti-inflammatory drug (NSAID). It is used to manage symptoms of various types of arthritis pain and in familial adenomatous polyposis (FAP) to reduce precancerous polyps in the colon. It is marketed by Pfizer under the brand name Celebrex, and was initially granted FDA approval in 1998. Interestingly, selective COX-2 inhibitors (especially celecoxib), have been evaluated as potential cancer chemopreventive and therapeutic drugs in clinical trials for a variety of malignancies.

Duvelisib

Duvelisib acts as a strong reversible inhibitor of the isoform gamma and delta of the phosphoinositide3-kinase (PI3K) [PI3K/AKT/mTOR].

Alpelisib

Alpelisib is an orally bioavailable phosphatidylinositol 3-kinase (PI3K) inhibitor with potential antineoplastic activity. Alpelisib specifically inhibits PIK3 in the PI3K/AKT kinase (or protein kinase B) signaling pathway, thereby inhibiting the activation of the PI3K signaling pathway. This may result in inhibition of tumor cell growth and survival in susceptible tumor cell populations. Activation of the PI3K signaling pathway is frequently associated with tumorigenesis. Dysregulated PI3K signaling may contribute to tumor resistance to a variety of antineoplastic agents.

Vismodegib

Vismodegib selectively binds to and inhibits the transmembrane protein Smoothened homologue (SMO) to inhibit the Hedgehog signalling pathway.

Mutations of the Hedgehog pathway may results in uncontrolled proliferation of skin basal cells. Vismodegib binds to and inhibits the transmembrane protein Smoothened homologue (SMO) to inhibit the Hedgehog signalling pathway.

Vismodegib inhibits the hedgehog signalling pathway and is indicated for treatment of adult basal cell carcinoma. FDA approved on Jan 30, 2012.

Sonidegib

Sonidegib has been shown to inhibit a transmembrane protein called SMO which plays a role in Hh signal transduction. This has resulted in inhibition of Hh signaling as well as antitumour activity in various animal models.

The hedgehog pathway is involved in many human cancers. Sonidegib effectively inhibits the regulator called smoothened (Smo), preventing the hedgehog pathway from functioning. As a result, tumours that depend on the hedgehog pathway are unable to grow.

Elacestrant

Elacestrant is an estrogen receptor antagonist used to treat ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

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.

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.

Everolimus

Everolimus is a PI3K/Akt/mTOR pathway inhitior. The PI3K/Akt/mTOR plays a cruitial role in trastuzumab resistance, dysregulating the HER2 downstream signal. The mTOR inhibitor everolimus inhibits the mTOR/S6K signal, and therefore improves fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. A concordant therapy using HER2-targeted agents and everolimus might lead to an improvement in therapy of HER2-positive gastric cancer.

Temsirolimus

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in vitro studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

Temsirolimus is indicated for the treatment of renal cell carcinoma (RCC). Also investigated for use/treatment in breast cancer, lymphoma (unspecified), rheumatoid arthritis, and multiple myeloma.

APR-246

APR-246 is a first-in-class agent targeting mutant p53. In vitro and in vivo preclinical models have demonstrated that APR-246 has excellent efficacy in OC (both adenocarcinoma and squamous cell carcinoma) and potently synergises with chemotherapies used in the treatment of OC, restoring sensitivity to chemotherapy-resistant tumours. An initial phase I clinical trial has shown APR-246 to be safe in humans and early results from a currently running phase Ib/II trial of APR-246 with carboplatin and liposomal doxorubicin in ovarian cancer have been promising. Together, these data provide a strong rationale for investigating the efficacy of APR-246 in OC.

APR-246 has been used in trials studying the treatment of Prostatic Neoplasms, Hematologic Neoplasms, and Platinum Sensitive Recurrent High-grade Serous Ovarian Cancer With Mutated p53.

APR-246 is an analogue of PRIMA-1, which modifies the core domain of mutant p53, resulting in restoration of wild-type p53 conformation and reactivation of normal p53 function, leading to increased cell cycle arrest and tumor cell death (PMID: 20498645).

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
https://clinicaltrials.gov/study/NCT05948826	Recruiting	A Phase 1, First in Human, Dose-Escalation Study of TORL-3-600 in Participants With Advanced Cancer	Colorectal Cancer	TORL-3-600	UCLA - JCCC Clinical Research Unit, Los Angeles, California 90095 Washington University School of Medicine-Siteman Cancer Center, Saint Louis, Missouri 63110 Mary Crowley Cancer Research, Dallas, Texas 75230

https://clinicaltrials.gov/study/NCT04976634	Recruiting	An Open-label, Multicenter, Phase 2 Study to Evaluate the Efficacy and Safety of Pembrolizumab Plus Lenvatinib in Combination With Belzutifan in Multiple Solid Tumors	Colorectal Cancer	Pembrolizumab	University of Arizona Cancer Center-University of Arizona Cancer Center - North Campus (Site 5047), Tucson, Arizona 85724 City of Hope Comprehensive Cancer Center (Site 5002), Duarte, California 91010 Cedars-Sinai Medical Center (Site 5045), Los Angeles, California 90048
https://clinicaltrials.gov/study/NCT03104439	Recruiting	Nivolumab and Ipilimumab and Radiation Therapy in Microsatellite Stable (MSS) and Microsatellite Instability (MSI) High Colorectal and Pancreatic Cancer	Colorectal Cancer	Nivolumab	Massachusetts general Hospital, Boston, Massachusetts 02214

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
RNF43	NP_060233.3:p.Gly659ValfsTer41	NM_017763.4:c.1976delG	G/X	gGt/gt	frameshift_variant	71.92	438	0
CREBBP	NP_004371.2:p.Ile1084SerfsTer15	NM_004380.2:c.3250delA	I/X	Atc/tc	"frameshift_variant, splice_region_variant"	69.56	391	0
PREX2	NP_079146.2:p.Ser565ArgfsTer10	NM_024870.2:c.1693delT	R/X	cgT/cg	frameshift_variant	54.65	741	0
APC	NP_000029.2:p.Arg302Ter	NM_000038.5:c.904C>T	R/*	Cga/Tga	stop_gained	53.03	379	0
CREBBP	NP_004371.2:p.Arg1985ThrfsTer356	NM_004380.2:c.5951dupG	G/GX	gga/ggGa	frameshift_variant	43.75	16	0
PIK3CG	NP_002640.2:p.Val763Ala	NM_002649.2:c.2288T>C	V/A	gTt/gCt	"missense_variant,splice_region_variant"	39.96	583	tolerated (1)
ABCB7	NP_004290.2:p.Arg314Trp	NM_004299.4:c.940C>T	R/W	Cgg/Tgg	missense_variant	39.95	388	deleterious (0)
CDKN1B	NP_004055.1:p.Gly97ValfsTer22	NM_004064.3:c.285delC	P/X	Ccc/cc	frameshift_variant	39.45	801	0
PPM1D	NP_003611.1:p.Arg248Gln	NM_003620.3:c.743G>A	R/Q	cGa/cAa	missense_variant	38.77	552	deleterious (0)
GLI1	NP_005260.1:p.Glu225ArgfsTer56	NM_005269.2:c.671_672dupAG	-/X	-/GA	frameshift_variant	38.41	565	0
ESR1	NP_001116214.1:p.Arg436His	NM_001122742.1:c.1307G>A	R/H	cGc/cAc	missense_variant	38.38	594	deleterious (0.01)

HOXB13	NP_006352.2:p.Arg25AlafsTer102	NM_006361.5:c.72dupG	-/X	-/G	frameshift_variant	38.27	810	0
FAM175A	NP_620775.2:p.Gly159AspfsTer8	NM_139076.2:c.474delA	K/X	aaA/aa	"frameshift_variant, splice_region_variant"	38.22	348	0
GNAS	NP_536350.2:p.Arg844His	NM_080425.2:c.2531G>A	R/H	cGt/cAt	missense_variant	38.19	309	deleterious (0.01)
PBRM1	NP_060783.3:p.Arg78Gln	NM_018313.4:c.233G>A	R/Q	cGa/cAa	missense_variant	37.2	785	deleterious (0)
BRAF	NP_004324.2:p.Val600Glu	NM_004333.4:c.1799T>A	V/E	gTg/gAg	missense_variant	37.19	777	deleterious (0)
MSH6	NP_000170.1:p.Arg911Ter	NM_000179.2:c.2731C>T	R/*	Cga/Tga	stop_gained	36.69	477	0
HRAS	NP_005334.1:p.Ala18Val	NM_005343.2:c.53C>T	A/V	gCg/gTg	missense_variant	36.62	426	deleterious (0)
TAL1	NP_003180.1:p.Arg189Cys	NM_003189.2:c.565C>T	R/C	Cgt/Tgt	missense_variant	36.56	930	deleterious (0)
TSC1	NP_000359.1:p.Leu264Pro	NM_000368.4:c.791T>C	L/P	cTg/cCg	missense_variant	36.48	540	deleterious (0)
TP53	NP_000537.3:p.Ser90ProfsTer33	NM_000546.5:c.267delC	P/X	ccC/cc	frameshift_variant	36.46	694	0
FANCM	NP_065988.1:p.Met2010Ile	NM_020937.2:c.6030G>A	M/I	atG/atA	missense_variant	36.42	453	tolerated (0.39)
DOT1L	NP_115871.1:p.Arg853Ser	NM_032482.2:c.2557C>A	R/S	Cgc/Agc	missense_variant	36.32	402	tolerated - low confidence (0.08)
RPTOR	NP_065812.1:p.Phe967LeufsTer6	NM_020761.2:c.2901delT	Y/X	taT/ta	frameshift_variant	35.9	702	0
GRM3	NP_000831.2:p.Pro342Thr	NM_000840.2:c.1024C>A	P/T	Ccc/Acc	missense_variant	35.87	577	tolerated (0.15)
PDGFRB	0	NM_002609.3:c.1807+2T>C	0	0	splice_donor_variant	35.66	258	0
GFI1B	NP_004179.3:p.Gly282Arg	NM_004188.4:c.844G>A	G/R	Gga/Aga	missense_variant	35.61	410	deleterious (0)
KIF23	NP_612565.1:p.Lys959SerfsTer18	NM_138555.3:c.2876delA	K/X	Aaa/aa	frameshift_variant	35.46	423	0
MED12	NP_005111.2:p.Ala1233Thr	NM_005120.2:c.3697G>A	A/T	Gcg/Acg	missense_variant	35.29	595	0
FANCA	NP_000126.2:p.Val107PhefsTer31	NM_000135.2:c.319delG	V/X	Gtt/tt	frameshift_variant	35.23	579	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. Borderline MSI results by NGS are confirmed by fragment analysis. 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 assays 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.

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. The poor coverage is primarily due to the inherent difficulty in obtaining adequate sequencing coverage in regions with high GC content. No well-characterized hotspots are present in these regions. 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 may contain 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	ATRX	BTK	CDKN2B	DKC1	FANCA	FLI1	GREM1	INPP4B	LIG4	MSH2	NSD2 (WHSC1)	POLE	RAF1	SDHD	STAG2	TP53

ABL1	AURKA	CALR	CDKN2C	DNM2	FANCB	FLT1	GRIN2A	IRF2	LMO1	MSH6	NTRK1	POT1	RANBP2	SEC23B	STAT3	TRAF3
ABL2	AURKB	CARD11	CEBPA	DNMT3A	FANCC	FLT3	GRM3	IRF4	LPIN2	MTOR	NTRK2	PPM1D	RARA	SETBP1	STAT4	TSC1
ABRAXAS1	AURKC	CBFB	CHD2	DOT1L	FANCD2	FLT4	GSK3B	IRS2	LRP1B	MUTYH	NTRK3	PPP2R1A	RB1	SETD2	STAT6	TSC2
ACD	AXIN1	CBL	CHD4	EED	FANCE	FOXL2	GSKIP	JAGN1	LYN	MVK	NUP93	PRDM1	RBBP6	SF3B1	STK11	TSHR
ACVR1B	AXIN2	CBLB	CHEK1	EGFR	FANCF	FOXP1	H3-3A (H3F3A)	JAK1	LYST	MYC	PAK3	PREX2	RBM10	SLIT2	SUFU	U2AF1
ADA	AXL	CBLC	CHEK2	EGLN1	FANCG	FRS2	H3C2	JAK2	LZTR1	MYCL	PALB2	PRKAR1A	RBM8A	SLX4	SUZ12	U2AF2
ADGRA2	B2M	CCN6 (WISP3)	CIC	ELANE	FANCI	FUBP1	HAX1	JAK3	MAGI2	MYCN	PAX5	PRKCI	REEP5	SMAD2	SYK	VEGFA
AK2	BAP1	CCND1	CREBBP	EMSY	FANCL	G6PC3	HGF	JUN	MAP2K1	MYD88	PBRM1	PRKDC	RET	SMAD3	TAF1	VHL
AKT1	BARD1	CCND2	CRKL	EP300	FANCM	GABRA6	HNF1A	KAT6A	MAP2K2	NBN	PDCD1LG2	PRKN (PARK2)	RHEB	SMAD4	TAL1	WAS
AKT2	BCL2	CCND3	CRLF2	EPAS1	FAS	GALNT12	HOXA11	KDM5A	MAP2K4	NF1	PDGFRA	PRSS1	RHOA	SMAD9	TBX3	WT1
AKT3	BCL2L1	CCNE1	CSF1R	EPCAM	FAT1	GATA1	HOXB13	KDM5C	MAP3K1	NF2	PDGFRB	PRSS8	RICTOR	SMARCA4	TCF3	XPO1
ALK	BCL2L2	CD274	CSF3R	EPHA3	FBXW7	GATA2	HRAS	KDM6A	MAP3K14	NFE2L2	PDK1	PSTPIP1	RIT1	SMARCB1	TCIRG1	XRCC2
AMER1	BCL6	CD79A	CTC1	EPHA5	FGF10	GATA3	HSD3B1	KDR	MAPK1	NFKBIA	PHF6	PTCH1	RNF168	SMC1A	TENT5C (FAM46C)	XRCC3
ANKRD26	BCOR	CD79B	CTCF	EPHA7	FGF14	GATA4	HSP90AA1	KEAP1	MCL1	NHP2	PIK3C2B	PTEN	RNF43	SMC3	TERC	ZBTB2
APC	BCORL1	CDAN1	CTNNA1	EPHB1	FGF19	GATA6	ID3	KEL	MDM2	NKX2-1	PIK3CA	PTPN11	ROS1	SMO	TERF1	ZNF217
AR	BCR	CDC73	CTNNB1	ERBB2	FGF23	GEN1	IDH1	KIF23	MDM4	NLRP3	PIK3CB	QKI	RPTOR	SNCAIP	TERF2	ZNF703
ARAF	BIRC3	CDH1	CUL3	ERBB3	FGF3	GFI1	IDH2	KIT	MED12	NME1	PIK3CG	RAB27A	RTEL1	SOCS1	TERF2IP	ZRSR2
ARFRP1	BLM	CDIN1 (C15orf41)	CUX1	ERBB4	FGF4	GFI1B	IGF1R	KLF1	MEF2B	NOP10	PIK3R1	RAC1	RUNX1	SOX10	TERT	-
ARID1A	BMPR1A	CDK12	CXCR4	ERCC4	FGF6	GID4	IGF2	KLHL6	MEFV	NOTCH1	PIK3R2	RAD21	RUNX1T1	SOX2	TET2	-
ARID1B	BRAF	CDK4	CYLD	ERG	FGFR1	GLI1	IKBKE	KLLN	MEN1	NOTCH2	PIM1	RAD50	SAMD9L	SOX9	TGFBR2	-
ARID2	BRCA1	CDK6	DAXX	ERRFI1	FGFR2	GLI2	IKZF1	KMT2A	MET	NOTCH3	PLCG1	RAD51	SBDS	SPEN	TNFAIP3	-
ASXL1	BRCA2	CDK8	DDR2	ESR1	FGFR3	GNA11	IKZF3	KMT2B	MITF	NPM1	PLCG2	RAD51B	SBF2	SPOP	TNFRSF14	-
ATG2B	BRD4	CDKN1A	DDX11	ETV6	FGFR4	GNA13	IL2RG	KMT2C	MLH1	NR0B1	PMS1	RAD51C	SDHA	SPTA1	TNFRSF1A	-
ATM	BRIP1	CDKN1B	DDX41	EXO1	FH	GNAQ	IL7R	KMT2D	MPL	NRAS	PMS2	RAD51D	SDHB	SRC	TOP1	-
ATR	BTG1	CDKN2A	DICER1	EZH2	FLCN	GNAS	INHBA	KRAS	MRE11	NSD1	POLD1	RAD54L	SDHC	SRSF2	TOP2A	-

RNA Fusions/Expression

Fusion/Expression													
ABL1	BCL6	CD274 (PD-L1)	EGFR	EWSR1	FLI1	IKZF3	MAP3K1	NRG1	NUP98	PML	RET	SS18	THADA
AKT3	BRAF	CIC	ERG	FGFR1	FOXO1	JAK2	MECOM	NTRK1	PAX8	PPARG	RHOA	STAT6	TMPRSS2
ALK	CAMTA1	CREB1	ETS1	FGFR2	FUS	KIAA1549	MYB	NTRK2	PDGFRA	PRKACA	ROS1	TAL1	YAP1
AR	CBFB	CREBBP	ETV1	FGFR3	GLI1	KMT2A	MYC	NTRK3	PDGFRB	RAF1	RUNX1	TCF3	YWHAE
BCL2	CCND1	ERBB2	ETV6	FIP1L1	HMGA2	MAML2	NOTCH1	NUP214	PICALM	RARA	RUNX1T1	TFG	ZFTA

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Electronic Signature

Ahmad Charifa, M.D.

The test (sample processing, sequencing and data generation) was performed at Genomic Testing Cooperative, LCA, 25371 Commercentre Drive Lake Forest, CA 92630. Medical Director Maher Albitar, M.D. Analysis of the data was performed by Genomic Testing Cooperative, LCA, 25371 Commercentre Drive, Lake Forest, CA 92630. 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.