25371 Commercentre Drive, Lake Forest, CA 92630
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CLIA #: 05D2111917 CAP #: 9441574

Solid Tumor Profile Plus

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

Collected Date:		Tumor Type:	Ovarian
Received Date:	M		
Reported Date:			

Detected Genomic Alterations				
Level 1 (FDA-Approved)	Level 2 (Standard of Care)	Level 3 (Clinical Evidence)	Level 4 (Biological Evidence)	Other
-BRCA1 (?germline) -Homologous recombination deficiency (HRD): Positive-High	-Tumor Mutation Burden Low: 6 Mut/Mb -No evidence of microsatellite instability	TP53, PIK3CA (2 mutations), XPO1, NOTCH1	CTC1, PAX5, TCIRG1, H3C2, RUNX1T1, KDM5A, FRS2	Autosomal chromosomal structural analysis shows numerous changes: 3q+ (distal), 4q-, 5q+ (proximal), 6p+, 6q-, 8q+ (MYC gain), 10q+, 11q+ (FGFR2 gain), 13q- (distal), 15q-, 17q- (proximal), 18q-, and others
FOLR1 FDA (ELAHERE™) testing by immunohistochemistry (IHC): Positive. Percentage of cells with 2+/3+ membrane staining: 95				

Results Summary

- **-Mutations in BRCA1, TP53, PIK3CA (2 mutations), CTC1, PAX5, XPO1, NOTCH1, TCIRG1, H3C2, RUNX1T1, KDM5A, and FRS2 genes**
  -Homologous recombination deficiency (HRD): Positive-High
  -Increased CA15-, CA-125, CK, FOLR1 mRNA
  -t(12;14)(q12;q24) ARID2::RAD51B fusion mRNA
  -Autosomal chromosomal structural analysis shows numerous changes: 3q+ (distal), 4q-, 5q+ (proximal), 6p+, 6q-, 8q+ (MYC gain), 10q+, 11q+ (FGFR2 gain), 13q- (distal), 15q-, 17q- (proximal), 18q-, and others
  -No evidence of microsatellite instability
  -Tumor Mutation Burden Low: 6 Mut/Mb
  -No evidence of fusion mRNA involving ALK, RET, ROS1, or NTRK
  -No evidence of PALB2 mutations

-EBV viral RNA: Not detected
-HPV viral RNA: Not detected
-TTV viral RNA: Not detected
-HLA Genotyping:
-HLA-A: A*24:443-A*68:02
-HLA-B: B*14:02-B*41:02
-HLA-C: C*17:03-C*08:02

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

-BRCA1 mutation suggests response to PARP inhibitors. The BRCA1 mutation is detected at a high level, suggestive of a germline variant. This mutation leads to early termination (loss of function). This mutation has been reported as a pathogenic mutation associated with predisposition to cancer.

-PIK3CA mutations suggest response to PI3K/mTOR inhibitors.

-XPO1 mutation suggests response to Selinexor.

-NOTCH1 mutation suggests sensitivity to NOTCH inhibitors.

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

See expression plots at the end of the report.

Tumor Heterogeneity

There is a dominant abnormal clone with BRCA1 and TP53 mutations. The PIK3CA (2 mutations), CTC1, PAX5, XPO1, NOTCH1, TCIRG1, H3C2, RUNX1T1, KDM5A, and FRS2 mutations are detected in subclones.

Expression

Increased CA15-, CA-125, CK, FOLR1 mRNA

Diagnostic Implications

BRCA1, TP53, PIK3CA (2 mutations), CTC1, PAX5, XPO1, NOTCH1, TCIRG1, H3C2, RUNX1T1, KDM5A, FRS2	The findings are consistent with ovarian cancer

FDA-Approved Therapeutics

HRD Positive	Niraparib + platinum-based chemotherapy
BRCA1	Niraparib, Olaparib, Olaparib + Bevacizumab, Rucaparib

FDA-Approved Therapeutics in Other Tumor Types	
PIK3CA	Inavolisib + Palbociclib + Fulvestrant, Capivasertib, Alpelisib

Relevant Alteration Associated with Resistance
TP53 mutation is associated with resistance to therapy.
PIK3CA mutations may predict resistance to anti-RTK therapy, including cetuximab, anti-EGFR TKIs, and trastuzumab and lapatinib.

Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence)	
BRCA1	PARP inhibitors
TP53	Aurora kinase A inhibitors, Wee1 inhibitors, Chk1 inhibitors, kevetrin, APR-246, nutlins, gene therapy
PIK3CA	PI3K, AKT, MTOR inhibitors
XPO1	Selective Inhibitors of Nuclear Export (SINE) compounds
NOTCH1	NOTCH inhibitors
HRD Positive	PARP Inhibitors & Platinum based chemotherapy

Relevant Genes with NO Alteration		
-No evidence of mutation in KRAS, NRAS, EGFR, BRAF, or BRCA2 -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

- BRCA1 mutations in the germline have become a hallmark for hereditary breast and ovarian cancers. Variants that have been demonstrated to reduce the function of the protein have been shown to increase the risk for these cancers, as well as prostate and pancreatic cancer. These findings have been the impetus for the increased popularity of genetic testing of healthy individuals to assess risk. Recent studies in ovarian cancer have also demonstrated that BRCA mutation status can predict treatment response. A number of trials assessing BRCA mutation status have shown an improved response to platinum agents, and more recently has led to the FDA-approval of PARP inhibitors for BRCA-positive ovarian cancers. These studies have resulted in the Society of Gynecologic Oncology to recommend germline BRCA testing in all patients with a diagnosis of ovarian cancer.This gene encodes a 190 kD nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor. The BRCA1 gene contains 22 exons spanning about 110 kb of DNA. The encoded protein combines with other tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). This gene product associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complexes. This protein thus plays a role in transcription, DNA repair of double-stranded breaks, and recombination. Mutations in this gene are responsible for approximately 40% of inherited breast cancers and more than

80% of inherited breast and ovarian cancers. Alternative splicing plays a role in modulating the subcellular localization and physiological function of this gene. Many alternatively spliced transcript variants, some of which are disease-associated mutations, have been described for this gene, but the full-length natures of only some of these variants has been described. A related pseudogene, which is also located on chromosome 17, has been identified. [provided by RefSeq, May 2020]

- 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]

- PIK3CA. Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. This gene has been found to be oncogenic and has been implicated in cervical cancers. A pseudogene of this gene has been defined on chromosome 22. [provided by RefSeq, Apr 2016]

- 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]

- PAX5. This gene encodes a member of the paired box (PAX) family of transcription factors. The central feature of this gene family is a novel, highly conserved DNA-binding motif, known as the paired box. Paired box transcription factors are important regulators in early development, and alterations in the expression of their genes are thought to contribute to neoplastic transformation. This gene encodes the B-cell lineage specific activator protein that is expressed at early, but not late stages of B-cell differentiation. Its expression has also been detected in developing CNS and testis and so the encoded protein may also play a role in neural development and spermatogenesis. This gene is located at 9p13, which is involved in t(9;14)(p13;q32) translocations recurring in small lymphocytic lymphomas of the plasmacytoid subtype, and in derived large-cell lymphomas. This translocation brings the potent E-mu enhancer of the IgH gene into close proximity of the PAX5 promoter, suggesting that the deregulation of transcription of this gene contributes to the pathogenesis of these lymphomas. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Jul 2013]

- XPO1. This cell-cycle-regulated gene encodes a protein that mediates leucine-rich nuclear export signal (NES)-dependent protein transport. The protein specifically inhibits the nuclear export of Rev and U snRNAs. It is involved in the control of several cellular processes by controlling the localization of cyclin B, MPAK, and MAPKAP kinase 2. This protein also regulates NFAT and AP-1. [provided by RefSeq, Jan 2015]

- NOTCH1. This gene encodes a member of the NOTCH family of proteins. Members of this Type I transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple different domain types. Notch signaling is an evolutionarily conserved intercellular signaling pathway that regulates interactions between physically adjacent cells through binding of Notch family receptors to their cognate ligands. The encoded preproprotein is proteolytically processed in the trans-Golgi network to generate two polypeptide chains that heterodimerize to form the mature cell-surface receptor. This receptor plays a role in the development of numerous cell and tissue types. Mutations in this gene are associated with aortic valve disease, Adams-Oliver syndrome, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and head and neck squamous cell carcinoma. [provided by RefSeq, Jan 2016]

- TCIRG1. This gene encodes a subunit of a large protein complex known as a vacuolar H+-ATPase (V-ATPase). The protein complex acts as a pump to move protons across the membrane. This movement of protons helps regulate the pH of cells and their surrounding environment. V-ATPase dependent organelle acidification is necessary for such intracellular processes as protein sorting, zymogen activation, and receptor-mediated endocytosis. V-ATPase is comprised of a cytosolic V1 domain and a transmembrane V0 domain. Alternative splicing results in multiple transcript variants. Mutations in this gene are associated with infantile malignant osteopetrosis. [provided by RefSeq, May 2017]

- H3C2. Histones are basic nuclear proteins that are responsible for the nucleosome structure of the chromosomal fiber in eukaryotes. This structure consists of approximately 146 bp of DNA wrapped around a nucleosome, an octamer composed of pairs of each of the four core histones (H2A, H2B, H3, and H4). The chromatin fiber is further compacted through the interaction of a linker histone, H1, with the DNA between the nucleosomes to form higher order chromatin structures. This gene is intronless and encodes a replication-dependent histone that is a member of the histone H3 family. Transcripts from this gene lack polyA tails; instead, they contain a palindromic termination element. This gene is found in the large histone gene cluster on chromosome 6p22-p21.3. [provided by RefSeq, Aug 2015]

- RUNX1T1. This gene encodes a member of the myeloid translocation gene family which interact with DNA-bound transcription factors and recruit a range of corepressors to facilitate transcriptional repression. The t(8;21)(q22;q22) translocation is one of the most frequent karyotypic abnormalities in acute myeloid leukemia. The translocation produces a chimeric gene made up of the 5'-region of the runt-related transcription factor 1 gene fused to the 3'-region of this gene. The chimeric protein is thought to associate with the nuclear corepressor/histone deacetylase complex to block hematopoietic differentiation. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Nov 2010]

- KDM5A. This gene encodes a member of the Jumonji, AT-rich interactive domain 1 (JARID1) histone demethylase protein family. The encoded protein plays a role in gene regulation through the histone code by specifically demethylating lysine 4 of histone H3. The encoded protein interacts with many other proteins, including retinoblastoma protein, and is implicated in the transcriptional regulation of Hox genes and

cytokines. This gene may play a role in tumor progression. [provided by RefSeq, Aug 2013]

- FRS2. Enables fibroblast growth factor receptor binding activity and neurotrophin TRKA receptor binding activity. Involved in negative regulation of cardiac muscle cell differentiation. Acts upstream of or within fibroblast growth factor receptor signaling pathway. Located in adherens junction. Biomarker of renal cell carcinoma. [provided by Alliance of Genome Resources, Apr 2022]

Drug Information

Olaparib (Lynparza)

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.

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 (Zejula)

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.

Rucaparib (Rubraca)

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.

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).

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.

Fulvestrant

Fulvestrant is a drug treatment of hormone receptor (HR)-positive metastatic breast cancer. It is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. While it is used as monotherapy for the treatment of breast cancers, it is also used in combination with alpelisib for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer.

Selinexor

Selinexor is a first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor functions by binding with, and inhibiting, the nuclear export protein, XPO1, leading to the accumulation of tumor suppressor proteins in the cell nucleus. This reinitiates and amplifies their tumor suppressor function and is believed to lead to the selective induction of apoptosis in cancer cells, while largely sparing normal cells.

Brontictuzumab

Brontictuzumab is a humanized monoclonal antibody directed against the Notch-1 receptor with potential antineoplastic activity. Upon administration, brontictuzumab binds to Notch-1 on the cell surface, thereby inhibiting Notch-mediated signaling and tumor cell proliferation. Notch 1, a type 1 transmembrane protein belonging to the Notch family, functions as a receptor for membrane bound ligands and has various roles during development; dysregulated Notch signaling is associated with increased cell growth and chemoresistance in cancers.

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
https://clinicaltrials.gov/study/NCT05983276	Recruiting	Combination of the Hypomethylating Agent Decitabine and the Nuclear Export Receptor XPO-1 Inhibitor Selinexor to Reverse Platinum Resistance in Relapsed/Refractory Epithelial Ovarian Cancer	Ovarian Cancer	Decitabine, Carboplatin, Paclitaxel, Selinexor	Loyola University Medical Center, Maywood, Illinois 60153
https://clinicaltrials.gov/study/NCT06646627	Recruiting	Phase I Clinical Trial of Autologous B7-H3 Chimeric Receptor (CAR) T Cells in Adults With Recurrent, Platinum Resistant Ovarian Tumors	Ovarian Cancer	B7-H3CART	Stanford University, Palo Alto, California 94304
https://clinicaltrials.gov/study/NCT05864144	Recruiting	A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of SNS-101 (Anti VISTA) as Monotherapy and in Combination With Cemiplimab in Patients With Advanced Solid Tumors	Ovarian Cancer	SNS-101 (anti-VISTA), Cemiplimab	Icahn School of Medicine at Mt. Sinai, New York, New York 10029 University of Pennsylvania, Perelman Center for Advanced Medicine, Philadelphia, Pennsylvania 19104 UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania 15232

https://clinicaltrials.gov/study/NCT05579366	Recruiting	Phase 1/2 Study of Rina-S in Patients With Locally Advanced and/or Metastatic Solid Tumors	Ovarian Cancer	Rina-S, Carboplatin, Bevacizumab, Pembrolizumab	Providence Medical Foundation, Santa Rosa, California 95403 USOR Sansum Clinic, Santa Barbara, California 93105 USOR Oncology Associates of Oregon, PC, Eugene, Oregon 97401

Detailed Results

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

Gene name	Hgvsp	Hgvsc	Amino acids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
BRCA1	NP_009231.2:p.Glu23ValfsTer17	NM_007300.3:c.68_69delAG	E/X	gAG/g	frameshift_variant	82.67	277	0
TP53	NP_000537.3:p.Cys135AlafsTer35	NM_000546.5:c.403delT	C/X	Tgc/gc	frameshift_variant	63.02	192	0
PIK3CA	NP_006209.2:p.Asn114Ser	NM_006218.2:c.341A>G	N/S	aAt/aGt	missense_variant	25.36	485	tolerated (0.08)
CTC1	NP_079375.3:p.Thr714Ile	NM_025099.5:c.2141C>T	T/I	aCa/aTa	missense_variant	23.05	256	tolerated (0.19)
PAX5	NP_057953.1:p.Phe341Ile	NM_016734.2:c.1021T>A	F/I	Ttt/Att	missense_variant	22.4	192	deleterious (0)
XPO1	NP_003391.1:p.Thr740Arg	NM_003400.3:c.2219C>G	T/R	aCa/aGa	missense_variant	18.61	532	deleterious (0)
NOTCH1	NP_060087.3:p.Val964Met	NM_017617.3:c.2890G>A	V/M	Gtg/Atg	missense_variant	18.13	182	deleterious (0)
TCIRG1	NP_006010.2:p.Arg660His	NM_006019.3:c.1979G>A	R/H	cGc/cAc	missense_variant	16.05	81	tolerated (0.3)
H3C2	NP_003528.1:p.Asp107Glu	NM_003537.3:c.321C>A	D/E	gaC/gaA	missense_variant	15.72	617	deleterious - low confidence (0)
PIK3CA	NP_006209.2:p.Glu542Lys	NM_006218.2:c.1624G>A	E/K	Gaa/Aaa	missense_variant	15.27	753	deleterious (0.04)
RUNX1T1	NP_001185608.1:p.Thr70Ala	NM_001198679.1:c.208A>G	T/A	Acc/Gcc	missense_variant	15.02	486	0
KDM5A	NP_001036068.1:p.Lys425_Arg428del	NM_001042603.1:c.1274_1285delAGGATGGGCGGA	KDGRR/R	aAGGATGGGCGGAga/aga	inframe_deletion	14.95	428	0
FRS2	NP_006645.3:p.Leu386Gln	NM_006654.4:c.1157T>A	L/Q	cTa/cAa	missense_variant	10.49	753	tolerated (0.68)

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)*

GENOMIC® TESTING COOPERATIVE
25371 Commercentre Drive, Lake Forest, CA 92630
Tel: 1-866-484-8870 www.genomictestingcooperative.com
CLIA #: 05D2111917 CAP #: 9441574

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

Reference

1. Molecular Subgroups of HRD Positive Ovarian Cancer and Their Prognostic Significance. Kekeeva T, Dudina I, Andreeva Y, Tanas A, Kalinkin A, Musatova V, Chernorubashkina N, Khokhlova S, Tikhomirova T, Volkonsky M, Kutsev S, Zaletaev D, Strelnikov V. Int J Mol Sci. 2024 Dec 18;25 (24):13549. doi: 10.3390/ijms252413549. PMID: 39769312.

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4. PARP inhibitors in ovarian cancer. Goldlust IS, Guidice E, Lee JM. Semin Oncol. 2024 Feb-Apr;51(1-2):45-57. doi: 10.1053/j.seminoncol.2024.01.001. Epub 2024 Jan 14. PMID: 38262776.

Electronic Signature

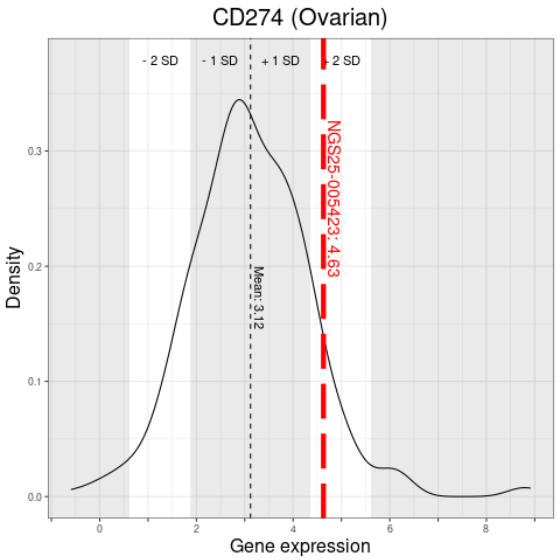
Ahmad Charifa, M.D.

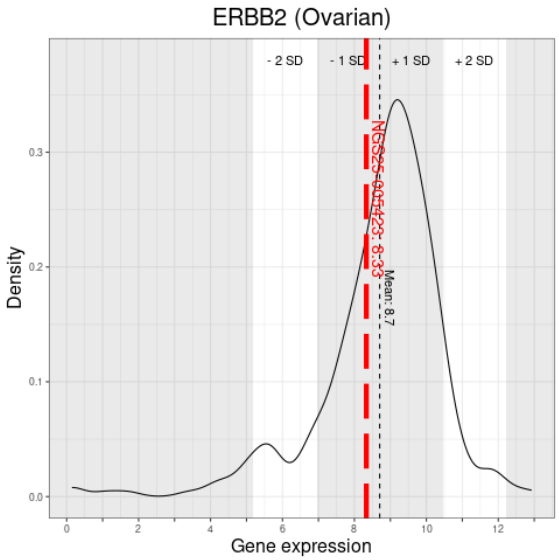
The test (sample processing, sequencing and data generation) was performed at Genomic Testing Cooperative, LCA, 25371 Commercentre Drive Lake Forest, CA 92630. Medical Director Maher Albitar, M.D. Analysis of the data was performed by Genomic Testing Cooperative, LCA, 25371 Commercentre Drive, Lake Forest,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

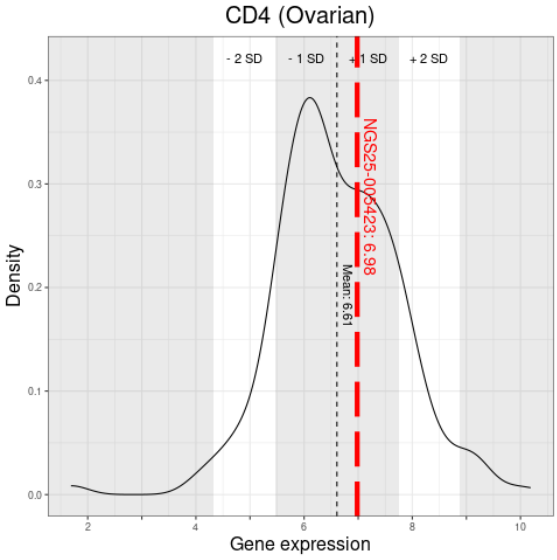
The test was developed and its performance characteristics have been determined by Genomic Testing Cooperative, LCA. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.

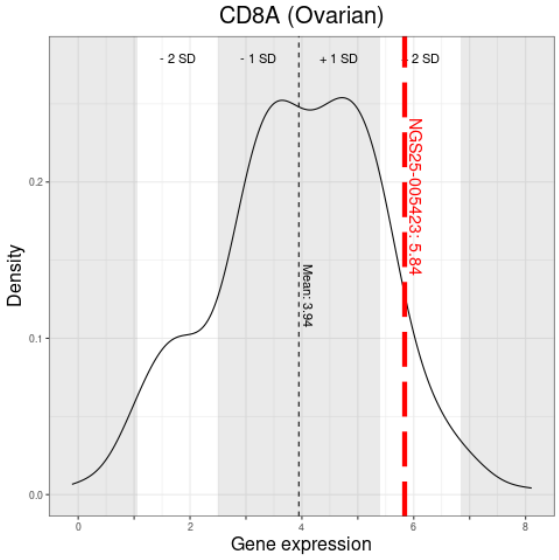
Additional Report Information

These plots represent the distribution of the expression in log2 transformed TPM (transcript per million) for each gene across GTC's history for the specified disease. The mean for each distribution is denoted by the black dotted line, while the alternating shaded areas depict the standard deviation. The expression for the current patient is marked by the red dotted line.

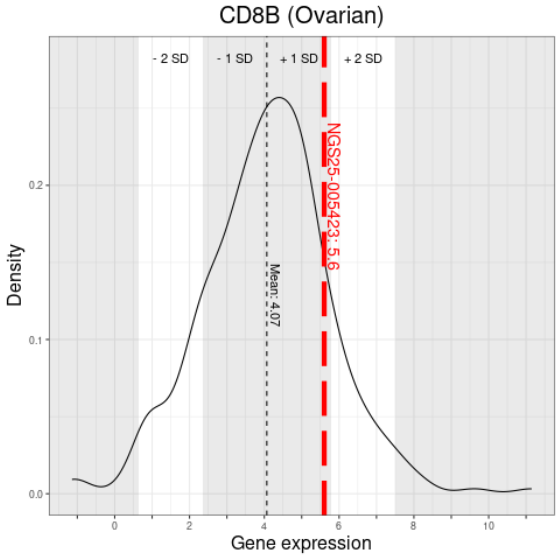


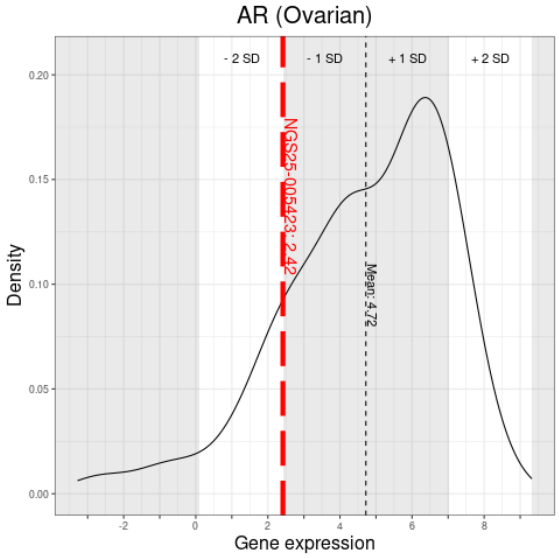


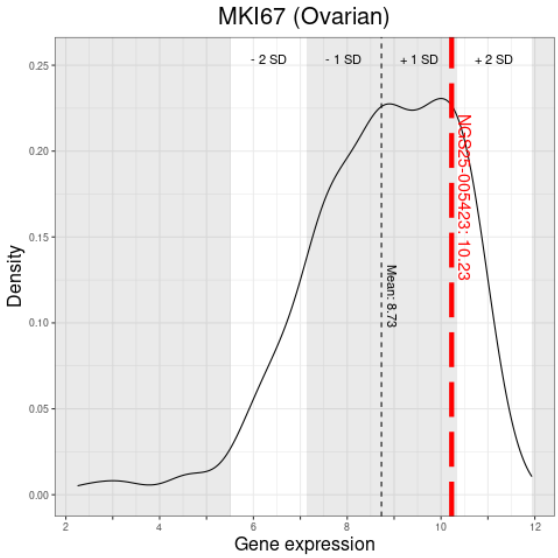


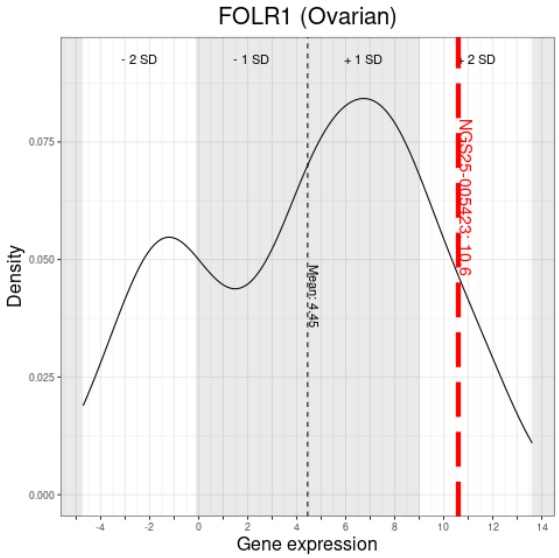


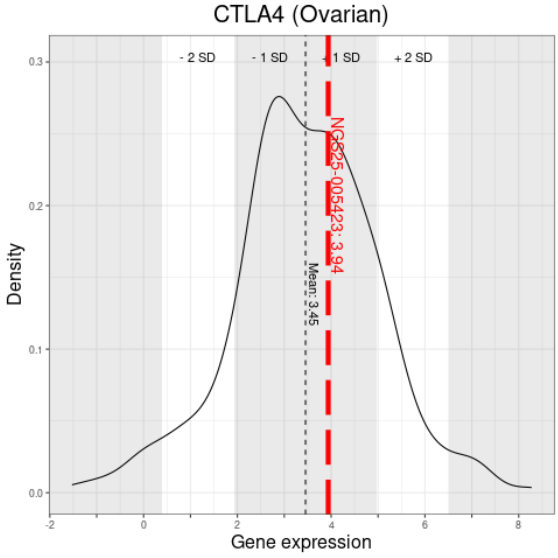
Additional Report Information

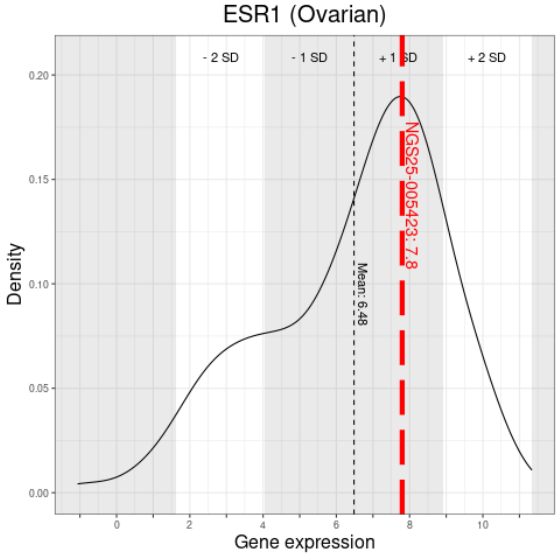












Additional Report Information