GENOMIC TESTING COOPERATIVE

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CLIA #: 05D2111917 CAP #: 9441574

Solid Tumor Profile Plus

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

MRN:				Indication for Testing:	C67.9 Malignant neoplasm of bladder unspecified
Collected Date:		Time:			
Received Date:		Time:			
Reported Date:	05/10/2025	Time:	01:45 PM		

Detected Genomic Alterations

Level 1 (FDA-Approved)	Level 2 (Standard of Care)	Level 3 (Clinical Evidence)	Level 4 (Biological Evidence)	Other
No evidence of microsatellite instability	-Homologous recombination deficiency (HRD): Positive-High -Tumor Mutation Burden Low: 8 Mut/Mb	MAP3K1, TP53, PDGFRA, MITF, MAP2K2, NTRK3, MAP2K1, ARID1A, GRIN2A, MAPK1, TSC2	TERT, KDM5A (2 mutations), IRF2, AXL, TCIRG1	-t(5;8)(q12;p11) CWC27::TACC1 fusion -Autosomal chromosomes show: +1, 2q-, -4, 5p+, 5q-, 8p-, 8q+, 10q+(proximal), 10q-(distal), 13q-, +18, 21q-, and -22.

Results Summary

- **-Mutations in MAP3K1, TP53, TERT, PDGFRA, MITF, MAP2K2, KDM5A (2 mutations), IRF2, NTRK3, MAP2K1, ARID1A, AXL, GRIN2A, MAPK1, TCIRG1, and TSC2 genes**
  -t(5;8)(q12;p11) CWC27::TACC1 fusion
  -Homologous recombination deficiency (HRD): Positive-High
  -No evidence of microsatellite instability
  -Tumor Mutation Burden Low: 8 Mut/Mb
  -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*02:844-A*68:01
  -HLA-B: B*55:01-B*51:01
  -HLA-C: C*03:03-C*02:02
  --Autosomal chromosomes show: +1, 2q-, -4, 5p+, 5q-, 8p-, 8q+, 10q+(proximal), 10q-(distal), 13q-, +18, 21q-, and -22.
  -Marked increase in Ki67 mRNA

-Increased synaptophysin

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

-MAP3K1 mutation suggests response to MEK-ERK/mTOR inhibitors.

-MAP2K1 mutation suggests response to MEK inhibitors (selumetinib, trametinib, binimetinib, vemurafenib, cobimetinib..).

-ARID1A mutation suggests increased sensitivity to radiation therapy and PARP inhibitors.

-TSC2 mutation suggests possible response to PI3K/AKT/MTOR inhibitors.

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

See chromosomal abnormality graph and expression plots at the end of the report.

Tumor Heterogeneity
There are dominant abnormal clones with MAP3K1 and TP53 mutations. The TERT, PDGFRA, MITF, MAP2K2, KDM5A (2 mutations), IRF2, NTRK3, MAP2K1, ARID1A, AXL, and GRIN2A mutations are detected in subclones. There are abnormal low-level clones with MAPK1, TCIRG1, and TSC2 mutations.

Expression	
Expression profiling suggests neuroendocrine tumor.	Marked increase in Ki67 mRNA
Increased synaptophysin	

Diagnostic Implications	
MAP3K1, TP53, TERT, PDGFRA, MITF, MAP2K2, KDM5A(2 mutations), IRF2, NTRK3, MAP2K1, ARID1A, AXL, GRIN2A, MAPK1, TCIRG1, TSC2	These findings are consistent with aggressive neoplasm.

FDA-Approved Therapeutics in Other Tumor Types	
HRD Positive-High	Niraparib + platinum-based chemotherapy
TSC2	Everolimus

Relevant Alteration Associated with Resistance
TP53 mutation is associated with resistance to therapy.

Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence)	
MAP3K1	MEK inhibitors
TP53	Aurora kinase A inhibitors, Wee1 inhibitors, Chk1 inhibitors, kevetrin, APR-246, nutlins, gene therapy
PDGFRA	Tyrosine Kinase Inhibitors
MITF	RAF inhibitors
MAP2K2	MEK inhibitors
MAP2K1	MEK inhibitors
ARID1A	sensitivity to radiation therapy and PARP inhibitors
GRIN2A	GRIN2A inhibitors
MAPK1	EGFR Inhibitors
TSC2	MTOR inhibitors
HRD Positive-High	PARP Inhibitors & Platinum based chemotherapy

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

- MAP3K1. The protein encoded by this gene is a serine/threonine kinase and is part of some signal transduction cascades, including the ERK and JNK kinase pathways as well as the NF-kappa-B pathway. The encoded protein is activated by autophosphorylation and requires magnesium as a cofactor in phosphorylating other proteins. This protein has E3 ligase activity conferred by a plant homeodomain (PHD) in its N-terminus and phospho-kinase activity conferred by a kinase domain in its C-terminus. [provided by RefSeq, Mar 2012]

- 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]

- TERT. Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by this gene, and an RNA component which serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis. Studies in mouse suggest that telomerase also participates in chromosomal repair, since de novo synthesis of telomere repeats may occur at double-stranded breaks. Alternatively spliced variants encoding different isoforms of telomerase reverse transcriptase have been identified; the full-length sequence of some variants has not been determined. Alternative splicing at this locus is thought to be one mechanism of regulation of telomerase activity. [provided by RefSeq, Jul 2008] In addition, recurring somatic mutations at multiple spots in the proximal promoter (particularly at 124bp and 146bp upstream of the translation start site) are found in tumors of many tissue origins. These mutations are thought to affect binding of Ets family proteins and nuclear factor kappa B and alter secondary structure and long-range interactions, leading to increased promoter activity. [provided by RefSeq, May 2023]

- PDGFRA. This gene encodes 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 or a heterodimer, composed of both platelet-derived growth factor receptor alpha and beta polypeptides. Studies suggest that this gene plays a role in organ development, wound healing, and tumor progression. Mutations in this gene have been associated with idiopathic hypereosinophilic syndrome, somatic and familial gastrointestinal stromal tumors, and a variety of other cancers. [provided by RefSeq, Mar 2012]

- MITF. The protein encoded by this gene is a transcription factor that contains both basic helix-loop-helix and leucine zipper structural features. The encoded protein regulates melanocyte development and is responsible for pigment cell-specific transcription of the melanogenesis enzyme genes. Heterozygous mutations in the this gene cause auditory-pigmentary syndromes, such as Waardenburg syndrome type 2 and Tietz syndrome. [provided by RefSeq, Aug 2017]

- MAP2K2. The protein encoded by this gene is a dual specificity protein kinase that belongs to the MAP kinase kinase family. This kinase is known to play a critical role in mitogen growth factor signal transduction. It phosphorylates and thus activates MAPK1/ERK2 and MAPK2/ERK3. The activation of this kinase itself is dependent on the Ser/Thr phosphorylation by MAP kinase kinase kinases. Mutations in this gene cause cardiofaciocutaneous syndrome (CFC syndrome), a disease characterized by heart defects, cognitive disability, and distinctive facial features similar to those found in Noonan syndrome. The inhibition or degradation of this kinase is also found to be involved in the pathogenesis of Yersinia and anthrax. A pseudogene, which is located on chromosome 7, has been identified for this gene. [provided by RefSeq, Jul 2008]

- 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]

- IRF2. IRF2 encodes interferon regulatory factor 2, a member of the interferon regulatory transcription factor (IRF) family. IRF2 competitively inhibits the IRF1-mediated transcriptional activation of interferons alpha and beta, and presumably other genes that employ IRF1 for transcription activation. However, IRF2 also functions as a transcriptional activator of histone H4. [provided by RefSeq, Jul 2008]

- NTRK3. This gene encodes a member of the neurotrophic tyrosine receptor kinase (NTRK) family. This kinase is a membrane-bound receptor that, upon neurotrophin binding, phosphorylates itself and members of the MAPK pathway. Signalling through this kinase leads to cell differentiation and may play a role in the development of proprioceptive neurons that sense body position. Mutations in this gene have been associated with medulloblastomas, secretory breast carcinomas and other cancers. Several transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2011]

- MAP2K1. The protein encoded by this gene is a member of the dual specificity protein kinase family, which acts as a mitogen-activated protein (MAP) kinase kinase. MAP kinases, also known as extracellular signal-regulated kinases (ERKs), act as an integration point for multiple biochemical signals. This protein kinase lies upstream of MAP kinases and stimulates the enzymatic activity of MAP kinases upon wide variety of extra- and intracellular signals. As an essential component of MAP kinase signal transduction pathway, this kinase is involved in many cellular processes such as proliferation, differentiation, transcription regulation and development. [provided by RefSeq, Jul 2008]

- ARID1A. This gene encodes a member of the SWI/SNF family, whose members have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. The encoded protein is part of the large ATP-dependent chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin. It possesses at least two conserved domains that could be important for its function. First, it has a DNA-binding domain that can specifically bind an AT-rich DNA sequence known to be recognized by a SNF/SWI complex at the beta-globin locus. Second, the C-terminus of the protein can stimulate glucocorticoid receptor-dependent transcriptional activation. It is thought that the protein encoded by this gene confers specificity to the SNF/SWI complex and may recruit the complex to its targets through either protein-DNA or protein-protein interactions. Two transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]

- AXL. The protein encoded by this gene is a member of the Tyro3-Axl-Mer (TAM) receptor tyrosine kinase subfamily. The encoded protein possesses an extracellular domain which is composed of two immunoglobulin-like motifs at the N-terminal, followed by two fibronectin type-III motifs. It transduces signals from the extracellular matrix into the cytoplasm by binding to the vitamin K-dependent protein growth arrest-specific 6 (Gas6). This gene may be involved in several cellular functions including growth, migration, aggregation and anti-inflammation in multiple cell types. The encoded protein acts as a host cell receptor for multiple viruses, including Marburg, Ebola and Lassa viruses and is a

candidate receptor for the SARS-CoV2 virus. [provided by RefSeq, Sep 2021]

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

- MAPK1. This gene encodes a member of the MAP kinase family. MAP kinases, also known as extracellular signal-regulated kinases (ERKs), act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. The activation of this kinase requires its phosphorylation by upstream kinases. Upon activation, this kinase translocates to the nucleus of the stimulated cells, where it phosphorylates nuclear targets. One study also suggests that this protein acts as a transcriptional repressor independent of its kinase activity. The encoded protein has been identified as a moonlighting protein based on its ability to perform mechanistically distinct functions. Two alternatively spliced transcript variants encoding the same protein, but differing in the UTRs, have been reported for this gene. [provided by RefSeq, Jan 2014]

- 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]

- TSC2. This gene is a tumor suppressor gene that encodes the growth inhibitory protein tuberin. Tuberin interacts with hamartin to form the TSC protein complex which functions in the control of cell growth. This TSC protein complex negatively regulates mammalian target of rapamycin complex 1 (mTORC1) signaling which is a major regulator of anabolic cell growth. Mutations in this gene have been associated with tuberous sclerosis and lymphangioleiomyomatosis. [provided by RefSeq, May 2022]

Drug Information

Trametinib

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

Binimetinib

Binimetinib is an orally available inhibitor of mitogen-activated protein kinase kinase 1 and 2 (MEK1/2) with potential antineoplastic activity. Binimetinib, noncompetitive with ATP, binds to and inhibits the activity of MEK1/2. Inhibition of MEK1/2 prevents the activation of MEK1/2-dependent effector proteins and transcription factors, which may result in the inhibition of growth factor-mediated cell signaling. This may eventually lead to an inhibition of tumor cell proliferation and an inhibition in production of various inflammatory cytokines including interleukin-1, -6 and tumor necrosis factor. MEK1/2 are dual-specificity threonine/tyrosine kinases that play key roles in the activation of the RAS/RAF/MEK/ERK pathway and are often upregulated in a variety of tumor cell types.

Cobimetinib

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

Selumetinib

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

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).

Avapritinib

Avapritinib is an orally bioavailable inhibitor of specific mutated forms of platelet-derived growth factor receptor alpha (PDGFR alpha; PDGFRa) and mast/stem cell factor receptor c-Kit (SCFR), with potential antineoplastic activity. Upon oral administration, avapritinib specifically binds to and inhibits specific mutant forms of PDGFRa and c-Kit, including the PDGFRa D842V mutant and various KIT exon 17 mutants. This results in the inhibition of PDGFRa- and c-Kit-mediated signal transduction pathways and the inhibition of proliferation in tumor cells that express these PDGFRa and c-Kit mutants. PDGFRa and c-Kit, protein tyrosine kinases and tumor-associated antigens (TAAs), are mutated in various tumor cell types; they play key roles in the regulation of cellular proliferation.

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.

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.

Olaparib

Olaparib (LYNPARZA) is an antineoplastic agent, Poly(ADP-ribose) Polymerase1;2;3 inhibitor. (PARP1;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.

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

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.

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
https://clinicaltrials.gov/study/NCT06041516	Recruiting	A First-in-Human Phase I Trial With Antibody Drug Conjugate ADCT-701 in Neuroendocrine Tumors and Carcinomas	Neuroendocrine Carcinoma	ADCT-701	National Institutes of Health Clinical Center, Bethesda, Maryland 20892
https://clinicaltrials.gov/study/NCT05882058	Recruiting	DAREON™-5: An Open-label, Multi-center Phase II Dose Selection Trial of Intravenous BI 764532, a DLL3-targeting T Cell Engager, in Patients With Relapsed/Refractory Extensive-stage Small Cell Lung Cancer and in Patients With Other Relapsed/Refractory Neuroendocrine Carcinomas	Neuroendocrine Carcinoma	BI 764532, dose 1, BI 764532, dose 2	Laura & Isaac Perlmutter Cancer Center at NYU Langone Health, New York, New York 10016 Montefiore Medical Center, Bronx, New York 10461 University of Maryland School of Medicine, Baltimore, Maryland 21201

https://clinicaltrials.gov/study/NCT02628067	Recruiting	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)	Neuroendocrine Carcinoma	pembrolizumab, pembrolizumab	Call for Information (Investigational Site 0008), New Brunswick, New Jersey 08903 MSD, Mexico City, MDS Colombia SAS, Bogota,

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
MAP3K1	NP_005912.1:p.Ser637Thr	NM_005921.1:c.1910G>C	S/T	aGc/aCc	missense_variant	91.61	441	deleterious (0.01)
TP53	NP_000537.3:p.His193Leu	NM_000546.5:c.578A>T	H/L	cAt/cTt	missense_variant	90.62	885	deleterious (0)
TERT	0	NM_198253.2:c.-124C>T	0	0	upstream_gene_variant	68.93	206	0
PDGFRA	NP_006197.1:p.Val546Phe	NM_006206.4:c.1636G>T	V/F	Gtt/Ttt	missense_variant	64.73	292	deleterious (0)
MITF	NP_937802.1:p.Glu419Lys	NM_198159.2:c.1255G>A	E/K	Gaa/Aaa	missense_variant	52.97	555	deleterious (0.04)
MAP2K2	NP_109587.1:p.Ala29Ser	NM_030662.3:c.85G>T	A/S	Gcc/Tcc	missense_variant	50.0	222	tolerated (0.74)
KDM5A	NP_001036068.1:p.Glu996Lys	NM_001042603.1:c.2986G>A	E/K	Gaa/Aaa	missense_variant	47.53	730	deleterious (0)
IRF2	NP_002190.2:p.Pro298Ser	NM_002199.3:c.892C>T	P/S	Ccg/Tcg	missense_variant	46.94	311	deleterious (0.03)
KDM5A	NP_001036068.1:p.Arg1157Cys	NM_001042603.1:c.3469C>T	R/C	Cgc/Tgc	missense_variant	46.78	977	deleterious (0.03)
NTRK3	NP_001012338.1:p.Pro239Ser	NM_001012338.2:c.715C>T	P/S	Cct/Tct	missense_variant	45.75	612	deleterious (0.03)
MAP2K1	NP_002746.1:p.Arg305Leu	NM_002755.3:c.914G>T	R/L	cGa/cTa	missense_variant	43.63	259	tolerated (0.16)
ARID1A	NP_006006.3:p.Ala325Ser	NM_006015.4:c.973G>T	A/S	Gcc/Tcc	missense_variant	42.65	619	0
AXL	NP_068713.2:p.Glu280ArgfsTer59	NM_021913.4:c.836dupC	D/DX	gac/gaCc	frameshift_variant	42.01	288	0
GRIN2A	NP_000824.1:p.Arg293Lys	NM_000833.3:c.878G>A	R/K	aGg/aAg	missense_variant	39.46	593	deleterious (0.02)
MAPK1	NP_002736.3:p.Arg135Thr	NM_002745.4:c.404G>C	R/T	aGa/aCa	missense_variant	19.62	418	deleterious (0)
TCIRG1	NP_006010.2:p.Leu12GlyfsTer44	NM_006019.3:c.29_32dupTGGC	V/VAX	gtg/gTGGCtg	frameshift_variant	14.63	287	0
TSC2	NP_000539.2:p.Ile606SerfsTer92	NM_000548.3:c.1816delA	P/X	ccA/cc	frameshift_variant	4.21	522	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

Reference

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3. Update in clinical management for gallbladder neuroendocrine carcinoma. Chu H, Shi Y, Liu J, Huang D, Zhang J, Dou C. Medicine (Baltimore). 2021 Apr 9;100(14):e25449. doi: 10.1097/MD.0000000000025449. PMID: 33832150.

4. Primary small-cell neuroendocrine carcinoma of the bladder: Case report and literature review. Olivieri V, Fortunati V, Bellei L, Massarelli M, Ruggiero G, Abate D, Serra N, Griffa D, Forte F, Corongiu E. Arch Ital Urol Androl. 2020 Oct 2;92(3). doi: 10.4081/aiua.2020.3.211. PMID: 33016048.

Electronic Signature

Maher Albitar, M.D.

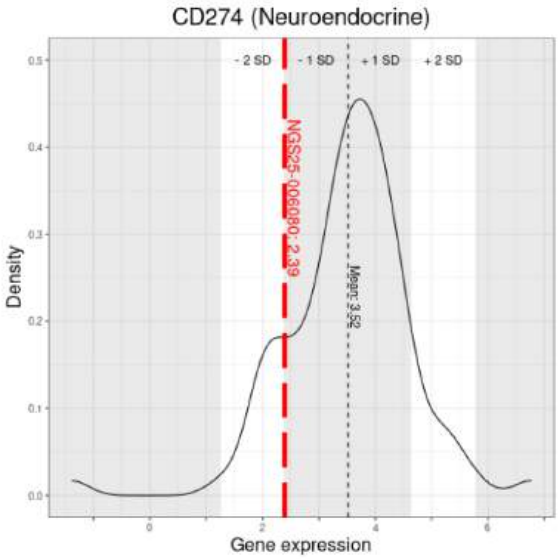
The test (sample processing, sequencing and data generation) was performed at Anthology Diagnostics-JFK Medical Center Lab, 80 James Street Edison, NJ 08820. Medical Director Clinton Ewing, M.D. Analysis of the data was performed by Genomic Testing Cooperative, LCA, 25371 Commercentre Drive, Lake Forest, CA 92630. Medical Director: Maher Albitar, M.D.

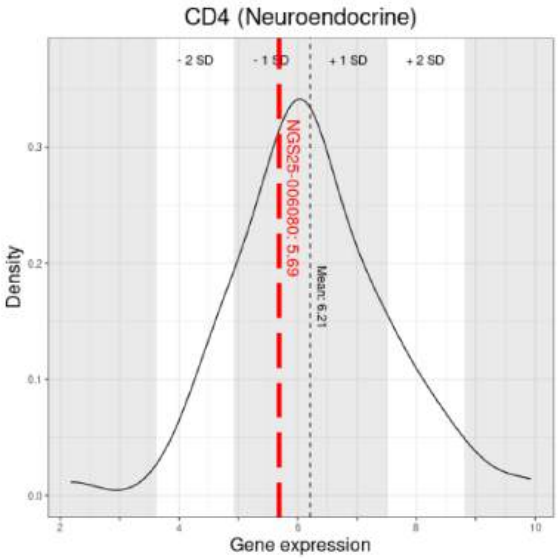
The test was developed and its performance characteristics have been determined by Anthology Diagnostics-JFK Medical Center Lab. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.

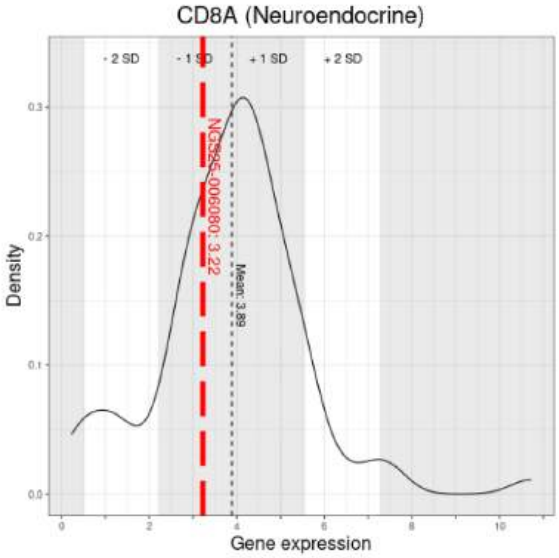
Additional Report Information

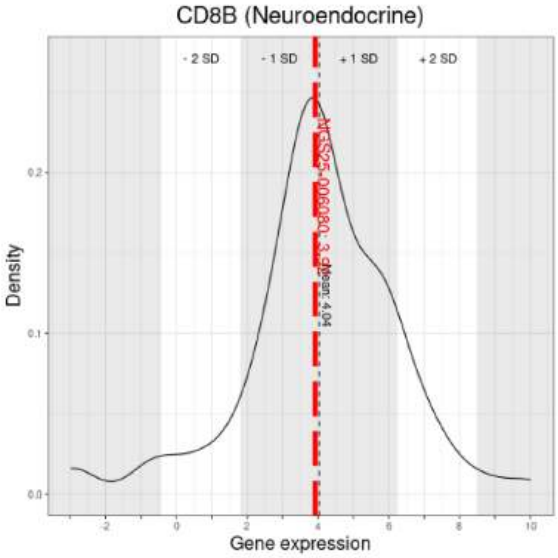
RNA Expression Plots

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.



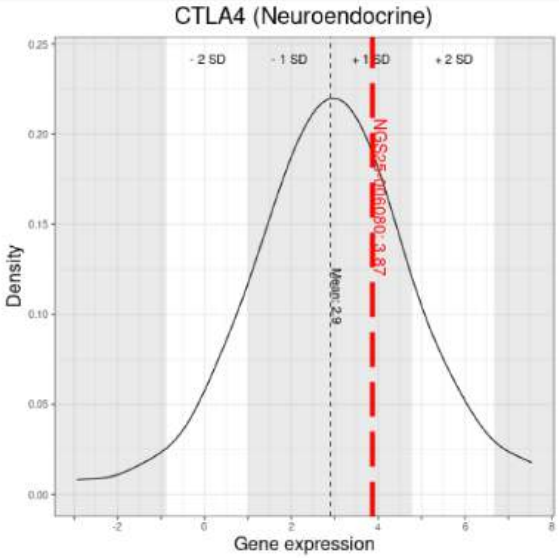


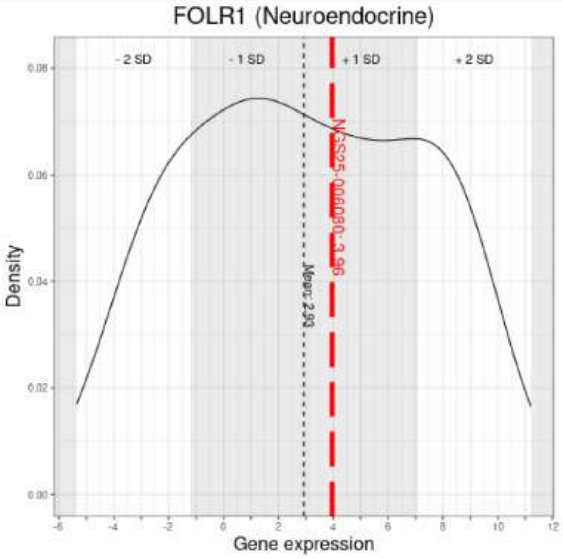


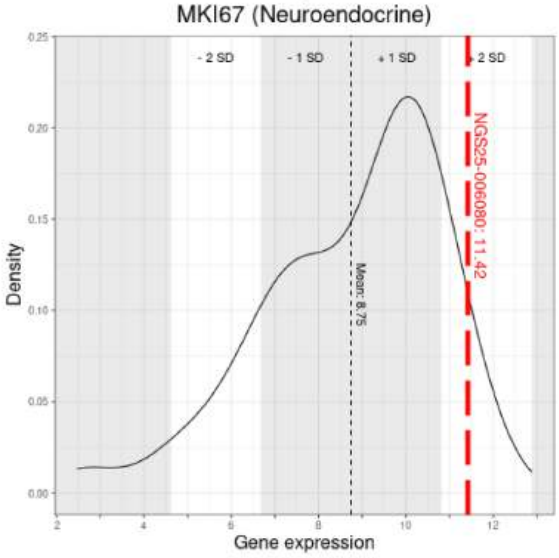


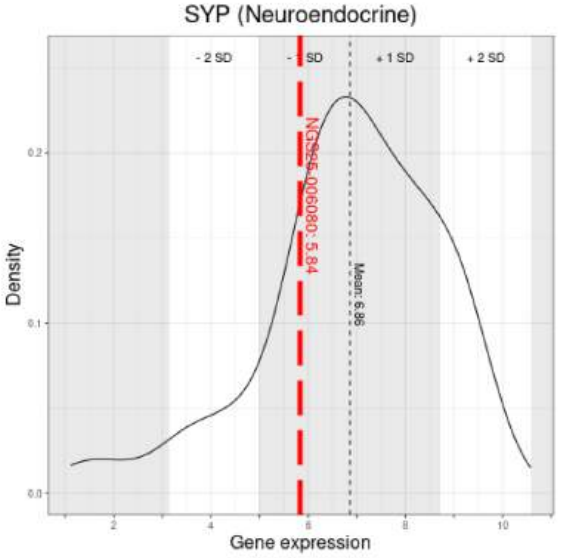
Additional Report Information

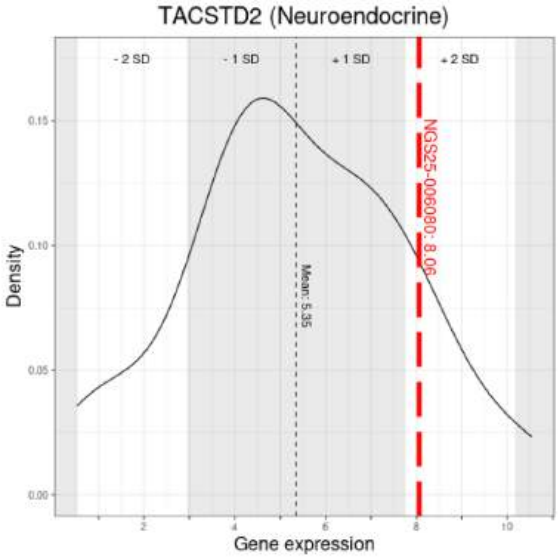
RNA Expression Plots











Additional Report Information

Chromosomal Abnormality Graph