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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: | | | |

| | | | |
|---|---|---|---|
| MRN: | | Indication for Testing: | C25.9 Malignant neoplasm of pancreas, unspecified |
| 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 |
|---|---|---|---|---|
| t(1;8)(q24;p12) ATP1B1::NRG1 fusion mRNA | -BRCA2<br>-Tumor Mutation Burden Low: 6 Mut/Mb<br>-Homologous recombination deficiency (HRD): Negative<br>-No evidence of microsatellite instability | JAK1, CHEK2, SMAD3, NOTCH1 | JUN, KMT2C, MYO18A (? Germline), KIF5B, SLC22A1 | Autosomal chromosomal structural analysis shows 1q+, +8, 12q-(distal) |

-PD-L1 testing by immunohistochemistry (IHC): Clone: ZR3; Tumor cells: 0%; Immune cells: 0%; Combined Positive Score (CPS): 0.

-CLDN18.2 FDA (Zolbetuximab™) testing by immunohistochemistry (IHC): Negative. Percentage of cells with 2+/3+membrane staining: 0%.

## Results Summary

- **-t(1;8)(q24;p12) ATP1B1::NRG1 fusion mRNA**
  **-Somatic mutations in JAK1, BRCA2, JUN, CHEK2, SMAD3, NOTCH1, KMT2C, KIF5B, and SLC22A1 genes**
  **-Possible germline mutation in MYO18A gene, heterozygous**
  **-No evidence of microsatellite instability**
  **-Tumor Mutation Burden Low: 6 Mut/Mb**
  **-Homologous recombination deficiency (HRD): Negative**
  **-No evidence of fusion mRNA involving ALK, RET, ROS1, or NTRK**
  **-No evidence of BRCA1 or PALB2 mutations**
  **-EBV, HPV, TTV, and HTLV1 viral mRNA: Not detected**

**-HLA Genotyping:**
**-HLA-A: A*80:01-A*30:01**
**-HLA-B: B*07:02-B*42:01**
**-HLA-C: C*17:01-C*17:01**
**-Autosomal chromosomal structural analysis shows 1q+, +8, 12q- (distal)**
**-Increased CA15-3, CK8/19, ERBB3, FGFR3, NRG1 mRNA**

-ATP1B1::NRG1 fusion suggest response to Zenocutuzumab.

-The FDA has approved NALIRIFOX (combination of liposomal irinotecan, 5-fluorouracil, and oxaliplatin) for the treatment of metastatic pancreatic cancer.

-JAK mutation suggests possible response to JAK inhibitors (filgotinib, baricitinib, tofacitinib, upadacitinib, ruxolitinib..).

-BRCA2 and CHEK2 mutations suggest response to PARP inhibitors.

-SMAD3 mutation suggests response to TGF-beta inhibitors, cisplatin and irinotecan as well as PI3K and MEK inhibitors.

-NOTCH1 mutation suggests sensitivity to NOTCH inhibitors.

-The MYO18A mutation is detected at high level, raising the possibility of a germline mutation. This mutation leads to early termination (loss of function). However, there is no data on its clinical relevance and should be classified as of "uncertain significance" at this time.

**See additional report information at the end of the report.**

## Tumor Heterogeneity

There are abnormal clones with JAK1, BRCA2, JUN, CHEK2, SMAD3, NOTCH1, KMT2C, KIF5B, and SLC22A1 mutations.
The MYO18A mutation is detected at a high level, possible germline abnormality.

## Expression

Increased CA15-3, CK8/19, ERBB3, FGFR3, NRG1 mRNA

## Diagnostic Implications

| | |
|---|---|
| JAK1, BRCA2, JUN, CHEK2, SMAD3, NOTCH1, KMT2C, MYO18A, KIF5B, SLC22A1 | -The findings are consistent with pancreatic cancer<br>-The MYO18A mutation is likely a germline variant. |

| FDA-Approved Therapeutics | |
|---|---|
| ATP1B1::NRG1 fusion | Zenocutuzumab |

| FDA-Approved Therapeutics in Other Tumor Types | |
|---|---|
| CHEK2 | Olaparib, Talazoparib + Enzalutamide |

| Levels 2, 3 & 4 (Standard of Care and Clinical/Biological Evidence) | |
|---|---|
| JAK1 | JAK inhibitors |
| BRCA2 | PARP inhibitors |
| CHEK2 | PARP inhibitors |
| SMAD3 | TGF-beta inhibitors, cisplatin and irinotecan and possible to PI3K and MEK inhibitors |
| NOTCH1 | NOTCH inhibitors |

| Relevant Genes with NO Alteration | | |
|---|---|---|
| -No evidence of mutation in KRAS, NRAS, EGFR, BRAF, TP53, or BRCA1<br>-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<br>-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, HTLV1, 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

- JAK1. This gene encodes a membrane protein that is a member of a class of protein-tyrosine kinases (PTK) characterized by the presence of a second phosphotransferase-related domain immediately N-terminal to the PTK domain. The encoded kinase phosphorylates STAT proteins (signal transducers and activators of transcription) and plays a key role in interferon-alpha/beta, interferon-gamma, and cytokine signal transduction. This gene plays a crucial role in effecting the expression of genes that mediate inflammation, epithelial remodeling, and metastatic cancer progression. This gene is a key component of the interleukin-6 (IL-6)/JAK1/STAT3 immune and inflammation response and is a therapeutic target for alleviating cytokine storms. The kinase activity of this gene is directly inhibited by the suppressor of cytokine signalling 1 (SOCS1) protein. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2020]

- BRCA2. Inherited mutations in BRCA1 and this gene, BRCA2, confer increased lifetime risk of developing breast or ovarian cancer. Both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The largest exon in both genes is exon 11, which harbors the most important and frequent mutations in breast cancer patients. The BRCA2 gene was found on chromosome 13q12.3 in human. The BRCA2 protein contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair. BRCA2 is considered a tumor suppressor gene, as tumors with BRCA2 mutations generally exhibit loss of heterozygosity (LOH) of the wild-type allele. [provided by RefSeq, May 2020]

- JUN. This gene is the putative transforming gene of avian sarcoma virus 17. It encodes a protein which is highly similar to the viral protein, and which interacts directly with specific target DNA sequences to regulate gene expression. This gene is intronless and is mapped to 1p32-p31, a

chromosomal region involved in both translocations and deletions in human malignancies. [provided by RefSeq, Jul 2008]

- CHEK2. In response to DNA damage and replication blocks, cell cycle progression is halted through the control of critical cell cycle regulators. The protein encoded by this gene is a cell cycle checkpoint regulator and putative tumor suppressor. It contains a forkhead-associated protein interaction domain essential for activation in response to DNA damage and is rapidly phosphorylated in response to replication blocks and DNA damage. When activated, the encoded protein is known to inhibit CDC25C phosphatase, preventing entry into mitosis, and has been shown to stabilize the tumor suppressor protein p53, leading to cell cycle arrest in G1. In addition, this protein interacts with and phosphorylates BRCA1, allowing BRCA1 to restore survival after DNA damage. Mutations in this gene have been linked with Li-Fraumeni syndrome, a highly penetrant familial cancer phenotype usually associated with inherited mutations in TP53. Also, mutations in this gene are thought to confer a predisposition to sarcomas, breast cancer, and brain tumors. This nuclear protein is a member of the CDS1 subfamily of serine/threonine protein kinases. Several transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Apr 2012]

- SMAD3. The SMAD family of proteins are a group of intracellular signal transducer proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (Mad) and the C. elegans gene Sma. The SMAD3 protein functions in the transforming growth factor-beta signaling pathway, and transmits signals from the cell surface to the nucleus, regulating gene activity and cell proliferation. It also functions as a tumor suppressor. Mutations in this gene are associated with aneurysms-osteoarthritis syndrome and Loeys-Dietz Syndrome 3. [provided by RefSeq, Nov 2019]

- 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]

- KMT2C. This gene is a member of the myeloid/lymphoid or mixed-lineage leukemia (MLL) family and encodes a nuclear protein with an AT hook DNA-binding domain, a DHHC-type zinc finger, six PHD-type zinc fingers, a SET domain, a post-SET domain and a RING-type zinc finger. This protein is a member of the ASC-2/NCOA6 complex (ASCOM), which possesses histone methylation activity and is involved in transcriptional coactivation. [provided by RefSeq, Jul 2008]

- MYO18A. The protein encoded by this gene can bind GOLPH3, linking the Golgi to the cytoskeleton and influencing Golgi membrane trafficking. The encoded protein is also part of a complex that assembles lamellar actomyosin bundles and may be required for cell migration. [provided by RefSeq, Oct 2016]

- KIF5B. Enables identical protein binding activity; microtubule binding activity; and microtubule motor activity. Involved in several processes, including lysosome localization; natural killer cell mediated cytotoxicity; and positive regulation of protein localization to plasma membrane. Located in centriolar satellite; cytosol; and vesicle. [provided by Alliance of Genome Resources, Apr 2022]

- SLC22A1. Polyspecific organic cation transporters in the liver, kidney, intestine, and other organs are critical for elimination of many endogenous small organic cations as well as a wide array of drugs and environmental toxins. This gene is one of three similar cation transporter genes located in a cluster on chromosome 6. The encoded protein contains twelve putative transmembrane domains and is a plasma integral membrane protein. Two transcript variants encoding two different isoforms have been found for this gene, but only the longer variant encodes a functional transporter. [provided by RefSeq, Jul 2008]

# Drug Information

## Irinotecan

Irinotecan is a topoisomerase inhibitor used for chemotherapy. It is a water-soluble analogue of camptothecin, which is extracted from Camptotheca acuminate tree. The bis-piperidine side chain in the structure of irinotecan bestows enhanced water solubility. As an anticancer drug, irinotecan was first commercially available in Japan in 1994 to treat various cancers such as lung, cervical and ovarian cancer. Approved by the FDA in 1996, irinotecan is used to treat colorectal cancer and pancreatic adenocarcinoma. Irinotecan liposome was approved by the FDA in February 2024.

## Tegafur

Tegafur (INN, BAN, USAN) is a prodrug of Fluorouracil (5-FU), an antineoplastic agent used as the treatment of various cancers such as advanced gastric and colorectal cancers. It is a pyrimidine analogue used in combination therapies as an active chemotherapeutic agent in conjunction with Gimeracil and Oteracil, or along with Fluorouracil as Tegafur-uracil. Tegafur is usually given in combination with other drugs that enhance the bioavailability of the 5-FU by blocking the enzyme responsible for its degradation, or serves to limit the toxicity of 5-FU by ensuring high concentrations of 5-FU at a lower dose of tegafur. When converted and bioactivated to 5-FU, the drug mediates an anticancer activity by inhibiting thymidylate synthase (TS) during the pyrimidine pathway involved in DNA synthesis.

## Oxaliplatin

Oxaliplatin is a platinum-based chemotherapy drug in the same family as cisplatin and carboplatin. Like most platinum-based compounds, oxaliplatin's mechanism of action is primarily through DNA damage through DNA crosslinking. However, due to the structure of oxaliplatin, its adducts make the binding of mismatch repair protein to DNA harder compared to cisplatin or carboplatin's adducts, resulting in greater cytotoxic effects. Oxaliplatin, in combination with infusional fluorouracil and leucovorin, is indicated for the treatment of advanced colorectal cancer and adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.

## Tofacitinib

Tofacitinib is a partial and reversible janus kinase (JAK) inihibitor that will prevent the body from responding to cytokine signals. By inhibiting JAKs, tofacitinib prevents the phosphorylation and activation of STATs. The JAK-STAT signalling pathway is involved in the transcription of cells involved in hematopoiesis, and immune cell function. Tofacitinib works therapeutically by inhibiting the JAK-STAT pathway to decrease the inflammatory response. However, there is evidence to suggest that it may also achieve efficacy via other pathways as well.

## 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).

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

## 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.

## Zenocutuzumab

Zenocutuzumab is a low-fucose humanized full-length immunoglobulin G1 (IgG1) bispecific HER2- and HER3-directed bispecific antibody. It works to attenuate aberrant cancer cell growth caused by genomic rearrangements involving the neuregulin 1 gene (NRG1), which is an oncogenic driver. Zenocutuzumab is also capable of promoting antibody-dependent cellular cytotoxicity in cancer cells.

# Potential Clinical Trials

| Trial URL | Status | Title | Disease | Drug | Sites |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| https://clinicaltrials.gov/study/NCT04753879 | Recruiting | Multi-agent Low Dose Chemotherapy (Gemcitabine, Nab-paclitaxel, Capecitabine, Cisplatin, Irinotecan) Followed by Maintenance Olaparib and Pembrolizumab in Untreated Metastatic Pancreatic Ductal Adenocarcinoma. | Metastatic Pancreatic Cancer | Nab-paclitaxel, Gemcitabine, Cisplatin, Irinotecan, Capecitabine, Pembrolizumab, Olaparib | Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland 21231 |
| https://clinicaltrials.gov/study/NCT04477343 | Recruiting | An Open-label Phase 1 Study to Evaluate the Safety and Tolerability of SX-682 in Combination With Nivolumab as a Maintenance Therapy in Patients With Metastatic Pancreatic Ductal Adenocarcinoma | Metastatic Pancreatic Cancer | SX-682, Nivolumab Injectable Product | University of Rochester, Rochester, New York 14642 |
| https://clinicaltrials.gov/study/NCT06941857 | Recruiting | A Phase 2 Study of NC410 and FOLFIRINOX in Combination With Nivolumab With or Without Ipilimumab in Patients With Treatment-naïve, Metastatic Pancreatic Cancer | Metastatic Pancreatic Cancer | Oxaliplatin, Irinotecan, Folinic Acid, 5-Fluorouracil (5-FU), NC410, Nivolumab, Ipilimumab | Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland 21231 |
| https://clinicaltrials.gov/study/NCT04543071 | Recruiting | A Phase 2 Study With Combination Chemotherapy (Gemcitabine and Nab-Paclitaxel), Chemokine (C-X-C) Motif Receptor 4 Inhibitor (BL-8040), and Immune Checkpoint Blockade (Cemiplimab) in METastatic Treatment naïve PANCreas Adenocarcinoma | Metastatic Pancreatic Cancer | Motixafortide, Cemiplimab, Gemcitabine, Nab paclitaxel | Columbia University Irving Medical Center, New York, New York 10032<br>Brown University, Providence, Rhode Island 02912<br>Medical College of Wisconsin, Wisconsin Diagnostic Labratories, Milwaukee, Wisconsin 53226 |

## 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 |
|---|---|---|---|---|---|---|---|---|
| JAK1 | NP_002218.2:p.Gly673Cys | NM_002227.2:c.2017G>T | G/C | Ggt/Tgt | missense_variant | 24.13 | 402 | deleterious |
| BRCA2 | NP_000050.2:p.Ser3241Phe | NM_000059.3:c.9722C>T | S/F | tCc/tTc | missense_variant | 21.03 | 252 | tolerated |
| JUN | NP_002219.1:p.Met142SerfsTer165 | NM_002228.3:c.424_431del | MVA/X | ATGGTGGCt/t | frameshift_variant | 20.31 | 586 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CHEK2 | NP_001005735.1:p.Ile409Leu | NM_001005735.1:c.1225A>C | I/L | Att/Ctt | "missense_variant,splice_region_variant" | 19.62 | 260 | tolerated |
| SMAD3 | NP_001138574.1:p.Ser320Phe | NM_001145102.1:c.959C>T | S/F | tCt/tTt | missense_variant | 19.27 | 327 | deleterious |
| NOTCH1 | NP_060087.3:p.Gly2292Glu | NM_017617.3:c.6875G>A | G/E | gGg/gAg | missense_variant | 15.57 | 1079 | tolerated |
| KMT2C | NP_733751.2:p.Cys302Ter | NM_170606.2:c.906T>A | C/* | tgT/tgA | stop_gained | 3.3 | 667 | 0 |
| MYO18A (RNA) | NP_510880.2:p.Thr2045ArgfsTer8 | NM_078471.3:c.6134_6135del | T/X | aCA/a | frameshift_variant | 42.78 | 942 | 0 |
| KIF5B (RNA) | NP_004512.1:p.Arg550ThrfsTer4 | NM_004521.2:c.1647dup | -/X | -/A | frameshift_variant | 12.1 | 1223 | 0 |
| SLC22A1 (RNA) | NP_003048.1:p.Arg294LysfsTer4 | NM_003057.2:c.880dup | Q/QX | caa/cAaa | frameshift_variant | 10.99 | 555 | 0 |

## Methodology and Test Background

This is a next generation sequencing (NGS) test that involves separate analysis of DNA and RNA panels for abnormalities that are reported to be altered in various types of solid tumors. The DNA panel is composed of 434 genes and the RNA panel is composed of >1600 genes. The DNA and RNA components of this assay were developed, validated, and set up as separate workflows, with independent extraction, library preparation, sequencing, and analysis pipelines. The NGS assay also detects several viruses that are important in oncology, including EBV, HPV, HTLV 1, 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), human T-lymphotropic virus type-1 (HTLV1), 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

1. Advances in pancreatic cancer early diagnosis, prevention, and treatment: The past, the present, and the future. Mannucci A, Goel A. CA Cancer J Clin. 2026 Jan-Feb;76(1):e70035. doi: 10.3322/caac.70035. Epub 2025 Sep 19. PMID: 40971231.

2. Pancreatic cancer - systemic treatment. Liberko M. Rozhl Chir. 2024;103(4):110-116. doi: 10.33699/PIS.2024.103.4.110-116. PMID: 39927503.

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4. Advancing Immunotherapy in Pancreatic Cancer. Hegazi A, Rager LE, Watkins DE, Su KH. Int J Mol Sci. 2024 Oct 28;25(21):11560. doi: 10.3390/ijms252111560. PMID: 39519112.

### Electronic Signature

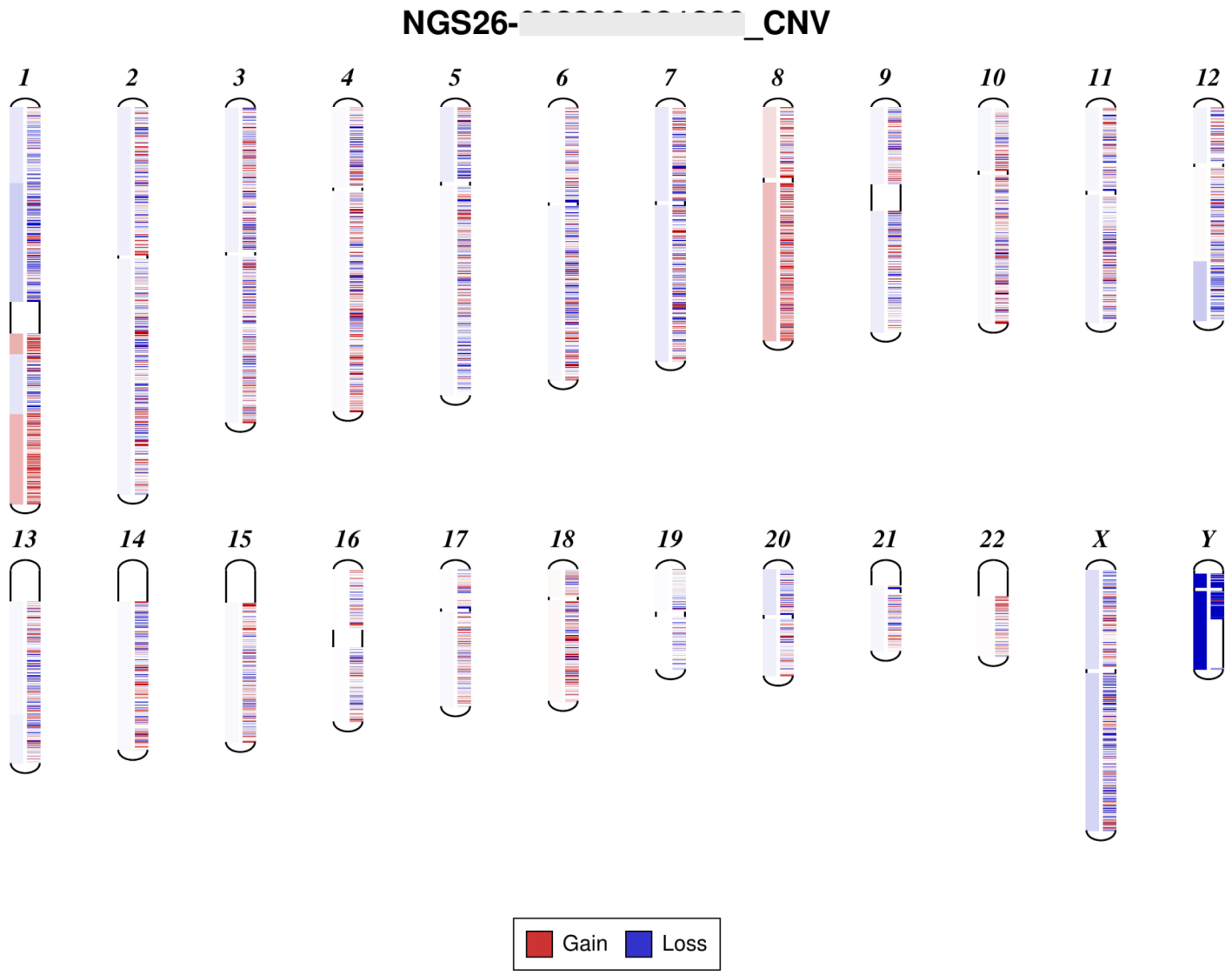
Ahmad Charifa, M.D.

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. (CLIA #: 05D2111917 CAP #: 9441574). The signing pathologist is fully responsible for the accuracy and interpretation of results and the release of this report.

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

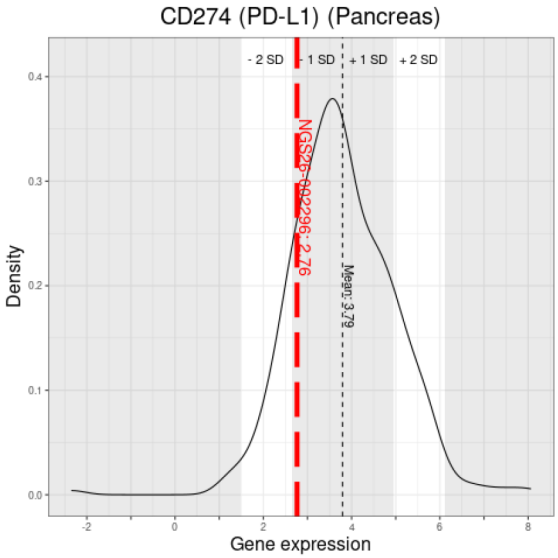
## Chromosomal Abnormality Graph

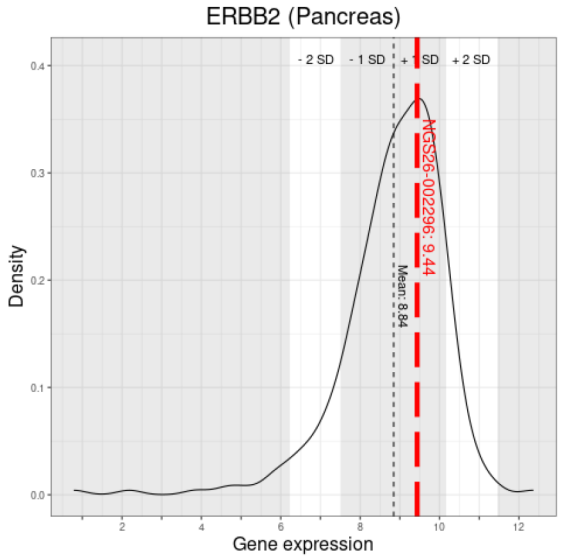


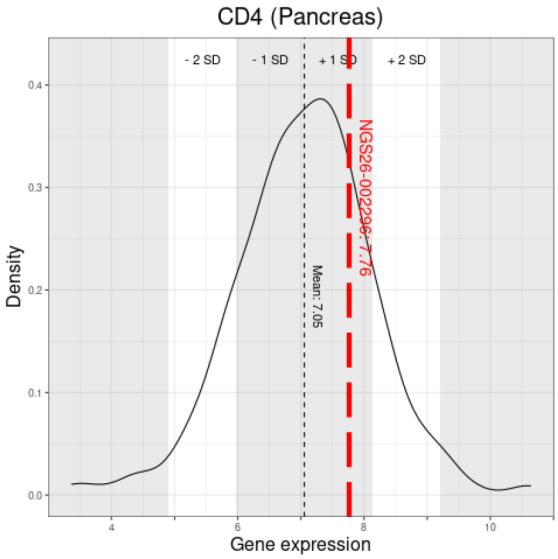
# Additional Report Information

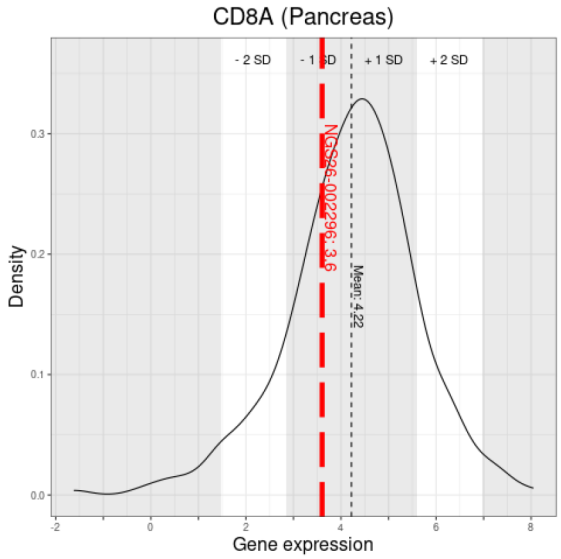
## RNA Expression Plots

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.



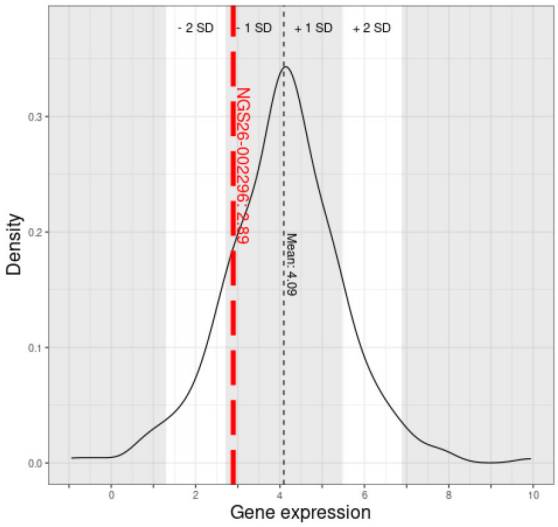



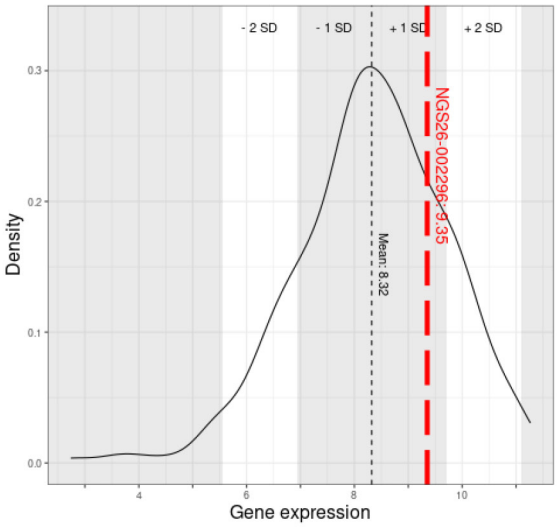
# Additional Report Information

## RNA Expression Plots

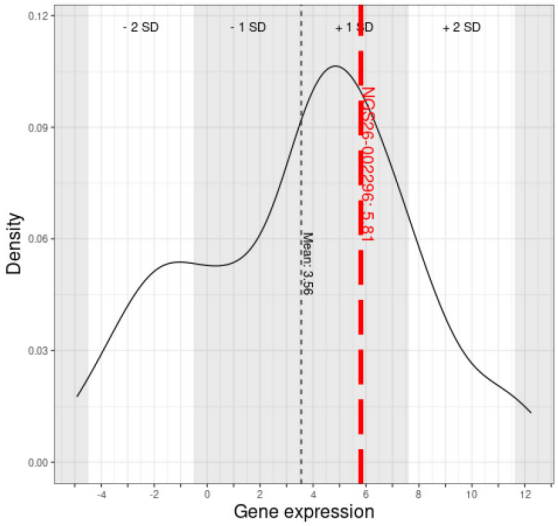
CD8B (Pancreas)



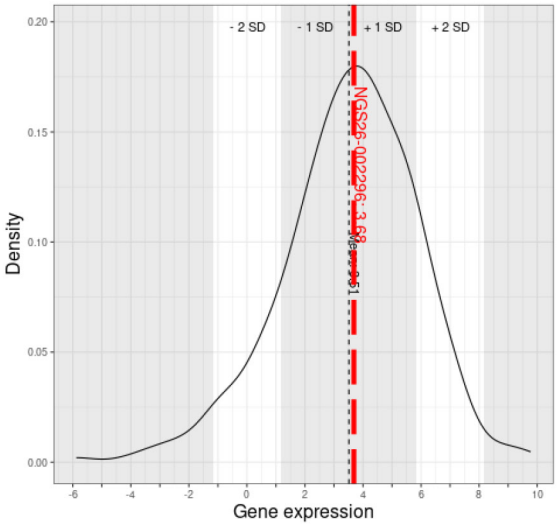

MKI67 (Ki67) (Pancreas)



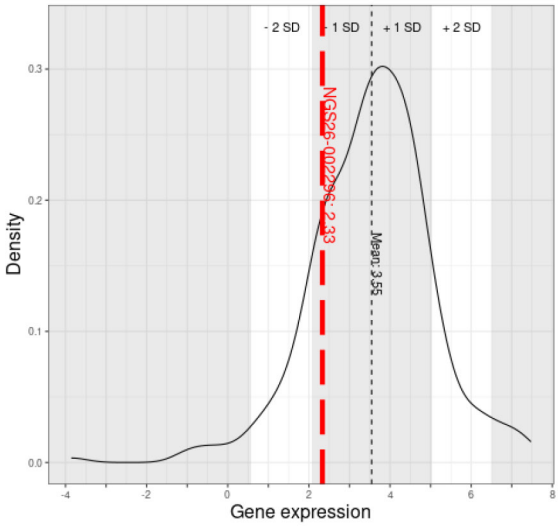

FOLR1 (Pancreas)




CDX2 (Pancreas)




CTLA4 (Pancreas)




TACSTD2 (TROP2) (Pancreas)