# Precision Panel- 50 Genes

## Test Description

The MolQ Precision Panel includes 50 genes, involving hotspot regions and 3159 unique variants, applicable to a wide range of tumor types for detection of SNV (single and multiple nucleotide variation), Insertion-Deletion, Copy Number Variation (CNV), and gene Fusions. Fusion and splice variants are detected in RNA.

## Patient Demographic

**Name**: Mr. Om Prakash
**Sex**: Male
**Date of Birth/Age**: 31 years
**Disease**: Colorectal Carcinoma

## Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Dr AV Institute of Personalized Cancer Therapy and Research
Pathologist: Not Provided

## Specimen

**Booking ID**: 012304270012
**Sample Type**: FFPE
**Tumor Content Percentage**: 10-15%
**Date of Collection**: 27-04-2023
**Date of Booking**: 27-04-2023

## CLINICAL SYNOPSIS

Om Prakash, is a known case of colorectal carcinoma. He has been evaluated for pathogenic variations in the genes listed in Appendix 2.

## RESULT SUMMARY

The assay has detected *KRAS* mutation (p.Gly12Asp, VAF = 35.02%). In addition, *PIK3CA* (p.His1047Arg, VAF =18.37%) is also present. Reports show that the coexistence of *KRAS* and *PIK3CA* mutations in cells implies potential synergistic hyperactivation of the Ras/MAPK and PI3K/Akt oncogenic pathways and indicates poor prognosis in colorectal carcinoma patients[1].

"*Important disclaimer: As a standard of care, reference laboratory case selection criteria for NGS run is ≥20% tumor content. The run was performed in this case after receiving informed consent from the clinician.*"

**RESULTS**

**Variants in *KRAS* and *PIK3CA* genes were detected.**

| Gene/ Transcript (Locus) | Variant ID | Variant | Allele Frequency | Variant Effect | *Relevant Therapies (In this cancer type) | *Relevant Therapies (In other cancer type) | Tier[2] |
|---|---|---|---|---|---|---|---|
| *KRAS* NM_033360.4 (chr12:25398284) | COSM522 | c.35G>C (p.Gly12Asp) | 35.02% | Missense | bevacizumab + chemotherapy | None | Ia |
| *PIK3CA* NM_006218.4 (chr3:178952085) | COSM775 | c.3140A>G (p.His1047Arg) | 18.37% | Missense | None | alpelisib + hormone therapy[i,ii] | IIc |
| *RET* | - | c.2428G>T (p.Gly810Cys) | 3.24% | - | None | selpercatinib[ii] vandetanib[ii] pralsetinib | IIc |
| *FGFR3* | - | Amplification | - | - | None | None | IIc |

| | | | | | | |
|---|---|---|---|---|---|---|
| *BRAF* | Wild Type | - | - | - | - | - |

* Public data sources included in relevant therapies: FDA[i], NCCN, EMA[ii], ESMO

## PREVALENT CANCER BIOMARKERS WITHOUT RELEVANT EVIDENCE BASED ON INCLUDED DATA SOURCES

***ERBB3*** amplification

## CLINICAL CORRELATION AND VARIANT INTERPRETATION

***KRAS*** **p.Gly12Asp**

***Gene description***: The *KRAS* proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the *RAS* superfamily which also includes *NRAS* and *HRAS*. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and surviva[3-5].

***Alterations and prevalence***: Recurrent mutations in *RAS* oncogenes cause constitutive activation and are found in 20-30% of cancers. *KRAS* mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[6]. The majority of *KRAS* mutations consist of point mutations occurring at G12, G13, and Q61[6-8]. Mutations at A59, K117, and A146 have also been observed but are less frequent[9,10].

***Potential relevance***: The FDA has approved the small molecule inhibitors, sotorasib[11] (2021) and adagrasib[12] (2022), for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has also granted breakthrough therapy designation (2022) to the *KRAS* G12C inhibitor, GDC-6036[13], for *KRAS* G12C mutation in non-small cell lung cancer. The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for *KRAS* G12V mutant non-small cell lung cancer or in combination with defactinib, for *KRAS* mutant endometrial carcinoma and *KRAS* G12V mutant non-small cell lung cancer[14]. The PLK1 inhibitor, onvansertib[15], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with *KRAS*-mutated metastatic colorectal cancer (mCRC). Additionally, the SHP2 inhibitor, BBP-398[16] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with *KRAS* G12C-mutated metastatic NSCLC. The EGFR antagonists, cetuximab[17] and panitumumab[18], are contraindicated for treatment of colorectal cancer patients with *KRAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[10]. Additionally, *KRAS* mutations are associated with poor prognosis in NSCLC[19].

***BRAF*** **Wild type**

***Gene description***: The *BRAF* gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/ threonine protein kinases which also includes ARAF and RAF1 (CRAF). *BRAF* is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through *BRAF* mutations and leads to an increase in cell division, dedifferentiation, and survival[20,21]. *BRAF* mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF3. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[22-24].

***Alterations and prevalence***: Recurrent somatic mutations in *BRAF* are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)[25-29]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic *BRAF* mutation across diverse cancer types[23,30]. Class 2 mutations include K601E/ N/T, L597Q/V, G469A/V/R/, G464V/E/, and *BRAF* fusions[23]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[23]. *BRAF* V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in

histiocytic neoplasms[31-33]. Other recurrent *BRAF* somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop[30]. In primary cancers, *BRAF* amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[26,29]. *BRAF* fusions are mutually exclusive to *BRAF* V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[34-38]. Part of the oncogenic mechanism of *BRAF* gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[24,34,36].

***Potential relevance***: Vemurafenib[39] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E mutation. *BRAF* class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[23]. BRAF kinase inhibitors including dabrafenib[40] (2013) and encorafenib[41] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E/K mutations. Encorafenib[41] is approved in combination with cetuximab[42] (2020) for the treatment of *BRAF* V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring *BRAF* alterations[23]. Trametinib[43] (2013) and binimetinib[44] (2018) were approved for the treatment of metastatic melanoma with *BRAF* V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib[45] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a *BRAF* V600E mutation. The PD-L1 antibody, atezolizumab[46], has also been approved in combination with cobimetinib and vemurafenib for *BRAF* V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib[47] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The pan-RAF kinase inhibitor, tovorafenib (DAY-101), was granted breakthrough therapy designation (2020) by the FDA for pediatric patients with advanced low-grade glioma harboring activating RAF alterations[48]. The ERK inhibitor ulixertinib[49] was also granted a fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring *BRAF* mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[50], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. *BRAF* fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[51]. Additional mechanisms of resistance to BRAF targeted therapy include *BRAF* amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in *KRAS*, *NRAS*, and *MAP2K1/2* (MEK1/2)[52-58]. Clinical responses to sorafenib and trametinib in limited case studies of patients with *BRAF* fusions have been reported[38].

### *ERBB2* Amplification

***Gene description***: The *ERBB3* gene encodes the erb-b2 receptor tyrosine kinase 3, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB3/HER3, EGFR/ERBB1/HER1, ERBB2/HER2, and ERBB4/HER4 make up the HER protein family[59]. ERBB3/ HER3 binds to extracellular factors, such as neuregulins, but has an impaired kinase domain[60]. Upon ligand binding, ERBB3 forms hetero-dimers with other ERBB/HER family members, including ERBB2/HER2 resulting in activation of tyrosine kinase activity primarily through its dimerization partner.

***Alterations and prevalence***: *ERBB3* gene amplification leading to an increase in expression occurs at low frequency (1-5%) in several cancer types including bladder, esophagus, lung adenocarcinoma, ovarian, pancreas, sarcoma, stomach, and uterine cancers[26,28,29,61-64]. *ERBB3* is also the target of relatively frequent (5-10%) and recurrent somatic mutations in diverse cancer types including bladder, cervical, colorectal, and stomach cancers[26,27,29,61,63]. Recurrent *ERBB3* mutations such as V104L/M, occur primarily in the extracellular domain.

***Potential relevance***: Currently, no therapies are approved for *ERBB3* aberrations. Overexpression and activation of ERBB3/HER3 is one mechanism of acquired resistance to therapies targeting EGFR and ERBB2/HER2[65,66]. Preclinical and translational research studies have characterized the oncogenic potential of recurrent *ERBB3* mutations and their sensitivity to anti-ERBB antibodies and small molecule inhibitors[67-70]. A phase I study exhibited progression-free survival (PFS) of 2.5 months and overall survival (OS) of 9 months in 25 patients with *ERBB3* mutations treated by anti-ERBB antibodies or molecular-targeted agents[71].

***FGFR3*** **Amplification**

***Gene description***: The *FGFR3* gene encodes fibroblast growth receptor 3, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 4. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[72-74].

***Alterations and prevalence***: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[75]. FGFR3 amplification is observed in up to 19% of uterine carcinoma, with somatic mutations occurring in 10-20% of bladder cancer[26,29,61]. Missense mutations that occur in the extracellular immunoglobulin-like and transmembrane domains of FGFR3, including S249C, R248C, and Y375C, cause ligand-independent dimerization and constitutive activation of FGFR3[76-78].

***Potential relevance***: The pan-FGFR inhibitor, erdafitinib[79], received FDA approval (2019) for the treatment of locally advanced or metastatic urothelial cancer that is positive for *FGFR2* fusions, *FGFR3* fusions including FGFR3-TACC3 and FGFR3-BAIAP2L1, and *FGFR3* gene mutations including R248C, S249C, G370C, and Y373C. The FGFR3 monoclonal antibody, vofatamab[80] was granted fast track designation (2019) by the FDA, for the treatment of advanced or metastatic bladder urothelial cell carcinoma that harbors *FGFR3* mutations or fusions. The FDA also granted fast track designation (2018) to Debio 1347[81] for solid tumors harboring *FGFR1*, *FGFR2*, or *FGFR3* aberrations. Unregulated activation of FGFR3 has been associated with resistance to tamoxifen in ER-positive breast cancer[82].

***PIK3CA*** **p.His1047Arg**

***Gene description***: The *PIK3CA* gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[83]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[84,85]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes *PIK3CA*, *PIK3CB*, *PIK3CD* and *PIK3CG*, respectively[84]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)- bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[86,87]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[86-89]. Recurrent somatic alterations in *PIK3CA* are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[90-92].

***Alterations and prevalence***: Recurrent somatic activating mutations in *PIK3CA* are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[26,29]. Activating mutations in *PIK3CA* commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[93,94]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[95-97]. *PIK3CA* resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[26,29].

***Potential relevance***: The PI3K inhibitor, alpelisib[98], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)- positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in *PIK3CA*-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[99]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[99]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with *PIK3CA* mutations[100]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in *PIK3CA* mutated refractory cancers[101,102].

***RET*** **p.Gly810Cys**

***Gene description***: The *RET* gene encodes the RET receptor tyrosine kinase which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[103]. *RET* is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact RET tyrosine kinase domain combined with several fusion partner genes. RET fusion kinases are constitutively activated and drive oncogenic transformation which can lead to activation of PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways resulting in cell survival and proliferation[104].

***Alterations and prevalence***: *RET* fusions occur in approximately 55% of papillary thyroid carcinomas (PTC) with even higher frequencies observed in PTC patients with radiation exposure[105-107]. *RET* rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[108]. Point mutations in *RET* are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[109]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[109].

***Potential relevance***: The FDA approved small-molecule tyrosine kinase inhibitor, cabozantinib (2012), is recommended for the treatment of NSCLC patients with *RET* rearrangements[110]. Cabozantinib has also demonstrated clinical benefit in *RET* mutated medullary thyroid cancer patients106. Selpercatinib[112] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer, and metastatic solid tumors that have progressed following systemic treatment. Selpercatinib[112] is also approved for *RET*-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[113], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as *RET* mutation-positive MTC. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[114,115]. *RET* mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[116].

## RECOMMENDATIONS

- Validation of the variant(s) by Sanger sequencing is recommended to rule out false positives.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.

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## APPENDIX 1: TEST METHODOLOGY

### Method

DNA and RNA were extracted from samples using the Qiagen FFPE DNA kit and Promega ReliaPrep FFPE Total RNA Miniprep system. Isolated DNA/RNA was directly loaded on Genexus Next Generation Sequencer and subjected to automated library preparation and template preparation followed by sequencing at average depth of ~4000X.
It utilizes unique molecular tags to enable high sensitivity detection of variants. Analysis is done using Ion Torrent Reporter Software, the data is visualized on Integrative Genomics Viewer (IGV) and analyzed. The final report is generated using Oncomine curated knowledgebase reporter and includes clinical trials information continuously being updated for the best of the patient management as per clinical guidelines.

## DISCLAIMER

- This report was generated using the materials and methods as recommended which required the use of quality reagents, protocols, instruments, software, databases and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases and/or other items may compromise the quality or accuracy of the report.
- The report has been created based on, or incorporated inferences to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the Report may be adversely impacted. MolQ Laboratory is not obligated to notify you of any of the impact that future scientific or medical findings may have on the report.
- The report must always be interpreted and considered within the clinical context, and a physician should always consider the report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis or developing and implementing a plan of care for the patient. The report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestations of many diseases are caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the report. This report is based on a Next Generation Assay which does not distinguish between a somatic and a germline variant. If germline variant is in question, further testing is recommended. The report provided by MolQ Laboratory is on a "as is" basis. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the report. In no event will MolQ Laboratory be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the report, your reliance on the report, or any defect or inaccurate information included within the report.
- Medical knowledge and annotation are constantly updated and reflects the current knowledge at the time.
- Due to inherent technology limitations of the assay, not all bases of the exome can be covered by this test. Accordingly, variants in regions of insufficient coverage may not be identified and/or interpreted. Therefore, it is possible that certain variants are present in one or more of the genes analyzed, but have not been detected. The variants not detected by the assay that was performed may/ may not impact the phenotype.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- The report shall be generated within turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MolQ Laboratory under no circumstances will be liable for any delay beyond afore mentioned TAT.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MolQ Laboratory hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MolQ Laboratory hereby disclaims all liability arising in connection with the report(s).
- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MolQ Laboratory. In case where any test provided by MolQ Laboratory fails for unforeseeable or unknown reasons that cannot be influenced by MolQ Laboratory in advance, MolQ Laboratory shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognized by MolQ Laboratory in advance.

- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory as required by the CLIA 1988 regulations. The report, and the tests used to generate the Report have not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The test results have scientifically shown to be clinically useful.

## APPENDIX 2: GENE LIST WITH COVERAGE

| DNA Hotspots | | | | | |
|---|---|---|---|---|---|
| *AKT1* | *AKT2* | *AKT3* | *ALK* | *AR* | *ARAF* |
| *BRAF* | *CDK4* | *CDKN2A* | *CHEK2* | *CTNNB1* | *EGFR* |
| *ERBB2* | *ERBB3* | *ERBB4* | *ESR1* | *FGFR1* | *FGFR2* |
| *FGFR3* | *FGFR4* | *FLT3* | *GNA11* | *GNAQ* | *GNAS* |
| *HRAS* | *IDH1* | *IDH2* | *KIT* | *KRAS* | *MAPK1* |
| *MAPK2* | *MET* | *MTOR* | *NRAS* | *NTRK1* | *NTRK2* |
| *NTRK3* | *PDGFRA* | *PIK3CA* | *PTEN* | *RAF1* | *RET* |
| *ROS1* | *SMO* | *TP53* | | | |
| **CNVs** | | | | | |
| *ALK* | *AR* | *CD274* | *CDKN2A* | *EGFR* | *ERBB2* |
| *ERBB3* | *FGFR1* | *FGFR2* | *FGFR3* | *KRAS* | *MET* |
| *PIK3CA* | *PTEN* | | | | |
| **Inter-genetic Fusions** | | | | | |
| *ALK* | BRAF | *ESR1* | *FGFR1* | *FGFR2* | *FGFR3* |
| *MET* | *NRG1* | *NTRK1* | *NTRK2* | *NTRK3* | *NUTM1* |
| *RET* | *ROS1* | *RSPO2* | *RSPO3* | | |
| **Intra-genetic Fusions** | | | | | |
| *AR* | *EGFR* | *MET* | | | |