TARGETED GENE PANEL: The ClearID standard panel targets 50 oncogenes and identifies the presence of over 4500 mutations that have been associated with cancer in clinical studies. Cynvenio also offers different oncogene panels tailored for different indications.

GENE	TARGETED THERAPIES	ROLE IN CANCER
ABL1	Saracatanib	The ABL1 oncogene is implicated in several human leukemias including 90-95% of chronic myelocytic leukemia (CML), 20-25% of adult acute lymphoblastic leukemia (ALL) and 2-5% of pediatric ALL. The molecular consequence of this translocation is the generation of a chimeric Bcr/c-Abl mRNA encoding activated Abl protein-tyrosine kinase.
AKT1	Triciribine, MK-2206, Ritonavir	AKT1 is a serine/threonine kinase that plays a key role in regulating cell survival, angiogenesis and tumor formation. Akt is a downstream mediator of PI3Kca in the mTOR pathway and is mutated in 3-5% of breast cancer patients.
ALK	LDK378, Crizotnib, X-396	The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of cancers. For example ALK fusions are found in anaplastic large cell lymphoma, colorectal cancer, inflammatory myofibroblastic tumor non-small cell lung cancer, and ovarian cancer. All ALK fusions contain the entire ALK tyrosine kinase domain. ALK fusions and copy number gains have been observed in renal cell carcinoma. Signaling downstream of ALK fusions results in activation of cellular pathways known to be involved in cell growth and cell proliferation.
APC	LGK974, WNT pathway inhibitors	Adenomatous polyposis coli (APC) defects cause familial adenomatous polyposis (FAP), an autosomal dominant pre-malignant disease that usually progresses to malignancy. Somatic mutations in APC occur in 2-40% of sporadic breast and colorectal tumors. APC mutations almost always result in a truncated protein product causing defective tumor suppressor function.
ATM	Therapeutic target	The tumor suppressor gene ATM (ataxia telangiectasia mutated) is a serine/threonine kinase that plays a critical role in coordinating the cellular response to DNA double-strand breaks. ATM is closely related to kinases that are activated by DNA damage. When activated, it leads to cell cycle arrest and either DNA repair or apoptosis. Mutations are reported in approximately 2.5% breast and 25% colorectal cancers.
BRAF	Trametinib, Vemurafenib, Dabrafenib, MEK & RAS inhibitors	BRAF belongs to the RAF family of serine-threonine protein kinases that activate MAPK/ERK signaling to regulate cell division and differentiation. BRAF mutations leading to constitutive kinase activation have been implicated in the pathogenesis of several cancers, including melanoma, non-small cell lung cancer, colorectal cancer, papillary thyroid cancer, and ovarian cancer with incidence ranging from 1 to 42%.
CDH1	Therapeutic target	Cadherin-1 (CDH1) is the epithelial representative of the Cadherin family of adhesion receptors. CDH1 mutations are correlated with breast and colorectal cancer with a 12-15% incidence. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis.
CDKN2A	Palbociclib, Dinaciclib	CDKN2A is a cyclin dependent kinase inhibitor that acts as a tumor suppressor by binding CDK4/6 and prohibiting cell cycle progression. It is frequently mutated or deleted in a wide variety of tumors including pancreatic and breast cancer.
CSF1R	Therapeutic target	Colony Stimulating Factor 1R (or cFMS) is a receptor tyrosine kinase. Mutations in CSF1R are associated with chronic myelomonocytic leukemia and acute myeloblastic leukemia.
CTNNB1	Therapeutic target	Catenin (CTNNB1) is both a structural protein and a transcription factor that associates with APC (see above). Mutations result in deregulated transcription and are associated with colorectal cancer (CRC), prostate and ovarian cancers.
EGFR	Erlotinib, Panitumumab, Cetuximab, Neratinib	The Epidermal Growth Factor Receptor (EGFR) belongs to a family of receptor tyrosine kinases that include EGFR and HER2/ERBB2/NEU. Activating mutations, which occur in 1-5% breast and colorectal cancers, cause misregulation of EGFR tyrosine kinase activity resulting in altered multiple downstream pathways involved in cell survival, and cell proliferation.
ERBB2	Trastuzumab, Lapitinib, Kadcyla, Pertuzumab, MGAH22, AMG 386, LJM 716, Neratiinib, Ganestespib, MM-302	HER2 belongs to a family of receptor tyrosine kinases that includes EGFR, HER2/ERBB2/NEU, and HER3/ERBB3. The gene for HER2 has been found to be genetically amplified/mutated in several human cancers including breast and ovarian cancers. HER2 over expression or activating mutations result in constitutive HER2 tyrosine kinase activity. Activated HER2 then regulates proliferation promoting tumorigenesis and pathogenesis.
ERBB4	Therapeutic target	This gene is a member of the Tyrosine protein kinase receptor family and the epidermal growth factor receptor subfamily. The protein binds to and is activated by neuregulins and other factors and induces a variety of cellular responses including mitogenesis and differentiation. Mutations in this gene have been associated with cancer.

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EZH2	Therapeutic target	Aberrant EZH2 function has been documented in several types of human cancer, most notably prostate and breast cancer but also acute lymphoblastic leukemia (ALL)and possibly other hematological malignancies. Levels of EZH2 expression strongly associate with the severity of malignant progression and poor prognosis in breast and prostate cancer.
FBXW7	Therapeutic target	FBXW7 protein is a member of the ubiquitin pathway responsible for degrading members of the cell cycle regulatory pathway. Mutations in this gene are reported approximately 1-10% of ovarian, breast and colorectal cancers, implicating a role in the pathogenesis of these diseases.
FGFR1	Dovotinib	The fibroblast growth factor receptor type 1 gene (FGFR1) encodes one member of the FGFR tyrosine kinase (TK) family. FGFR TKs play crucial roles in development and have been shown to be deregulated by either amplification, point mutation, or translocation in cancer. Alterations of FGFR1 has been reported in many cancers including oral squamous cell carcinoma, breast cancer, esophageal squamous cell carcinoma, ovarian, bladder, prostate, and lung cancer, predominantly in the squamous subtype.
FGFR2	FGFR inhibitors and antibodies	The fibroblast growth factor receptor type 2 gene (FGFR2) encodes the second member of the FGFR tyrosine kinase (TK) family. This protein is involved in cell division, regulation of cell growth and maturation, formation of blood vessels, wound healing, and embryonic development. Alterations in the activity (expression) of the FGFR2 gene are associated with certain cancers. The altered gene expression may enhance several cancer-related events such as cell division (proliferation), cell movement, and the development of new blood vessels that nourish a growing tumor.
FGFR3	ENMD-2076	FGF receptor 3 (FGFR3) is activated by mutation or over-expression in many bladder cancers. Chromosomal translocations that fuse FGFR3 to the transforming acidic coiled-coil (TACC) coding domains of TACC3 have been observed in glioblastoma multiforme (GBM)
FLT3	FLT3	FLT3 is a receptor tyrosine kinase plays an important role in the maintenance, proliferation and differentiation of hematopoiesis. FLT3 is also expressed in acute myeloid leukemia (AML) and B-lineage acute lymphoblastic leukemia cells. Mutations in the FLT3 gene can lead to the development of leukemias or cancers of bone marrow hematopoietic progenitors. FLT3 length mutations are the most common mutations associated with acute myelogenous leukemia (AML) and are prognostic indicators associated with adverse disease outcome.
GNA11	Therapeutic target	Guanine nucleotide binding proteins (G proteins) are a family of heterotrimeric proteins which couple seven-transmembrane domain receptors to intracellular cascades, including neurotransmitter, growth factor, and hormone signaling pathways. Heterotrimeric G proteins are composed of three subunits, Gα, Gß, and Gγ, of which GNA11 is the gene for subunit alpha-11. Receptor activation catalyzes the exchange of GDP (guanosine diphosphate) to GTP (guanosine triphosphate) on the Gα subunit. Each sub unit can then activate downstream cellular signaling pathways.
GNAQ	Therapeutic target	Guanine nucleotide binding proteins (G proteins) are a family of heterotrimeric proteins which couple seven-transmembrane domain receptors to intracellular signaling pathways. Heterotrimeric G proteins are composed of three subunits: Gα, Gß, and Gγ. GNAQ encodes a Gα subunit. Receptor activation catalyzes the dephosphorylation of GTP and the resulting activation of the Gα subunit. Gα can then activate downstream cellular signaling pathways. Oncogenic mutations result in a loss of this intrinsic GTPase activity, resulting in a constitutively active Gα subunit.
GNAS	Therapeutic target	Somatically acquired, activating mutations of GNAS, the gene encoding the stimulatory G-protein Gsα subunit, have been identified in kidney, thyroid, pituitary, leydig cells, adrenocortical and, more recently, in colorectal tumours
HNF1A	Therapeutic target	The protein encoded by this gene is a transcription factor required for the expression of several liver-specific genes. Defects in this gene are a cause of maturity onset diabetes of the young type 3 and also can result in the appearance of hepatic adenomas. HNF1A functions as a tumor suppressor by regulating expression of the polycystic kidney and hepatic disease gene 1 (PKHD1).
HRAS	Trametinib, MEK & RAS inhibitors	HRAS gene mutations that occur in bladder cells have been associated with some cases of bladder cancer. Mutations in the HRAS gene also have been associated with the progression of bladder cancer and an increased risk of tumor recurrence after treatment.
IDH1	Therapeutic target	The IDH1 gene provides instructions for making an enzyme called isocitrate dehydrogenase 1. The mutated form of IDH1 produces a metabolite, 2-hydroxyglutarate, which may contribute to the formation and malignant progression of gliomas, the most common type of brain cancers.
IDH2	Therapeutic target	The IDH2 gene provides instructions for making an enzyme called isocitrate dehydrogenase 2. Within mitochondria, the enzyme participates in reactions that produce energy for cell activities. Mutations in the IDH2 gene have been associated with cytogenetically normal acute myeloid leukemia (CN-AML). While large chromosomal abnormalities can be involved in the development of acute myeloid leukemia, about half of cases do not have these abnormalities; these are classified as CN-AML. Nearly 20 percent of people with CN-AML have a mutation in the IDH2 gene.

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JAK2	Ruxolitinib, JAK-STAT inhibitors, STAT decoys	Janus kinase 2 (JAK2) encodes for a protein tyrosine kinase involved in cytokine receptor signaling. Mutations in JAK2 have been identified in ALL and other hematologic malignancies. Preclinical models have been used to test efficacy of mTOR and JAK inhibitors where the upstream regulator is altered (CRLF2) or JAK2 is mutated in high-risk precursor B-cell ALL.
JAK3	(same as above)	The protein encoded by this gene is a member of the Janus kinase (JAK) family of tyrosine kinases involved in cytokine receptor-mediated intracellular signal transduction. It is predominantly expressed in immune cells and transduces a signal in response to its activation via tyrosine phosphorylation by interleukin receptors. Mutations in this gene are associated with autosomal SCID (severe combined immunodeficiency disease).
KDR	VEGF inhibitors & antibodies	Vascular endothelial growth factor (VEGF) is a major growth factor for endothelial cells. This gene encodes one of the two receptors of the VEGF. It functions as the main mediator of VEGF-induced endothelial proliferation, survival, migration, tubular morphogenesis and sprouting. Mutations of this gene are implicated in infantile capillary hemangiomas. It plays a major role in tumor angiogenesis.
KIT	Pazopanib, Imatinib	KIT (also called CD117), is a receptor tyrosine kinase bound by stem cell factor (SCF). Activating mutations cause misregulation of multiple downstream signaling pathways all of which promote growth and survival signals. Mutant KIT has been implicated in the pathogenesis of several cancers including large intestine (13%) and breast (1.5%).
KRAS	Trametinib, MEK & RAS inhibitors	KRAS protein is a central mediator of growth factor receptor signaling for cell proliferation, survival, and differentiation. KRAS has been implicated in the pathogenesis of several cancers. Activating mutations within the KRAS gene result in constitutive activation and sustained proliferation signals. KRAS is recurrently mutated in several malignancies including colon cancer, breast cancer, lung cancer, and pancreatic cancer.
MET	Cabozantinib, Crizotinib	The MET gene encodes a receptor tyrosine kinase (RTK) belonging to the MET/RON family of RTKs. In the context of malignancy, aberrant signaling through the MET receptor promotes pleiotrophic effects including growth, survival, invasion, migration, angiogenesis and metastasis.The MET receptor and/or its ligand HGF have been reported to be aberrantly activated in many human cancers. Germline mutations in the tyrosine kinase domain of MET occur in 100% of hereditary papillary renal cell carcinoma, and somatic mutations in MET are found in 10–15% of sporadic papillary renal cell carcinoma.
MLH1	Therapeutic target	The MLH1 gene provides instructions for making a protein that plays an essential role in DNA repair. The MLH1 protein joins with another protein, PMS2, to form a protein complex. This complex coordinates the activities of other proteins that repair mistakes made during DNA replication. The repairs are made by removing a section of DNA that contains mistakes and replacing the section with a corrected DNA sequence.
MPL	JAK-STAT inhibitors	The MPL gene provides instructions for making the thrombopoietin receptor protein, which promotes the growth and proliferation of cells. The thrombopoietin receptor is activated when bound by thrombopoietin. The activated thrombopoietin receptor stimulates a signaling pathway through the JAK/STAT pathway, which transmits signals important for controlling the production of blood cells.
NOTCH1	BMS-906024, RO4929097	The Notch1 gene encodes a transcription factor that functions as a tumor suppressor through negative regulation of kinase signaling in epithelial cancers and squamous cell carcinomas characterized by transcriptional down regulation. Conversely, activating mutations in Notch1 occur in the associated hematologic cancers such as T and B cell lymphoblastic and lymphocytic leukemias. Notch1 mutations have been reported in approximately 17% of hematopoietic cancers, 10% esophageal cancer, and 7% of colorectal cancer.
NPM1	Therapeutic target	The NPM1 gene encodes a protein called nucleophosmin. It is thought to play a part in many cellular functions, including processes involved in protein formation, DNA replication, and progression through the cell cycle. In the nucleolus, nucleophosmin attaches to another protein called ARF, keeping it in the proper location and protecting it from being broken down. The ARF protein, a tumor suppressor, prevents cells from growing and dividing in an uncontrolled way.
NRAS	Trametinib, MEK & RAS inhibitors	RAS has been implicated in the pathogenesis of several cancers. Activating mutations within the RAS gene result in constitutive activation of the RAS GTPase, even in the absence of growth factor signaling. The result is a sustained proliferation signal within the cell. Specific RAS genes are recurrently mutated in different malignancies. NRAS mutations are particularly common in melanoma, hepatocellular carcinoma, myeloid leukemias, and thyroid carcinoma.
PDGFRA	Apatinib, Sunitinib, Sorafenib, Pazopanib, Imatinib	The platelet derived growth factor receptor alpha (PDGFRA) belongs to a family of receptor tyrosine kinases (RTKs) that include PDGFRA and PDGFRB. The binding of ligands, such as platelet derived growth factor (PDGF), induces a conformational change that facilitates receptor homo- or heterodimer formation, thereby resulting in activation of PDGFRA tyrosine kinase activity. Mutant PDGFRA has been implicated in the pathogenesis of a number of cancers. For example, mutations are found in gastrointestinal stromal tumors (GIST), and fusions in hypereosinophilic syndrome and dermatofibrosarcoma protuberans.

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PIK3CA	BKM120, MK-2206, BYL719, BEZ235, GDC-0032, GDC-0941, GDC-0980, Everolimus, CC-122, Temsirolimus, AMG479, CC-223,	PIK3CA is the gene for the catalytic subunit of the phosphoinositide 3-kinase, a lipid kinase that regulates many cellular processes including growth, proliferation, differentiation, motility and survival. Mutant PIK3ca has been implicated in the pathogenesis of several cancers including breast cancer (25%), colon cancer (14%), gastric (9%), lung (4%) and endometrial cancers (23%).
PTEN	GSK2636771, MK-2206, PIK3 inhibitors	PTEN is lipid protein phosphatase that has a role in growth, proliferation and maintenance of genomic integrity. PTEN functions as a tumor suppressor by negatively regulating the AKT/PIK3ca/mTOR pathway. Somatic mutations occur in multiple malignancies including breast (4%), prostate (10%), and colorectal (11%) cancers.
PTPN11	Therapeutic target	PTPN11 is a non-receptor protein tyrosine phosphatase. Activating mutations in PTPN11 are associated with activation of the RAS/RAF/MAPK and PI3K/Akt pathways. Somatic mutations in PTPN11 have been reported most frequently in leukemias (7%) as well as cancer of the large intestine (6%) and endoetrial cancers (4%)and infrequently in breast cancers, reported in less than 1% of samples. Germline mutations in PTPN11 are associated with the developmental disorder, Noonan syndrome, which has been linked to a predisposition to several cancers.
RB1	Therapeutic target	The retinoblastoma protein (RB1) is a tumor suppressor protein. It inhibits cell cycle progression in cells with damaged DNA; loss or mutation of RB1 may result in genomic instability and excessive cell proliferation. Mutations of RB1 have been reported in approximately 50% of cancers of the eye, 21% urinary tract carcinoma, and 15% of endometrial and colorectal cancer and about 3% of breast cancers.
RET	RET inhibitors	The RET gene ("rearranged during transfection") encodes a receptor tyrosine kinase (RTK) belonging to the RET family of RTKs. This gene plays a crucial role in neural crest development. Activated RET then phosphorylates its substrates, resulting in activation of multiple downstream cellular pathways. RET aberrations are predominantly found in thyroid cancers. Somatic and germline point mutations are associated with sporadic and familial medullary thyroid cancers, respectively. RET fusions are also found in some lung adenocarcinomas.
SMAD4	Fresolimumab	SMAD4 is the central mediator for downstream transcriptional output in the TGF-β family signaling pathways. The TGF-β pathway plays a complex role in cancer development, progression, and metastasis. Mutations in SMAD4 are involved in several hereditary syndromes with cancer predisposition, including juvenile polyposis syndrome and hemorrhagic hereditary telangiectasia (HHT) syndrome. SMAD4 loss or mutation is also seen in approximately 25% of pancreatic tumors and in 15–65% of invasive CRC.
SMARCB1	Therapeutic target	The SMARCB1 gene encodes a protein that forms one subunit of several different SWI/SNF protein complexes. Through their ability to regulate gene activity, SWI/SNF complexes are involved in many processes, including repairing damaged DNA; DNA replication; and controlling the growth, division, and differentiation of cells. The SMARCB1 protein and other SWI/SNF subunits are thought to act as tumor suppressors.
SMO	GDC-0449, LDE225, Hedgehog inhibitors	SMO is a component of the Hedgehog signaling pathway. Mutations in PTCH1 or SMO that lead to constitutive activation of SMO are known to play a role in carcinogenesis of basal cell carcinoma, glioblastoma, medulloblastoma, and rhabdomyosarcoma. The Hedgehog signaling pathway is a critical part of embryonic development. After embryonic development, the Hedgehog pathway is not active in most human tissues. Reactivation of this pathway can lead or contribute to carcinogenesis.
SRC	Saracatanib, Dasatinib	This proto-oncogene may play a role in the regulation of embryonic development and cell growth. The protein encoded by this gene is a tyrosine-protein kinase whose activity can be inhibited by phosphorylation by c-SRC kinase. Mutations in this gene could be involved in the malignant progression of colon cancer. SRC kinase activity has been shown to be increased in several tumor tissues and tumor cell lines such as colon carcinoma cells.
STK11	Therapeutic target	Serine Threonine Kinase 11 (STK11) is a tumor suppressor identified by frequent inactivations by deletion. Mutations of STK11 have been reported in approximately 24% of gastrointestinal cancers, 8% Lung cancer, and 5% of skin and colorectal cancer.
TP53	Therapeutic target	TP53 is a tumor suppressor gene; loss or mutation of TP53 protein may result in genomic instability and excessive cell proliferation. Mutations of TP53 have been reported in approximately 30% of all cancer including 44% of large intestine carcinoma, 18% prostate and 22% of breast cancer.
VHL	Sorafenib, Sunitinib, Pazopanib, Axitinib, Bevacizumab, Rapamycin, Evorolimus, Temsirolimus	VHL (Von Hippel-Lindau) functions as a tumor suppressor by cooperating with TP53 as a component of the transactivation complex during the DNA damage response thus playing an important role in cell cycle regulation. Inactivation of the VHL tumor suppressor gene is an early, causal event in the development of clear cell renal cell carcinomas in both hereditary and nonhereditary forms. Somatic alterations are also found in colorectal (13%) and endometrial (2%) cancer.