CANCER 50 GENE PANEL

CANCER 50 GENE PANEL - (Next Gen Sequencing)

Note: The Ion AmpliSeq ™Cancer Hotspot Panel v2 is a multiplex PCR-based library preparation method by which 207 amplicons covering approximately 2,800 COSMIC mutations from 50 oncogenes and tumor suppressor genes are selectively analyzed. *For a complete list of the genes assayed, please see below.*

TUMOR TYPE: Free text

RESULT:

Genomic Alteration Identified*:

*Identified variants detected with minimum 50X read depth and 25% frequency; variants present at lower frequency are not detected. See Appendix A below for detailed findings.

THERAPEUTIC IMPLICATIONS (AS OF FEBRUARY 4, 2014)*:

Genomic Alterations Detected for Which There Are FDA- Approved Mutation-Targeted Therapies	FDA-Approved Mutation-Targeted Therapies For Patient's Tumor Type	FDA-Approved Mutation-Targeted Therapies For Other Tumor Types	FDA-Approved Mutation-Targeted Therapies Associated with Lack of Response

Comment: Free text

*THIS REPORT DESCRIBES ONLY THOSE FDA-APPROVED TREATMENTS TARGETED TO THE SPECIFIC GENOMIC ALTERATIONS IDENTIFIED. CLINICAL TRIALS TESTING THERAPIES TARGETING ONE OR MORE OF THE SPECIFIC GENOMIC ALTERATIONS IDENTIFIED MAY BE IN PROGRESS; HOWEVER, SUCH CLINICAL TRIALS ARE NOT DESCRIBED IN THIS REPORT.

GENES ASSAYED

The Ion AmpliSeq™ Cancer Hotspot Panel v2 assay interrogates the following 50 cancer-related genes/biomarkers.

ABL1	FGFR3	NOTCH1
AKT1	FLT3	NPM1
ALK	GNA11	NRAS
APC	GNAQ	PDGFRA
ATM	GNAS	PIK3CA
BRAF	HNF1A	PTEN
CDH1	HRAS	PTPN11
CDKN2A	IDH1	RB1
CSFIR	IDH2	RET
CTNNB1	JAK2	SMAD4
EGFR	JAK3	SMARCB1
ERBB2	KDR	SMO
ERBB4	KIT	SRC
EZH2	KRAS	STK11
FBXW7	MET	TP53
FGFR1	MLH1	VHL
FGFR2	MPL	

See Appendix B below for a description of each gene/biomarker.

Disclaimer

THIS REPORT DOCUMENTS THE GENETIC ALTERATIONS DETECTED IN THE SUBMITTED SAMPLE MATERIAL.
[ ] THERE ARE NO FDA-APPROVED THERAPIES THAT ARE SPECIFIC TO THE REPORTED GENETIC ALTERATIONS.
[ ] THIS REPORT DESCRIBES FDA-APPROVED THERAPIES THAT ARE SPECIFIC TO THE REPORTED GENETIC ALTERATIONS. THE GENETIC ALTERATIONS DETECTED MAY BE ASSOCIATED WITH THE ACTIVITY OF CERTAIN FDA-APPROVED THERAPIES;
HOWEVER, THE THERAPEUTIC AGENTS LISTED IN THIS REPORT MAY HAVE VARIED CLINICAL EVIDENCE IN THE PATIENT ÕR TUMOR TYPE. THE LISTED THERAPEUTIC AGENTS ARE NOT RANKED IN ORDER OF POTENTIAL OR PREDICTED EFFICACY FOR THIS PATIENT, NOR ARE THEY RANKED IN ORDER OF LEVEL OF EVIDENCE FOR THIS PATIENT OR TUMOR TYPE.

DRUGS REFERENCED IN THIS REPORT MAY NOT BE SUITABLE FOR A PARTICULAR PATIENT. THE SELECTION OF ANY, ALL OR NONE OF THE DRUGS ASSOCIATED WITH POTENTIAL CLINICAL BENEFIT OR POTENTIAL LACK OF CLINICAL BENEFIT RESIDES ENTIRELY WITHIN THE DISCRETION OF THE PATIENT OR TREATING PHYSICIAN.

THE REPORT PROVIDED IS FOR INFORMATION PURPOSES ONLY AND THE DATA SHOULD BE INTERPRETED IN CONJUNCTION WITH RELEVANT CLINICAL INFORMATION.

DECISIONS ON PATIENT CARE AND TREATMENT MUST BE BASED ON THE INDEPENDENT MEDICAL JUDGMENT OF THE TREATING PHYSICIAN, TAKING INTO CONSIDERATION ALL APPLICABLE INFORMATION CONCERNING THE PATIENT CONDITION, FAMILY HISTORY, PHYSICIAN EXAMINATIONS, DIAGNOSTIC TESTS, AND PATIENT PREFERENCES, IN ACCORDANCE WITH THE STANDARD OF CARE IN A GIVEN COMMUNITY. A TREATING PHYSICIAN'S DECISION SHOULD NOT BE BASED ON A SINGLE TEST OR ON THE INFORMATION CONTAINED IN THIS REPORT.

THE INFORMATION IN THIS REPORT DOES NOT CONSTITUTE A TREATMENT RECOMMENDATION EITHER TO USE OR NOT TO USE ANY SPECIFIC THERAPEUTIC AGENT, AND SHOULD NOT BE INTERPRETED AS TREATMENT ADVICE. DECISIONS CONCERNING PATIENT CARE AND TREATMENT REST SOLELY WITHIN THE DISCRETION OF THE TREATING PHYSICIAN.

Appendix A: Detail on Coding Variants and Non-Coding Variants

Coding Variants detected with minimum 50X read depth and 5% frequency

Gene	Chromosome	Locus	Position	Ref	Variant	AA Change	Variant Allele
ALK	chr2	p23.2					
EGFR	chr7	p11.2					
GNAQ	chr9	q21.2					
KDR	chr4	q12					
KRAS	chr12	p12.1					
RB1	chr13	q14.2					
SMAD74	chr18	q21.2					
SMAD4	chr18	q21.2					
TP53	chr17	p13.1					

Non-coding Variants detected with minimum 50X read depth and 5% frequency

Gene	Chromosome	Locus	Position	Ref	Variant	Region	Variant Allele Frequency
ABL1	chr9	q34.12	133750318				
APC	chr5	q22.2	112175770				
ATM	chr11	q22.3	108122119				
CSF1R	chr5	q32	149433597				
EGFR	chr7	p11.2	55249063				
EGFR-AS1	chr7	p11.2	55249174				
ERBB2	chr17	q12	37881388				
ERBB4	chr2	q34	212812097				

FGFR3	chr4	p16.3	1807894				
FGFR3	chr4	p16.3	1807922				
FLT3	chr13	q12.2	28610183				
KDR	chr4	q12	55980239				
PDGFRA	chr4	q12	55141055				
PIK3CA	chr3	q26.32	178917005				
PIK3CA	chr3	q26.32	178952020				

Non-coding Variants detected with minimum 50X read depth and 5% frequency

Gene	Chromosome	Locus	Position	Ref	Variant	Region	Variant Allele Frequency
RET	chr10	q11.21	43613843				
SMARCB1	chr22	q11.23	24176287				
VHL	chr3	p25.3	10188193				

A synonymous substitution is a substitution of one base for another in an exon of a gene coding for a protein, such that the amino acid sequence is not modified. Synonymous substitutions and mutations are known as silent mutations.

Appendix B: Description of Biomarkers

BIOMARKER	DESCRIPTION
ABL1	The ABL1 protooncogene encodes a cytoplasmic and nuclear protein tyrosine kinase that has been implicated in processes of cell differentiation, cell division, cell adhesion, and stress response. Activity of c-Abl protein is negatively regulated by its SH3 domain, and deletion of the SH3 domain turns ABL1 into an oncogene. The t(9;22) translocation results in the head-to-tail fusion of the BCR (MIM:151410) and ABL1 genes present in many cases of chronic myelogeneous leukemia. The DNA-binding activity of the ubiquitously expressed ABL1 tyrosine kinase is regulated by CDC2-mediated phosphorylation, suggesting a cell cycle function for ABL1. The ABL1 gene is expressed as either a 6- or 7-kb mRNA transcript, with alternatively spliced first exons spliced to the common exons 2-11. (provided by RefSeq,Jul 2008)
AKT1	The serine-threonine protein kinase encoded by the AKT1 gene is catalytically inactive in serum-starved primary and immortalized fibroblasts. AKT1 and the related AKT2 are activated by platelet-derived growth factor. The activation is rapid and specific, and it is abrogated by mutations in the pleckstrin homology domain of AKT1. It was shown that the activation occurs through phosphatidylinositol 3-kinase. In the developing nervous system AKT is a critical mediator of growth factor-induced neuronal survival. Survival factors can suppress apoptosis in a transcription-independent manner by activating the serine/threonine kinase AKT1, which then phosphorylates and inactivates components of the apoptotic machinery. Mutations in this gene have been associated with the Proteus syndrome. Multiple alternatively spliced transcript variants have been found for this gene. (provided by RefSeq, Jul 2011)

ALK	This gene encodes a receptor tyrosine kinase, which belongs to the insulin receptor superfamily. This protein comprises an extracellular domain, an hydrophobic stretch corresponding to a single pass transmembrane region, and an intracellular kinase domain. It plays an important role in the development of the brain and exerts its effects on specific neurons in the nervous system. This gene has been found to be rearranged, mutated, or amplified in a series of tumours including anaplastic large cell lymphomas, neuroblastoma, and non-small cell lung cancer. The chromosomal rearrangements are the most common genetic alterations in this gene, which result in creation of multiple fusion genes in tumourigenesis, including ALK (chromosome 2)/EML4 (chromosome 2), ALK/RANBP2 (chromosome 2), ALK/ATIC (chromosome 2), ALK/TFG (chromosome 3), ALK/NPM1 (chromosome 5), ALK/SQSTM1 (chromosome 5), ALK/KIF5B n(chromosome 10), ALK/CLTC (chromosome 17), ALK/TPM4 (chromosome 19), and ALK/MSN (chromosome X),(provided by RefSeq, Jan 2011)
APC	This gene encodes a tumor suppressor protein that acts as an antagonist of the Wnt signaling pathway. It is also involved in other processes including cell migration and adhesion, transcriptional activation, and apoptosis. Defects in this gene cause familial adenomatous polyposis (FAP), an autosomal dominant pre-malignant disease that usually progresses to malignancy. Disease-associated mutations tend to be clustered in a small region designated the mutation cluster region(MCR) and result in a truncated protein product. (provided by RefSeq, Jul 2008)
ATM	The protein encoded by this gene belongs to the PI3/PI4-kinase family. This protein is an important cell cycle checkpoint kinase that phosphorylates; thus, it functions as a regulator of a wide variety of downstream proteins, including tumor suppressor proteins p53 and BRCA1, checkpoint kinase CHK2, checkpoint proteins RAD17 and RAD9, and DNA repair protein NBS1. This protein and the closely related kinase ATR are thought to be master controllers of cell cycle checkpoint signaling pathways that are required for cell response to DNA damage and for genome stability, Mutations in this gene are associated with ataxia telangiectasia, and autosomal recessive disorder, (provided by RefSeq, Aug2010)
BRAF	This gene encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion. Mutations in this gene are associated with cardiofaciocutaneous syndrome, a disease characterized by heart defects, mental retardation and a distinctive facial appearance. Mutations in this gene have also been associated with various cancers, including non- Hodgkin lymphoma, colorectal cancer, malignant melanoma, thyroid carcinoma, non-small cell lung carcinoma, and adenocarcinoma of lung. A pseudogene, which is located on chromosome X, has been identified for this gene. (provided by RefSeq, Jul 2008
CHD1	This gene is a classical cadherin from the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. Mutations in this gene are correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization. Identified transcript variants arise from mutation at consensus splice sites. (provided by RefSeq, Jul 2008)
CDKN2A	This gene generates several transcript variants which differ in their first exons. At least three alternatively spliced variants encoding distinct proteins have been reported, two of which encode structurally related isoforms known to function as inhibitors of CDK4 kinase. The remaining transcript includes an alternate first exon located 20 Kb upstream of the remainder of the gene; this transcript contains an alternate open reading frame (ARF) that specifies a protein which is structurally unrelated to the products of the other variants. This ARF product functions as a stabilizer of the tumor suppressor protein p53 as it can interact

	with, and sequester, the E3 ubiquitin-protein ligase MDM2, a protein responsible for the degradation of p53. In spite of the structural and functional differences, the CDK inhibitor isoforms and the ARF product encoded by this gene, through the regulatory roles of CDK4 and p53 in cell cycle G1 progression, share a common functionality in cell cycle G1 control. This gene is frequently mutated or deleted in a wide variety of tumors, and is known to be an important tumor suppressor gene. (provided by RefSeq, Sep 2012)
CSF1R	The protein encoded by this gene is the receptor for colony stimulating factor 1, a cytokine which controls the production, differentiation, and function of macrophages. This receptor mediates most if not all of the biological effects of this cytokine. Ligand binding activates the receptor kinase through a process of oligomerization and transphosphorylation. The encoded protein is a tyrosine kinase transmembrane receptor and member of the CSF1/PDGF receptor family of tyrosine-protein kinases. Mutations in this gene have been associated with a predisposition to myeloid malignancy. The first intron of this gene contains a transcriptionally inactive ribosomal protein L7 processed pseudogene oriented in the opposite direction. (provided by RefSeq, Jul 2008)
CTNNB1	The protein encoded by this gene is part of a complex of proteins that constitute adherens junctions (AJs). AJs are necessary for the creation and maintenance of epithelial cell layers by regulating cell growth and adhesion between cells. The encoded protein also anchors the actin cytoskeleton and may be responsible for transmitting the contact inhibition signal that causes cells to stop dividing once the epithelial sheet is complete. Finally, this protein binds to the product of the APC gene, which is mutated in adenomatous polyposis of the colon. Mutations in this gene are a cause of colorectal cancer (CRC), pilomatrixoma (PTR), medulloblastoma (MDB), and ovarian cancer. Three transcript variants encoding the same protein have been found for this gene.(provided by RefSeq, Oct 2009)
EGGR	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer. Multiple alternatively spliced transcript variants that encode different protein isoforms have been found for this gene. (provided by RefSeq, Jul 2010)
ERBB2	This gene encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. This protein has no ligand binding domain of its own and therefore cannot bind growth factors. However, it does bind tightly to other ligand-bound EGF receptor family members to form a heterodimer, stabilizing ligand binding and enhancing kinase-mediated activation of downstream signalling pathways, such as those involving mitogen-activated protein kinase and phosphatidylinositol-3 kinase. Allelic variations at amino acid positions 654 and 655 of isoform a (positions 624 and 625 of isoform b) have been reported, with the most common allele, Ile654/Ile655, shown here. Amplification and/or overexpression of this gene has been reported in numerous cancers, including breast and ovarian tumors. Alternative splicing results in several additional transcript variants, some encoding different isoforms and others that have not been fully characterized. (provided by RefSeq, Jul 2008)
ERBB4	This gene is a member of the Tyr protein kinase family and the epidermal growth factor receptor subfamily. It encodes a single-pass type I membrane protein with multiple cysteine rich domains, a transmembrane domain, a tyrosine kinase domain, a phosphotidylinositol-3 kinase binding site and a PDZ domain binding motif. The protein binds to and is activated by neuregulins and other factors and induces a variety of cellular responses including mitogenesis and differentiation. Multiple proteolytic events allow for the release of a cytoplasmic fragment and an extracellular fragment. Mutations in this gene have been associated with cancer. Alternatively spliced variants which encode different protein

	isoforms have been described; however, not all variants have been fully characterized. (provided by RefSeq, Jul 2008)
FBXW7	This gene encodes a member of the F-box protein family which is characterized by an approximately 40 amino acid motif, the F-box. The F-box proteins constitute one of the four subunits of ubiquitin protein ligase complex called SCFs (SKP1-cullin-F-box), which function in phosphorylation-dependent ubiquitination. The F-box proteins are divided into 3 classes: Fbws containing WD-40 domains, Fbls containing leucine-rich repeats, and Fbxs containing either different protein-protein interaction modules or no recognizable motifs. The protein encoded by this gene was previously referred to as FBX30, and belongs to the Fbws class; in addition to an F-box, this protein contains 7 tandem WD40 repeats. This protein binds directly to cyclin E and probably targets cyclin E for ubiquitin-mediated degradation. Mutations in this gene are detected in ovarian and breast cancer cell lines, implicating the gene's potential role in the pathogenesis of human cancers. Multiple transcript variants encoding different isoforms have been found for this gene. (provided by RefSeq, Mar 2012)
FGFR1	The protein encoded by this gene is a member of the fibroblast growth factor receptor (FGFR) family, where amino acid sequence is highly conserved between members and throughout evolution. FGFR family members differ from one another in their ligand affinities and tissue distribution. A full-length representative protein consists of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation. This particular family member binds both acidic and basic fibroblast growth factors and is involved in limb induction. Mutations in this gene have been associated with Pfeiffer syndrome, Jackson-Weiss syndrome, Antley-Bixler syndrome osteoglophonic dysplasia, and autosomal dominant Kallmann syndrome 2. Chromosomal aberrations involving this gene are associated with stem cell myeloproliferative disorder and stem cell leukemia lymphoma syndrome. Alternatively spliced variants which encode different protein isoforms have been described; however, not all variants have been fully characterized. (provided by RefSeq, Jul 2008)
FGFR2	The protein encoded by this gene is a member of the fibroblast growth factor receptor family, where amino acid sequence is highly conserved between members and throughout evolution. FGFR family members differ from one another in their ligand affinities and tissue distribution. A full-length representative protein consists of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation. This particular family member is a high-affinity receptor for acidic, basic and/or keratinocyte growth factor, depending on the isoform. Mutations in this gene are associated with Crouzon syndrome, Pfeiffer syndrome, Craniosynostosis, Apert syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrata syndrome, Saethre-Chotzen syndrome, and syndromic craniosynostosis. Multiple alternatively spliced transcript variants encoding different isoforms have been noted for this gene. (provided by RefSeq, Jan 2009)
FGFR3	This gene encodes a member of the fibroblast growth factor receptor (FGFR) family, with its amino acid sequence being highly conserved between members and among divergent species. FGFR family members differ from one another in their ligand affinities and tissue distribution. A full-length representative protein would consist of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation. This particular family member binds acidic and basic fibroblast growth hormone and plays a role in bone development and

	maintenance. Mutations in this gene lead to craniosynostosis and multiple types of skeletal dysplasia. Three alternatively spliced transcript variants that encode different protein isoforms have been described. (provided by RefSeq, Jul 2009)
FLT3	This gene encodes a class III receptor tyrosine kinase that regulates hematopoiesis. The receptor consists of an extracellular domain composed of five immunoglobulin-like domains, one transmembrane region, and a cytoplasmic kinase domain split into two parts by a kinase-insert domain. The receptor is activated by binding of the fms-related tyrosine kinase 3 ligand to the extracellular domain, which induces homodimer formation in the plasma membrane leading to autophosphorylation of the receptor. The activated receptor kinase subsequently phosphorylates and activates multiple cytoplasmic effector molecules in pathways involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow. Mutations that result in the constitutive activation of this receptor result in acute myeloid leukemia and acute lymphoblastic leukemia. (provided by RefSeq, Jul 2008)
GNAS	This locus has a highly complex imprinted expression pattern. It gives rise to maternally, paternally, and biallelically expressed transcripts that are derived from four alternative promoters and 5' exons. Some transcripts contain a differentially methylated region (DMR) at their 5' exons, and this DMR is commonly found in imprinted genes and correlates with transcript expression. An antisense transcript is produced from an overlapping locus on the opposite strand. One of the transcripts produced from this locus, and the antisense transcript, are paternally expressed noncoding RNAs, and may regulate imprinting in this region. In addition, one of the transcripts contains a second overlapping ORF, which encodes a structurally unrelated protein - Alex. Alternative splicing of downstream exons is also observed, which results in different forms of the stimulatory G-protein alpha subunit, a key element of the classical signal transduction pathway linking receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular reponses. Multiple transcript variants encoding different isoforms have been found for this gene. Mutations in this gene result in pseudohypoparathyroidism type 1a, pseudohypoparathyroidism type 1b, Albright hereditary osteodystrophy, pseudopseudohypoparathyroidism, McCune-Albright syndrome, progressive osseus heteroplasia, polyostotic fibrous dysplasia of bone, and some pituitary tumors. (provided by RefSeq, Aug 2012)
HNF1A	The protein encoded by this gene is a transcription factor required for the expression of several liver- specific genes. The encoded protein functions as a homodimer and binds to the inverted palindrome 5'-GTTAATNATTAAC-3'. Defects in this gene are a cause of maturity onset diabetes of the young type 3 (MODY3) and also can result in the appearance of hepatic adenomas. (provided by RefSeq, Mar 2009)
HRAS	This gene belongs to the Ras oncogene family, whose members are related to the transforming genes of mammalian sarcoma retroviruses. The products encoded by these genes function in signal transduction pathways. These proteins can bind GTP and GDP, and they have intrinsic GTPase activity. This protein undergoes a continuous cycle of de- and re-palmitoylation, which regulates its rapid exchange between the plasma membrane and the Golgi apparatus. Mutations in this gene cause Costello syndrome, a disease characterized by increased growth at the prenatal stage, growth deficiency at the postnatal stage, predisposition to tumor formation, mental retardation, skin and musculoskeletal abnormalities, distinctive facial appearance and cardiovascular abnormalities. Defects in this gene are implicated in a variety of cancers, including bladder cancer, follicular thyroid cancer, and oral squamous cell carcinoma. Multiple transcript variants, which encode different isoforms, have been identified for this gene. (provided by RefSeq, Jul 2008)
IDH1	Isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate. These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)- dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)- dependent isocitrate dehydrogenases, one of

	which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the cytoplasm and peroxisomes. It contains the PTS -1 peroxisomal targeting signal sequence. The presence of this enzyme in peroxisomes suggests roles in the regeneration of NADPH for intraperoxisomal reductions, such as the conversion of 2, 4-dienoyl-CoAs to 3-enoyl-CoAs, as well as in peroxisomal reactions that consume 2-oxoglutarate, namely the alpha-hydroxylation of phytanic acid. The cytoplasmic enzyme serves a significant role in cytoplasmic NADPH production. (provided by RefSeq, Jul 2008)
JAK2	This gene product is a protein tyrosine kinase involved in a specific subset of cytokine receptor signaling pathways. It has been found to be constituitively associated with the prolactin receptor and is required for responses to gamma interferon. Mice that do not express an active protein for this gene exhibit embryonic lethality associated with the absence of definitive erythropoiesis. (provided by RefSeq, Jul 2008
JAK3	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). (provided by RefSeq, Jul 2008)
KDR	Vascular endothelial growth factor (VEGF) is a major growth factor for endothelial cells. This gene encodes one of the two receptors of the VEGF. This receptor, known as kinase insert domain receptor, is a type III receptor tyrosine kinase. It functions as the main mediator of VEGF-induced endothelial proliferation, survival, migration, tubular morphogenesis and sprouting. The signalling and trafficking of this receptor are regulated by multiple factors, including Rab GTPase, P2Y purine nucleotide receptor, integrin alphaVbeta3, T-cell protein tyrosine phosphatase, etc.. Mutations of this gene are implicated in infantile capillary hemangiomas. (provided by RefSeq, May 2009)
KIT	This gene encodes the human homolog of the proto-oncogene c-kit. C-kit was first identified as the cellular homolog of the feline sarcoma viral oncogene v-kit. This protein is a type 3 transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor). Mutations in this gene are associated with gastrointestinal stromal tumors, mast cell disease, acute myelogenous lukemia, and piebaldism. Multiple transcript variants encoding different isoforms have been found for this gene. (provided by RefSeq, Jul 2008)
KRAS	This gene, a Kirsten ras oncogene homolog from the mammalian ras gene family, encodes a protein that is a member of the small GTPase superfamily. A single amino acid substitution is responsible for an activating mutation. The transforming protein that results is implicated in various malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal carcinoma. Alternative splicing leads to variants encoding two isoforms that differ in the C-terminal region. (provided by RefSeq, Jul 2008)
MET	The proto-oncogene MET product is the hepatocyte growth factor receptor and encodes tyrosinekinase activity. The primary single chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits, which are disulfide linked to form the mature receptor. Various mutations in the MET gene are associated with papillary renal carcinoma. Two transcript variants encoding different isoforms have been found for this gene. (provided by RefSeq, Jul 2008)
MLH1	This gene was identified as a locus frequently mutated in hereditary nonpolyposis colon cancer (HNPCC). It is a human homolog of the E. coli DNA mismatch repair gene mutL, consistent with the characteristic alterations in microsatellite sequences (RER+phenotype) found in HNPCC. Alternative splicing results in multiple transcript variants encoding distinct isoforms. Additional transcript variants have been described, but their full-length natures have not been determined.(provided by RefSeq, Nov 2009)

MPL	In 1990 an oncogene, v-mpl, was identified from the murine myeloproliferative leukemia virus that was capable of immortalizing bone marrow hematopoietic cells from different lineages. In 1992 the human homologue, named, c-mpl, was cloned. Sequence data revealed that c-mpl encoded a protein that was homologous with members of the hematopoietic receptor superfamily. Presence of anti-sense oligodeoxynucleotides of c-mpl inhibited megakaryocyte colony formation. The ligand for c-mpl, thrombopoietin, was cloned in 1994. Thrombopoietin was shown to be the major regulator of megakaryocytopoiesis and platelet formation. The protein encoded by the c-mpl gene, CD110, is a 635 amino acid transmembrane domain, with two extracellular cytokine receptor domains and two intracellular cytokine receptor box motifs . TPO-R deficient mice were severely thrombocytopenic, emphasizing the important role of CD110 and thrombopoietin in megakaryocyte and platelet formation. Upon binding of thrombopoietin CD110 is dimerized and the JAK family of non-receptor tyrosine kinases, as well as the STAT family, the MAPK family, the adaptor protein Shc and the receptors themselves become tyrosine phosphorylated. (provided by RefSeq, Jul 2008)
NOTCH1	This gene encodes a member of the Notch family. Members of this Type 1 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 family members play a role in a variety of developmental processes by controlling cell fate decisions. The Notch signaling network is an evolutionarily conserved intercellular signaling pathway which regulates interactions between physically adjacent cells. In Drosophilia, notch interaction with its cell-bound ligands (delta, serrate) establishes an intercellular signaling pathway that plays a key role in development. Homologues of the notch-ligands have also been identified in human, but precise interactions between these ligands and the human notch homologues remain to be determined. This protein is cleaved in the trans-Golgi network, and presented on the cell surface as a heterodimer. This protein functions as a receptor for membrane bound ligands, and may play multiple roles during development. (provided by RefSeq, Jul 2008)
NPM1	This gene encodes a phosphoprotein which moves between the nucleus and the cytoplasm. The gene product is thought to be involved in several processes including regulation of the ARF/p53 pathway. A number of genes are fusion partners have been characterized, in particular the anaplastic lymphoma kinase gene on chromosome 2. Mutations in this gene are associated with acute myeloid leukemia. More than a dozen pseudogenes of this gene have been identified. Alternative splicing results in multiple transcript variants.(provided by RefSeq, Nov 2009)
NRAS	This is an N-ras oncogene encoding a membrane protein that shuttles between the Golgi apparatus and the plasma membrane. This shuttling is regulated through palmitoylation and depalmitoylation by the ZDHHC9-GOLGA7 complex. The encoded protein, which has intrinsic GTPase activity, is activated by a guanine nucleotide-exchange factor and inactivated by a GTPase activating protein. Mutations in this gene have been associated with somatic rectal cancer, follicular thyroid cancer, autoimmune lymphoproliferative syndrome, Noonan syndrome, and juvenile myelomonocytic leukemia. (provided by RefSeq, Jun 2011)
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)
PIK3CA	Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. This gene has been found to be oncogenic and has been implicated in cervical cancers. (provided by RefSeq, Jul

	2008)
PTEN	This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase.It contains a tensin like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway (provided by RefSeq, Jul 2008)
PTPN11	The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This PTP contains two tandem Src homology-2 domains, which function as phospho-tyrosine binding domains and mediate the interaction of this PTP with its substrates. This PTP is widely expressed in most tissues and plays a regulatory role in various cell signaling events that are important for a diversity of cell functions, such as mitogenic activation, metabolic control, transcription regulation, and cell migration. Mutations in this gene are a cause of Noonan syndrome as well as acute myeloid leukemia. Two transcript variants encoding different isoforms have been found for this gene. (provided by RefSeq, May 2012)
RB1	The protein encoded by this gene is a negative regulator of the cell cycle and was the first tumor suppressor gene found. The encoded protein also stabilizes constitutive heterochromatin to maintain the overall chromatin structure. The active, hypophosphorylated form of the protein binds transcription factor E2F1. Defects in this gene are a cause of childhood cancer retinoblastoma (RB), bladder cancer, and osteogenic sarcoma. (provided by RefSeq, Jul 2008)
RET	This gene, a member of the cadherin superfamily, encodes one of the receptor tyrosine kinases, which are cell-surface molecules that transduce signals for cell growth and differentiation. This gene plays a crucial role in neural crest development, and it can undergo oncogenic activation in vivo and in vitro by cytogenetic rearrangement. Mutations in this gene are associated with the disorders multiple endocrine neoplasia, type IIA, multiple endocrine neoplasia, type IIB, Hirschsprung disease, and medullary thyroid carcinoma. Two transcript variants encoding different isoforms have been found for this gene. Additional transcript variants have been described but their biological validity has not been confirmed. (provided by RefSeq, Jul 2008)
SMAD4	This gene encodes a member of the Smad family of signal transduction proteins. Smad proteins are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to TGF-beta signaling. The product of this gene forms homomeric complexes and heteromeric complexes with other activated Smad proteins, which then accumulate in the nucleus and regulate the transcription of target genes. This protein binds to DNA and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad-binding element (SBE). The Smad proteins are subject to complex regulation by post-translational modifications. Mutations or deletions in this gene have been shown to result in pancreatic cancer, juvenile polyposis syndrome, and hereditary hemorrhagic telangiectasia syndrome. (provided by RefSeq, Oct 2009)
SMARCB1	The protein encoded by this gene is part of a complex that relieves repressive chromatin structures, allowing the transcriptional machinery to access its targets more effectively. The encoded nuclear protein may also bind to and enhance the DNA joining activity of HIV-1 integrase. This gene has been found to be a tumor suppressor, and mutations in it have been associated with malignant rhabdoid tumors. Two transcript variants encoding different isoforms have been found for this gene. (provided by RefSeq, Jul 2008)
SMO	The protein encoded by this gene is a G protein-coupled receptor that interacts with the patched protein, a receptor for hedgehog proteins. The encoded protein tranduces signals to other proteins after activation by a hedgehog protein/patched protein complex. (provided by RefSeq, Jul 2010)
SRC	This gene is highly similar to the v-src gene of Rous sarcoma virus. 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. Two transcript variants encoding the same protein have been found for this gene. (provided by RefSeq, Jul 2008)
STK11	This gene, which encodes a member of the serine/threonine kinase family, regulates cell polarity and functions as a tumor suppressor. Mutations in this gene have been associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by the growth of polyps in the gastrointestinal tract, pigmented macules on the skin and mouth, and other neoplasms. Alternate transcriptional splice variants of this gene have been observed but have not been thoroughly characterized. (provided by RefSeq, Jul 2008)
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 use of alternate start codons (PMIDs: 12032546, 20937277).(provided by RefSeq, Feb 2013)