SearchLight DNA™
Orientation

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The SearchLight DNA™ report is designed to describe the mutations identified in a pet's tumor. It also describes diagnostic, prognostic, and treatment-related biomarker associations with those mutations that are based on curation of more than 274 primary canine publications and inference from human cancer biomarker publications and databases. The report is thus built on a foundation of peer-reviewed research to support clinical decision-making. The front pages summarize actionable mutations and their associations. These pages are followed by in-depth biomarker summaries, evidence statements, and links to supporting articles.
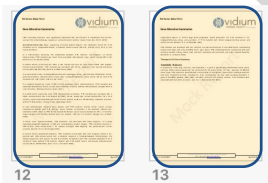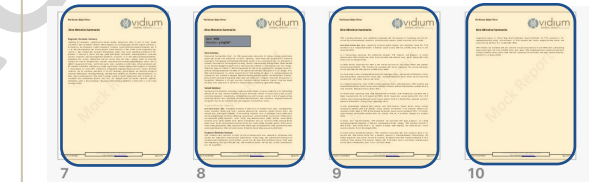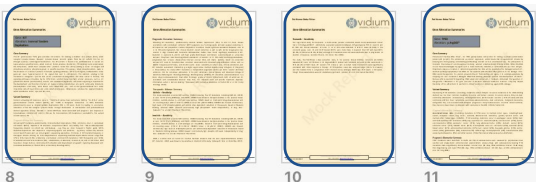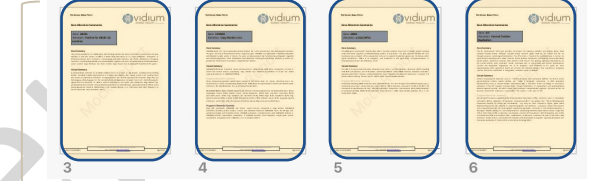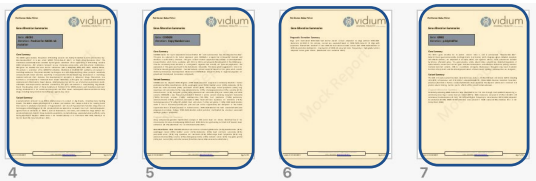
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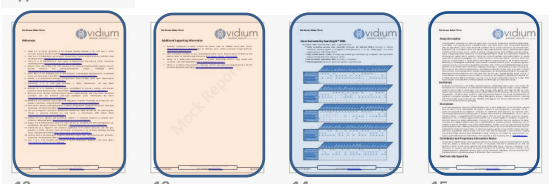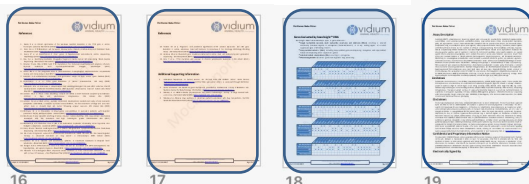
SearchLight DNA^{TM} Client Report

SearchLight DNA^{TM}
Client Report

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Pet Name: Boba Fisher
Breed: Australian Shepherd
Sex: M/N
Date of Birth: August 2012
Owner: George Fisher

Veterinarian: Dr. Aphra
Veterinary Clinic: Veterinary Specialty Hospitals
Sample Collection Date: 2020-03-10
Sample Received Date: 2020-03-20
Report Date: 2020-03-30

Diagnosis: Cutaneous Mast Cell Tumor
Specimen Location: Skin of Lip
Specimen Type: Fine Needle Aspirate
Client Accession #: 54321

Overview: This test evaluated 120 cancer genes in Boba's tumor sample. Four alterations were identified of potential clinical significance for cancer diagnosis, prognosis, or treatment.

Summary of Key Findings

Therapeutically Actionable Genomic Findings	**Tumor Histology-Related Findings**
1 Pharmacogenomic Biomarker	4 Diagnostic Biomarkers
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Therapeutically Actionable Genomic Findings

Pharmacogenomic Biomarker

Gene	Alteration	Pharmacogenomic Association

Tumor Histology-Related Findings

Diagnostic Biomarkers

Gene	Alteration	Diagnostic Role in Dog Cancers	Diagnostic Role in Human Cancers
CDKN2B	Copy Number Loss	✔	✔
GNB1	p.Gly116Phe	✔	-
KIT	Internal Tandem Duplication	✔	-
TP53	p.Arg265*	-	✔

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Prognostic Biomarkers

Gene	Alteration	Prognostic Role in Dog Cancers	Prognostic Role in Human Cancers
CDKN2B	Copy Number Loss	Poor Outcome	-
KIT	Internal Tandem Duplication	Poor Outcome	-
TP53	p.Arg265*	Poor Outcome	Poor Outcome

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Gene Alteration Summaries

> Gene: **CDKN2B**
> Alteration: **Copy Number Loss**

Gene Summary
CDKN2B stands for "cyclin dependent kinase inhibitor 2B" and is pronounced "See-Dee-Kay-Enn-Too-Bee". This gene lies next to the important tumor suppressor gene CDKN2A, in a region that is frequently mutated and deleted in a wide variety of tumors. This gene encodes a protein that functions as a cell growth regulator and controls progression of the cell division cycle. Mutations in this gene may disrupt its ability to control cell growth and thereby lead to excessive cell growth and division.

Variant Summary
CDKN2A/CDKN2B are located on canine chromosome 11. CDKN2A and CDKN2B are disrupted in a variety of canine and human tumors, typically by copy number loss. Deletion is predicted to disrupt the tumor suppressor function of CDKN2A/CDKN2B.

Diagnostic Biomarker Summary
Array comparative genomic hybridization analysis of 109 canine mast cell tumors identified loss of the chromosome 11 locus encompassing CDKN2A and CDKN2B to be significantly enriched in KIT-mutant mast cell tumors (21.2%). (Mochizuki H et al. Chromosome Res 2017).

Associated human data. CDKN2B deletions are common in human glioblastoma (55%), mesothelioma (43%), esophageal cancer (35%), bladder cancer (31%), melanoma (29%), head and neck carcinoma (28%), pancreatic cancer (27%), lung squamous cell carcinoma (26%), diffuse large B-cell lymphoma (25%), lung adenocarcinoma (16%), sarcoma (15%), cholangiocarcinoma (14%), stomach cancer (11%), low grade glioma (11%), liver cancer (5%), and other cancers (TCGA Pan-Cancer Atlas accessed via cBioPortal).

Prognostic Biomarker Summary
Dogs with inactivated CDKN2A/B had shorter overall survival compared to dogs without CDKN2A/B alterations (p=0.02). In this analysis, survival was evaluated based on CDKN2A/B status for 40 dogs with lymphoma treated with standard of care. CDKN2A inactivation included tumors with CDKN2A/B deletion or CDKN2A promoter methylation. Inactivation of CDKN2A occurred more frequently in high-grade tumors compared to low-grade tumors. (Modiano JF et al. Leukemia 2007).

Gene Alteration Summaries

Gene: **GNB1**
Alteration: **p.Gly116Phe**

Gene Summary

The GNB1 gene (pronounced "Gee-Enn-Bee-Won") encodes a protein that is part of a larger protein complex inside cells called a guanine nucleotide-binding protein, or "G protein". This gene encodes the beta sub-unit. G proteins are a vital part of the process that cells use to respond to external signals, like hormones, called signal transduction. GNB1 is an oncogene, and mutations in this gene result in hyperactivation of downstream processes and ultimately, cancer.

Variant Summary

This GNB1 missense variant has been detected in one study in 12.3% of 81 mast cell tumors (MCT) including 11% (8/72) of cutaneous and 22% (2/9) of subcutaneous MCTs. These GNB1 missense mutations have been previously identified in human acute lymphoblastic B-cell leukemia. The adjacent amino acid is involved in G protein subunit binding, but the specific effects of this variant remain unknown.

Diagnostic Biomarker Summary

Potentially activating GNB1 mutations were identified for the first time through multi-platform sequencing as commonly occurring in canine mast cell tumors (MCTs). GNB1 mutations occurred in 17.3% of 81 MCTs (72 cutaneous, 9 subcutaneous; 48 fresh, 33 FFPE) with higher frequency in subcutaneous MCTs (44%) compared to cutaneous (13.9%). GNB1 G116F mutations were present in 10/81 cases (12.3%). (Vozdova M et al. Vet Comp Oncol 2020).

Gene Alteration Summaries

Gene: **KIT**
Alteration: **Internal Tandem Duplication**

Gene Summary

The KIT (pronounced "Kit") gene provides instructions for making a member of a protein family called receptor tyrosine kinases. Receptor tyrosine kinases transmit signals from the cell surface into the cell through a process called signal transduction. The KIT protein is found in the cell membrane of certain cell types where a specific protein, called stem cell factor, attaches (binds) to it. This binding turns on (activates) the KIT protein, which then activates other proteins inside the cell. The signaling pathways stimulated by the KIT protein control many important cellular processes such as cell growth and division (proliferation), survival, and movement (migration). KIT is an oncogene, and mutations in this gene can cause hyperactivation of the signals that lead to cell division. The common analogy is that mutations in oncogenes "put the foot on the accelerator of cell growth", and allow cancer to develop.

Variant Summary

Somatic activating KIT mutations occur in ~13-50% of canine mast cell tumors (MCTs), ~35-74% of canine gastrointestinal stromal tumors (GISTs), and ~2-8% of malignant melanomas. In MCT, mutations predominantly occur as internal tandem duplications (ITD) in KIT exons 8 and 11, leading to constitutive activation of the KIT receptor tyrosine kinase through modulation of extracellular and juxtamembrane domain regulatory activity. KIT ITDs in canine MCT have been associated with prognosis. KIT exon 11 ITDs are the most common KIT mutations in canine MCTs. This variant is a KIT exon 11 ITD.

Diagnostic Biomarker Summary

Activating KIT mutations, predominantly internal tandem duplications (ITDs), commonly occur in canine mast cell tumors (MCTs). Reports of KIT mutation frequencies in MCT vary widely, from ~9% to 50%. Reported frequencies depend on cohort size and makeup - e.g. they are more frequent in higher grade MCTs. Reported frequencies also depend on sequencing regions and platforms - e.g. many studies only evaluate one or two KIT exons and use only targeted sequencing approaches. Estimates of KIT mutation frequency in the largest cohorts utilizing the most comprehensive sequencing methods report a more narrow range from 17% to 30%. Exon 11 ITDs or deletions are the most common KIT mutations in MCT followed by exon 8 ITDs or substitutions and rare mutations (ITDs, substitutions, or deletions) in exons 9, 12, and 17. KIT ITDs in MCT have been shown to drive constitutive KIT activation and downstream pro-growth signaling. (Reviewed with Consensus Guidelines in Thamm DH et al. Vet Comp Oncology 2019).

Gene Alteration Summaries

Prognostic Biomarker Summary

Activating KIT mutations, predominantly internal tandem duplications (ITDs) in exon 11, have shown associations with canine mast cell tumor (MCT) prognosis (i.e. histologic grade and post-surgical outcomes) in retrospective and prospective studies. Prospective trials have found significant association between exon 8 or 11 ITDs and progression-free interval (but not overall outcome) as well as with shorter progression-free survival in dogs treated with toceranib. Retrospective studies have found significant association of KIT mutation in exons 8, 9, and 11 with high grade (both Kiupel and Patnaik systems) based on univariate analyses. They have also found significant association of exon 11 or 12 ITDs with recurrence, metastasis, progression-free survival, disease-free interval, survival time, and death, typically based on univariate analyses. KIT exon 11 mutations have also been associated with increased cell proliferation indices such as AgNOR frequency, Ki67 index, and mitotic counts. Given variability in cohort sizes, clinical annotation, and KIT mutation assessment methods (e.g. a single region versus multiple regions versus all regions of the gene) in these studies, the status of KIT mutations as independent prognostic factors are still in need of definitive validation. Per the consensus publication of the joint Veterinary Cancer Society and American College of Veterinary Pathologists' Oncology-Pathology Working Group (OPWG), KIT "mutation presence/absence is a more objective measurement than either histologic grade or mitotic index/count, both of which can be associated with considerable observer bias. Thus, this measure could still provide important objective information useful in decision-making." (Reviewed with Consensus Guidelines in Thamm DH et al. Vet Comp Oncology 2019).

Gene Alteration Summaries

> Gene: **TP53**
> Alteration: **p.Arg265***

Gene Summary

Pronounced "Tee-Pee-Fifty-Three", the TP53 gene provides instructions for making a protein called tumor protein p53 (or p53). This protein acts as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing (proliferating) too fast or in an uncontrolled way. The p53 protein is located in the nucleus of cells throughout the body, where it attaches (binds) directly to DNA. When the DNA in a cell becomes damaged by agents such as toxic chemicals, radiation, or ultraviolet (UV) rays from sunlight, this protein plays a critical role in determining whether the DNA will be repaired or the damaged cell will self-destruct (undergo apoptosis). If the DNA can be repaired, p53 activates other genes to fix the damage. If the DNA cannot be repaired, this protein prevents the cell from dividing and signals it to undergo apoptosis. By stopping cells with mutated or damaged DNA from dividing, p53 helps prevent the development of tumors. Because p53 is essential for regulating DNA repair and cell division, it has been nicknamed the "guardian of the genome." Mutations in this gene are some of the most common mutations in cancer. They may impact the ability of the p53 protein to perform its critical functions in protecting against DNA damage.

Variant Summary

Inactivating TP53 mutations (truncating mutations and/or hotspot missense mutations in the DNA-binding domain) are the most common mutations in canine and human cancers. In canine cancers, they are most commonly observed in osteosarcoma, hemangiosarcoma, and histiocytic sarcoma (>40% of cases) and less commonly (<20%) in B-cell lymphoma, pulmonary adenocarcinoma, mast cell tumors, malignant melanoma, and glioma. They are also associated with poor prognosis in many human cancers.

Diagnostic Biomarker Summary

Associated human data. Truncating mutations in TP53 occur in multiple tumor types, including breast cancer, colorectal cancer, lung cancer, sarcoma, adrenocortical carcinoma, glioma, Spitzoid tumor, and multiple other tumor types (COSMIC). TP53 truncating mutations occur in esophageal cancer (34%), head and neck squamous cell carcinoma (32%), lung squamous cell carcinoma (30%), ovarian cancer (27%), uterine carcinosarcoma (23%), pancreatic cancer (22%), lung adenocarcinoma (20%), stomach cancer (18%), colorectal cancer (17%), bladder cancer (16%), chromophobe renal cell carcinoma (15%), sarcomas (13%), breast cancer (12%), adrenocortical carcinoma (12%), liver cancer (12%), low grade gliomas (11%), uterine cancer (10%), glioblastoma (8%), melanoma (7%), diffuse large B-cell lymphoma (5%), mesothelioma (5%), acute myeloid leukemia (5%), and other cancers. (TCGA Pan-Cancer Atlas accessed via cBioPortal).

Prognostic Biomarker Summary

TP53 mutations were identified in 24/59 (40.7%) of osteosarcoma cases assessed by polymerase chain reaction and single-strand conformational polymorphism analysis. Dogs with osteosarcoma bearing TP53 mutations had a significantly shorter median survival time (81 days, 95% confidence interval: 73-89 days) than dogs bearing wild-type TP53 (256 days, 95% confidence interval: 119-392 days, p=.026). (Kirpensteijn J et al. Vet Surg 2008).

Gene Alteration Summaries

TP53 truncating mutations were significantly associated with the presence of metastases, but not with survival time or chemotherapy response in canine histiocytic sarcoma. (Asada H et al. Res Vet Sci 2019).

Associated human data. Deep sequencing of human splenic marginal zone lymphoma found that TP53 mutations are an independent marker of reduced overall survival (HR 2.36, p=0.03). (Parry M et al. Clin Cancer Res 2015).

In a meta-analysis evaluating the relationship between TP53 mutation and prognosis in human osteosarcoma, TP53 mutation was found to be associated with reduced 2-year overall survival (RR=1.79). (Chen Z et al. Dis Markers 2016).

In a meta-analysis of patients with EGFR or ALK mutant non-small cell lung cancer treated with targeted tyrosine kinase inhibitors, TP53 mutation was associated with shorter progression free survival and overall survival (HR=1.88, HR=1.92). (Qin K et al. BMC Cancer 2020).

In a meta-analysis study including 888 patients with esophageal cancer, patients with TP53 mutant tumors were found to have reduced overall survival when compared to patients whose tumors did not have TP53 mutations (HR 1.48). (Fisher OM et al. Gut 2017).

In a targeted sequencing study of 283 primary pancreatic ductal adenocarcinoma, TP53 mutation was associated with reduced overall survival when compared to tumors without TP53 mutations (median OS 37.4 vs 65.0 months). (McIntyre CA et al. Cancer 2020).

In a whole exome sequencing study of 87 hepatocellular carcinomas, TP53 mutation was associated with a higher recurrence rate (89 vs 40 percent, p=0.006), shorter disease-free survival (median DFS 7.9 vs 42.9 months), and a trend toward reduced overall survival (median OS 26.0 vs 83.2 months), compared to tumors without TP53 mutations. (Cleary SP et al. Hepatology 2013).

In acute lymphoblastic leukemia (ALL), patients with TP53 mutation showed shorter overall survival, compared to patients with TP53 wildtype tumors (median 11.5 months vs not reached). Patients with alterations in both alleles of TP53 (2 hits) showed the shortest overall survival (median OS 2 hits, 7.1 months, single mutation, 63.5 months, deletion alone, not reached, TP53 wt, 75.5 months). (Stengel A et al. Blood 2014).

In human acute myeloid leukemia, TP53 mutations are associated with worse prognosis. In a study evaluating prognostic subgroups of AML with myelodysplasia-related changes, TP53 mutations occurred in 22% of cases, were mostly found in the complex karyotype AML subgroup, and predicted poor clinical outcome. (Devillier R et al. Oncotarget 2015).

In human chronic lymphocytic leukemia, TP53 mutation is associated with poor prognosis. None of the patients with TP53-mutant tumors had a complete response to fludarabine-based chemotherapy. The median progression-free survival for was 23.3 months for patients with TP53 mutation compared to 62.2 months for those without TP53 mutation. Patients with TP53 mutant tumors also showed reduced overall survival (29.2 vs 84.6 months). (Zenz T et al. J Clin Oncol 2010).

Gene Alteration Summaries

Longitudinal analysis of diffuse large B-cell lymphomas found enrichment for TP53 mutations in the relapsed/refractory setting, and association of TP53 mutation with inferior progression-free survival and overall survival. (Rushton CK et al. Blood Adv 2020).

TP53 mutation was associated with poor outcome in a pan-cancer analysis of over 3000 tumors representing twelve tumor types (HR 1.19, p=0.049). Tumor types where TP53 showed significant associations with poor outcome included kidney cancer, head and neck squamous cell carcinoma, and acute myeloid leukemia. (Kandoth C et al. Nature 2013).

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Appendix

Variants of Uncertain Significance

The following variants were detected in Boba's tumor sample. These variants are considered variants of uncertain significance, meaning the functional impact of the alteration on gene function is unknown or the role of the mutation in tumor diagnosis, prognosis, or treatment is unknown. Future research may reveal a role for these mutations in cancer.

ATR (Copy Number Loss)
ATR is the gene that encodes the ATR serine/threonine kinase, and is pronounced "Ay-Tee-Ahr". This protein has several functions in the cell, including as a DNA damage sensor, and it can inhibit DNA replication if that DNA is damaged in certain ways. It can also promote DNA repair mechanisms. In some cases of extreme damage, the gene can trigger apoptosis, or normal, programmed cell death. ATR is classified as a tumor suppressor gene, since its normal functions reduce the chance a cell will become cancerous. The common analogy is that mutations in tumor suppressor genes are like "taking the foot off the brake pedal of cell division" and cancer may result.

EGFR (p.Ile287Val)
The EGFR gene provides instructions for making a protein called the epidermal growth factor (EGF) receptor, and is pronounced "Ee-Jee-Eff-Ahr". The receptor for EGF spans the cell's membrane so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning allows the receptor to attach (bind) to other proteins, called ligands, outside the cell and to receive signals that help the cell respond to its environment. Ligands and receptors fit together like keys into locks. Epidermal growth factor receptor binds to at least seven different ligands. The binding of a ligand to epidermal growth factor receptor allows it to attach to another nearby receptor protein and activate the receptor complex. As a result, signaling pathways within the cell are triggered that promote cell growth and division (proliferation) and cell survival. EGFR is an oncogene. Mutations in the gene that make EGFR protein less likely to turn off or more likely to turn on can cause proliferation and tumorigenesis.

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Additional Supporting Information

1. Alteration frequencies in human cancers are derived from the COSMIC Cancer Gene Census (https://cancer.sanger.ac.uk/census) and the TCGA pan-cancer cohort, as accessed through cBioPortal (https://www.cbioportal.org)

2. Gene summaries are based on gene descriptions provided by the National Library of Medicine and National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/gene)

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Genes Evaluated by SearchLight™ DNA

SearchLight DNA™ detects multiple types of gene mutations:

- **Single nucleotide variants, small nucleotide insertions and deletions (SNVs)** occurring in selected commonly mutated regions in oncogenes ("Selected Exons") or in any coding region of a tumor suppressor gene ("All Coding Exons").

- **Copy number variants (CNVs)** including copy number gains encompassing oncogenes and copy number losses encompassing tumor suppressor genes.

- **Internal tandem duplications (ITDs)** occurring in oncogenes.

- **Pharmacogenomic** variants in genes that regulate drug processing.

	ABCB1	AKT1	AKT3	ALK	APC	ARAF	ARID1A	ASXL1	ATM	ATR	ATRX	BAP1	BRAF	BRCA1	BRCA2	BTK	CALR	CBL	CCND1	CCND2	CCND3	CCNE1	CDK12	CDK4
SNV Selected Exons		●	●	●									●		●	●	●	●						
SNV All Coding Exons					●		●	●	●			●											●	
CNV		●		●	●				●						●				●	●	●	●		●
ITD																								
Pharmacogenomic	●																							

	CDK6	CDKN2A	CDKN2B	CHEK2	CRK	CSF3R	CTNNB1	DDR2	DNMT3A	EGFR	ERBB2	ERRFI1	ESR1	EZH2	FANCA	FANCC	FANCG	FANCL	FBXW7	FGF3	FGFR1	FGFR2	FGFR3	FLCN
SNV Selected Exons										●			●								●	●	●	
SNV All Coding Exons		●	●	●				●		●						●								
CNV	●	●	●					●		●	●			●					●	●	●			
ITD																								
Pharmacogenomic																								

	FLT3	FOXL2	GNAQ	GNAS	GNB1	H3F3A	HRAS	IDH1	IDH2	IKZF1	JAK1	JAK2	KDR	KIT	KMT2D	KRAS	MAP2K1	MAP2K2	MAPK1	MDM2	MDM4	MEN1	MET	MLH1
SNV Selected Exons	●	●	●	●	●	●	●	●	●		●	●	●	●		●	●	●					●	
SNV All Coding Exons																						●		●
CNV									●			●		●		●			●	●	●		●	
ITD	●													●										
Pharmacogenomic																								

	MSH2	MSH3	MSH6	MTOR	MYC	MYCN	MYD88	NF1	NF2	NFE2L2	NOTCH1	NPM1	NRAS	NT5C2	PALB2	PDGFRA	PIK3CA	PIK3R1	PMS2	POLD1	POLE	PTCH1	PTEN	PTPN11
SNV Selected Exons				●						●		●	●			●	●							●
SNV All Coding Exons	●	●	●					●	●		●				●			●	●	●	●	●	●	
CNV	●		●	●	●	●		●						●	●	●	●	●		●		●	●	
ITD																								
Pharmacogenomic																								

	RAC1	RAF1	RB1	REL	RET	RICTOR	RUNX1	SDHB	SDHD	SETD2	SF3B1	SMAD4	SMARCA4	SMARCB1	SMO	STAT3	STK11	TP53	TRAF3	TSC1	TSC2	U2AF1	VEGFA	VHL
SNV Selected Exons	●	●			●						●				●	●				●		●		
SNV All Coding Exons			●				●	●	●	●		●	●	●			●	●			●			●
CNV		●	●	●	●	●		●	●		●	●	●		●	●	●	●	●		●		●	
ITD																								
Pharmacogenomic																								

Assay Description

SearchLight DNA™ is a Next Generation Sequencing targeted tumor-only assay that provides for the detection of single nucleotide variants (SNVs), small nucleotide insertions and deletions (indels), copy number variants (CNVs), internal tandem duplications (ITDs), and polymorphisms in tumor tissue. Genomic DNA is extracted from the patient's tumor samples and the isolated DNA is then prepared using a custom hybrid capture panel (Agilent). Library preparation includes shearing, purification, adaptor ligation and PCR amplification. Libraries are then clustered on a flow cell and sequenced using the Illumina MiSeq or NextSeq. Sequence data are analyzed using validated bioinformatics tools (SearchLight DNA™ Pipeline 1.0) and canine polymorphism databases. The reference genome assembly used for alignment is CanFam 3.1. Each tumor's candidate cancer-specific mutations are queried against Vidium's proprietary knowledgebase which contains thousands of canine cancer biomarker associations derived from primary peer-reviewed literature to identify potential pharmacogenomic, diagnostic, prognostic, and therapeutic associations. Additionally, this knowledgebase contains human cancer biomarker associations inferred via genomic and proteomic alignments and conservation scores from the Clinical Interpretation of Variants in Cancer (CIViC version 05/01/20) and Catalogue of Somatic Mutations in Cancer (COSMIC version 91) databases. ABCB1 germline genotype is determined based on tumor-only sequencing. SNVs are reported when present at ≥ 3% allele fraction. Allele fractions are dependent on tumor purity. Tumor purity is not taken into account when calculating allele fractions. Reported CNVs (gains/losses) are identified based on comparison to a copy number baseline generated from normal tissues across major breed clades and tissue types. Reported CNVs may be focal, arm-level, or chromosome-level. ITDs are reported only for KIT and FLT3 in selected exons. Pharmacogenomic polymorphisms are reported only for ABCB1 (also known as MDR1). Indeterminate results may occur due to poor sample quality or sequencing coverage. Mean target coverage for tumor sample DNA is ≥ 200x (unique reads) and ≥ 89% of target bases bear ≥ 100x coverage.

Limitations

Samples with a tumor content less than 30% may have reduced sensitivity and lead to false negative results. It is also possible that the sample contains a mutation below our established limit of detection or in a genetic region not included in our assay. Alterations present in repetitive or high GC content region or non-coding areas may not be detected. Indels larger than 40bp may not be detected. Copy number signal relative to background noise inherent in DNA from FFPE samples may affect sensitivity of reporting CNV gains/losses. The lack of a variant call does not necessarily indicate the absence of a variant since technical limitations to acquire data in some genetic regions may limit assay detection. ABCB1 germline genotype is inferred from tumor-only sequencing and it remains possible, though unlikely, that either ABCB1 loss of heterozygosity in the tumor or somatic acquisition of an ABCB1 mutation could interfere with accurate genotyping.

Disclaimers

This test was developed, and performance characterics determined, by Vidium Animal Health. This test has not been approved by the U.S. FDA. The FDA has determined that such clearance or approval for veterinary diagnostics is not necessary. This test is used for clinical purposes for veterinary patients. It should also be noted that the data interpretations are based on our current understanding of genes and variants and are current as of the report date. Alterations are listed alphabetically, and not in order of strength of evidence or appropriateness for the patient's disease. When the report does identify variants with therapeutic implications, this does not promise or guarantee that a particular drug or treatment regimen will be effective or helpful in the treatment of disease in any patient, and the selection of any drug for patient treatment is done at the discretion of the treating veterinarian. These treatment options are based solely on published biomarker associations and do not include dosing, safety, or combinatorial guidelines. Please refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Use caution when combining multiple drugs and be aware of potential drug interactions. Genomic alterations should be considered in the context of the patient's history, risk factors and any previous genomic testing. Variants of Unknown Significance (VUS) may be associated with potential therapies in the future. Vidium does not update reports or send notification regarding reclassification of these alterations. Vidium Animal Health's services, including but not limited to the results contained in this report, are governed by Vidium's Terms & Conditions, which are available by email by requesting them at vidiuminfo@tgen.org.

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