ONCOLOGY genpath an OPKO Health Company

OnkoSight™ Advanced CNS NGS Report

Final Report

SAMPLE, PHYSICIAN
ONCOLOGY HOSPITAL
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ANYTOWN, USA 00000
Acct#:
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Patient Name: SAMPLE, PATIENT
DOB: 01/04/1964 **Age:** 57 Y **Sex:** M
Surgical #:
Patient ID:

Specimen ID: XXXXXXXXX
Date of Report: 07/03/2021 12:21 PM EDT
Date Collected: 06/22/2021
Date Received: 06/24/2021
Specimen Source: Solid Tumor
Specimen Tumor %: >50%

RESULT SUMMARY: ABNORMAL

DETECTED GENOMIC ALTERATIONS:

Tier I: Variants of Strong Clinical Significance

BRAF p.(Val600Glu)

Tier II: Variants of Potential Clinical Significance

PIK3CA Amplification

PTEN p.(Tyr336Ter)

TERT C228T

Tier III: Variants of Unknown Clinical Significance

NTRK1 p.(Ala107Val)

TUMOR TYPE: Glioblastoma

CLINICAL INFORMATION:

Brain biopsy showed glioblastoma (Testing performed on # xx-xxxx-xxxx-xxxx).

IMMUNOTHERAPY BIOMARKERS:

TUMOR MUTATION BURDEN: LOW (3.9 MUTATIONS / MB)

MICROSATELLITE INSTABILITY: MSI NEGATIVE

PERTINENT NEGATIVE RESULTS:

The following genes are NEGATIVE for clinically relevant mutations. Mutational hotspots and surrounding exonic regions were interrogated for DNA level point mutations and indels (fusions not assayed).

APC, ATRX, CDKN2A, CTNNB1, EGFR, ERBB2, H3F3A, H3F3B, H3F3C, HIST1H3B, HIST1H3C, IDH1, IDH2, MYC, NF1,NF2, PDGFRA, SMARCA4, SMARCB1, TP53, VHL

TECHNICAL SUMMARY

Gene	Alteration	AMP Tier	Chr	Pos	Ref	Alt	Coverage	Allele Freq. or Fold Change	cDNA Change	Exon
BRAF	p.(Val600Glu)	I	7	140453136	A	T	652	20%	c.1799T>A	15
PIK3CA	Amplification	II	0	0	-	-	-	2.845x	-	-
PTEN	p.(Tyr336Ter)	II	10	89720857	C	G	215	72%	c.1008C>G	8
TERT	C228T	II	5	1295228	G	A	91	33%	c.-124C>T	-
NTRK1	p.(Ala107Val)	III	1	156834552	C	T	903	41%	c.320C>T	3

THERAPEUTIC ASSOCIATIONS

In Patient's Tumor Type

	Gene / Locus	Alteration	Potential Therapeutic Response / Drug Class	Disease Association
✓	BRAF	p.Val600Glu	Associated with sensitivity to BRAF/MEK inhibitors	Glioma

INTERPRETATION SUMMARY

An amplification in PIK3CA was detected in this patient's sample.

PIK3CA is frequently mutated in a diverse range of cancers including gastric cancers, implying an important role of PIK3CA mutations in gastric carcinogenesis. In addition to mutations, genomic amplification of PIK3CA has been reported in various human cancers, including ovarian cancer, cervical cancer, thyroid cancer, and non-small cell lung cancer (NSCLC). Increased copy number of PIK3CA is closely associated with elevated mRNA or protein expression (9916799; 10851074; 17317825; 21507233). Importantly, PIK3CA overexpression caused by gene amplification increases PI3-kinase activity and phosphorylated Akt level, which was associated with aberrant cell proliferation and apoptosis, both of which are directly linked to tumorigenesis (9916799; 10851074; 11959846). However, association of PIK3CA alterations with lung cancer require further verification in more rigorous studies with consistent and standardized methodology. PIK3CA amplification status has not been explicitly or formally incorporated into diagnostic, prognostic, or therapeutic algorithms for glioblastoma (NCCN Guidelines, Central Nervous System Cancers, Version 1.2021)

A mutation in PTEN (p.(Tyr336Ter)) was detected in this patient's sample.

PTEN is one of the most important tumor suppressor genes, and it is highly mutated in various types of cancers including brain, breast, kidney, lung and uterine cancers (18794877; 9072974; 18455982). Many patients with brain tumours carry mutations in the PTEN genes (18794877; 10564676). Among these, glioblastoma (GBM) has a very high frequency of mutation (~35%) in the PTEN gene (18772890; 21727940). In several study, PTEN deficiency in GBM has been associated with poor survival (12006525; 16530701). At current time, PTEN mutations have not been explicitly or formally incorporated into diagnostic, prognostic, or therapeutic algorithms for central nervous system cancers (NCCN Guidelines, Central Nervous System Cancers, Version 1.2021)

Clinical and pathologic correlation is required to interpret these findings.

A BRAF p.Val600Glu (V600E) mutation was detected in this patient's sample.

BRAF V600E has been detected in approximately 20-75% of gliomas, and more frequently in lower grade tumors (21274720; 21479234; 22492957; 23547069; NCCN Guidelines, Central Nervous System Cancers, Version 1.2021). Clinical studies investigating prognosis in BRAF V600E mutated gliomas have been conflicting and research is ongoing (28534272; 25667294; 23609006; 22492957; NCCN Guidelines, Central Nervous System Cancers, Version 1.2021). Therapy with BRAF inhibitors, dabrafenib and vemurafenib, has been successful in patients with BRAF V600E mutated melanoma that metastasized to the brain (21639808; 23051966; 24295639; 24508103; NCCN Guidelines, Central Nervous System Cancers, Version 1.2021). Use of BRAF inhibitors, such as vemurafenib and dabrafenib, as treatment for BRAF V600E mutated gliomas has been promising in early studies and clinical trials are ongoing (23358987; 25524464; 24725538; 28062673; 27781490; 27799506; 25092772; 25944653; NCCN Guidelines, Central Nervous System Cancers, Version 1.2021). Clinical studies investigating the use of MEK inhibitors, such as selumetinib, are also under investigation (27217440).

A hotspot promoter mutation in TERT (C228T) was detected in this patient's sample.

Hotspot mutations involving c.-124 or c.-146 positions upstream of the TERT transcriptional start site (C228T or C250T mutations, respectively), have been reported in a wide variety of solid tumor types including NSCLC, colorectal cancer, malignant melanomas, high grade CNS neoplasms, thyroid cancer, hepatocellular carcinoma, bladder cancer, basal cell carcinoma, and cutaneous squamous cell carcinomas, among others, where these alterations typically confer enhanced TERT promoter activity. TERT encodes the catalytic active site telomerase, the enzyme responsible for maintaining telomere length in dividing cells. In the absence of an IDH mutation, TERT mutations in diffusely infiltrative gliomas are associated with reduced overall survival compared to gliomas lacking TERT promoter methylation (NCCN Guidelines, Central Nervous System Cancers, Version 1.2021).

An unclear variant in NTRK1 p.(Ala107Val) was detected in this patient's sample.

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LEGEND:	Likely Response for defined therapy	Unlikely Response for defined therapy	Unknown therapeutic response	Associated with increased survival	Associated with decreased survival	Investigational agent available
	✓	✗	?	↑	↓	

This variant has been reported in a limited number of tumor samples (COSMIC) but has also been reported as an extremely rare population variant (gnomAD). Therefore, although likely disease-associated, due to the paucity of functional and clinical evidence, its significance is currently unclear.

The present sample analysis is NEGATIVE for evidence of high level Tumor Mutation Burden or high level microsatellite instability.

The present sample analysis is negative for high level Tumor Mutation Burden. Presence of >10 mutations / megabase has been reported to be therapeutically predictive of favorable clinical outcomes and responsiveness to immune checkpoint inhibitors, according to some studies (29658845; 30395155). TMB is an evolving biomarker, and consensus standardization for this biomarker remains an ongoing imperative (30664300). To date, the median TMB for all tumor types tested by OnkoSight Advanced in general, is approximately 3.9 mutations / megabase, and 3.9 mutations / megabase for CNS cancers, in particular. According to some large scale cohorts published in the primary literature, a median TMB value of 2.7 mutations / megabase has been reported for glioblastoma (28420421).

The present sample analysis is also negative for high level microsatellite instability.

Clinical and pathologic correlation is required to interpret these findings.

DETAILED GENETIC INTERPRETATION

Alteration	Interpretation
PIK3CA **Amplification** **-** **2.845x fold change** **Exon -** **NM_006218.2**	An amplification of PIK3CA corresponding to an increase in the total number of reads covering the amplicons of this gene was detected. This increase in read depth demonstrates that additional genomic material was present for these regions of this sample, but the total number of additional copies present in any one cell cannot be determined with this methodology. The increase may represent a very high level amplification in a subset of cells tested, or a low level amplification in many cells. The PIK3CA gene (phosphatidylinositol-4,5-Bisphosphate 3-kinase, catalytic subunit alpha) is located on chromosome 3q26.32. The gene encodes the p110alpha catalytic subunit of class I phosphatidylinositol 3-kinase (PI3K), a key component of the PI3K/AKT/mTOR cell survival pathway. PIK3CA mutations lead to constitutive activation of the p110 catalytic activity, AKT signaling, and ligand-independent growth. Somatic missense mutations in the PIK3CA have been reported in a variety of tumor types, and most often target residues E542 and E545 in the helical domain and residue H1047 in the kinase domain of the protein (16341083; 17561399).
PTEN **p.(Tyr336Ter)** **c.1008C>G** **72% allele frequency** **Exon 8** **NM_000314.4**	p.(Tyr336Ter) represents a nonsense mutation in exon 8 of PTEN converting the wild type residue, Tyrosine, into a premature stop codon at amino acid 336 of the protein. The introduction of a stop codon at this position results in a truncated form of the protein. This mutation leads to partial deletion of the membrane-binding C2 domain and is expected to lead to loss of function. This mutation has also been detected as a germline mutation in multiple different hereditary cancer-predisposing syndromes (ClinVar). The phosphatase and tensin homolog (PTEN) is located on chromosome 10q23.31 and encodes a dual-specificity phosphatase. PTEN functions as a tumor suppressor and a negative regulator of the PI3K-AKT-mTOR signaling pathway by dephosphorylating phosphatidylinositol-3,4,5-trisphosphate (PIP3) (22473468). Somatic mutations in the PTEN gene have been reported in a variety of cancers (21430697). Mutations (mostly missense or nonsense) occur throughout the entire gene, although often target the phosphatase catalytic core (PTP) domain and, less frequently, membrane-binding C2 domain (22473468; 24766807; 21828076), leading to loss of function and PI3K activation.
BRAF **p.(Val600Glu)** **c.1799T>A** **20% allele frequency** **Exon 15**	p.Val600Glu represents a hotspot missense mutation in exon 15 of BRAF converting the wild type residue, Valine, into a Glutamic Acid at amino acid 600. The BRAF V600 residue is located in the activation segment of the kinase domain, close to a conserved DFG motif which is essential for transition to an active catalytic state. The V600E substitution destabilizes the hydrophobic interactions between the glycine-rich loop and activation segment of the BRAF kinase domain, and restores the active orientation of the catalytic site, leading an increase in kinase activity in vitro

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Alteration	Interpretation
NM_004333.4	(21388974; 24388103). This mutation predicts response to RAF inhibitors in a variety of tumor types. The V-Raf murine sarcoma viral oncogene homolog B (BRAF) is located on chromosome 7q34. The gene encodes a member of the raf/mil family of serine/threonine protein kinases, and is involved in the MAP kinase/ERKs signaling pathway. BRAF mutations have been identified in a wide range of cancers, including colorectal cancer, malig-t melanoma, papillary thyroid cancer, non-small cell lung carcinoma and hairy cell leukemia, among other tumors (12068308; 12460918; 21663470; 23668556). Most BRAF mutations destabilize the interaction between two regions of the kinase domain (Glycine rich loop and activation segment), resulting in constitutive increase in kinase activity (24388103; 21388974; 15035987). The most common BRAF missense mutation (V600E) accounts for over 90% of all reported somatic BRAF mutations, and consists of a single base substitution in exon 15 (c.1799T>A), leading to a substitution of Valine by a Glutamic acid at position 600.
NTRK1 **p.(Ala107Val)** **c.320C>T** **41% allele frequency** **Exon 3** **NM_002529.3**	p.(Ala107Val) represents a missense mutation in exon 3 of NTRK1 at amino acid 107 converting the wild type residue, Alanine, into a Valine. This variant has been reported in a limited number of tumor samples (COSMIC) but has also been reported as an extremely rare population variant (gnomAD). Therefore, although likely disease-associated, due to the paucity of functional and clinical evidence, its significance is currently unclear.
TERT **C228T** **c.-124C>T** **33% allele frequency** **Exon -** **promoter**	TERT Promoter Mutation This variant has not been reported in publicly available databases (COSMIC; gnomAD). Functional studies suggest this mutation creates a new CCGGAA/T general binding motifs for E-twenty six/ternary complex factor (Ets/TCF) transcription factors,and is believed to contribute the tumorgenesis in melanoma (26928778; 25159205).

CLINICAL TRIALS

Context	NCTID	Title	Conditions	Location	Sponsor
BRAF - p.Val600Glu	NCT02684058	Phase II Pediatric Study With Dabrafenib in Combination With Trametinib in Patients With HGG and LGG	Multiple Disease Types	Multiple locations in Argentina, Australia, Belgium, Brazil, Canada, Czechia, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Russian Federation, Spain, Sweden, Switzerland, United Kingdom, United States	Novartis Pharmaceuticals
	NCT02840409	Vinblastine +/- Bevacizumab in Children With Unresectable or Progressive Low Grade Glioma (LGG)	Low Grade Glioma	Toronto, Ontario, Canada	The Hospital for Sick Children
	NCT03429803	TAK-580 In Gliomas and Other Tumors	Low-grade Glioma	Multiple locations in United States	Karen D. Wright MD
	NCT02285439	Phase I/II Study of MEK162 for Children With Ras/Raf Pathway Activated Tumors	Multiple Disease Types	Multiple locations in United States	Children's Hospital Los Angeles
	NCT03220035	Vemurafenib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With BRAF V600 Mutations (A Pediatric MATCH Treatment Trial)	Multiple Disease Types	Multiple locations in Puerto Rico, United States	National Cancer Institute (NCI)

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Context	NCTID	Title	Conditions	Location	Sponsor
	NCT03155620	Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial)	Multiple Disease Types	Multiple locations in Puerto Rico, United States	National Cancer Institute (NCI)
	NCT02455245	A Study Comparing Two Carboplatin Containing Regimens for Children and Young Adults With Previously Untreated Low Grade Glioma	Low Grade Glioma	Multiple locations in United States	Natasha Pillay Smiley
	NCT01089101	Selumetinib in Treating Young Patients With Recurrent or Refractory Low Grade Glioma	Multiple Disease Types	Multiple locations in United States	National Cancer Institute (NCI)
	NCT02465060	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	Multiple Disease Types	Multiple locations in Puerto Rico, United States	National Cancer Institute (NCI)

MUTATIONAL HOTSPOTS:

The following recurrently mutated codons demonstrated adequate sequencing coverage depths and show wild type sequences only.

Gene	Codons	Gene	Codons	Gene	Codons
APC	1367, 1378, 1429	ATRX	1426	BRAF	466, 469, 581, 594, 597, 600, 601
CDKN2A	50, 51, 58, 80, 83, 84, 88, 108, 110, 114, 120, 153	CTNNB1	32, 33, 34, 37, 41, 45, 335, 387	EGFR	62, 108, 222, 252, 289, 598, 709, 719, 768, 790, 858, 861
ERBB2	310, 678, 755, 769, 777, 842	H3F3A	28, 35	HIST1H3B	28
IDH1	132	IDH2	140, 172	MYC	44, 74
NF1	440, 2450	PDGFRA	842	PIK3CA	38, 81, 88, 93, 104, 106, 108, 111, 118, 344, 345, 350, 420, 453, 542, 545, 546, 726, 901, 1007, 1021, 1043, 1044, 1047, 1049
PTEN	68, 70, 92, 93, 130, 132, 136, 173, 212, 233, 343	SMARCA4	910, 1192, 1232	SMARCB1	377
TP53	175, 213, 220, 245, 248, 273, 282	VHL	65, 80, 89, 114, 155		

The following recurrently mutated codons demonstrated inadequate sequencing coverage depths (<100x), and the possibility of undersensitive detection cannot be excluded.

N/A

TRANSCRIPT ACCESSIONS FOR INTERROGATED GENES:

Gene	Transcript ID	Gene	Transcript ID	Gene	Transcript ID
APC	NM_000038.5	ATRX	NM_000489.4	BRAF	NM_004333.4
CDKN2A	NM_000077.4	CTNNB1	NM_001904.3	EGFR	NM_005228.3

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ERBB2	NM_004448.3	H3F3A	NM_002107.4	H3F3B	NM_005324.4
H3F3C	NM_001013699.2	HIST1H3B	NM_003537.3	HIST1H3C	NM_003531.2
IDH1	NM_005896.3	IDH2	NM_002168.3	MYC	NM_002467.4
NF1	NM_001042492.2	NF2	NM_000268.3	NTRK1	NM_002529.3
PDGFRA	NM_006206.4	PIK3CA	NM_006218.2	PTEN	NM_000314.4
SMARCA4	NM_001128849.3	SMARCB1	NM_003073.4	TERT	promoter
TP53	NM_000546.5	VHL	NM_000551.3		

COVERAGE DEPTH QC:

Among the following targeted exons, >50% of coding sequences failed to achieve >100x coverage depths. Analytic sensitivity for potentially relevant genomic alterations may therefore be limited among the following interrogated loci:

Gene	Exons
ATRX	1

METHODS

Tissue microdissection and DNA isolation from tumor enriched areas are based on histologic review by an appropriately board certified pathologist; specimens with minimal tumor cellularity may be rejected. DNA is extracted and fragmented by Covaris shearing. DNA molecules from each sample are uniquely identified by ligation of a short oligonucleotide, sample specific barcodes. Each genomic DNA fragment is also tagged with a unique molecular identifier sequence (UMI) to collapse PCR duplicates and facilitate error corrected sequencing. Exons of 523 genes are enriched by hybridization to oligonucleotide synthetic probes, and PCR is performed to further amplify captured sequences. Amplified DNA is sequenced using Illumina sequencing-by-synthesis methodology. The assay interrogates whole exons and selected intronic regions across 523 genes to detect single base substitutions, insertion/deletions, and gene amplifications, targeting 1.94 million bases, encompassing 1.28 Mb of exonic sequence. The software requires a minimum number of 100 unique reads (after removal of PCR duplicates) to detect a mutation. An automated process that takes into account statistical confidence of base calling, alignment, and mapping quality, identifies variants (TSO500 Local App Software Release Notes V2.1.0; April 17, 2020). Following mapping of the read data to the human genome (reference build GRCh37/hg19), single nucleotide variants (SNVs), and insertion deletion events (Indels) with an allele frequency greater than 4% are detected. Detection of Insertions and Deletions larger than 29 bases have not been validated. 1.5x, 3x, and 5x fold changes have been validated with this assay to correspondent to high level FISH amplification for ERBB2, MET, and EGFR, respectively; fold changes for other genes are reported if in excess of 2.5x. Reported variants include known disease associated mutations and unclear variants with little or no literature support. Benign population polymorphisms or likely benign variants are not included in the report. Variant Tier categorizations are clinically reported in accordance with the AMP/ASCO/CAP consensus recommendations indicated in Li et. al. (27993330). Tumor Mutation Burden (TMB) is calculated as the number of mutations / megabase, and 1.94 megabases of genomic coding sequence are targeted for analysis. A cutoff of 10 mutations / MB is employed to report TMB as either high or low. Standardization for this biomarker remains an ongoing imperative, and further generation of assay specific, laboratory specific percentile cutoffs for individual tumor types has not yet been established. Median tumor mutation burden specific for tumor type is referenced from large scale patient cohorts in published studies (28420421). The assay interrogates 130 microsatellite regions to determine microsatellite instability class (MSI-Positive or MSI-Negative). Data from a minimum of 40 regions is needed to calculate an MSI score. A sample is classified as MSI-POSITIVE if 30% or more of the microsatellite regions are unstable (24310308; 29665853). Reportable Range: For full listings of interrogated genes please refer to: https://www.genpathdiagnostics.com/oncology/ngspersonalized-medicine/.

OnkoSight Advanced was developed and its performance characteristics were determined by GenPath, a division of BioReference Laboratories. This test has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such a clearance or approval is not necessary. Pursuant to the requirements of CLIA88, this laboratory has established and verified the test's accuracy and precision. However, a false positive or false negative result incurred during any phase of the testing cannot be completely excluded. Large insertion/deletion events may not be detected by this assay due to the limit of sequencing read length and bioinformatics processing. This assay does not detect translocation/gene fusion. This assay does not determine variant causality, or whether a variant is inherited or somatically acquired. These results may be used for clinical or research purposes and therefore should be carefully considered within the context of other clinical and laboratory data. In the absence of an appropriate clinical context, the clinical utility of OnkoSight ™ testing is not clearly defined. The information contained in this report reflects the current interpretation of the findings as of the date of the report, based on the available scientific information. This information, which comes from numerous sources, is subject to change over time in response to future scientific and medical findings and correlations. BioReference Laboratories, Inc. makes no representation or warranty of any kind regarding the accuracy of information provided or contained in these manuscripts, references or other sources of information. If any of the information provided by or contained in the referenced material is later deemed to be inaccurate, this may impact the accuracy of this report and interpretation of the findings. BioReference Laboratories, Inc. is not obligated to notify you of any impact that additional or modified information, or future scientific or medical research may have on this report. The laboratory is not responsible for reanalysis of the data or updated classification of this report or past reports' findings as the knowledge evolves. A medical provider can request a reassessment of clinical significance of variants and/or re-review of the clinical interpretation of the findings. Additional charges may apply for the

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updated report.Please contact the laboratory for more information if update is requested.This assay has been approved by the NYS DOH based on initial validation; orthogonal testing for full validation is currently ongoing. Please contact the laboratory for more information if update is requested.

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