OHSU Knight Cancer Institute
KNIGHT DIAGNOSTIC LABORATORIES

2525 SW 3rd Ave, STE 350
Portland, OR 97201
Phone: 855-535-1522 I Fax: 855-535-1329
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Patient Name:	Beaker, Bonnie Jean	Accession #:	**21KD-281P0001**
Medical Record #:	12345678		
Account #:	2000000000		
Date of Birth:	1/2/1965		
Sex:	Female	Reference Lab no.:	
Referral Source:	Clark Kent, DO OHSU PATIENT	Physician(s):	

GENETRAILS COMPREHENSIVE SOLID TUMOR PANEL (Final result)

GENETRAILS COMPREHENSIVE SOLID TUMOR PANEL

Positive.

SAMPLE TESTED

Lymph Node, right axilla

INTERPRETATION

DIAGNOSIS REPORTED: Metastatic adenocarcinoma, compatible with pulmonary primary

MICROSATELLITE INSTABILITY STATUS: **Negative (MSS).**

ESTIMATED TUMOR MUTATION BURDEN (TMB): **4.9 mutations/Mb.**

Comment: In lung adenocarcinoma, a TMB value ≥9.8 mutations/Mb correlates with a greater likelihood of benefit from immune checkpoint inhibitor therapy (PMID: 30643254).

Alteration(s) of Strong Clinical Significance (Tier I*)

ERBB2 p.A775_G776insYVMA. Based on pre-clinical studies, exon 20 insertions of this type cause activation of the HER2 kinase. They are resistant to EGFR inhibitors erlotinib and gefitinib. In a retrospective analysis of 6 patients with this mutation treated with afatinib, the response rate was 33% and the disease control rate was 100% (median time to treatment failure was 9.6 months; Peters et al. J Thoracic Onc; Vol 13, Issue 12, Pages 1897–1905). There is one case report of this mutation showing no response to neratinib. Cell lines harboring exon 20 insertions appear to be sensitive to trastuzumab, and there is one case report of a response to the combination of trastuzumab with lapatinib.

Alteration(s) of Potential Clinical Significance (Tier II*)

TP53 p.R273C. This is a known hotspot mutation in TP53. However, based on its allele fraction it is likely subclonal in the current specimen. The TP53 gene encodes a tumor suppressor protein that responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle

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arrest, apoptosis, senescence, DNA repair, or changes in metabolism.

Alteration(s) of Unknown Significance (Tier III*)

MSH3 p.S173N
BAP1 p.P584S

*Genomic variants classified in accordance with recommendations by AMP/ASCO/CAP (PMID: 27993330).

No gene fusions or clinically informative splice alterations identified in the genes listed below.

AKT3	ALK	BRAF	EGFR	ERBB4
ERG	FGFR1	FGFR2	FGFR3	MET
NOTCH1	NOTCH2	NRG1	NTRK1	NTRK2
NTRK3	NUTM1	PDGFRA	RAF1	RET
ROS1				

CLINICAL TRIALS

NCT01376505 - Phase I Active Immunotherapy Trial With a Combination of Two Chimeric (Trastuzumab-like and Pertuzumab-like)Human Epidermal Growth Factor Receptor 2 (HER-2) B Cell Peptide Vaccine Emulsified in ISA 720 and Nor-MDP Adjuvant in Patients With Advanced Solid Tumors
Phase: Phase 1 **Location(s):** OH
Gene(s): EGFR, ERBB2, CDK4, MTOR
Genotype(s): ERBB2 Amplification
Drug(s): Almurtide, Montanide ISA, Peptide, HER-2 Vaccine, Sirolimus

NCT02091141 - My Pathway: An Open-Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib, and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents
Phase: Phase 2 **Location(s):** OK, AR, TX, SD, CO, TN, MN, WI, IL, NM, ND, OH, GA, AZ, PA, NC, FL, VA, MD, CA, NY, CT, OR, WA, MO
Gene(s): NRAS, POLE, ERBB2, SMO, PTCH1, BRAF, EGFR, CD274, PDCD1, PDCD1LG2, ALK, CYP3A4, RAF1, TNFRSF9, KRAS
Genotype(s): EGFR exon 20 mutation, BRAF V600, BRAF V600E, ERBB2 G309A, ERBB2

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G309E, ERBB2 P780_Y781insGSP, ERBB2 V777L, ERBB2 V842I, ERBB2 exon 20 insertion, EGFR exon 19
deletion, PTCH1 Loss
Drug(s): Pertuzumab, Vismodegib, Gdc-0973, Vemurafenib + Cobimetinib, Vemurafenib, Erlotinib hydrochloride, RG7446, Alectinib, Trastuzumab, Sodium lactate, Cobimetinib + atezolizumab

NCT02387216 - SHERLOC: A Phase 2 Study of MM-121 in Combination With Docetaxel Versus Docetaxel Alone in Patients With Heregulin Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer
Phase: Phase 2 **Location(s):** IL, IN, TN, AZ, PA, VA, FL, CA, NY, MA, WA, ON
Gene(s): ERBB3, ERBB2, ALK
Drug(s): Docetaxel anhydrous, MM-121

NCT02465060 - Molecular Analysis for Therapy Choice (MATCH)
Phase: Phase 2 **Location(s): Oregon**
Gene(s): NF2, KIT, PTEN, FRS2, ERBB2, FGFR1, SMO, NRAS, HRAS, GNA11, GNAQ, KRAS, BRAF, AKT1, ARID1A, PTCH1, FGFR3, FGFR2, EGFR, PIK3R1, INPP4B, PIK3CA, TSC1, TSC2, AKT3, AKT2, PIK3CD, CYP3A4, MET, PIK3CB, ROS1, CD274, PDCD1, PDCD1LG2, Wild-Type ALK, Wild-Type EGFR, ALK, CDK6, CCND1, BRCA1, BRCA, BRCA2, MTOR, CD4, CDK4, NTRK3, NTRK2, NTRK1, FGFR4, STK11, FBXW7, Wild-Type RB1, CDKN2B, CDKN2A, MLH1, MSH2, NF1, DDR2, PI3K
Drug(s): Dasatinib, Pertuzumab, Ado-trastuzumab emtansine, Trametinib, Azd-5363, Vismodegib, Azd-4547, Azd-9291, Bay 80-6946, Gdc-0068, Gdc-0032, Gsk-2636771, PD-332991, PF-5280014, Dabrafenib, Bvd-523, ABP 980, Afatinib, nivolumab, Crizotinib, Sunitinib malate, Trastuzumab, LOXO-101, Jnj-42756493, Mln0128, Mk-1775, Mek-162, Pd-0332991, Vs-6063, Pf 573228,
Ulixertinib, Trametinib + Dabrafenib

NCT02500199 - A Two-part Phase I, Open Label, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Pyrotinib in Patients With HER2-positive Solid Tumors Whose Disease Progressed on Prior HER2 Targeted Therapy
Phase: Phase 1 **Location(s):** MO, TN, TX, MI, FL, CA, NY, MA
Gene(s): ERBB2, CYP3A4
Genotype(s): ERBB2 Amplification, HER2 Mutations
Drug(s): Pyrotinib, Mitomycin, Surgery

NCT03219268 - A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of MGD013, A Bispecific DART® Protein Binding PD-1 and LAG-3 in Patients With

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Unresectable or Metastatic Neoplasms
Phase: Phase 1 **Location(s):** OK, IL, TX, TN, OH, AZ, NC, MD, FL, PA, CA, MA
Gene(s): CD274, ERBB2, PDCD1, LAG3
Drug(s): Margetuximab, Oxygen compressed, Surgery

Test information: The following genes were negative in this analysis, unless otherwise listed above.

ACVR1	CCND1	ERCC2	HLA-A	MDC1	PDGFRA	RB1	SOCS1
AKT1	CCND2	ERCC3	HLA-B	MDH2	PIK3CA	RECQL	SPEN
AKT2	CCND3	ERCC5	HLA-C	MDM2	PIK3CB	RET	SPOP
AKT3	CCNE1	ESR1	HOXB13	MDM4	PIK3R1	REV7	STAG2
ALK	CD274 (PD-L1)	FAM175A	HRAS	MEN1	PLAG1	RHEB	STAT3
AMER1	CDH1	FANCA	IDH1	MET	PLCG1	RICTOR	STK11
APC	CDK12	FANCC	IDH2	MLH1	PMS1	RINT1	SUFU
APLNR	CDK4	FANCD2	IDO1	MLH3	PMS2	RIT1	TAP1
AR	CDK6	FANCE	IDO2	MRE11A	POLE	RNF139	TAP2
ARAF	CDKN1B	FANCF	IFNGR1	MSH2	PPM1D	RNF43	TAPBP
ARID1A	CDKN2A	FANCG	IFNGR2	MSH3	PPP2R1A	ROS1	TCEB1
ARID2	CHD4	FANCM	INPP4B	MSH6	PPP6C	RPTOR	TERT
ASF1A	CHEK1	FBXW7	IRF1	MTAP	PRKAR1A	RRAS	TMEM127
ATM	CHEK2	FGF19	JAK1	MTOR	PRKCA	SDHA	TP53
ATR	CIC	FGF3	JAK2	MUTYH	PSMB5	SDHAF1	TP53BP1
ATRX	COL2A1	FGF4	KDR	MYC	PTCH1	SDHAF2	TRAF7
AURKA	CTNNB1	FGFR1	KEAP1	MYCN	PTEN	SDHAF3	TSC1
AXIN1	DDR2	FGFR2	KIF1B	MYOD1	PTPN11	SDHAF4	TSC2
B2M	DDX11	FGFR3	KIT	NBN	PTPRB	SDHB	VHL
BAP1	DDX3X	FGFR4	KLF4	NDUFAB1	RAC1	SDHC	XRCC1
BARD1	DICER1	FH	KRAS	NF1	RAD50	SDHD	YAP1
BRAF	EGFR	FUBP1	LZTR1	NF2	RAD51	SETD2	YES1
BRCA1	EGLN1	GATA3	MAP2K1 (MEK1)	NRAS	RAD51B	SF3B1	
BRCA2	EGLN2	GNA11	MAP2K2 (MEK2)	NTRK1	RAD51C	SMAD4	
BRD4	EIF1AX	GNAQ	MAP2K4	NTRK2	RAD51D	SMARCA2	
BRIP1	EPAS1	GNAS	MAP3K1	NTRK3	RAD52	SMARCA4	
BUB1B	ERBB2	H3F3A	MAPK1	PALB2	RAD54L	SMARCB1	
EMSY	ERBB3	HIST1H3B	MAX	PBRM1	RAF1	SMARCE1	
CASP8	ERBB4	HIST1H3C	MC1R	PDCD1LG2	RASA1	SMO	

Assay QC: Estimated tumor content in material tested: 80%

DNA Panel Information: Average read depth: 6,116 per targeted gene region
The DNA panel is designed to detect alterations in the above listed genes, which are known to play a role in cancer growth. Each specimen is examined microscopically and genomic DNA is extracted from dissected, tumor-rich areas. Mutations are screened by massively parallel sequencing using a

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combination of multiplexed PCR and sequencing on an Illumina platform. The panel covers target exons and portions of flanking intronic sequences for all of the listed genes, with the exception of a few minor coverage gaps (further information available upon request). The minimum detectable variant allele fraction (VAF) ranges between 2% and 5%, depending on sequence read depth. The minimum required coverage is 250 reads per gene segment (limit of detection = 5% VAF). It should be noted in regard to insertions and deletions that this test is biased toward shorter alterations. Gene copy loss is reported when there are <0.5 copies (corrected for tumor fraction) and copy gain is reported for >5 copies.

Microsatellite instability: Short repeat sequences included in the panel are analyzed using a custom algorithm. This tumor has a score of 0.00%. A score >5% is required for MSI-high.
MSI Total
Sites=227
MSI Somatic
Sites=0
MSI Percent Somatic=0.00%

Tumor mutation burden (TMB) is based on the total number of nonsynonymous variants (including VUS) that are deemed unlikely to be germline based on allele fraction and review of public databases (e.g. dbSNP, ExaC, etc.). TMB is calculated as the number of variants/0.61 Mb (the size of this panel) and reported as mutations/Mb. Based on the publication by Samstein et al. (PMID: 30643254), a TMB in the top 20th percentile is significantly correlated with a benefit of immune checkpoint inhibitor therapy for the following cancers: Bladder Carcinoma (≥16.4 mutations/Mb); Head & Neck Squamous Carcinoma (≥9.8 mutations/Mb); Lung Adenocarcinoma (≥13.1 mutations/Mb); Cutaneous Melanoma (≥18.0 mutations/Mb). For all other cancers, the clinical significance of the top 20th percentile – or any other cut-off – has not been fully established.

RNA Gene Fusion Panel Information: Total on-target unique reads: 569,490
This test is designed to detect fusions involving the genes listed above, and is agnostic with respect to fusion partners. EGFRvIII and splice variants causing MET exon 14 skipping are also tested. All of the driver genes are known to play a role in cancer growth, and most of them are actionable with one or more targeted therapies. Submitted samples are examined microscopically and genomic RNA is extracted and purified from dissected, tumor-rich areas. Sequencing libraries are prepared from cDNA using an amplicon-based methodology and are sequenced by massively parallel sequencing on an Illumina NextSeq500/550. The gene fusions can be detected to the range of approximately 1-5% of input cells.

Additional Details on Mutations Identified:

Gene	Transcript	cDNA Var	Genome	Chrom	Start	End	Ref	Var
TP53	NM_000546	c.817C>T	hg19	chr17	7577121	7577121	G	A

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BAP1	CCDS2853.1	c.1750C>T	hg19	chr3	52437294	52437294	G	A
ERBB2	CCDS32642.1	c.2313_2314insTACGT GATGGCT	hg19	chr17	37880984	37880984	A	ATACGTGATGGCT
MSH3	CCDS34195.1	c.518G>A	hg19	chr5	79961121	79961121	G	A

DNA SUMMARY
DNA QC

RNA SUMMARY
RNA QC

DISCLAIMER
This test was developed and its performance characteristics determined by the OHSU Knight Diagnostic Laboratories. It has not been cleared or approved by the Food and Drug Administration. FDA approval is not required for the clinical use of the test, and therefore validation was done as required under the requirements of the Clinical Laboratory Improvement Act of 1988 (CLIA). The OHSU Knight Diagnostics Laboratories are fully licensed by the state of Oregon under CLIA and are accredited by the College of American Pathologists (CAP). Laboratory Director: Christopher Corless, M.D., Ph.D.

Reviewed and electronically signed by GEORGE V THOMAS, MD
10/8/2021 10:11 AM

Slide-Block specimen 21KD-281P0001 from Slide-Block Unspecified. Ordered by Clark Kent, DO. Authorized by Clark Kent, DO. Collected: 10/8/2021 0947 Received: 0947. Verified: 10/8/2021 1011. Resulted by OHSU-KNIGHT DIAGNOSTIC LABORATORIES.

Specimen Details

	Submitter ID	Tests
21KD-281P0001		GENETRAILS COMPREHENSIVE SOLID TUMOR PANEL

Submitter

OHSU PATIENT

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