Patient		Sample		Physician	
Name	**Jane Jones**	Specimen Type	**Blood**	Ordering Physician	**John Smith**
Date of Birth (Age)	**11/27/1940 (83 yrs)**	Collection Date	**01/05/2024**	Medical Facility	**BillionToOne Inc**
Assigned Sex at Birth	**Female**	Receipt Date	**01/06/2024**	Address	**1035 O'Brien Drive Menlo Park, California 94025**
Diagnosis	**Non-Small Cell Lung Carcinoma**	Accession ID	**V010900AA001-1**	Phone	**(833) 537-1819**
Medical Record #	**ID400231**	Report Date	**02/01/2024**	Fax	**(833) 874-0918**
Internal Patient ID	**10000090**	Test Number	**1**		

Northstar Select Results

3 **informative genomic alterations identified**

Summary of Informative Genomic Alterations

Detected Genomic Findings[§]	Associated FDA-Approved and/or Guideline Recommended Therapies			Clinical Trials[§§]	VAF / Copy number
	✓ **Approved** in indication	✓ **Approved** in other indication	⊗ Associated with **resistance**		
CHEK2 R145W		• **enzalutamide/talazoparib** • **olaparib**		**5**	0.74%
KRAS G13C			• **afatinib**[G] • **erlotinib**[G] • **gefitinib**[G] • **osimertinib**[G] • **panitumumab**	**5**	0.25%
MET V1206L				**0**	0.09%

[G] Treatment listed is based upon recommendation from professional guidelines only. Please consult professional guidelines and FDA indications for complete details.

[§] For additional variant information, please see the **Variant Details** section of the report. **Variants of Unknown Significance (VUS)** and **Genes with copy number signal indicating potential for aneuploidy** are reported after the Variant Details section of the report.

[§§] Clinical trials are matched within 500 miles of the ordering physician, based on detected genomic alterations and provided patient demographics. For additional options, please visit **www.clinicaltrials.gov**.

Microsatellite Instability-High

Microsatellite Instability-High (MSI-H) is reported here as detected/not detected based upon mutation analysis at curated genomewide MSI sites and subsequent bioinformatic algorithm calculation.

Not Detected Detected

Summary of Guideline-Recommended Genes Evaluated

The following guideline-recommended genes for Non-Small Cell Lung Carcinoma were evaluated. Variants not listed in the tables above are considered 'Not Detected'. For a complete list of genes tested, refer to the Methods section of the report.

ALK *BRAF* *EGFR* *ERBB2 (HER2)* *KRAS* *MET* *NTRK* *RET* *ROS1*

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Clinical Trial Availability

Clinical trial matches are displayed based upon somatic variant detection and patient demographic and diagnostic information provided on the test requisition form. Trials are matched within 500 miles of the ordering provider's location. This list is neither comprehensive nor a guarantee of eligibility, as many other requirements must be met prior to enrollment.

For further details on eligibility, please visit **www.clinicaltrials.gov** and enter the NCT#.

Phase 3 NCT05633602	Pragmatica-Lung: A Prospective Randomized Study of Ramucirumab (LY3009806; NSC 749128) Plus Pembrolizumab (MK-3475; NSC 776864) Versus Standard of Care for Participants Previously Treated With Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer **KRAS G13C**	**Weaverville, North Carolina (28787)** AdventHealth Infusion Center Weaverville
Phase 2 NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial **CHEK2 R145W**	**London, Ontario (N6A 5W9)** London Regional Cancer Program
Phase 2 NCT04550494	A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response **CHEK2 R145W**	**Bethesda, Maryland (20892)** National Cancer Institute Developmental Therapeutics Clinic
Phase 2 NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study **CHEK2 R145W**	**Charlotte, North Carolina (28277)** Atrium Health's Levine Cancer Institute
Phase 2 NCT03808558	A Phase 2 Multi-center Pharmacodynamics Study of TVB-2640 in KRAS Mutant Non-small Cell Lung Carcinomas **KRAS G13C**	**Cincinnati, Ohio (45267)** University of Cincinnati
Phase 1/Phase 2 NCT04826341	A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer, Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors **CHEK2 R145W**	**Bethesda, Maryland (20892)** National Institutes of Health Clinical Center
Phase 1/Phase 2 NCT05898399	A Phase I/IIa, Open-label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of the DNA Polymerase Theta Inhibitor ART6043 Administered Orally as Monotherapy and in Combination to Patients With Advanced or Metastatic Solid Tumors **CHEK2 R145W**	**Grand Rapids, Michigan (49546)** South Texas Accelerated Research Therapeutics (START) - Midwest
Phase 1/Phase 2 NCT04092673	A Phase 1-2 Dose-Escalation and Cohort-Expansion Study of Intravenous Zotatifin (eFT226) in Subjects With Selected Advanced Solid Tumor Malignancies **KRAS G13C**	**Fairfax, Virginia (22031)** Virginia Cancer Specialists
Phase 1 NCT05631574	A Phase 1/1b Dose Finding Study of BMF-219, an Oral Covalent Menin Inhibitor, in Adult Patients With Unresectable, Locally Advanced, or Metastatic Non-small Cell Lung Cancer (NSCLC), Pancreatic Cancer (PDAC), and Colorectal Cancer (CRC). **KRAS G13C**	**Atlanta, Georgia** Cancer Treatment Centers of America - Atlanta
Phase 1 NCT05379985	A Multicenter Open-Label Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS **KRAS G13C**	**Cincinnati, Ohio (45219)** Christ Hospital Cancer Center

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Variant Details

CHEK2

CHEK2 encodes the tumor suppressor, checkpoint kinase 2 (Chk2), a serine/threonine kinase that plays an important role in cell cycle arrest in response to DNA damage [1, 2, 3, 4]. Depletion of CHEK2 has been reported to increase sensitivity to PARP inhibitors in preclinical models and PARP inhibitors are in clinical trials in cancers with DNA repair deficiencies, including CHEK2 alterations [5]. The PARP inhibitors olaparib, rucaparib, and talazoparib have been approved for certain indications in the context of BRCA1 or BRCA2 mutation, or alteration in one or more homologous recombination repair genes, including CHEK2 mutation [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16].

CHEK2 R145W

Gene	**CHEK2**
Nucleotide	**NM_007194.4: c.433C>T**
Amino Acid	**p.R145W**
Exon	**3**
Biomarker Type	**inactivating**

CHEK2 R145W is a missense alteration within the FHA domain of the Chk2 protein (UniProt). This alteration has been reported to destabilize the Chk2 protein, and result in reduced catalytic activity and Chk2 activation following radiation [17, 18, 19, 20].

KRAS

KRAS encodes the signaling protein K-Ras, a member of the Ras family; activating KRAS alterations may result in activation of downstream signaling pathways, including the Raf/MEK/ERK pathway [21, 22]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant [23, 24, 25, 26, 27, 28, 29, 30]. Other clinical approaches are also under investigation in the context of KRAS -mutant tumors, including FAK and Shp-2 inhibitors [31, 32, 33, 34, 35, 36]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically [37, 38, 39, 40]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy [41, 42]. In addition, the combination of adagrasib with cetuximab has been reported to provide clinical benefit in colorectal carcinoma patients with KRAS G12C mutation and has been granted “breakthrough” designation by the FDA for accelerated review [43].

KRAS G13C

Gene	**KRAS**
Nucleotide	**NM_004985.5: c.37G>T**
Amino Acid	**p.G13C**
Exon	**2**
Biomarker Type	**activating**

The KRAS G13C mutation lies within the first "G box" domain of the K-Ras protein, one of several conserved regions responsible for GTP binding and hydrolysis [44]. Mutation of the adjacent codon 12 creates a protein that is defective for GTP hydrolysis and is therefore constitutively active [45]. While KRAS codon 13 mutations, including G13C, have been reported to be activating, cells transformed with a codon 13 mutant gene grew less aggressively than cells transformed with KRAS codon 12 mutants [46, 47]. KRAS G13C has been assigned a clinical significance of pathogenic/likely pathogenic based on eight submissions with a two-star review status last evaluated on 2023/01/03 (ClinVar, Jun 2023). In addition, KRAS G13C has been reported as a germline alteration in patients with RAS-associated autoimmune leukoproliferative disease (RALD) [47, 48].

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MET

Aberrant activation of Met in cancer can occur through MET gene mutation or amplification, or excessive/inappropriate signaling via the Met receptor's ligand, HGF [49]. Cabozantinib, which targets Met and other kinases, has been approved for certain indications [50, 51, 52, 53]. Crizotinib, a kinase inhibitor that has been approved for treatment of ALK - and ROS1 -rearranged non-small cell lung cancer, also targets Met [54, 55, 56]. In addition, the kinase inhibitors capmatinib and tepotinib have been approved by the FDA, EMA and PMDA, for the treatment of adult patients with metastatic non-small cell lung cancer and a MET exon 14 skipping mutation [57, 58].

MET V1206L

Gene	**MET**
Nucleotide	**NM_001127500.3: c.3616G>C**
Amino Acid	**p.V1206L**
Exon	**18**
Biomarker Type	**activating**

MET V1206L is a missense alteration occurring in the kinase domain of the Met protein (UniProt) [59]. MET V1206L has been reported as a germline alteration in a papillary renal carcinoma patient, and was reported to increase Met kinase activity and xenograft tumor formation, but did not alter cell transformation, as compared with wild-type protein [60, 61]. Preclinical studies have reported that MET V1206L resulted in resistance to EMD1214063 (tepotinib), but retained sensitivity to SU11274 in cell models [62, 63].

Variants of Unknown Significance (VUS)

The clinical relevance of these variants is currently unknown. Therefore, the functional impact of targeting these variants cannot be determined at this time.

CDK12 c.1810C>T (p.P604S), 0.21%

Genes with copy number signal indicating potential for aneuploidy

Changes in copy number due to biological factors including aneuploidy can confound the accurate detection of clinically informative copy number alterations (CNAs). The following genes have deviations in copy number signal but are not called for copy number amplification/loss due to observed patterns of copy number signal (i.e. aneuploidy) within the chromosomal arm and/or other chromosomal arms of the sample.

Copy number signal indicating potential aneuploidy was not detected in any gene.

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Interpretation

Genomic alterations (SNVs/indels/fusions) were detected in the cell-free DNA (cfDNA) isolated from the patient's blood specimen. The variant frequency of the mutations, reported as variant allele fraction (VAF), is calculated and reported for detected SNVs and indels. These alterations may be informative to cancer treatment response and/or clinical trial eligibility. While somatic actionability is of primary concern when determining report inclusion, some variants may be included without matched actionable outcomes. These variants may be critical to carcinogenesis in the patient's tumor.

Methods and Limitations

Northstar Select™ is a next generation sequencing (NGS)-based in vitro diagnostic test for detection of substitutions (SNVs), small insertion and deletion alterations (indels), selected genes' copy number alterations (CNAs, including amplifications and deletions) and selected gene-rearrangements in a total of 84 genes (Table 1), as well as microsatellite instability status. Cell-free DNA (cfDNA) is extracted from plasma, and the targeted regions, encompassing >250kb, are amplified and sequenced. The sensitivity of the test is 100% (95% CI: [99.84%,100.00%]) for SNVs and indels for variant allele fraction (VAF) ≥0.5% and fusions examined in the assay analytical validation, and 100% (95% CI: [76.84%,100.00%]) for CNAs. The limit of detection for the assay is 0.13-0.16% (VAF) for SNVs and indels. However, key actionable variants may be reported at lower VAFs where technically feasible. The overall base-wise specificity of the Northstar Select™ test is >99.99%, leading to high confidence in true positive reporting for variants with VAF >0.2%, despite the expansive genomic loci targeted and assayed. For CNAs, the LOD for gene amplifications is 2.125-2.16 copies and for loss is 1.78 copies. CNA LOD is subject to aneuploidy noise, with less aneuploid samples having a superior LOD. Observed increased or decreased copy number may not be called as CNAs despite potentially reflecting a characteristic (ie aneuploidy) of the tumor biology. These genes with copy number signal indicating potential for aneuploidy are listed in the corresponding section of the report (except for the AR gene located on the X-chromosome, which will not be subject to this additional analysis). MSI score is calculated using a count of somatic indel mutations in targeted microsatellite sites; based upon meeting threshold, MSI-H status is reported when detected. The sensitivity of the MSI component is 100% (95% CI: [97.72%,100.00%]) for MSI-H at a tumor fraction of ≥0.5%, and the limit of detection of the assay for MSI-H is 0.07-0.4% tumor fraction. An MSI-Indeterminate result is an inconclusive result as it does not suggest the presence or absence of MSI-H in the patient. For certain cfDNA sample or variant characteristics, such as low cfDNA input or high level of cancer-associated chromosomal copy abnormality, the analytical sensitivity may be reduced.

Variants detected in the cfDNA are aligned to the hg19 reference genome. Informative genomic alterations are potentially actionable or biologically relevant variants based on evidence from medical and scientific literature. Variants of unknown significance (VUS) are genomic alterations that do not have sufficient evidence to determine biological/clinical significance.

Genomic profiling of tumors can detect alterations not associated with the tumor itself but due to clonal hematopoiesis (CH). This assay cannot definitively differentiate whether variants detected in the cfDNA are derived from a patient's solid tumor or clonal blood cells. Variants indicating CH, which are found in specific genes, may be detected, especially in older individuals. Although the list is not exhaustive, the following genes are the most prevalent in CH and are tested on the Northstar Select™ panel: ATM, CHEK2, JAK2, NF1, SF3B1, and TP53 [64][65]. This report should not be used in place of a dedicated hematological evaluation. Any interpretations should take into consideration the patient's clinical context.

Reported treatments and trials should be comprehensively evaluated by the medical provider, as inclusion in the report is neither a guarantee of treatment/trial match, nor intended to be fully comprehensive. Treatments and trials are reported based upon the information provided at the time of test requisition, including diagnosis, sex, age, and location, and may not account for all elements of the patient's medical history. Certain treatments may have specifications surrounding other clinical factors, such as HR/HER2-status or germline mutation origin. The ordering provider should consult official FDA-approval information for full approval specifications, as well as professional guidelines for complete recommendations. Inclusion in Northstar Select™ does not guarantee that reported treatments or trials will have an impact on clinical outcome.

This assay is validated for the detection of somatic variants, but was not developed to distinguish germline variants, which may predispose the patient to certain types of cancer, from detected somatic variants. For variants with a VAF reported between 40-60%, separate germline testing may be recommended to identify and characterize such variants that may have hereditary implications.

Table 1: Genes on the Northstar Select™ panel

Northstar Select™ reports single nucleotide variants, insertion and deletion variants (indels), and splice site mutations for clinically relevant exons in 82 genes, copy number amplifications in 19 genes, and copy number loss in 5 genes, and fusion events in 9 genes, as detailed in the table below. This assay was designed for blood-based molecular profiling of solid tumors; while indicated for use, gene coverage may not meet guideline recommendations for certain cancer types such as sarcomas and lymphomas.

AKT1, AKT2, ALK$^{\wedge}$, APC, AR^{+}, ARAF, ARID1A, ATM^{-}, BRAF$^{\wedge+}$, BRCA1^{-}, BRCA2^{-}, BRIP1, CCND1, CCND2, CCNE1^{+}, CD274^{+}, CDH1, CDK12, CDK4^{+}, CDK6^{+}, CDKN2A^{-}, CDKN2B, CHEK2, CTNNB1, DDR2, EGFR^{+}, ERBB2^{+}, ESR1^{+}, EZH2, FANCA, FBXW7, FGFR1^{+}, FGFR2$^{\wedge+}$, FGFR3$^{\wedge}$, FGFR4, GATA3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, JAK2, JAK3, KIT^{+}, KRAS^{+}, MAP2K1, MAP2K2, MET^{+}, MLH1, MPL, MSH2, MSH6, MTOR, MYC^{+}, NF1, NOTCH1, NPM1, NRAS, NTRK1$^{\wedge}$, NTRK2$^{\wedge\wedge}$, NTRK3$^{\wedge\wedge}$, PALB2, PDGFRA^{+}, PIK3CA^{+}, PMS2, PTEN^{-}, PTPN11, RAD51C, RAD51D, RAF1^{+}, RB1, RET$^{\wedge+}$, RHOA, RIT1, ROS1$^{\wedge}$, SF3B1, SMAD4, SMO, STK11, TERT, TP53, TSC1, VHL

$^{\wedge}$ Northstar Select™ also reports fusion events for this gene
$^{\wedge\wedge}$ Northstar Select™ reports only reports only fusion events for these genes, no SNVs and indels will be reported; NTRK3 is limited to NTRK3-ETV6 fusions only
$^{+}$ Northstar Select™ also reports copy number amplifications of this gene
$^{-}$ Northstar Select™ also reports copy number deletions of this gene

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This NGS-based assay was developed and its performance characteristics determined by BillionToOne, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration. BillionToOne, Inc. is regulated under CLIA. This test is used for clinical purposes. It should not be regarded as investigational or for research. This test was performed using BillionToOne's patented technology (www.billiontoone.com/patents).

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