GUARDANT 360 Liquid
Powered by Guardant Infinity

Malagrino, James (A1473811)
Patient MRN: 443449 // DOB: Jun 9th, 1942 // Sex: M
Diagnosis: Non-small cell lung carcinoma (NSCLC)

Reporting

Report Date: Jul 28th, 2025
Receipt Date: Jul 18th, 2025
Collection Date: Jul 17th, 2025
Specimen: Blood
Status: FINAL

Sameer Desai

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Additional Recipient: N/A

Complete Tumor Response Map on page 4

Summary of Genomic & Epigenetic Biomarkers with Associated Treatment Options

✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 5)	% CFDNA OR COPY NUMBER
***PTEN* Loss (Single Copy Deletion)**	~ Capivasertib	Yes	DETECTED
***TP53* Y205C**	None	Yes	22.3%
***ATM* Loss (Single Copy Deletion)**	None	Yes	DETECTED
***PALB2* Loss (Single Copy Deletion)**	None	Yes	DETECTED
***RB1* Biallelic Loss (Homozygous Deletion)**	None	No	DETECTED

Variants of uncertain clinical significance listed on following pages.

Additional Biomarkers

Tumor Mutational Burden (TMB)	5.69 mut/Mb
MSI-High	NOT DETECTED
Confidence Patient is Biomarker Negative	≥99% - Likelihood that the patient is free of biomarkers associated with FDA-approved therapies.
Tumor Fraction#	42.5% - Based on 1099 patient-specific biomarkers

Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

Patient Biomarkers

Pharmacogenomics

CYP2D6	*1/*41	Normal metabolizer

This genotype results in normal CYP2D6 enzyme activity. Activity score: 1.25

TPMT	*1/*3C	Intermediate metabolizer

This genotype results in an intermediate metabolizer phenotype and may require dose reduction when prescribed azathioprine, 6-mercaptopurine (6-MP), and thioguanine. See guidelines (pharmgkb.org) for additional information.

UGT1A1	*1/*28	Intermediate metabolizer

This genotype results in intermediate UGT1A1 enzyme activity. Irinotecan is expected to be metabolized at a level between normal and poor metabolizers leading to increased toxicity, such as neutropenia or hyperbilirubinemia. See guidelines (pharmgkb.org) for additional information.

DPYD, HLA-B	No abnormal variant detected in reportable alleles (see Interpretations)

Human Leukocyte Antigen (HLA) Genotyping

HLA-A:	A*23:01, A*68:01
HLA-B:	B*18:01, B*37:01
HLA-C:	C*06:02, C*07:01

Results reflect evaluable alleles in *HLA-A*, *-B*, and *-C*. HLA Class I results are intended as an aid for oncology therapy selection and/or clinical trial matching and are not validated for transplant allele typing.

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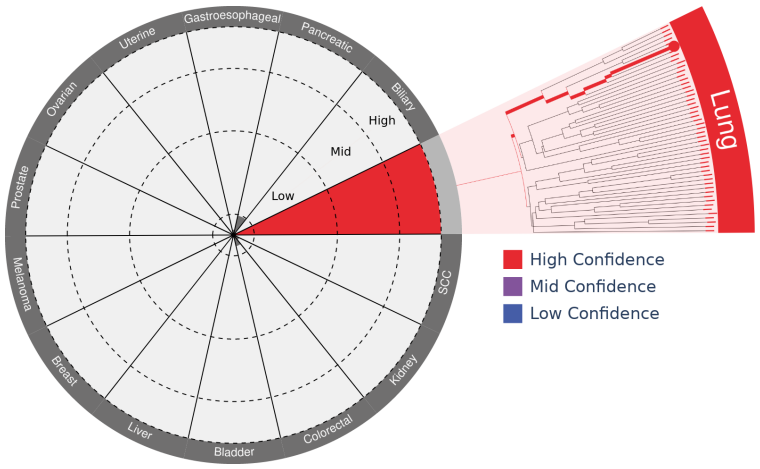
Molecular Tumor Type

These findings are not a diagnosis of cancer and should be interpreted in the context of other clinical information, by a qualified medical professional.



Molecular Tumor Typing

Primary Prediction: **Lung, 100%**

Percentage represents confidence level in tumor type prediction

Molecular Lung Subtype

Lung adenocarcinoma: <10%
Lung squamous cell carcinoma: <10%
Small cell lung carcinoma: >90%

Percentage represents proportional contribution of each subtype

A molecular prediction of tumor type and/or subtype based on DNA methylation signatures is provided as a supplement and not a replacement of standard clinical and pathologic evaluation. These results are not considered diagnostic and should be interpreted in the context of other clinical information by a qualified medical professional. Confirmatory microscopic evaluation of the tumor may be considered if clinically indicated.

Comments

Reported by: SYS

Variants of Uncertain Clinical Significance

ATM E2290D (3.1%)	*GSK3B* G34Afs*4 (2.6%)	*LTK* L684F (13.4%)	*RAF1* K493Q (24.3%)
DNMT3B H677Y (0.3%)	*HRAS* G151V (0.3%)	*NOTCH3* D2010D (0.2%)	
FZD8 E8E (0.3%)	*JAK2* Q175P (19.1%)	*PTPRD* A945A (2.2%)	

Variants of Uncertain Clinical Significance: The functional consequences and/or clinical significance of these alterations is uncertain. Relevance of therapies targeting these alterations is unknown.

Variants of Potential Clonal Hematopoiesis

DNMT3A R771Q (0.5%)	*KMT2C* Y2218* (0.9%)	*SF3B1* K666N (0.5%)

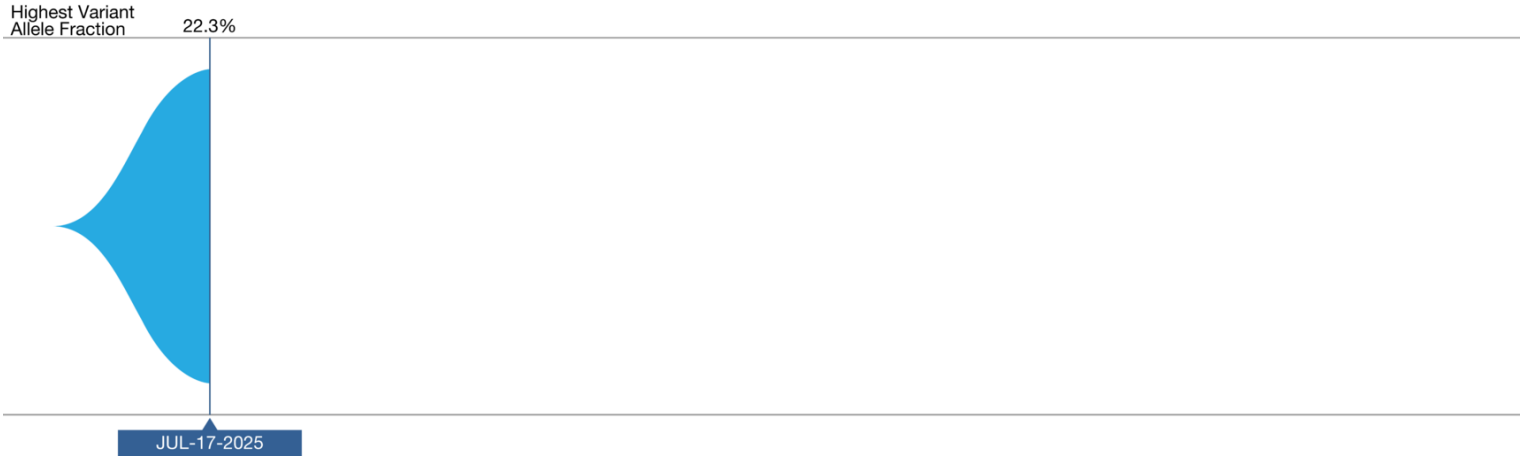
Variants are categorized as of potential clonal hematopoietic origin using a proprietary algorithm that discriminates variants of non-solid-tumor origin, the majority of which are likely to arise from hematopoietic sources. The specificity of the test for annotating clonal hematopoiesis in cfDNA is >98%.

We evaluated this sample for MSI, TMB, and alterations in 744 genes, including the following guideline-recommended genes for NSCLC

ALK	*BRAF*	*EGFR*	*ERBB2 (HER2)*	*KRAS*	*MET*	*NRG1*	*NTRK*	*RET*	*ROS1*

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (**portal.guardanthealth.com**) for the Tumor Response Map with all test dates.



DETECTED ALTERATION(S) / BIOMARKER(S)	% CFDNA OR COPY NUMBER	
Tumor Fraction	42.5%	
TP53 Y205C	22.3%	
ATM Loss (Single Copy Deletion) Deletions not graphed above	DETECTED Plasma Copy Number 1.7	
DNMT3A R771Q	0.5%	Variant of Potential Clonal Hematopoiesis §
KMT2C Y2218*	0.9%	Variant of Potential Clonal Hematopoiesis §
PALB2 Loss (Single Copy Deletion) Deletions not graphed above	DETECTED Plasma Copy Number 1.6	
PTEN Loss (Single Copy Deletion) Deletions not graphed above	DETECTED Plasma Copy Number 1.6	
RB1 Biallelic Loss (Homozygous Deletion) Deletions not graphed above	DETECTED Plasma Copy Number 1.2	
SF3B1 K666N	0.5%	Variant of Potential Clonal Hematopoiesis §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1473811 in the subject line of the email, for additional trials.

ALTERATION	TRIAL ID / CONTACT	TITLE	PHASE	SITE(S)
PTEN Loss (Single Copy Deletion)	NCT03994796 Priscilla Brastianos, MD,pbrastianos@partners.org,617-724-1074	Genetic Testing in Guiding Treatment for Patients With Brain Metastases	Phase 2	Neptune, NJ Summit, NJ Pennington, NJ
	NCT05238922 Incyte Corporation Call Center (US), medinfo@incyte.com,1.855.463.3463	Study of INCB123667 in Subjects With Advanced Solid Tumors	Phase 1	Hackensack, NJ
	NCT05932862 Exelixis Clinical Trials,druginfo@exelixis.com,1-888-393-5494)	A Phase 1 Study of XL309 (ISM3091) Alone and in Combination in Patients With Advanced Solid Tumors	Phase 1	New Brunswick, NJ
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
ATM Loss (Single Copy Deletion)	NCT05238922 Incyte Corporation Call Center (US), medinfo@incyte.com,1.855.463.3463	Study of INCB123667 in Subjects With Advanced Solid Tumors	Phase 1	Hackensack, NJ
	NCT05566574 Nancy Lee, MD,leen2@mskcc.org,212-639-3341	A Study of RP-3500 in Combination With Standard Radiation Therapy in People With Solid Tumor Cancer	Phase 1 /Phase 2	Basking Ridge, NJ Montvale, NJ Middletown, NJ
	NCT05932862 Exelixis Clinical Trials,druginfo@exelixis.com,1-888-393-5494)	A Phase 1 Study of XL309 (ISM3091) Alone and in Combination in Patients With Advanced Solid Tumors	Phase 1	New Brunswick, NJ
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
PALB2 Loss (Single Copy Deletion)	NCT05238922 Incyte Corporation Call Center (US), medinfo@incyte.com,1.855.463.3463	Study of INCB123667 in Subjects With Advanced Solid Tumors	Phase 1	Hackensack, NJ
	NCT05932862 Exelixis Clinical Trials,druginfo@exelixis.com,1-888-393-5494)	A Phase 1 Study of XL309 (ISM3091) Alone and in Combination in Patients With Advanced Solid Tumors	Phase 1	New Brunswick, NJ
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 Y205C	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
More clinical trial options available at **portal.guardanthealth.com**				

Interpretation

Somatic Alterations: Guardant360 detects somatic alterations in circulating cell-free DNA isolated from a patient's blood specimen in the genes listed in Table 1. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Amplification: Guardant360 detects amplifications in the genes listed in Table 1. Gene amplification results in increased copies of the gene present in the cfDNA. The reported absolute copy number value represents the average copy number for the detected gene that was detected in circulating cfDNA. With the exception of sex-linked genes such as *AR*, 2 copies are expected in the absence of amplification. As the absolute number of copies in circulation is dependent on both tumor fraction and the magnitude of the tumor amplification, amplifications are reported on a semi-quantitative scale.

Amplifications are reported in two levels:

Medium (++): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.

High (+++): Amplification magnitude is above the 50th percentile.

Unlike tissue based gene amplification tests (e.g. IHC or FISH), Guardant360 assesses the total representation of a given gene in all circulating cell-free DNA present in the patient's blood sample including material derived from the tumor and healthy tissue alike. As such, the absolute level of amplification present in the blood depends both on the tumor-derived cfDNA content and on the degree of amplification within that fraction and cannot be inferred from bulk cfDNA interrogation. For example, a positive Guardant360 test could represent a small population of cells with extremely high levels of the detected gene amplification. Alternatively, it could represent a large population of cells with low to medium levels of the detected gene amplifications. The exact correlation between amplification detected by Guardant360 compared to IHC or FISH and how each test differentially guides patient management is an area of active investigation.

Biomarker Negative: Guardant360 assesses the level of certainty (confidence score) that the sample is negative for clonal/driver FDA-approved genomic biomarkers in that tumor type (see https://www.guardantcomplete.com/hcp/solutions/guardant360 for a list of eligible biomarkers in lung and colorectal cancers). It is intended to support clinical decision making regarding further diagnostic procedures. Therapy annotations and wildtype status are provided only for colorectal samples with confidence scores >95%.The algorithm is based on biomarker prevalence from the literature, modified by the specific test result, based on analytical test characteristics and a large tissue-plasma concordance training set. For lung cancer and colorectal cancer samples that are determined to be FDA-approved biomarker negative on Guardant360 with confidence scores >90%, the concordance with tissue, i.e. the predictive value of the negative result, is 96%. As subclonal alterations may exist at any variant allele fraction, the algorithm result applies only to clonal/driver alterations. Samples with confidence scores <90% have >10% chance for being positive for relevant biomarkers in the tumor; therefore consideration for further testing by tissue is recommended as clinically indicated.

Clonal Hematopoiesis (CH): All SNVs and Indels detected on the Guardant 360 assay will be evaluated for the likelihood that they are derived from hematopoietic sources. The categorization of these variants as potential clonal hematopoietic origin by an algorithm is not intended to be used for the diagnosis of a hematolymphoid malignancy. The clinical significance of these variants requires evaluation of other clinical and laboratory parameters, such as peripheral blood counts, patient age, and treatment history. Non-tumor derived variants may arise from hematolymphoid tissues, such as those associated with clonal hematopoiesis, and/or include variants from clonal processes in other organ sites.

Deletion (Del): Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

Fusion: Fusion events are gene rearrangements that fuse two previously distinct genes into a single genetic unit. Guardant360 detects fusions in the genes listed in Table 1.

Genomic Instability Status (GIS): Homologous recombination deficiency (HRD) is characterized by inability to accurately repair double-stranded breaks in DNA and sensitivity to DNA-damaging agents such as platinum-based chemotherapy and poly-ADP ribose polymerase (PARP) inhibitors. HRD status can be determined by testing for either deleterious mutations in homologous recombination repair (HRR) genes or genomic instability (PMID: 37769224). Guardant360 reports a qualitative genomic instability status (GIS) in prostate, breast, ovarian, and pancreatic cancers based on a probabilistic prediction measured by a combination of genomic instability biomarkers, including loss of heterozygosity, large-scale state transitions, telomere allelic imbalance, and specific SNV signatures. The positive agreement of GIS with HRD status as assessed by mutations in HRR genes is 79.5%, and the negative agreement is 97.6% . A "Not Detected" result indicates that signal in the plasma sample did not exceed a predefined threshold, and does preclude genomic instability in the tumor. A "Not evaluable" result is returned for samples with large discordances in observed and expected copy numbers or germline variant allele fraction distributions, indicating low confidence of background signal assessment and potentially inconclusive results.

Homozygous Deletion: Homozygous deletion results when both copies of a gene are lost.

Human Leukocyte Antigen: All samples are evaluated for germline MHC Class I genes in the *HLA-A*, *HLA-B*, and *HLA-C* loci at two-field high resolution (IPD-IMGT/HLA release 3.44.0) from cfDNA. The accuracy of Guardant360 for HLA detection compared to orthogonal methods is 97.3%. The assay cannot differentiate between loss of heterozygosity and homozygosity when only one allele is detected in samples with very high tumor fractions where the majority of cfDNA is tumor derived. A Not Evaluable result indicates ambiguous support for multiple alleles. HLA alleletyping results are intended as a supplement to standard of care in therapy selection and/or an aid in clinical trial eligibility assessment, not a replacement for standard methodologies in immunohistocompatibility testing (PMID 34551229 & 37328642).

Indel: Guardant360 detects short insertions or deletions in the exons of certain genes (see Table 1). This type of variant represents frameshift, in-frame and complex alterations comprising both an insertion and a deletion. These variants can result in the substitution of one or more amino acids with the reading frame preserved (in-frame), or disrupt the reading frame (frameshift) leading to a premature stop codon.

Insertion (Ins): Guardant360 detects short insertions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

***MET* exon 14 skipping:** This type of genomic alteration is predicted to result in the skipping of *MET* exon 14 during RNA splicing, resulting in oncogenic activation of the *MET* protein.

Molecular Breast Subtype: Guardant360 evaluates the methylation profile of the sample across target panel regions to infer tumor-associated DNA methylation changes. In breast cancer patients, distinct cfDNA methylation signatures characterize hormone receptor (HR), HER2-positive, and triple negative breast cancer (TNBC) subtypes. Guardant360 reports the level of certainty (confidence score) for the presence of these subtypes, when the tumor fraction in blood is >0.5%. The accuracy for detecting HR, HER2, and TNBC status compared to standard of care methodologies such as immunohistochemistry (IHC) and in-situ hybridization (ISH) is 85.7%, 86.3%, and 91.9%, respectively. Detection of the HER2-positive subtype was developed and validated in cases with high HER2 expression (IHC 3+, IHC 2+, or ISH+ in paired tissue); the test has not been validated for detection of HER2-low or HER2-ultralow disease. When the confidence score for any subtype is reported as <10%, the signal in plasma is below the detection limit of the assay; this does not preclude the presence of the subtype in the patient's tumor. The molecular breast tumor subtyping provided by Guardant360 is intended to be a supplement rather than replacement for standard of care methodologies. If clinically indicated, confirmatory testing with a validated standard assay is recommended.

Molecular Lung Subtype: Guardant360 evaluates the methylation profile of a sample across target panel regions to infer tumor-associated DNA methylation changes. In lung cancer patients, histologic subtypes (adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and small cell carcinoma (SCLC)) are associated with distinct cfDNA methylation signatures (PMID: 30317601, PMID: 35941262). Guardant360 assesses the relative proportional contribution of each lung subtype to the unique methylation signature to the tumor, when the tumor fraction in blood is >0.1%. The accuracy for detecting the predominant subtype for LUAD, LUSC and SCLC is 93.44%, 83.51%, 81.08%, respectively. The estimated proportions for each subtype are provided as an annotation and not intended to be a quantitative output. When the estimated proportion for any subtype is reported as <10%, the signal in plasma is below the detection limit of the assay; this does not preclude the presence of that subtype in the tumor. This prediction is intended to supplement histologic characterization and confirmatory tissue evaluation may be warranted if clinically indicated.

Molecular Tumor Type: Molecular Tumor Type (MTT) is a prediction of tumor type based on DNA methylation signatures. Primary and secondary MTT predictions, along with an associated confidence score, are provided as an annotation to supplement standard clinical and pathologic diagnostic evaluation, particularly for adjudication of carcinoma of unknown primary (CUP). The associated confidence scores represent the level of certainty of the MTT prediction: 0.1-0.5 (Low), 0.5-0.8 (Mid), 0.8-1.0 (High). The MTT algorithm has demonstrated 88.5%-100% agreement between MTT predictions and clinicopathologic diagnosis depending on tumor type. MTT predictions are not provided if the confidence score is below predefined thresholds or the patient's tumor type is not supported by the algorithm (see https://www.guardantcomplete.com/hcp/solutions/guardant360). The presence of two CSO predictions does not necessarily indicate that multiple primary cancers are present.

Nonsense Mutation: A point mutation that results in a premature stop gain.

Pharmacogenomics: All samples are evaluated for germline variants in Tier 1 and select Tier 2 alleles that modulate toxicity/sensitivity to chemotherapeutic agents in *CYP2D6*, *DPYD*, *TPMT*, *UGT1A1*, and the HLA allele *HLA-B**57:01 *(*for more information including reportable alleles and therapy indications see https://www.guardantcomplete.com/hcp/solutions /guardant360). Germline alleletype is inferred based on cfDNA sequencing data and metabolizer status is a prediction based on the diplotype. Interpretations are limited to oncologic therapies. Activity scores are calculated using CPIC guidelines. The accuracy of Guardant360 for Pharmacogenomics alleletyping compared to PCR-based methods is 96.3%. A Not Evaluable result indicates that the copy number of the gene cannot be determined and/or there is ambiguous support for multiple alleles. As the test does not detect all variants, *1 represents the absence of a detectable variant. *CYP2D6* hybrid and duplicate alleles will be represented with 3 values (*1/*2/*3) and complex alleles are not reported. Only the HLA allele *HLA-B**57:01 associated with increased risk of drug hypersensitivity will be reported if detected. Drug response can be influenced by other clinical factors and therapy decisions should take these variables into consideration. Functional confirmation is recommended when conflicting evidence exists in the literature.

Promoter Methylation: Guardant360 detects promoter methylation in the genes listed in Table 1. Hypermethylation of normally unmethylated CpG islands located in gene promoters correlates with transcriptional repression that can serve as an alternative to coding region mutations for inactivation of tumor suppressor genes (Baylin et al., 1997). DNA methylation of key CG dinucleotides within the promoter blocks accessibility of transcription factors to their binding motifs, thereby silencing gene expression. DNA hypermethylation occurs early in tumorigenesis and typically increases with tumor progression (Ehrlich 2019).

Rearrangement: Guardant360 detects rearrangements in the genes listed in Table 1. Rearrangement refers to large genomic events that result in single or multi-exon deletions (>3Kb in size) or gene fusions.

Reversion: Reversions are secondary mutations, often small indels, that convert an initial frameshift mutation into an in-frame internal deletion that still produces a partly functional protein product.

Single Copy Deletion + Co-Occurring Loss of Function (LOF) Variant: Occurs when a single copy of a gene is lost due to whole gene deletion in the presence of a loss-of-function variant in the same gene.

Single Copy Deletion: Occurs when a single copy of a gene is lost due to a whole gene deletion.

Somatic Alterations Not Detected (ND): In some cases, Guardant360 does not detect any somatic alterations. Somatic alterations may be present that are below the limit of detection of this test. Certain sample or variant characteristics may result in reduced analytic sensitivity. The absence of detectable somatic alterations in circulating cell-free DNA does not preclude the presence of somatic alterations in the tumor.

Splice Site: Splice site variants disrupt the donor and/or acceptor splice site(s), leading to abnormal mRNA splicing and altered protein levels and/or function.

Synonymous Alteration: This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Tumor Mutational Burden (TMB): Checkpoint inhibition has been FDA-approved for patients who have no satisfactory alternative treatment option with a tissue TMB score of 10 mut/Mb or higher. In a large clinical study of blood TMB in patients with newly diagnosed non-small cell lung cancer (NSCLC) using Guardant360, Guardant360 TMB score of 16 mut /Mb, 76th percentile, correlates with a tissue TMB score of 10 mut/Mb (Rizvi, N.A., et al. JAMA Oncology, 2020). The distribution of tissue TMB scores has been shown to differ across tumor types (Samstein, R.M, et al. Nature Genetics, 2019). Similarly, in a landscape analysis of Guardant360 TMB, 80th percentile corresponds to the following TMB scores: NSCLC - 20.2 mut/Mb; colorectal cancer - 20.1 mut/Mb; breast cancer- 15.3 mut/Mb; prostate cancer - 13.4 mut/Mb; pancreatic cancer - 11.4 mut/Mb; head and neck squamous cell cancer (HNSCC)- 17.4 mut/Mb; cholangiocarcinoma - 10.5 mut/Mb.

Variants of Uncertain Clinical Significance: The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Viral Status: Guardant360 targets viral genome sequences from *EBV* and 14 strains of high-risk HPV (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, and HPV68). The reportable range for *EBV* is ≥10.64 normalized viral genome copies, and the reportable range for HPV is ≥3.6 normalized viral genome copies. The intended use population for *EBV* viral genome detection are patients with advanced-stage gastric and nasopharyngeal carcinoma, and for HPV is patients with advanced-stage HPV-mediated malignancies in the head and neck and lower anogenital tract. Both viruses are reported in carcinoma of unknown primary. The sensitivity of Guardant360 for viral detection compared to standard of care methods is 93.6%, and the specificity is 96.6%. The test cannot distinguish between infectious and neoplastic sources of viral DNA and is not a substitute for diagnostic tissue-based testing for newly-diagnosed cancers.

About the Test

The Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The laboratory report should be interpreted in the context of other clinical information and laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drug and trial information are based on the diagnosis written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies. Some drugs listed in this report may not be approved or cleared by the FDA for the indicated use. Guardant Health makes no endorsement, expressed or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing Performed at: Guardant Health

Laboratory Director: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

Method and Limitations

Guardant360 sequences 744 cancer-associated genes to identify somatic and germline alterations. Cell-free DNA (cfDNA) is extracted from plasma, partitioned based on methylation status, enriched for targeted regions, and sequenced using the Illumina platform and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variants (SNVs), gene amplifications, fusions/rearrangements, short insertions /deletions (indels, longest detected, 87 base pairs), copy number deletions, promoter methylation and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. Tumor mutational burden (TMB) score is calculated for all cancer types from somatic SNVs and indels in exons of 497 genes detected in cfDNA, followed by adjusting for tumor shedding levels and the size of the panel. A "Not Evaluable" result is an inconclusive result in samples where the evidence of tumor shedding is insufficient and it does not preclude TMB-High status in tissue. Promoter methylation status is assessed for all cancer types by calculating the % cfDNA methylated molecules overlapping defined promoter regions of 47 genes and is reported as Detected or Not Detected based on the established sensitivity. Promoter methylation may not always be associated with gene inactivation; orthogonal confirmation and clinical correlation are recommended as indicated. Methylation-based tumor fraction is estimated in all cancer types by evaluating multiple patient-specific differentially methylated regions associated with cancer. The quantifiable range for tumor fraction ranges from 0.05% to 90%. Tumor fractions less than 0.05% are reported as <0.05%, those higher than 90% are indicated as >90%. All SNVs and Indels detected on the Guardant360 assay will be evaluated for the likelihood that they are derived from hematopoietic sources by a proprietary algorithm that identifies variants of nonsolid- tumor origin that may originate from hematopoietic or non-hematopoietic clonal processes. The test is not intended to be used for the diagnosis of hematolymphoid malignancy. Certain sample or variant characteristics, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Additional information is available

Therapeutic annotations are based on publicly available information. A more detailed Guardant360 report (including Additional Clinical Trials, Detailed Therapy Results, Relevance of Detected Alterations, and References) is available through our online portal at **portal.guardanthealth.com**. To set up an account, contact Client Services at **855.698.8887** or **clientservices@guardanthealth.com**.

If you would like to receive this additional information for this report, or with every Guardant360 report, contact Client Services.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants, splice site mutations, and insertion and deletion variants (indels) in the genes listed below and reports other variant types in select genes as indicated.

ABCB1	*BRD2*	*CRTC1*	*EML4*	*FGF7*	*HLA-C* [h §]	*LGR6*	*NF1* [^]	*PIK3R2*	*RB1* [* ^ #]	*SMARCE1*	*TP63*
ABL1	*BRD3*	*CSF1R*	*EMSY*	*FGF8*	*HNF1A*	*LIG1*	*NF2* [^]	*PIK3R3*	*RBBP6*	*SMC1A*	*TP73*
ABL2	*BRD4*	*CSF3R*	*EP300*	*FGF9*	*HNRNPDL*	*LIG4*	*NFE2L2*	*PIM1*	*RBM10*	*SMC3*	*TPMT* [p]
ABRAXAS1	*BRIP1* [^]	*CTC1*	*EPCAM*	*FGFR1* [† #]	*HOXB13*	*LMO1*	*NFKBIA*	*PIN1*	*RBMX*	*SMO*	*TRAF2*
ACVR1	*BSG*	*CTCF*	*EPHA3*	*FGFR2* [† #]	HPV (high-risk) [~ §]	*LRP1B*	*NHEJ1*	*PKM*	*RECQL*	*SNCAIP*	*TRAF3*
ACVR1B	*BTG1*	*CTLA4*	*EPHA5*	*FGFR3* [#]	*HRAS*	*LRP2*	*NKX2-1*	*PLCG2*	*RECQL4*	*SOCS1*	*TRAF7*
ACVR2A	*BTG2*	*CTNNA1*	*EPHA7*	*FGFR4*	*HSD3B1*	*LRP5*	*NOTCH1*	*PLEKHS1*	*RET* [#]	*SOCS3*	*TRIM24*
ADARB2	*BTK*	*CTNNB1*	*EPHB1*	*FH*	*HSP90AA1*	*LRP6*	*NOTCH2*	*PLRG1*	*REV3L*	*SOS1*	*TRIP13*
ADGRA2	*BUB1B*	*CUL3*	*ERBB2* [†]	*FLCN*	*ICOSLG*	*LTK*	*NOTCH3*	*PMS1*	*RGS1*	*SOX10*	*TSC1*
ADGRG4	*C9orf78*	*CUL4A*	*ERBB3*	*FLT1*	*ID3*	*LYN*	*NOTCH4*	*PMS2* [^]	*RHEB*	*SOX17*	*TSC2* [^]
AFDN	*CALR*	*CUX1*	*ERBB4*	*FLT3*	*IDH1*	*LZTR1*	*NOVA1*	*POLA1*	*RHOA*	*SOX2*	*TSHR*
AGGF1	*CARD11*	*CWC22*	*ERCC1*	*FLT4*	*IDH2*	*MAD2L2*	*NPM1*	*POLD1*	*RHOB*	*SOX9*	*TSHZ2*
AIP	*CASP8*	*CXCR4*	*ERCC2*	*FOXA1*	*IDO1*	*MALT1*	*NPRL2*	*POLE* [^]	*RICTOR*	*SPEN*	*TYMP*
AKT1	*CASR*	*CYLD*	*ERCC3*	*FOXL2*	*IFNG*	*MAP2K1*	*NPRL3*	*POLH*	*RIF1*	*SPOP*	*TYMS*
AKT1S1	*CAV1*	*CYP17A1*	*ERCC4*	*FOXO1*	*IFNGR1*	*MAP2K2*	*NRAS*	*POLQ*	*RILPL1*	*SRC*	*TYRO3*
AKT2	*CBFB*	*CYP19A1*	*ERCC5*	*FOXP1*	*IFNGR2*	*MAP2K4*	*NRG1* [#]	*POT1*	*RIT1*	*SRSF2*	*U2AF1*
AKT3	*CBL*	*CYP2C19*	*ERCC6*	*FRS2*	*IFNW1*	*MAP3K1*	*NSD1*	*POU2F2*	*RNASEH2B*	*SRY*	*UBE2T*
ALB	*CBLB*	*CYP2D6* [p §]	*ERCC6L2*	*FUBP1*	*IGF1*	*MAP3K13*	*NSD2*	*PPARG*	*RNF43*	*SS18*	*UGT1A1* [p]
ALK [#]	*CCAR1*	*CYP3A4*	*ERCC8*	*FUBP3*	*IGF1R*	*MAP4K3*	*NSD3*	*PPIG*	*ROBO1*	*STAG2*	*UIMC1*
ALOX12B	*CCN6*	*DAXX*	*EREG*	*FUS*	*IGF2*	*MAPK1*	*NSRP1*	*PPM1D*	*ROBO2*	*STAT1*	*ULBP1*
ALOX15B	*CCNA2*	*DCUN1D1*	*ERF*	*FYN*	*IGF2BP3*	*MAPK3*	*NTHL1*	*PPP2CA*	*ROS1* [#]	*STAT3*	*ULBP3*
ALOX5	*CCNB1*	*DDIT3*	*ERG*	*FZD1*	*IGF2R*	*MAPKAP1*	*NTRK1* [#]	*PPP2R1A*	*RPA1*	*STAT4*	*USP28*
AMER1	*CCND1* [†]	*DDR1*	*ERRFI1*	*FZD10*	*IKBKE*	*MARK2*	*NTRK2* [#]	*PPP2R2A*	*RPS27A*	*STK11* [* ^ #]	*USP7*
APC [^]	*CCND2* [†]	*DDR2*	*ESR1* [† #]	*FZD2*	*IKZF1*	*MAX*	*NTRK3* [#]	*PPP3CA*	*RPS6KA3*	*STK19*	*USP9X*
APEX1	*CCND3*	*DDX17*	*ETS1*	*FZD3*	*IL1R1*	*MCL1*	*NUMA1*	*PPP6C*	*RPS6KB1*	*STK40*	*VEGFA*
APLNR	*CCNE1* [†]	*DDX18*	*ETV1*	*FZD4*	*IL2RA*	*MDC1*	*NUMB*	*PRDM1*	*RPS6KB2*	*STN1*	*VEGFB*
AR [†]	*CCNE2*	*DDX27*	*ETV4*	*FZD5*	*IL2RB*	*MDM2*	*NUP93*	*PREX1*	*RPTOR*	*SUFU*	*VHL*
ARAF	*CD274*	*DDX3X*	*ETV5*	*FZD6*	*IL2RG*	*MDM4*	*NUTM1*	*PREX2*	*RRAGC*	*SYK*	*VIRMA*
ARFRP1	*CD276*	*DDX41*	*ETV6*	*FZD7*	*IL7R*	*MED12*	*P2RY8*	*PRKAR1A*	*RSPO1*	*SYNCRIP*	*WBP11*
ARHGAP35	*CD74*	*DEPDC5*	*EWSR1*	*FZD8*	*INHBA*	*MEF2B*	*PABPC1*	*PRKCI*	*RSPO2*	*TACSTD2*	*WEE1*
ARID1A [^]	*CD79A*	*DEPTOR*	*EXO1*	*FZD9*	*INPP4B*	*MEN1*	*PAK1*	*PRKDC*	*RSPO4*	*TAF1L*	*WRN*
ARID1B [^]	*CD79B*	*DHX15*	*EZH1*	*GAS6*	*INTS6L*	*MERTK*	*PAK3*	*PRKN*	*RUNX1*	*TAP1*	*WT1*
ARID2	*CDC27*	*DHX16*	*EZH2*	*GATA1*	*IRF1*	*MET* [† #]	*PALB2* [* ^ #]	*PRMT5*	*RUNX1T1*	*TAP2*	*WWP1*
ASXL1	*CDC5L*	*DHX36*	*FAAP100*	*GATA2*	*IRF2*	*MGA*	*PARG*	*PRPF40B*	*RXRA*	*TAPBP*	*XBP1*
ATM [* ^ #]	*CDC7*	*DHX9*	*FAAP20*	*GATA3*	*IRF4*	*MGMT* [^ §]	*PARP1*	*PRPF4B*	*RYBP*	*TBC1D7*	*XPA*
ATMIN	*CDC73*	*DICER1*	*FAAP24*	*GATA4*	*IRS2*	*MITF*	*PARP2*	*PSENEN*	*SAMHD1*	*TBX3*	*XPC*
ATR [^]	*CDH1* [^]	*DIS3L2*	*FANCA* [^]	*GATA6*	*JAK1*	*MKNK1*	*PAX3*	*PSMB10*	*SDC4*	*TCERG1*	*XPO1*
ATRX	*CDH6*	*DLL4*	*FANCB*	*GEN1*	*JAK2*	*MLH1* [^]	*PAX5*	*PSMB8*	*SDHA* [^]	*TCF7L2*	*XRCC1*
AURKA	*CDK11A*	*DNAJB1*	*FANCC*	*GID4*	*JAK3*	*MLH3*	*PAX7*	*PSMB9*	*SDHAF2*	*TEK*	*XRCC2*
AURKB	*CDK12* [* ^ #]	*DNMT1*	*FANCD2*	*GLI1*	*JUN*	*MLST8*	*PAX8*	*PTCH1*	*SDHB* [^]	*TEN1*	*XRCC3*
AURKC	*CDK4* [†]	*DNMT3A*	*FANCE* [^]	*GNA11*	*KAT6A*	*MPL*	*PAXIP1* [^]	*PTDSS1*	*SDHC* [^]	*TENT5C*	*XRCC4*
AXIN1	*CDK6* [†]	*DNMT3B*	*FANCF* [^]	*GNA13*	*KAT6B*	*MRAS*	*PBRM1* [^]	*PTEN* [* ^ #]	*SDHD* [^]	*TERT* [‡]	*XRCC5*
AXIN2	*CDK7*	*DOT1L*	*FANCG* [^]	*GNAQ*	*KDM4A*	*MRE11*	*PCBP1*	*PTPN11*	*SEM1*	*TET1*	*XRCC6*
AXL	*CDK8*	*DPYD* [p]	*FANCI*	*GNAS*	*KDM5A*	*MSH2* [^]	*PCBP2*	*PTPN2*	*SERPINB3*	*TET2*	*YAP1*
B2M [^]	*CDKN1A*	*DUSP4*	*FANCL* [^]	*GPATCH8*	*KDM5B*	*MSH3*	*PCDH15*	*PTPRD*	*SERPINB4*	*TFE3*	*YES1*
BABAM1	*CDKN1B* [^]	*DYNLL1*	*FANCM*	*GPC3*	*KDM5C*	*MSH6* [^]	*PDCD1*	*PTPRS*	*SESN2*	*TFRC*	*ZC3H13*
BABAM2	*CDKN1C*	*DYRK2*	*FAS*	*GREM1*	*KDM6A*	*MTAP* [* ^ #]	*PDCD1LG2*	*PTPRT*	*SETD2*	*TGFBR1*	*ZC3H18*
BAP1	*CDKN2A* [* ^ #]	*E2F3*	*FAT1*	*GRIN2A*	*KDR*	*MTHFR*	*PDE7A*	*QKI*	*SF3B1*	*TGFBR2*	*ZC3H4*
BARD1	*CDKN2B*	*EBV* [~ §]	*FBXW7*	*GSK3B*	*KEAP1* [* ^ #]	*MTOR*	*PDGFRA* [†]	*RAB35*	*SF3B3*	*THRAP3*	*ZMYM3*
BCL2	*CDKN2C*	*ECT2L*	*FCGR2A*	*GSTM1*	*KIN*	*MUTYH* [^]	*PDGFRB*	*RAC1*	*SH2D1A*	*TIA1*	*ZNF217*
BCL2L1	*CEBPA*	*EFTUD2*	*FCGR3A*	*GSTP1*	*KIT* [†]	*MYB*	*PDK1*	*RAD18*	*SHLD1*	*TIPARP*	*ZNF703*
BCL2L2	*CELF4*	*EGFR* [† #]	*FEN1*	*H3-4*	*KLF4*	*MYC* [†]	*PDPK1*	*RAD21*	*SHLD2*	*TMEM127*	*ZNRF3*
BCL6	*CEP295*	*EIF1AX*	*FGF1*	*H3F3A*	*KLHL6*	*MYCL*	*PHF6*	*RAD50* [^]	*SLC34A2*	*TMPRSS2*	*ZRSR2*
BCOR	*CFAP20*	*EIF4A1*	*FGF10*	*HACD4*	*KLHL9*	*MYCN*	*PHLPP1*	*RAD51* [^]	*SLFN11*	*TNFAIP3*	
BCORL1	*CHD4*	*EIF4A2*	*FGF12*	*HDAC2*	*KMT2A*	*MYD88*	*PHLPP2*	*RAD51B*	*SLIT2*	*TNFRSF14*	
BCR	*CHEK1* [^]	*EIF4A3*	*FGF14*	*HDAC6*	*KMT2B*	*MYOD1*	*PHOX2B*	*RAD51C* [* ^ #]	*SMAD2*	*TNFRSF1A*	
BIRC5	*CHEK2* [* ^ #]	*EIF4B*	*FGF19*	*HELQ*	*KMT2C*	*NAB2*	*PIAS4*	*RAD51D* [* ^ #]	*SMAD3*	*TNK2*	
BLM	*CIC*	*EIF4E*	*FGF2*	*HES1*	*KMT2D*	*NBN*	*PIK3C2B*	*RAD52*	*SMAD4* [^]	*TNPO1*	
BMPR1A	*CMTM4*	*EIF4E2*	*FGF23*	*HEY1*	*KNSTRN*	*NCOR1*	*PIK3CA* [†]	*RAD54L*	*SMARCA2*	*TOP1*	
BRAF [† #]	*CMTM6*	*ELAVL1*	*FGF3*	*HEYL*	*KRAS* [†]	*NCR1*	*PIK3CB*	*RAET1E*	*SMARCA4*	*TOP2A*	
BRCA1 [* ^ #]	*CNOT3*	*ELAVL2*	*FGF4*	*HGF*	*LATS1*	*NCR3*	*PIK3CD*	*RAF1* [†]	*SMARCAL1*	*TOPAZ1*	
BRCA2 [* ^ #]	*CREBBP*	*ELF3*	*FGF5*	*HLA-A* [h §]	*LGR4*	*NEGR1*	*PIK3CG*	*RARA*	*SMARCB1*	*TP53* [^]	
BRCC3	*CRKL*	*ELOC*	*FGF6*	*HLA-B* [p h §]	*LGR5*	*NELFE*	*PIK3R1*	*RASA1*	*SMARCD1*	*TP53BP1*	

‡ Guardant360 reports alterations in the promoter region of this gene.
† Guardant360 reports amplifications of this gene.
* Guardant360 reports copy number deletions in this gene.
# Guardant360 reports rearrangements in this gene.
§ Guardant360 does not report SNVs or indels from this feature.
^ Guardant360 reports promoter methylation of this gene.
~ Guardant360 reports detection of this virus.
h Guardant360 reports HLA alleles for this gene.
p Guardant360 reports pharmacogenomics results of this gene.