PATIENT & PHYSICIAN INFORMATION

Patient: First Last
MRN: MRN-XX
Physician: Dr. First Last

Date of Birth: Jan 3, 1952
Gender: Male
Facility: Facility Name

Tumor: Lung
Specimen Type: Whole Blood
Address: Facility Address, Town, NY, Zip Code

GSNGS Accession No: GNGSXXXXXXXX
Stage: Advanced Stage
Phone: XXX-XXX-XXXX
Fax: XXX-XXX-XXXX

External Specimen ID: N/A
Date Collected: Jul 1, 2024
Date Received: Jul 2, 2024
Date Reported: Jul 3, 2024

GENESTRAT NGS® TEST RESULTS

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EML4::ALK fusion*	**alectinib** [1] **brigatinib** [1] **ceritinib** [1] **crizotinib** [1] **ensartinib** [1] **lorlatinib** [1]	**crizotinib** [1] alectinib brigatinib ceritinib lorlatinib	17

Public data sources included in relevant therapies: FDA[1], NCCN

See "Classification and Levels of Evidence" section for tier definitions.

Alerts informed by public data sources: Contraindicated, Resistance, Breakthrough, Fast Track, Not recommended

EML4::ALK fusion	**neladalkib** [1]

Public data sources included in alerts: FDA[1], NCCN

LABORATORY DIRECTOR

Gary Pestano, Ph.D., New York State Laboratory Director

The Laboratory Director approval applies to the detection of the molecular variants in this assay.

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Louisville, CO 80027

GENESTRAT NGS® PANEL DETAILS

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	***EML4::ALK fusion***	MET	None detected
BRAF	None detected	NTRK1	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected

Genes Assayed

Single Nucleotide Variants (SNVs) and Insertion/Deletions (Indels): AKT1, ALK, APC, AR, ARAF, BRAF, CHEK2, CTNNB1, DDR2, EGFR, ERBB2 (HER2), ERBB3, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FBXW7, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SF3B1, SMAD4, SMO, TP53

Fusions and Skipping Variants: ALK, BRAF, ERG, ETV1, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK3, RET, ROS1

Copy Number Amplifications: CCND1, CCND2, CCND3, CDK4, CDK6, EGFR, ERBB2 (HER2), FGFR1, FGFR2, FGFR3, MET, MYC

Biomarker Descriptions

EML4::ALK fusion

ALK receptor tyrosine kinase, echinoderm microtubule associated protein like 4

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK) with sequence similarity to the insulin receptor subfamily of kinases[1]. ALK is the target of recurrent alterations in cancer, the most common being chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with multiple partner genes[2]. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways[2,3,4,5].

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin (NPM) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of anaplastic large cell lymphoma cases (ALCL)[1,6]. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1[7,8,9].

Potential relevance: The first generation small molecule tyrosine kinase inhibitor (TKI), crizotinib[10], was FDA approved (2011) for the treatment of ALK positive advanced NSCLC as well as ALK positive ALCL or inflammatory myofibroblastic tumor (IMT). Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants have been shown to confer acquired resistance to crizotinib in ALK positive NSCLC[11,12,13,14]. Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R[15]. In order to overcome acquired resistance,

Biomarker Descriptions (continued)

second and third-generation ALK inhibitors including ceritinib[16] (2014), alectinib[17] (2015), brigatinib[18] (2017), lorlatinib[19] (2018), and ensartinib[20] (2024) were developed and approved by the FDA. Two phase III trials evaluating crizotinib and alectinib as first line therapy in NSCLC, including patients with asymptomatic central nervous system (CNS) disease, were conducted and both studies showed consistent higher objective response rates (ORR) with alectinib relative to crizotinib[21,22]. For this reason, alectinib is a preferred first-line treatment of ALK positive NSCLC[23]. The FDA granted breakthrough therapy designation (2024) to NVL-655 for locally advanced or metastatic ALK-positive NSCLC patients who have been previously treated with two or more ALK TKIs[24].

Clinical Trials Summary

EML4::ALK fusion

NCT ID	Title	Phase
NCT02201992	A Randomized Phase III Trial for Surgically Resected Early Stage Non-small Cell Lung Cancer: Crizotinib Versus Observation for Patients With Tumors Harboring the Anaplastic Lymphoma Kinase (ALK) Fusion Protein	III
NCT05170204	A Phase I-III, Multicenter Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Patients Selected According to Biomarker Status, With Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer	III
NCT06765109	A Phase III Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 Compared to Alectinib in First-Line Treatment of Patients With ALK-Positive Advanced Non-Small Cell Lung Cancer (ALKAZAR)	III
NCT06074588	A Randomized, Open-label, Phase III Study of MK-2870 vs Chemotherapy (Docetaxel or Pemetrexed) in Previously Treated Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer (NSCLC) With EGFR Mutations or Other Genomic Alterations	III
NCT06012435	A Randomized, Phase III, Open-label Study to Evaluate SGN-B6A Compared With Docetaxel in Adult Subjects With Previously Treated Non-small Cell Lung Cancer	III
NCT04302025	NAUTIKA1: Multicenter, Phase II, Neoadjuvant and Adjuvant Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III Non-Small Cell Lung Cancer	II
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT06522360	Brigatinib Plus Chemotherapy or Local Consolidation Therapy in ALK Positive Advanced Non-small Cell Lung Cancer (BrightStar-2)	II
NCT05845671	A Phase I/II , Open Label, Study of Amivantamab (JNJ-61186372) Among Participants With Advanced NSCLC Harboring ALK, ROS1, and RET Gene Fusions in Combination With Tyrosine Kinase Inhibitors	I/II

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Clinical Trials Summary (continued)

EML4::ALK fusion (continued)

NCT ID	Title	Phase
NCT05384626	A Phase I/II Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 in Patients With Advanced NSCLC and Other Solid Tumors (ALKOVE-1)	I/II
NCT06007937	A Phase I/II Study of Combination Lorlatinib and Ramucirumab in Patients With Advanced ALK-rearranged Lung Cancers	I/II
NCT06225427	Phase I Study of Gilteritinib for ALK Positive Non-Small Cell Lung Cancer	I
NCT05769075	A Phase I, Multicenter, Open-label Study of TY-2136b, Administered Orally in Patients With Advanced or Metastatic Solid Tumors Harboring ALK, ROS1 or NTRK1-3 Alterations	I
NCT04693468	Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)	I
NCT05669846	Phase II Feasibility Study of Responder-derived FMT (R-FMT) and Pembrolizumab in Relapsed/ Refractory PD-L1 Positive NSCLC	II
NCT06598371	A Phase I/II Study of KSQ-004EX, Autologous Tumor Infiltrating Lymphocytes Engineered to Inactivate Genes Encoding SOCS1 and Regnase-1, in Patients With Select Advanced Solid Tumors	I/II
NCT04094610	A Phase I/II, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations	I/II

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CLASSIFICATION AND LEVELS OF EVIDENCE

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IA	IB	IIC	IID
Variants with strong clinical significance	*Variants with strong clinical significance*	*Variants with potential clinical significance*	*Variants with potential clinical significance*
Level A variants have an FDA-approved therapy and are included in professional guidelines for patient's tumor type.	Level B variants have well-powered studies with consensus from experts in the field for patient's tumor type.	Level C variants have FDA-approved therapies for different tumor types or investigational therapies. Multiple small, published studies with some consensus.	Level D variants have preclinical trials or a few case reports without consensus.

III: Variants of unknown clinical significance. | **IV:** Variants deemed benign or likely benign.

References: Li M. et al. *JMD.* Volume 19, Issue 1, P4-23, January 2017. | Li M. et al. *JMD.* Volume 25, Issue 2, P69-86, February 2023.

GENESTRAT NGS® ANALYSIS DESCRIPTION

TEST DESCRIPTION: The GeneStrat NGS genomic test is a qualitative laboratory developed test designed to aid physicians by providing molecular characterization of cancer patients' disease. The test has been validated for the detection of somatic mutations from cell-free DNA and RNA (cfDNA and cfRNA) derived from plasma samples using established targeted next generation sequencing methodology.

LIMITATIONS AND DISCLAIMER:

- Specific validated SNV and indel variant types relevant to oncology are reported from the genes assayed.
- The test has been validated to 0.5% Variant Allele Frequency for SNVs and indels.
- The limit of detection for fusion/skipping variants and copy number amplifications were 42 copies and 1.4 fold change, respectively.
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- Variants found in circulation may be due to clonal hematopoiesis of indeterminate potential (CHIP). Accordingly, results are adjunctive to the ordering physician's workup and should be evaluated by a qualified healthcare professional in combination with the patient's clinical history, other diagnostic tests, and clinicopathological factors.
- For patients that test negative for all variants, tissue based testing is recommended.
- The GeneStrat NGS genomic test was developed and its performance characteristics determined by Biodesix, Inc. as a laboratory developed test. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes and should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity clinical laboratory testing.
- The GeneStrat NGS genomic test results are intended to assist with decisions related to patient management and provide supplementary information. This test is not a stand-alone diagnostic assay.
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References

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References (continued)

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MRN-XX

Physician:
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Date of Birth:
Jan 2, 1951

Gender:
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Facility:
Facility Name

Tumor:
Lung

Specimen Type:
Whole Blood

Address:
Facility Address, Town, State, Zip Code

GSNGS Accession No:
GNGSXXXXXXXX

Stage:
Advanced Stage

Phone:
XXX-XXX-XXXX

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External Specimen ID:
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GENESTRAT NGS® TEST RESULTS

Relevant Biomarkers

No relevant genomic findings were identified in this specimen. Consider tumor tissue testing if clinically indicated.

LABORATORY DIRECTOR

Donald Joe Chaffin, M.D., CAP Accredited CLIA Laboratory Director

The Laboratory Director approval applies to the detection of the molecular variants in this assay.

GENESTRAT NGS® PANEL DETAILS

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NTRK1	None detected
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Genes Assayed

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