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FINAL REPORT

PATIENT
MRN:

DOB:
Age: | Sex:

PHYSICIAN	SAMPLE	CLINICAL BACKGROUND
DOCTOR CLINIC Account ID:	LUCENCE ID: CS-26-XXXXX Date of Report: May 04 2026 Date Collected: Apr 28 2026 Date Received: Apr 29 2026 Type: Cerebrospinal fluid in Sterile Container (6.5 mL)	Indication: Lung Adenocarcinoma Diagnosis: Metastatic Stage IV Lung Adenocarcinoma Biomarker: NA

ctDNA - SUMMARY OF FINDINGS

ALTERATION† VAF / Fold Change	FDA-APPROVED THERAPIES (This Indication)	OTHER THERAPIES	CLINICAL TRIALS
EGFR P753_I759delinsG Exon 19 Inframe indel 45.42%	SENSITIVE Afatinib, Amivantamab, Amivantamab + Lazertinib, Dacomitinib, Datopotamab Deruxtecan, Erlotinib, Erlotinib + Ramucirumab, Gefitinib, Osimertinib	SENSITIVE (Other Indications) Bevacizumab + Erlotinib (Guidelines)	Yes

- Uncertain clinical actionability:
  - o EGFR A289T (38.02%)
  - o CTNNB1 G34E (28.12%)
  - o CDKN2A Copy Number Loss (1.89 Fold)
  - o EGFR Copy Number Gain (1.53 Fold)
- Microsatellite Status: MS Stable
- No ctDNA alterations were found in the following treatment-relevant genes: *ALK*, *BRAF*, *ERBB2*, *KRAS*, *MET*, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, *ROS1*
- FDA-approved therapies are available in Lung Adenocarcinoma associated with these Genomic Findings. See Section on Genomic Findings With Clinical Actionability (ctDNA) for more details.

NOTE

- † FDA Approval, Breakthrough Designation, Professional Guidelines Recommendations, Phase III Clinical Trials Results, or Compelling Clinical Evidence. Refer to DEFINITIONS for details of the levels of clinical actionability of findings.
- Some findings may have Actionability Evidence from Clinical Trials (Phase I-II), Clinical Studies or Case Reports. Refer to the Appendix section for more information.
- This test is not intended for, and cannot confirm germline status in any manner. Variants detected may be of tumor-derived somatic, germline, or non-tumor somatic origins, including mosaicism and clonal hematopoiesis of indeterminate potential (CHIP).
- It is possible that there are alterations in targets not included in the panel or others not detectable by this analysis due to inherent analytical limitations. Clinical correlation is recommended.

Laboratory Director Joseph Michael Anderson, MD, FCAP
CLIA ID Number: 05D2200843 D TBC-LHI V1.0

Lucence Health Inc. 3520 West Bayshore Road, Palo Alto, CA 94303, USA
Tel: +1-(888)-LUCENCE (582-3623) Email: inquiry.us@lucence.com

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GENOMIC FINDINGS WITH CLINICAL ACTIONABILITY† (ctDNA)

Alteration	In Lung Adenocarcinoma or Related	In Other Indications
EGFR P753_I759delinsG (45.42%)	**Sensitive:** **Dacomitinib** (NSCLC, FDA Approval), **Erlotinib** (NSCLC, FDA Approval), **Gefitinib** (NSCLC, FDA Approval), **Afatinib** (NSCLC, FDA Approval), **Osimertinib** (NSCLC, FDA Approval), **Erlotinib + Ramucirumab** (NSCLC, FDA Approval), **Amivantamab + Lazertinib** (NSCLC, FDA Approval), **Amivantamab** (NSCLC, FDA Approval), **Datopotamab Deruxtecan** (NSCLC, FDA Approval),	**Sensitive:** **Bevacizumab + Erlotinib** (Lung Non-Squamous Non-Small Cell Carcinoma, Guidelines)

† FDA Approval, Breakthrough Designation, Professional Guidelines Recommendations, Phase III Clinical Trials Results, or Compelling Clinical Evidence.

GENOMIC FINDINGS WITH UNCERTAIN CLINICAL ACTIONABILITY (ctDNA)

Alteration	VAF % or Fold Change
EGFR A289T	38.02%
CTNNB1 G34E	28.12%
CDKN2A Copy Number Loss	1.89 Fold
EGFR Copy Number Gain	1.53 Fold

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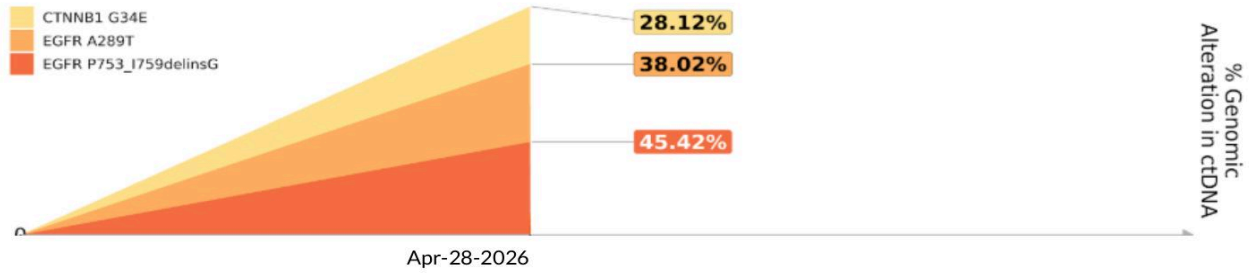
ctDNA PERCENTAGE MAP

The ctDNA percentage map shows the frequency of observed genomic alterations in circulating tumor DNA (%ctDNA) at the time point that the patient's sample was tested. Only selected single nucleotide variants / small indels of potentially somatic status have been presented. Certain variant types like ctDNA copy number alterations (CNAs) and microsatellite instability (MSI) are not plotted on this same map. ctDNA percentage map is for visualization purposes only and is not drawn to scale. Clinical correlation is advised.



ctDNA PERCENTAGE TABLE

The ctDNA percentage table shows the genomic findings and its associated variant allele frequency (%) / copy number fold change from ctDNA at the testing time point.

Alteration	CS-SG-26-XXXXX Apr-28-2026
EGFR P753_I759delinsG	45.42%
EGFR A289T	38.02%
CTNNB1 G34E	28.12%
CDKN2A Copy Number Loss	1.89 fold
EGFR Copy Number Gain	1.53 fold

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TARGETED CLINICAL TRIALS FOR GENOMIC FINDINGS (ctDNA)

Clinical trials that meet inclusion and exclusion criteria for genomic findings from ctDNA, and selected biomarkers are ranked by proximity of trial location to ordering medical facility and phase of trial. This is not a comprehensive list of all clinical trials available. Details are provided for top 20 trial matches and up to 30 additional trials are listed. Listed trials may have additional criteria from medical and treatment history required for final eligibility.

NCT05401110: Study of Osimertinib With Carotuximab in Advanced, EGFR-mutated Non-Small Cell Lung Cancer	**Phase:** Phase1. **Status:** Recruiting. **Locations:** California. **Disease Inclusions:** Lung Non-Small Cell Carcinoma, Lung Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation.
NCT04412616: ZZ06 in Adult Patients With Advanced EGFR Positive Solid Tumor Malignancies	**Phase:** Phase1. **Status:** Recruiting. **Locations:** California, Jilin, Kansas, New York. **Disease Inclusions:** Malignant Solid Neoplasm. **Variant Inclusions:** EGFR Mutation.
NCT04429542: Study of Safety and Tolerability of BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-driven Advanced Solid Tumors	**Phase:** Phase1. **Status:** Recruiting. **Locations:** California, Florida, Massachusetts, New South Wales, New York, North Carolina, Ohio, Ontario, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Victoria. **Disease Inclusions:** Malignant Solid Neoplasm. **Variant Inclusions:** EGFR Mutation.
NCT05315700: Study of ORIC-114 in Patients With Advanced Solid Tumors Harboring an EGFR or HER2 Alteration	**Phase:** Phase1/Phase2. **Status:** Recruiting. **Locations:** California, Connecticut, District of Columbia, England, Florida, Illinois, Massachusetts, Minnesota, New York, North Carolina, Ontario, Pahang, Pennsylvania, Pulau Pinang, Sarawak, South Carolina, Virginia. **Disease Inclusions:** Malignant Solid Neoplasm. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Leptomeninges, Malignant Central Nervous System Neoplasm. **Variant Inclusions:** EGFR Mutation. **Variant Exclusions:** EGFR T790M.
NCT06417814: A Phase III, Open-label, Sponsor-blind, Randomized Study of Dato-DXd With or Without Osimertinib Versus Platinum-based Doublet Chemotherapy for Participants With EGFR-mutated Locally Advanced or Metastatic Non-small Cell Lung Cancer Whose Disease Has Progressed on Prior Osimertinib Treatment (TROPION-Lung15)	**Phase:** Phase3. **Status:** Recruiting. **Locations:** Arkansas, California, Colorado, Florida, Georgia, Illinois, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Nebraska, New Jersey, New York, Ohio, Ontario, Pennsylvania, Quebec, Tennessee, Virginia, Washington. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Brain, Metastatic Malignant Neoplasm in the Leptomeninges. **Variant Inclusions:** EGFR Exon 19 Deletion.
NCT06745908: ResQ201A: Randomized, Open-Label, Phase 3 Clinical Trial of N-803 Plus Tislelizumab and Docetaxel Versus Docetaxel Monotherapy in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Acquired Resistance to Immune Checkpoint	**Phase:** Phase3. **Status:** Recruiting. **Locations:** Arkansas, California, Florida, Georgia, Ohio, Tennessee. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation. **Variant Exclusions:** ALK Fusion.

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Inhibitor Therapy	
NCT07100080: IZABRIGHT-Lung01: A Randomized, Open-label, Phase 2/3 Study of Izalontamab Brengitecan (BMS-986507) Versus Platinum-based Chemotherapy in Patients With EGFR-mutated Non-small Cell Lung Cancer and Disease Progression on EGFR Tyrosine Kinase Inhibitor Therapy	**Phase:** Phase2/Phase3. **Status:** Recruiting. **Locations:** Aichi-ken, Alberta, Alsace, Antwerpen, Attikí, Baden-Wurttemberg, Bangkok, Barcelona [Barcelona], Bavaria, Beijing Municipality, Bruxelles-Capitale, Région de, București, Buenos Aires, Buenos Aires F.D., Buskerud, California, Canton of Aargau, Canton of St. Gallen, Catalunya [Cataluña], Cesar Department, Changwat Khon Kaen, Chiba, Chongqing Municipality, Chungcheongbuk-do [Chungbuk], Cluj, Colorado, Cundinamarca, Córdoba Province, Departamento de Córdoba, Dolj, Ehime, Emilia-Romagna, Florida, Friuli Venezia Giulia, Fujian, Fukuoka, Gelderland, Georgia, Glasgow City, Guangdong, Gujarat, Haryana, Haute-Garonne, Hauts-de-France, Henan, Hokkaido, Hordaland, Hubei, Hunan, Hyōgo, Illinois, Isère, Jiangsu, Jiangxi, Jilin, Kanagawa, Karnataka, Kensington and Chelsea, Kentrikí Makedonía, Kyŏnggi-do, Liaoning, Loire-Atlantique, London, City of, Lower Saxony, Lublin Voivodeship, Madrid, Comunidad de, Maharashtra, Massachusetts, Mexico City, Missouri, Miyagi, Namur, National Capital Territory of Delhi, Nevada, New York, North Holland, North Rhine-Westphalia, Oaxaca, Ohio, Okayama-ken, Ontario, Oost-Vlaanderen, Oregon, Osaka, Pennsylvania, Piedmont, Pomeranian Voivodeship, Quebec, Rhône, Saitama, Santiago Metropolitan, Saxony, Schleswig-Holstein, Seoul-teukbyeolsi [Seoul], Shandong, Shanghai Municipality, Shanxi, Shizuoka, Tennessee, Texas, Thessaloníki, Tokyo, Torino, Val-de-Marne, Valle del Cauca Department, Virginia, West Bengal, Zhejiang. **Disease Inclusions:** Lung Non-Squamous Non-Small Cell Carcinoma. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Leptomeninges, Metastatic Malignant Neoplasm in the Spinal Cord. **Variant Inclusions:** EGFR Exon 19 Deletion.
NCT06868485: A Phase II, Open Label, Multicenter, Single Arm Study of WSD0922-FU for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with First-Line Osimertinib Treatment and Harbor a C797S Mutation	**Phase:** Phase2. **Status:** Recruiting. **Locations:** California, Florida, Fujian, Hubei, Ille-et-Vilaine, Michigan, New Jersey, Normandy, Nouvelle-Aquitaine, Ohio, Pennsylvania, Shanghai Municipality, Texas, Tianjin Municipality, Var, Virginia. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation.
NCT05579366: Phase 1/2 Study of PRO1184 in Patients With Locally Advanced and/or Metastatic Solid Tumors	**Phase:** Phase1/Phase2. **Status:** Recruiting. **Locations:** Arizona, Beijing Municipality, California, China, Chongqing Municipality, Florida, Fukushima, Georgia, Gunma, Hokkaido, Hunan, Hyōgo, Jiangxi, Jilin, Kansas, Maryland, Massachusetts, Michigan, Minnesota, New Jersey, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, Saitama, Shanghai Municipality, Shizuoka, Sichuan, Tennessee, Texas, Tokyo, Utah, Virginia, Washington, Yamagata, Zhejiang. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Mutation, EGFR Sensitizing Mutation.
NCT06706076: A Phase 1/2 Open-Label, Multicenter, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BH-30643 in Subjects with Locally Advanced or Metastatic NSCLC Harboring EGFR And/or HER2 Mutations (SOLARA)	**Phase:** Phase1/Phase2. **Status:** Recruiting. **Locations:** Alberta, Arizona, California, Chiba, Connecticut, District of Columbia, Florida, Illinois, Massachusetts, Michigan, Minnesota, New Territories, Ontario, Osaka, Pennsylvania, Sarawak, Tennessee, Texas, Tokyo, Victoria, Virginia, Washington. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Lung Small Cell Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation. **Variant Exclusions:** BRAF Predefined Mutation, MET Exon 14 Skipping, MET Copy Number Gain, ALK Fusion, RET Fusion, ROS1 Fusion, NTRK1 Fusion, NTRK2 Fusion, NTRK3 Fusion, KRAS G12C.

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NCT06956690: A First-in-Human, Open-label, Phase 1/2 Clinical Trial to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of ENV-501 in Patients With Advanced-Stage, Relapsed/Refractory HER3-Expressing Solid Tumors	**Phase:** Phase1/Phase2. **Status:** Recruiting. **Locations:** California, Indiana, Michigan, New South Wales, Texas. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Leptomeninges, Metastatic Malignant Neoplasm in the Brain. **Variant Inclusions:** EGFR Sensitizing Mutation.
NCT04181060: AZD9291 (Osimertinib) With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer	**Phase:** Phase3. **Status:** Recruiting. **Locations:** Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Virginia, Washington, West Virginia, Wisconsin, Wyoming. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Lung Squamous Cell Carcinoma. **Variant Inclusions:** EGFR Activation Mutation. **Variant Exclusions:** EGFR Exon 20 Insertion.
NCT05261399: Savolitinib Plus Osimertinib Versus Platinum-based Doublet Chemotherapy in Participants With Non-Small Cell Lung Cancer Who Have Progressed on Osimertinib Treatment (SAFFRON)	**Phase:** Phase3. **Status:** Recruiting. **Locations:** Alberta, California, Florida, Hawaii, Illinois, Massachusetts, Michigan, New Jersey, New York, Ohio, Ontario, Quebec, Tennessee. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Lung Squamous Cell Carcinoma, Lung Small Cell Carcinoma, Metastatic Malignant Neoplasm in the Leptomeninges. **Variant Inclusions:** EGFR Sensitizing Mutation.
NCT06350097: A Phase III, Open-label, Randomised Study of Osimertinib With or Without Datopotamab Deruxtecan (Dato-DXd), as First-line Treatment in Participants With Epidermal Growth Factor Receptor (EGFR) Mutation-positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer	**Phase:** Phase3. **Status:** Recruiting. **Locations:** Alberta, California, Connecticut, District of Columbia, Florida, Hawaii, Illinois, Indiana, Maryland, Michigan, Minnesota, Missouri, Nevada, New York, Quebec, Texas, Virginia, Washington, Wisconsin. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Brain. **Variant Inclusions:** EGFR Exon 19 Deletion.
NCT04410796: Osimertinib Alone or With Chemotherapy for EGFR-Mutant Lung Cancers	**Phase:** Phase2. **Status:** Recruiting. **Locations:** California, Florida, Maryland, Massachusetts, New Jersey, New York, Tennessee, Texas, Washington. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Activation Mutation.
NCT05456256: Phase II Trial of LP-300 in Combination With Carboplatin and Pemetrexed in Never Smoker Patients With Relapsed Advanced Primary Adenocarcinoma of the Lung After Treatment With Tyrosine Kinase Inhibitors (The HARMONIC Study)	**Phase:** Phase2. **Status:** Recruiting. **Locations:** California, Hokkaido, Kanagawa, Miyagi, Okayama-ken, Pennsylvania, Texas, Tokyo, Virginia. **Disease Inclusions:** Lung Adenocarcinoma. **Disease Exclusions:** Lung Small Cell Carcinoma, Lung Squamous Cell Carcinoma, Lung Large Cell Carcinoma, Malignant Mesothelioma, Combined Lung Small Cell Carcinoma and Lung Adenocarcinoma, Adenosquamous Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation.

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NCT05498428: A Study of Amivantamab in Participants With Advanced or Metastatic Solid Tumors Including Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer (PALOMA-2)	**Phase:** Phase2. **Status:** Recruiting. **Locations:** California, District of Columbia, Florida, Kansas, Maryland, Massachusetts, Missouri, New Jersey, New York, North Carolina, Ohio, Utah, Virginia, Washington. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Disease Exclusions:** Metastatic Malignant Neoplasm in the Brain. **Variant Inclusions:** EGFR Exon 19 Deletion.
NCT05642572: Comparing Combinations of Targeted Drugs for Advanced Non-Small Cell Lung Cancer That Has EGFR and MET Gene Changes (A Lung-MAP Treatment Trial)	**Phase:** Phase2. **Status:** Recruiting. **Locations:** Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Sensitizing Mutation.
NCT05967689: An Open-Label, Phase 2b, Global Multicenter Cohort Trial to Assess the Safety and Efficacy of Zipalertinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer With Exon 20 Insertion and Uncommon/Single or Compound Epidermal Growth Factor Receptor Mutations	**Phase:** Phase2. **Status:** Recruiting. **Locations:** Aichi-ken, Alabama, Aslace, Auvergne-Rhône-Alpes, Basse-Normandie, California, Chiba, England, Florence, Forli-Cesena, Gyeonggi-do, Gyeongsangnamdo [Kyongsangnam-do], Hassen, Hong Kong Island, Hukuoka, Incheon Gwang'yeogsi [Inch'on-Kwangyokshi], Istanbul, Jeollanam-do, Limousin, Malaga, Massachusetts, Miyagi, Nevada, New Jersey, New South Wales, New York, Niigata, Nouvelle-Aquitaine, Ohio, Osaka, Provence-Alpes-Côte d'Azur Region, Seoul Teugbyeolsi [Seoul-T'ukpyolshi], Shizuoka, Tennessee, Texas, Tokyo, Virginia, Western Australia, Wisconsin, Île-de-France Region. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Mutation.
NCT06010329: A Multicenter, Open-label, Phase 2 Study to Evaluate the Efficacy and Safety of Sutetinib Maleate Capsule in Locally Advanced or Metastatic NSCLC (Uncommon EGFR Mutations Only)	**Phase:** Phase2. **Status:** Recruiting. **Locations:** California, Florida, Georgia, Iowa, Kentucky, New York, Texas. **Disease Inclusions:** Lung Non-Small Cell Carcinoma. **Variant Inclusions:** EGFR Mutation. **Variant Exclusions:** EGFR Resistance Mutation.

More:

NCT06014827, NCT06120140, NCT04486833, NCT05519293, NCT05394831, NCT04085315, NCT05083481, NCT05948865, NCT05983432, NCT06507306, NCT06804824, NCT07155187, NCT06741085, NCT06567015, NCT06618287, NCT06685718, NCT06905197, NCT07315113, NCT03586453, NCT03797391, NCT05068024, NCT03891615, NCT04762199, NCT04780568, NCT05076760, NCT06043713, NCT07111520

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ctDNA SEQUENCING PERFORMANCE SPECIFICATIONS

	SNVs/Indels
Raw on-target reads	15,316,629
Unique on-target reads (non-duplicates)	2,541,272
Mean depth of coverage	8,410.53
Uniformity: Pct reads > 0.2*Mean	99.38%
Coverage	99.76% (50x), 99.76% (100x), 98.76% (1000x)

DEFINITIONS

LEVELS OF CLINICAL ACTIONABILITY OF GENOMIC FINDINGS

Categorization of Clinical actionability is guided by AMP/ASCO/CAP consensus recommendation for the interpretation and reporting of sequence variants in cancer (PMID: 27993330, PMID: 32246132). Clinical actionability corresponds to Tier 1 evidence level (FDA, guidelines, well-powered studies with expert consensus), of the AMP/ASCO/CAP consensus recommendations.

Description	Therapy association with Finding	Criteria
CLINICAL ACTIONABILITY	Sensitive	Therapies with FDA Approval, FDA Breakthrough Designation, from Professional Guidelines, or with results from Phase III trials in Relevant Indication or in Other Indications available for Genomic findings.
	Resistance	Therapies with FDA Approval, FDA Breakthrough Designation, from Professional Guidelines, or with results from Phase III trials or Compelling Clinical Evidence from Clinical Studies and/or Case Reports in Relevant Indication or in Other Indications available for Genomic findings.
UNCERTAIN CLINICAL ACTIONABILITY	-	No therapies meeting criteria for Clinical Actionability / Evidence are available, although such Genomic findings may have prognostic impact in Relevant Indication. A subset of findings may have Evidence from Clinical Trials, Studies or Reports, which are provided.

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TEST DETAILS

The LiquidHALLMARK® CSF assay is a next-generation sequencing (NGS) based test that identifies targeted somatic genomic alterations including single nucleotide variations, copy number variations, and microsatellite instability (MSI) in circulating tumor DNA (ctDNA) (PMID: 35486650).

This clinical test was developed and its performance characteristics determined by Lucence Health Inc. It has not been cleared or approved by the US 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, unless otherwise stated above. Lucence Health Inc. is a Clinical Laboratory Improvement Amendments (CLIA)-certified clinical diagnostic laboratory (CLIA ID Number: 05D2200843) and is accredited to College of American Pathologists (CAP) laboratory quality standards.

VALIDATED GENOMIC ALTERATIONS TESTED (ctDNA)(v1)

SINGLE NUCLEOTIDE VARIANTS, INDELS AND GENE COPY NUMBER ALTERATIONS*

ABL1	*CDKN2A* #	*GNA11*	*KEAP1*[1]	*NRAS* #	*RIT1*
AKT1 [1]	*CREBBP*	*GNAQ*	*KIT* #	*NTRK1*	*ROS1*
ALK #	*CTNNB1*	*GNAS*	*KRAS* #	*NTRK3*	*SF3B1*
APC	*EGFR* #†	*H3-3A*	*MAP2K1* (MEK1)	*PDGFRA* #	*SMAD4* #1
AR #	*ERBB2* (HER2) #	*H3-3B*	*MAP2K2* (MEK2)	*PIK3CA* #1	*SMO*
ARAF	*ERCC2*	*H3C2*	*MAPK1* (ERK2)	*PIK3R1*	*SPOP*
ATM #	*ESR1* #	*H3C3*	*MED12*	*PPP2R1A*	*STK11*
BRAF #	*EZH2*	*HNF1A*	*MET* #	*PTEN* #^	*TERT*
BRCA1 #1	*FBXW7* #	*HRAS*	*MLH1*	*PTPN11*	*TP53* #1
BRCA2 #1	*FGFR1* #	*IDH1*	*MTOR*	*RAF1*	*U2AF1*
CCND1 #	*FGFR2* #	*IDH2*	*MYC* #	*RB1* #	*VHL*
CCND2 #1	*FGFR3* #	*JAK1*	*NF1*	*RET*	
CDH1	*FLT3*	*JAK2*	*NFE2L2*	*RHEB*	
CDK6 #1	*GATA3*	*JAK3*	*NOTCH1*	*RHOA*	

*Targeted regions selected to maximize detection of known hotspot mutations, in all clinically relevant exons of tested genes.
†Includes sequencing of EGFR kinase and extracellular domain mutations.
Includes detection of gene copy number alterations.
^Full coverage, [1]>97% coverage of coding exons.

MICROSATELLITE INSTABILITY (MSI)

BAT25	BAT26	NR21	NR24	NR27	MONO27

TARGETED GENES REFERENCE TRANSCRIPTS

ABL1	NM_005157.6	*EZH2*	NM_004456.5	*JAK3*	NM_000215.4	*PIK3R1*	NM_181523.3
AKT1	NM_001014432.2	*FBXW7*	NM_033632.3	*KEAP1*	NM_203500.2	*PPP2R1A*	NM_014225.6
ALK	NM_004304.5	*FGFR1*	NM_023110.3	*KIT*	NM_000222.3	*PTEN*	NM_000314.8
APC	NM_000038.6	*FGFR2*	NM_000141.5	*KRAS*	NM_033360.4	*PTPN11*	NM_002834.5
AR	NM_000044.6	*FGFR3*	NM_000142.5	*MAP2K1*	NM_002755.4	*RAF1*	NM_002880.4
ARAF	NM_001654.5	*FLT3*	NM_004119.3	*MAP2K2*	NM_030662.4	*RB1*	NM_000321.3
ATM	NM_000051.4	*GATA3*	NM_001002295.2	*MAPK1*	NM_002745.5	*RET*	NM_020975.6
BRAF	NM_004333.6	*GNA11*	NM_002067.5	*MED12*	NM_005120.3	*RHEB*	NM_005614.4
BRCA1	NM_007294.4	*GNAQ*	NM_002072.5	*MET*	NM_000245.4	*RHOA*	NM_001664.4
BRCA2	NM_000059.4	*GNAS*	NM_000516.7	*MLH1*	NM_000249.4	*RIT1*	NM_006912.6
CCND1	NM_053056.3	*H3-3A*	NM_002107.7	*MTOR*	NM_004958.4	*ROS1*	NM_002944.3
CCND2	NM_001759.4	*H3-3B*	NM_005324.5	*MYC*	NM_002467.6	*SF3B1*	NM_012433.4
CDH1	NM_004360.5	*H3C2*	NM_003537.4	*NF1*	NM_001042492.3	*SMAD4*	NM_005359.6
CDK6	NM_001145306.2	*H3C3*	NM_003531.3	*NFE2L2*	NM_006164.5	*SMO*	NM_005631.5

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CDKN2A	NM_000077.5	*HNF1A*	NM_000545.8	*NOTCH1*	NM_017617.5	*SPOP*	NM_001007228.2
CREBBP	NM_004380.3	*HRAS*	NM_005343.4	*NRAS*	NM_002524.5	*STK11*	NM_000455.5
CTNNB1	NM_001904.4	*IDH1*	NM_005896.4	*NTRK1*	NM_002529.4	*TERT*	NM_198253.3
EGFR	NM_005228.5	*IDH2*	NM_002168.4	*NTRK3*	NM_001012338.3	*TP53*	NM_000546.6
ERBB2	NM_004448.4	*JAK1*	NM_002227.4	*PDGFRA*	NM_006206.6	*U2AF1*	NM_006758.3
ERCC2	NM_000400.4	*JAK2*	NM_004972.4	*PIK3CA*	NM_006218.4	*VHL*	NM_000551.4
ESR1	NM_000125.4						

METHODS

Amplicon-based sequencing analysis is carried out by proprietary technology owned by Lucence. Nucleic acid (cfDNA) is extracted from the cerebrospinal fluid (CSF) sample. The extracted DNA undergoes sequencing library construction for genes targeted in the LiquidHALLMARK® CSF assay. Quality and concentration of constructed libraries are determined and then sequenced on an Illumina NextSeq/NovaSeq instrument with 2x150 paired-end reads. Targeted regions listed in the Tested Genomic Alterations (ctDNA) section or a relevant subset of the list, selected to maximize detection of known hotspot mutations, are analyzed for sequence variants. List available on physician request. Six microsatellite loci (BAT25, BAT26, NR21, NR24, NR27, MONO27) are analyzed for insertions/deletions in homopolymeric regions. Samples with microsatellite instability (MSI) detected in two or more of six sites are considered MSI-High (MSI-H) and those with MSI detected in one of six sites are considered MSI-Low (MSI-L). Sequences are aligned to reference sequences based on human genome build GRCh37/UCSC hg19. Data is analyzed using in-house bioinformatics pipelines, and proprietary sequencing error-correction methodology is applied on raw sequencing data. Copy number changes are calculated based on adjusted read count, and its variation from normalized baseline read count determined across control samples. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines as published in PMID: 26931183 (HGVS nomenclature v15.11, 2016). Clinical actionability of genomic findings is determined based on curated databases from publicly available data sources, including peer-reviewed publications of genomic alterations and biomarkers and associated drugs. Tiering of clinical actionability is based on AMP/ASCO/CAP consensus recommendation (PMID: 27993330, PMID: 32246132) where clinical actionability are based on Tier 1 evidence level (FDA, guidelines, Phase III trials, well-powered studies with expert consensus). Drug and clinical trial information are obtained from curated databases including NCI thesaurus and ClinicalTrials.gov. Clinical trial curated database is updated with trials verified within the last month.

ANALYTICAL AND CLINICAL PERFORMANCE SPECIFICATIONS

Test performance specifications are determined using commercial ctDNA standards, contrived samples including cell line DNA, and CSF clinical samples for specific variants at varying allele frequencies described below. Specificity has been determined for the entirety of bases targeted in the assay and it is not variant- or hotspot-specific. The limit of detection for SNVs/indels is determined to be 0.1% and 0.75% based on 25ng and 5ng input, respectively. For copy number alterations, the limit of detection has been determined to be an excess of 2 copies for a copy number gain of 2-fold (2 vs. 4), and a deficiency of 1 copy for a copy number loss of 2-fold (2 vs. 1). The limit of detection for microsatellite instability is determined to be 5% DNA with insertions/deletions in the microsatellite loci in the background of normal DNA.

Input DNA (ng)	Mutation Class	Sensitivity By Mutant Allele Frequency					Specificity
		0.1%	0.5%	0.75%	2.5%	5%	
25	SNVs	>90%	>99%	-	-	>99%	>95%
	Indels	>93%	>99%	-	-	>99%	>91%
5	SNVs	-	-	>99%	>99%	-	>95%
	Indels	-	-	>98%	>99%	-	>91%

The clinical performance characteristics of this test are based on known associations with genomic alterations and response to or selection for therapy in the clinical literature, professional society guidelines and clinical trials databases (PMID: 26378224, PMID: 28365644, PMID: 27601506, PMID: 35426374, PMID: 27993330, clinicaltrials.gov).

This report has been reviewed and approved by	Date and Time
Joseph Michael Anderson, MD, FCAP Laboratory Director	May 04 2026, 1930 hrs (PDT)

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PATIENT
MRN:

DOB:
Age: | Sex:

APPENDIX

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FINDINGS WITH ACTIONABILITY EVIDENCE FROM CLINICAL TRIALS (PHASE I-II), CLINICAL STUDIES, OR CASE REPORTS

GENOMIC FINDINGS (ctDNA)

Alteration	In Lung Adenocarcinoma or Related
EGFR P753_I759delinsG (45.42%)	**Sensitive:** **Gefitinib + Metformin** (Phase 2), **Erlotinib + Metformin** (Phase 2), **Afatinib + Metformin** (Phase 2), **Tesevatinib** (NSCLC, Phase 2), **Lazertinib** (NSCLC, Early Trials), **Osimertinib + Selumetinib** (NSCLC, Phase 1), **Erlotinib + Nimotuzumab** (Case Report), **TAS-121** (NSCLC, Case Report)
EGFR A289T (38.02%)	**Sensitive:** **Icotinib** (NSCLC, Case Report)
CDKN2A Copy Number Loss (1.89 Fold)	**Sensitive:** **Palbociclib** (Clinical Study)

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DESCRIPTION OF GENOMIC FINDINGS (ctDNA)

Gene: EGFR

EGFR (epidermal growth factor receptor) is an oncogene (PMID:25979928). Somatic alterations in EGFR commonly occur in glioma and NSCLC. Germline alterations in EGFR are also common in NSCLC. Frequent alterations of EGFR in cancer include amplification (PMID:9790506), overexpression (PMID:15142631), missense mutations (PMID:9790506, PMID:27727438), and inframe indels (PMID:9790506).

EGFR in Lung Cancer

EGFR is a trans-membrane glycoprotein which regulates several signalling pathways to control cellular proliferation, once ligand binding in its extracellular domain triggers cytoplasmic kinase activity of its tyrosine kinase (TK) domain (PMID:22263017). Mutations in the EGFR TK domain can result in constitutive activation of signal transduction pathways, leading to cell proliferation or anti-apoptosis, regardless of the presence of any extracellular ligand. EGFR alterations leading to increased tyrosine kinase activity are implicated in the development and progression of many types of cancer. The majority of EGFR alterations cluster around the ATP-binding pocket within exons 18-21. Better prognosis is generally observed in EGFR-mutant NSCLC (including EGFR L858R) compared to EGFR wild type NSCLC (PMID:17285735, PMID:28826599, PMID:19096302, PMID:18303429).

Roles of EGFR in the Hallmarks of Cancer

EGFR plays a role in 5 of the 10 hallmarks of cancer described by Hanahan and Weinberg (PMID:21376230), as demonstrated in the functional assays in vitro and in vivo.

- **Sustaining proliferative signaling:** Promotes cell proliferation (PMID:15142631); MiR-133a inhibits cervical cancer growth by targeting EGFR (PMID:26134491)
- **Activating invasion & metastasis:** EGFR-L858R mutant enhances lung adenocarcinoma cell invasive ability and promotes malignant pleural effusion formation through activation of the CXCL12-CXCR4 pathway (PMID:26338423); Upregulation of EGFR and c-Met is associated with epithelial mesenchymal transition in response to increased matrix rigidity in lung adenocarcinoma (PMID:26000960); Promotes metastasis by altering mitochondrial dynamics in NSCLC (PMID:26497368)
- **Inducing angiogenesis:** Activation of the EGFR pathway is involved in tumour associated angiogenesis (PMID:16152621)
- **Resisting cell death:** Activation of EGFR protects against anoikis (PMID:12517767); Activating mutations within the tyrosine kinase domain activate anti-apoptotic pathways (PMID:15284455)
- **Deregulating cellular energetics:** EGFR inhibitors reverse Warburg effect and reactivate oxidative phosphorylation of cancer cells in NSCLC (PMID:26216352); EGFR signalling enhances aerobic glycolysis in Triple-Negative Breast Cancer cells to promote tumour growth and immune escape (PMID:26759242); Stimulates mitochondrial fission and redistribution in the lamellipodia, upregulates cellular ATP production, and enhances motility in vitro and in vivo in NSCLC (PMID:26497368)

EGFR Mutation Frequencies in Cancer

From the latest release of COSMIC (v98, PMID:30371878), of 209516 samples sequenced for EGFR for all cancer types, 15% or 30468 were reported to have somatic mutations in EGFR. The most frequently reported EGFR mutations are EGFR L858R and exon 19 deletion mutations.

EGFR exon 19 deletion and EGFR L858R mutations are the most common EGFR mutations in NSCLC (26-40%) in Asian and North American populations (PMID:18458038, PMID:23242437, PMID:23207445, PMID:15604253, PMID:15681531), and has been reported to be as high as 62.5% (PMID:26933124). EGFR exon 20 mutations are rare but account for about 9% of all EGFR mutated lung adenocarcinomas (PMID:23371856).

Among solid tumors, 15% (30220 of 196837) samples had EGFR mutations, and among hematological cancers, 1.6% (183 of 11766) samples had EGFR mutations.

EGFR Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, EGFR mutations have been reported at a frequency of 30% (16028 of 52833 samples). In samples other than Lung Adenocarcinoma, the frequency of EGFR mutations is 9.2% (14440 of 156683 samples).

Drug Actionability of EGFR

Alterations in EGFR are used to guide selection of patients for treatment for Lung Non-Small Cell Carcinoma with Icotinib, Erlotinib, Dacomitinib, Gefitinib, and Afatinib (FDA, FDA, FDA, FDA, PMID:34327360) and Lung Non-Squamous Non-Small Cell Carcinoma with Amivantamab and Bevacizumab + Erlotinib (PMID:38754467), among others.

Furthermore, EGFR is the subject of active investigation for multiple targeted therapies in early trials or preclinical studies, including for Lung Adenocarcinoma (PMID:22982663, PMID:28676220, PMID:30746257), Lung Non-Small Cell Carcinoma (PMID:22722787, PMID:27928026, PMID:30351341), Colorectal Carcinoma (PMID:22270724, PMID:24894453, PMID:25962717), Glioblastoma (PMID:31154523, PMID:32034072), and Breast Carcinoma (PMID:29533458).

In addition to being actionable drug targets, EGFR mutations are also correlated with resistance to targeted therapies in Colorectal Carcinoma (PMID:25623215, PMID:26059438), Lung Adenocarcinoma (PMID:27499993, PMID:35712479), and Lung Non-Small Cell Carcinoma (PMID:29857056, PMID:38754467).

Alteration: EGFR P753_I759delinsG

EGFR P753_I759delinsG is a gain of function and oncogenic inframe deletion within exon 19 of EGFR. This mutation has not been observed as germline polymorphism among samples documented in GnomAD (GnomAD v2.1.1).

Clinical Actionability

Inframe indel

Mutation Frequencies in Cancer

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MRN: Age: | Sex:

HGVS:
chr7:g.55242486_55242507delinsCGGA,
NP_005219.2:p.Pro753_Ile759delinsGly,
NM_005228.5:c.2256_2277delinsCGGA

VAF %: 45.42%

From the latest release of COSMIC (v98, PMID:30371878), EGFR P753_I759delinsG has been reported in none of the 209516 samples of all cancer types tested for mutations in EGFR.

Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, EGFR P753_I759delinsG has been reported in 0% of samples (0 of 52833), compared to 0% of samples (0 of 156683) belonging to all other cancer types.

Alteration: EGFR A289T

Uncertain Clinical Actionability

Missense variant

HGVS:
chr7:g.55221821G>A,
NP_005219.2:p.Ala289Thr,
NM_005228.5:c.865G>A

VAF %: 38.02%

EGFR A289T is a gain of function and oncogenic mutation within exon 7 of EGFR. In the ClinVar database, EGFR A289T is classified as a variant of uncertain significance (ClinVar ID: 376395). This mutation has not been observed as germline polymorphism among samples documented in GnomAD (GnomAD v2.1.1).

Mutation Frequencies in Cancer

From the latest release of COSMIC (v98, PMID:30371878), EGFR A289T has been reported in 0.017% (35 of 209516) samples of all cancer types tested for mutations in EGFR. Among samples positive for EGFR A289T, the most frequent cancer types annotated are: Brain Glioblastoma (71%), Cerebral Glioblastoma (5.7%), Anaplastic Astrocytoma (5.7%), and Esophageal Leukoplakia (5.7%).

The frequency of EGFR A289T among solid tumors is 0.017% (33 of 196837 samples), and among hematological cancers the frequency is 0% (0 of 11766 samples).

Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, EGFR A289T has been reported in 0.0019% of samples (1 of 52833), compared to 0.022% of samples (34 of 156683) belonging to all other cancer types.

Alteration: EGFR Copy Number Gain

Uncertain Clinical Actionability

Copy number change: 1.53 Fold

EGFR Copy Number Gain involves the increase in genomic copy number of EGFR, including amplifications.

EGFR gene amplification has been reported in 26 of 290 (9.0%) non-small cell lung cancer (NSCLC) patients, and was more frequently seen in patients harboring EGFR mutation (exon 19 deletion or L858R) than those with wild-type EGFR (41.2% vs. 7.0%) (PMID:26722081). EGFR wild-type allele amplification is a potential mechanism of resistance to third-generation TKI osimertinib (PMID:28202511, PMID:26473643, IASLC).

EGFR copy number gain has been observed in several cancer types including central nervous system cancer (28.64%), esophageal cancer (10.38%), upper aerodigestive tract cancer (9.53%), lung cancer (7.26%), and urinary tract cancer (5.04%) in the COSMIC database (v98, PMID: 30371878).

Gene: CDKN2A

CDKN2A (cyclin dependent kinase inhibitor 2A) is a tumor suppressor gene (PMID:12789286). Somatic alterations in CDKN2A commonly occur in melanoma and multiple other tumour types. Germline alterations in CDKN2A are also

common in melanoma and pancreatic cancer. Frequent alterations of CDKN2A in cancer include deletion (PMID:27727438), missense mutations (PMID:27727438), and truncating mutations (PMID:27727438).

CDKN2A encodes two alternate reading frame proteins, p16INK4a and p14ARF (PMID:9823374). The specific binding of the p16INK4a protein to CDK4 or CDK6 induces an allosteric conformational change in these proteins and inhibits the formation of the complex between CDK4 or 6 and cyclin D (PMID:8259215). With the lack of complex formation, the retinoblastoma protein (Rb) is retained at its hypo-phosphorylated and growth-suppressive states, thus leading to the induction of G1 phase cell cycle arrest through the formation of the Rb/E2Fs-repressive complex (PMID:7736585).

The loss of p16INK4a is increasingly common with advancing stages of various neoplasms (PMID:27428416). In various cancers, frequent inactivation of $p16^{INK4a}$ is reported to be induced by homozygous deletion or promoter hypermethylation and point mutation (PMID:27428416). Multiple studies in gastric, colorectal, and prostate cancers have described the associations of several genetic and epigenetic alterations of CDKN2A with enhanced tumorigenesis and metastasis, cancer recurrence and poor prognosis (PMID:24744581, PMID:23669186, PMID:26157509, PMID:23358881).

Roles of CDKN2A in the Hallmarks of Cancer

CDKN2A plays a role in 4 of the 10 hallmarks of cancer described by Hanahan and Weinberg (PMID:21376230), as demonstrated in the functional assays in vitro and in vivo.

- **Evading growth suppressors:** P14(ARF) inhibits the growth of human tumour cells lacking functional p53 by inducing a transient G(2) arrest and subsequently apoptosis (PMID:12660818); Inhibits cell proliferation through induction of cell-cycle arrest (PMID:8761411)
- **Activating invasion & metastasis:** P16(INK4A) inhibits the pro-metastatic potential of osteosarcoma cells through targeting the ERK pathway and TGF-beta 1 (PMID:25728247)
- **Inducing angiogenesis:** P16-negative tumours associate with increased circulating levels of pro-angiogenic VEGF and angiopoietin-1 in HNC (PMID:26171937)
- **Resisting cell death:** P14(ARF) prevents proliferation of aneuploid cells by activating p53-dependent apoptosis (PMID:25752701); P14(ARF) inhibits the growth of human tumour cells lacking functional p53 by inducing a transient G(2) arrest and subsequently apoptosis (PMID:12660818)

CDKN2A Mutation Frequencies in Cancer

From the latest release of COSMIC (v98, PMID:30371878), of 114406 samples sequenced for CDKN2A for all cancer types, 6.5% or 7489 were reported to have somatic mutations in CDKN2A. CDKN2A mutations are frequently observed in central nervous system, non-small cell lung and biliary tract cancers (PMID:30371878) and common alterations include truncating mutation, copy number loss and loss of heterozygosity (PMID:27428416). The most common

somatic mutation sites in CDKN2A are R80*, R58*, H83Y, W110*, and P114L (PMID:30371878).

Among solid tumors, 6.9% (6420 of 92593) samples had CDKN2A mutations, and among hematological cancers, 4.7% (955 of 20502) samples had CDKN2A mutations.

CDKN2A Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, CDKN2A mutations have been reported at a frequency of 5.9% (250 of 4205 samples). In samples other than Lung Adenocarcinoma, the frequency of CDKN2A mutations is 6.6% (7239 of 110201 samples).

Drug Actionability of CDKN2A

CDKN2A is the subject of active investigation for multiple targeted therapies in early trials or preclinical studies, including for Lung Adenocarcinoma (PMID:32669708) and Lung Squamous Cell Carcinoma (PMID:32669708).

Alteration: CDKN2A Copy Number Loss

Uncertain Clinical Actionability

Copy number change: 1.89 Fold

CDKN2A Copy Number Loss involves the decrease in genomic copy number of CDKN2A.

CDKN2A/p16 homozygous deletion, promoter methylation and more rarely, point mutations are commonly observed in non-small cell lung cancer (NSCLC) and lead to the inactivation of CDKN2A/p16 tumor suppressor. CDKN2A/p16 homozygous deletion is reported to be detected in 29% of NSCLC (PMID:18559592).

Coexistence of CDKN2A/p16 homozygous deletion and activating EGFR mutations is associated with a poor response to EGFR inhibitors (PMID:27987577, PMID:29106415). In a retrospective review of 127 NSCLC patients with activating EGFR mutations treated with either erlotinib or gefitinib, overall response rate in patients with and without CDKN2A homozygous deletion was 48.4% and 78.1% respectively (P=0.0027), and median progression-free survival was 5.3 months (95% CI, 4.582–6.018) and 10.5 months (95% CI, 9.365–11.635) respectively (PMID:27987577). CDKN2A/2B copy number loss has been reported in 3 cases of acquired resistance and 1 case of primary resistance to lorlatinib (PMID:29650534). In a case of lung carcinoma, CDKN2A loss was associated with sensitivity to palbociclib (PMID:32669708).

CDKN2A copy number loss has been observed in several cancer types including central nervous system cancer (34.73%), esophageal cancer (32.79%), urinary tract cancer (30.73%), skin cancer (27.71%), and pancreatic cancer (25.00%) in the COSMIC database (v98, PMID: 30371878).

Gene: CTNNB1

CTNNB1 (catenin beta 1) is an oncogene (PMID:26815163, PMID:10398436). Somatic alterations in CTNNB1 commonly occur in colorectal, ovarian cancer, hepatoblastoma, pleomorphic salivary gland adenoma, and other tumour types.

CTNNB1 (Beta-catenin) is a transcriptional activator, part of the canonical Wnt signaling pathway. Normally in the absence of Wnt signaling, glycogen synthase

kinase-3 (GSK-3) phosphorylates the beta catenin protein, targeting it for degradation via the ubiquitin-proteasome system. Most beta-catenin mutations occur in or around exon 3 of the CTNNB1 gene, affecting the putative phosphorylation sites for GSK-3, making it refractory to degradation, leading to increased transcription of downstream target genes of T-cell factor/lymphoid enhancing factor (TCF/LEF), for which beta-catenin is a co-factor (PMID:12781368). Activating mutations in CTNNB1 are implicated in the pathogenesis of melanoma, colorectal cancer, hepatocellular carcinoma, and ovarian cancer (PMID:12781368).

Roles of CTNNB1 in the Hallmarks of Cancer

CTNNB1 plays a role in 8 of the 10 hallmarks of cancer described by Hanahan and Weinberg (PMID:21376230), as demonstrated in the functional assays in vitro and in vivo.

- **Sustaining proliferative signaling:** Induced expression of stabilized beta-catenin results in exhibited increased proliferation in mouse fibroblasts (PMID:11983872); Knockdown significantly inhibits cell proliferation in mantle cell lymphoma (PMID:26227550); Knockdown decreases cell proliferation in mouse pituitary adenoma (PMID:25646597); Promotes cell proliferation in multiple myeloma (PMID:15067127)
- **Evading growth suppressors:** Elevated levels of nuclear beta-catenin in both primary tumors and metastases correlate with reduced expression of a marker of proliferation and with improved survival in melanoma (PMID:19144919)
- **Enabling replicative immortality:** Crucial for high-TERT-expression-mediated Cancer Stem Cell traits in prostate cancer (PMID:28209613); Regulates self-renewal networks and plays a central role in the control of pluripotency genes in nasopharyngeal carcinoma (PMID:24073846)
- **Activating invasion & metastasis:** Promotes metastasis in melanoma (PMID:22172720); Activated by hypoxia contributes to enhanced metastatic potential in hepatocellular carcinoma (PMID:20460486); Promotes EMT in breast cancer (PMID:17072303); Knockdown decreases cell decreases cell invasiveness in mouse pituitary adenoma (PMID:25646597)
- **Inducing angiogenesis:** Stimulates the expression of the angiogenic factors, MMP-2, MMP-9, VEGF-A, VEGF-C and bFGF in hepatocellular carcinoma (PMID:24944688); Activating mutations are associated with increased macro- and microvascular invasion in hepatocellular carcinoma (PMID:19101982)
- **Genome instability & mutation:** Knockdown significantly enhances formation of covalent DNA adducts by benzo[a]pyrene due to deregulation of cytochrome CYP1A1 in colon cancer (PMID:25805023); Required for activation of the Ku70/Ku80 DNA repair machinery upon irradiation (PMID:26713771)
- **Resisting cell death:** Knockdown increases the rate of apoptosis in multiple myeloma (PMID:28105169); Knockdown induces apoptosis in mantle cell lymphoma (PMID:26227550); Blocks anoikis and promotes

anchorage-independent growth by down-regulating death-associated protein kinase-2 (DAPk-2) (PMID:18957423)

- **Deregulating cellular energetics:** Knockdown induces autophagy in multiple myeloma (PMID:28105169); Knockdown results in loss of mitochondrial mass and membrane potential, downregulates the expression of proteins involved in carbohydrate metabolism and tricarboxylic acid cycle and upregulates proteins associated to lipid metabolism in breast cancer (PMID:28798698)

CTNNB1 Mutation Frequencies in Cancer

From the latest release of COSMIC (v98, PMID:30371878), of 121404 samples sequenced for CTNNB1 for all cancer types, 7.3% or 8805 were reported to have somatic mutations in CTNNB1. CTNNB1 mutations frequently occur in codons between 29 and 48 in exon 3 of CTNNB1 (PMID:30699286).

Among solid tumors, 7.9% (8632 of 109686) samples had CTNNB1 mutations, and among hematological cancers, 0.54% (52 of 9687) samples had CTNNB1 mutations.

CTNNB1 Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, CTNNB1 mutations have been reported at a frequency of 3.4% (133 of 3926 samples). In samples other than Lung Adenocarcinoma, the frequency of CTNNB1 mutations is 7.4% (8672 of 117478 samples).

Alteration: CTNNB1 G34E

Uncertain Clinical Actionability

Missense variant

HGVS:
chr3:g.41266104G>A,
NP_001895.1:p.Gly34Glu,
NM_001904.4:c.101G>A

VAF %: 28.12%

CTNNB1 G34E is a gain of function mutation within exon 3 of CTNNB1. This mutation has not been observed as germline polymorphism among samples documented in GnomAD (GnomAD v2.1.1).

Mutation Frequencies in Cancer

From the latest release of COSMIC (v98, PMID:30371878), CTNNB1 G34E has been reported in 0.13% (158 of 121404) samples of all cancer types tested for mutations in CTNNB1. Among samples positive for CTNNB1 G34E, the most frequent cancer types annotated are: Hepatocellular Carcinoma (16%), Endometrial Endometrioid Adenocarcinoma (13%), Hepatoblastoma (8.2%), and Adamantinomatous Craniopharyngioma (5.7%).

The frequency of CTNNB1 G34E among solid tumors is 0.14% (153 of 109686 samples), and among hematological cancers the frequency is 0.01% (1 of 9687 samples).

Mutation Frequencies in Lung Adenocarcinoma

In samples of Lung Adenocarcinoma, CTNNB1 G34E has been reported in 0.051% of samples (2 of 3926), compared to 0.13% of samples (156 of 117478) belonging to all other cancer types.

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TARGETED THERAPIES RECOMMENDED FOR GENOMIC FINDINGS WITH CLINICAL ACTIONABILITY IN RELEVANT INDICATION (ctDNA)

Only therapies with FDA Approval, FDA Breakthrough Designation, from Professional Guidelines or with results from Phase III trials in Relevant Indication are described.

Dacomitinib

Description:
Dacomitinib is an orally bioavailable, highly selective, second-generation small-molecule inhibitor of the pan-epidermal growth factor receptor (EGFR) family of tyrosine kinases (ErbB family) with potential antineoplastic activity. Dacomitinib specifically and irreversibly binds to and inhibits human EGFR subtypes, resulting in inhibition of proliferation and induction of apoptosis in EGFR-expressing tumor cells. EGFRs play major roles in tumor cell proliferation and tumor vascularization, and are often overexpressed or mutated in various tumor cell types.

Gene Association:
Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions and exon 21 L858R mutations have shown sensitivity to dacomitinib.

Supporting Data:
Dacomitinib is FDA approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations (FDA). The approval is based on the results obtained from a phase 3 randomized, prospective, active-controlled study (ARCHER 1050) in 452 NSCLC patients with EGFR-activating mutations (exon 19 deletion or exon 21 L858R mutation). The evaluation of first-line use of dacomitinib vs. gefitinib showed that dacomitinib has a significant improvement in progression-free survival (PFS) as compared to gefitinib (median PFS -14.7 vs 9.2 months; hazard ratio 0.59; 95% CI, 0.47 - 0.74; p < 0.0001) (PMID:28958502). No improvement in overall response rate was demonstrated. In the mature overall survival (OS) analysis, median OS was 34.1 months (95% CI, 30.1 months to not reached) with dacomitinib and 26.8 months with gefitinib (95% CI, 25.0 months to not reached) (PMID:29864379).

Erlotinib

Description:
Erlotinib is the hydrochloride salt of a quinazoline derivative with antineoplastic properties. Competing with adenosine triphosphate, erlotinib reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

Gene Association:
Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions and exon 21 L858R mutations have shown sensitivity to erlotinib. EGFR T790M is the most common secondary mutation which is responsible for >50% of all resistance to erlotinib and gefitinib (PMID:15728811,

PMID:19010870).

Supporting Data:
Erlotinib is FDA approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations (FDA). The approval is based on the results obtained from EURTAC study (European cohort), a phase 3 randomized, prospective, placebo-controlled trial in 174 NSCLC patients with EGFR-activating mutations (exon 19 deletion or exon 21 L858R mutation). The evaluation of first-line use of erlotinib vs. platinum based chemotherapy showed that erlotinib has a significant improvement in PFS as compared to chemotherapy (10.4 vs 5.2 months), with ORR of 65% for erlotinib arm and 16% for chemotherapy arm (PMID:22285168).

Phase III trial (OPTIMAL) evaluated erlotinib vs chemotherapy as first-line treatment in Asian patients whose tumors have harbored EGFR mutations (exon 19 deletion or exon 21 L858R mutation) demonstrated that erlotinib conferred a significant progression-free survival benefit (13.1 vs 4.6 months) (PMID:21783417).

Erlotinib is also FDA-approved for treatment of locally advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine in the first line setting (FDA).

Gefitinib

Description:
Gefitinib is an anilinoquinazoline with antineoplastic activity. Gefitinib inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis.

Gene Association:
Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions and exon 21 L858R mutations have shown sensitivity to gefitinib.

Supporting Data:
Gefitinib is FDA approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations (FDA). The approval is based on the results obtained from a multicentre, single-arm, open label study (IFUM) in 106 metastatic NSCLC treatment naïve patients with EGFR-activating mutations (exon 19 deletion or exon 21 L858R mutation). The blinded independent central review (BICR) objective response rate (ORR) observed was 50% (95% CI, 41–59) with a median duration of response of 6.0 months (PMID:26980062).

A supporting retrospective analysis on 186 EGFR mutant positive metastatic NSCLC patients, a subset of a randomized, multicenter, open-label trial, demonstrated an improvement in progression-free survival (PFS) for gefitinib-treated patients as compared to carboplatin/paclitaxel-treated patients (median PFS-10.9 vs 7.4 months; hazard ratio 0.54; 95% CI, 0.38–0.79)

(PMID:26980062). The ORR for gefitinib was 67% (95% CI, 56–77) as compared to 41% (95% CI, 31–51) for carboplatin-paclitaxel chemotherapy (PMID:26980062).

Another phase 3, open-label study (IPASS) conducted in East Asia, in a subset of 261 EGFR mutant positive advanced pulmonary adenocarcinoma, PFS was significantly longer in gefitinib-treated patients as compared to carboplatin-paclitaxel-treated patients (HR for progression or death, 0.48; 95% CI, 0.36 to 0.64; p < 0.001) (PMID:19692680).

Afatinib

Description:
Afatinib is an orally available inhibitor of the receptor tyrosine kinase (RTK) epidermal growth factor receptor (ErbB; EGFR) family, with antineoplastic activity. Upon administration, afatinib selectively and irreversibly binds to and inhibits the epidermal growth factor receptors 1 (ErbB1; EGFR), 2 (ErbB2; HER2), and 4 (ErbB4; HER4), and certain EGFR mutants, including those caused by EGFR exon 19 deletion mutations or exon 21 (L858R) mutations. This may result in the inhibition of tumor growth and angiogenesis in tumor cells overexpressing these RTKs. Additionally, afatinib inhibits the EGFR T790M gatekeeper mutation which is resistant to treatment with first-generation EGFR inhibitors. EGFR, HER2 and HER4 are RTKs that belong to the EGFR superfamily; they play major roles in both tumor cell proliferation and tumor vascularization and are overexpressed in many cancer cell types.

Gene Association:
Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R as well as less common EGFR S768I, L861Q, and/or G719X mutations have shown sensitivity to afatinib.

Supporting Data:
Afatinib is FDA approved for metastatic NSCLC as a first line treatment in patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (FDA). FDA approval is based on a multi-center international open-label randomized trial of 345 patients with metastatic NSCLC carrying EGFR mutations (exon 19 deletion, L858R or other). Patients treated with afatinib had a 11.5 months median PFS as compared to 6.9 months in patients treated with chemotherapy. Objective response rates were 50.4% in patients treated with afatinib and 19.1% in patients treated with chemotherapy (PMID:23816960, PMID:23816967).

Afatinib is also FDA approved for a broadened indication in first-line treatment of NSCLC patients with EGFR S768I, L861Q, and/or G719X mutations (FDA). Approval was based on the findings in a subset of 32 afatinib-treated patients with metastatic NSCLC harboring EGFR mutations (S768I, L861Q, and/or G719X) other than exon 19 deletions or exon 21 L858R substitutions enrolled in either the LUX-Lung 2, LUX-Lung 3 or LUX-Lung 6 clinical trials. 14 patients with G719X had an objective response (77.8%, 95% CI:52.4-93.6), as did 9 with L861Q (56.3%, 95%:CI 29.9-80.2), and 8 with S768I (100.0%, 95% CI:63.1-100.0) (PMID:26051236).

Osimertinib

Description:
Osimertinib is an orally available, irreversible, third-generation,

mutant-selective epidermal growth factor receptor (EGFR) inhibitor, with potential antineoplastic activity. Upon oral administration, osimertinib selectively and covalently binds to and inhibits the activity of the mutant forms of EGFR, including the T790M EGFR mutant form, thereby preventing EGFR-mediated signaling. This may both induce cell death and inhibit tumor growth in EGFR-overexpressing tumor cells. EGFR, a receptor tyrosine kinase overexpressed or mutated in many types of cancers, plays a key role in tumor cell proliferation and tumor vascularization. As osimertinib inhibits T790M, a secondarily acquired resistance mutation, this agent may have therapeutic benefits in tumors with T790M-mediated resistance. As this agent is selective towards mutant forms of EGFR, its toxicity profile may be reduced as compared to non-selective EGFR inhibitors, which also inhibit wild-type EGFR.

Gene Association:
Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 20 T790M and exon 21 L858R mutations have shown sensitivity to osimertinib.

Supporting Data:
Osimertinib is FDA-approved for the treatment of patients with metastatic EGFR T790M-mutant NSCLC, who have progressed on or after EGFR tyrosine kinase inhibitor therapy (FDA). Approval was based on findings in an open-label phase III trial (AURA3) in patients with metastatic EGFR T790M-mutation-positive NSCLC who had progressive disease following first-line EGFR tyrosine kinase inhibitor therapy (PMID:27959700). Patients were randomized, in a 2:1 ratio, to oral osimertinib or chemotherapy (pemetrexed plus either carboplatin or cisplatin every 3 weeks for up to six cycles, maintenance pemetrexed was allowed). Primary end point was progression free survival (PFS), which was significantly longer with osimertinib than with chemotherapy (10.1 months vs. 4.4 months). Objective response rate was significantly better with osimertinib (71%) than with chemotherapy (31%) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; $p < 0.001$).

Osimertinib is also FDA-approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test (FDA). Approval was based on findings in a double-blind phase III trial (FLAURA) in patients with EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC who had not received previous systemic treatment for advanced disease (PMID:29151359). Patients were randomized in a 1:1 ratio to receive oral osimertinib or standard EGFR-TKI (oral gefitinib or erlotinib) once daily. Primary end point was PFS, which was significantly longer with osimertinib than with standard EGFR-TKI (18.9 months vs. 10.2 months). Objective response rate was similar: osimertinib (80%) and standard EGFR-TKIs (76%) (odds ratio for objective response, 1.27; 95% CI, 0.85 to 1.90; P=0.24). Median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs.

Osimertinib in combination with pemetrexed and platinum-based chemotherapy is also FDA-approved for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or

	exon 21 L858R mutations, as detected by an FDA-approved test (FDA). Approval was based on findings in an open-label, randomized phase III trial (FLAURA 2) in patients with EGFR mutation-positive (exon 19 deletion or L858R) locally advanced or metastatic NSCLC who had not received previous systemic treatment for advanced disease (PMID:37937763). Patients were randomized 1:1 to receive either osimertinib with platinum-based chemotherapy or osimertinib monotherapy. Osimertinib plus platinum-based chemotherapy demonstrated a statistically significant improvement in PFS compared to osimertinib monotherapy with a hazard ratio of 0.62 (95% CI: 0.49, 0.79; two-sided p-value p < 0.0001). The median PFS was 25.5 months (95% CI: 24.7, NE) and 16.7 months (95% CI: 14.1, 21.3) in the respective arms. Osimertinib is also FDA-approved for adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations (FDA). This approval was based on a randomized, double-blind, placebo-controlled trial (ADAURA, NCT02511106) (PMID:32955177). Patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy, were randomized (1:1) to receive osimertinib 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy, if given. Median disease-free survival (DFS) was not reached (38.8, NE) in patients on the osimertinib arm compared with 19.6 months (16.6, 24.5) on the placebo arm (HR 0.17; 95% CI: 0.12, 0.23; p < 0.0001).
Erlotinib + Ramucirumab	**Description:** Erlotinib is the hydrochloride salt of a quinazoline derivative with antineoplastic properties. Competing with adenosine triphosphate, erlotinib reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation. Ramucirumab is a recombinant, fully human monoclonal antibody directed against human vascular endothelial growth factor receptor 2 (VEGFR-2) with antiangiogenesis activity. Ramucirumab specifically binds to and inhibits VEGFR-2, which may result in an inhibition of tumor angiogenesis and a decrease in tumor nutrient supply. VEGFR-2 is a pro-angiogenic growth factor receptor tyrosine kinase expressed by endothelial cells. **Gene Association:** Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions and exon 21 L858R mutations have shown sensitivity to ramucirumab in combination with erlotinib. **Supporting Data:** Ramucirumab in combination with erlotinib is FDA approved for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations (FDA). The approval was based on the data from RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study in patients with previously untreated metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. The median progression-free survival (PFS) was 19.4 months in the

	ramucirumab plus erlotinib arm compared with 12.4 months in the placebo plus erlotinib arm (HR 0.59; 95% CI: 0.46, 0.76; p < 0.0001). The ORR and median duration of response (DoR) were 76% and 18.0 months, respectively, for ramucirumab plus erlotinib arm, whereas the ORR and DoR were 75% and 11.1 months, respectively, for the placebo plus erlotinib arm (PMID:31591063).
Amivantamab + Lazertinib	**Description:** Amivantamab is a human bispecific antibody targeting both epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (HGFR; cMet), with potential antineoplastic activity. Upon administration, amivantamab simultaneously targets and binds to wild-type or certain mutant forms of both EGFR and cMet expressed on cancer cells, thereby preventing receptor phosphorylation. This prevents the activation of both EGFR- and cMet-mediated signaling pathways. In addition, binding results in receptor degradation, which further inhibits EGFR- and cMet-mediated signaling. JNJ-61186372 also causes antibody-dependent cellular cytotoxicity (ADCC). Altogether, this results in the inhibition of tumor cell proliferation. EGFR and cMet, both upregulated or mutated in a variety of tumor cell types, play key roles in tumor cell proliferation. Lazertinib is an orally available third-generation, selective inhibitor of certain forms of the epidermal growth factor receptor (EGFR) with activating mutations, including the resistance mutation T790M, exon 19 deletions (Del19), and the L858R mutation, with potential antineoplastic activity. Upon administration, lazertinib specifically and irreversibly binds to and inhibits selective EGFR mutants, which prevents EGFR mutant-mediated signaling and leads to cell death in EGFR mutant-expressing tumor cells. Lazertinib may inhibit programmed cell death-1 ligand 1 (PD-L1) and inflammatory cytokines in specific cancer cells harboring certain EGFR mutations. Compared to some other EGFR inhibitors, lazertinib may have therapeutic benefits in tumors with T790M- or L858R-mediated drug resistance. In addition, lazertinib penetrates the blood-brain barrier (BBB). This agent shows minimal activity against wild-type EGFR (wtEGFR), and does not cause dose-limiting toxicities, which occur during the use of non-selective EGFR inhibitors and inhibit wtEGFR. EGFR, a receptor tyrosine kinase (RTK) mutated in many tumor cell types, plays a key role in tumor cell proliferation and tumor vascularization. **Gene Association:** Non-small cell lung cancer (NSCLC) patients with EGFR exon 19 deletions or EGFR L858R mutation have shown sensitivity to the combination of amivantamab and lazertinib. **Supporting Data:** Amivantamab, in combination with lazertinib, has been approved by the FDA for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or EGFR L858R mutation, as detected by an FDA-approved test (FDA). Approval was based on MARIPOSA, a randomized, active-controlled, multicenter clinical trial (NCT04487080) of which efficacy was evaluated in previously untreated EGFR-mutated (exon 19 deletion or L858R), locally advanced or metastatic NSCLC patients who were randomized (2:2:1) to receive amivantamab in combination with lazertinib (N=429), osimertinib monotherapy (N=429), or lazertinib monotherapy (216) until disease progression or unacceptable toxicity. The median progression-free survival (PFS)

was significantly longer in the amivantamab + lazertinib group than in the osimertinib group (23.7 vs. 16.6 months; HR =0.70; 95% CI: 0.58, 0.85; p < 0.001). An objective response was observed in 86% of the patients (95% CI: 83, 89) in the amivantamab-lazertinib group and in 85% of those (95% CI: 81, 88) in the osimertinib group. Among patients with a confirmed response (336 in the amivantamab + lazertinib group and 314 in the osimertinib group), the median response duration was 25.8 months (95% CI: 20.1, could not be estimated) and 16.8 months (95% CI: 14.8, 18.5), respectively (PMID:38924756).

Amivantamab

Description:
Amivantamab (JNJ-6372/JNJ-61186372) is a human bispecific antibody targeting both epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (HGFR; cMet), with potential antineoplastic activity. Upon administration, amivantamab simultaneously targets and binds to wild-type or certain mutant forms of both EGFR and cMet expressed on cancer cells, thereby preventing receptor phosphorylation. This prevents the activation of both EGFR- and cMet-mediated signaling pathways. In addition, binding results in receptor degradation, which further inhibits EGFR- and cMet-mediated signaling. JNJ-61186372 also causes antibody-dependent cellular cytotoxicity (ADCC). Altogether, this results in the inhibition of tumor cell proliferation. EGFR and cMet, both upregulated or mutated in a variety of tumor cell types, play key roles in tumor cell proliferation.

Gene Association:
Non-small cell lung cancer (NSCLC) patients with EGFR exon 20 insertion mutations, EGFR exon 19 deletions, or EGFR L858R mutation have shown sensitivity to amivantamab.

Supporting Data:
Amivantamab has been granted approval by the FDA for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy (FDA). Approval was based on CHRYSALIS, a multicenter, non-randomized, open label, multicohort clinical trial (NCT02609776) of which efficacy was evaluated in 81 patients who received amivantamab-vmjw once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. Overall response rate (ORR) was 40% (95% CI: 29%, 51%) with a median response duration of 11.1 months (95% CI: 6.9, not evaluable) (PMID:34339292).

Amivantamab with carboplatin and pemetrexed has been granted approval by the FDA for treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test. (FDA). Approval was based on PAPILLON (NCT04538664), a randomized, open-label multicenter trial of 308 patients with EGFR exon 20 insertion mutations. Patients were randomized 1:1 to receive amivantamab-vmjw with carboplatin and pemetrexed or carboplatin and pemetrexed. A statistically significant improvement in the progression-free survival (PFS) in the Amivantamab-vmjw plus carboplatin and pemetrexed group compared with carboplatin and pemetrexed with a hazard ratio of 0.40 (95% CI: 0.30, 0.53). The median PFS was 11.4 months (95% CI: 9.8, 13.7) and 6.7 months (95% CI: 5.6, 7.3) in the respective arms (PMID:37923902).

	Amivantamab with carboplatin and pemetrexed has been granted approval by the FDA for treatment of locally advanced or metastatic NSCLC with EGFR exon 19 deletions or EGFR L858R mutation, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor (FDA). Approval was based on MARIPOSA-2 (NCT04988295), a randomized, open-label, multicenter trial in 657 patients with EGFR exon 19 deletions or exon 21 L858R substitution mutations and disease progression on or after receiving Osimertinib. Patients were randomized to receive amivantamab-vmjw with carboplatin and pemetrexed or carboplatin and pemetrexed. A statistically significant improvement in the progression-free survival (PFS) in the amivantamab-vmjw plus carboplatin and pemetrexed group compared with carboplatin and pemetrexed with a hazard ratio of 0.48 (95% CI: 0.36, 0.64). The median PFS was 6.3 months (95% CI: 5.6, 8.4) and 4.2 months (95% CI: 4.0, 4.4) in the respective arms. The confirmed overall response rate (ORR) was 53% (95% CI: 44, 62) in the amivantamab plus carboplatin and pemetrexed group whereas 29% (95% CI: 23, 35) in the carboplatin and pemetrexed group (PMID:37879444).
Datopotamab Deruxtecan	**Description:** Datopotamab deruxtecan is an antibody-drug conjugate (ADC) composed of a humanized monoclonal antibody against tumor-associated antigen (TAA) trophoblast cell surface protein 2 (calcium signal transducer 2; TROP2; TROP-2; TACSTD2) conjugated, via an enzymatically cleavable tetrapeptide-based linker, to the cytotoxic DNA topoisomerase I inhibitor and exatecan (DX-8951) derivative DXd (MAAA-1181a; MAAA-1181), with potential antineoplastic activity. Upon administration of the datopotamab deruxtecan, the anti-TROP2 antibody targets and binds to TROP2 expressed on tumor cells. Upon cellular uptake and lysosomal degradation of the linker, DXd targets and binds to DNA topoisomerase I, thereby stabilizing the cleavable complex between topoisomerase I and DNA, resulting in DNA breaks, inhibition of DNA replication and apoptosis. This inhibits tumor cell proliferation of TROP2-expressing tumor cells. TROP2 is a transmembrane protein overexpressed in various tumors while its expression is low and/or restricted in normal, healthy tissues. Its expression is associated with enhanced tumor aggressiveness, metastasis, drug resistance and increased tumor cell survival. The ADC allows for reduced systemic exposure and enhanced delivery of the cytotoxic agent DXd. **Gene Association:** Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR mutations have shown sensitivity to datopotamab deruxtecan. **Supporting Data:** Datopotamab deruxtecan has been granted FDA accelerated approval for the treatment of patients with locally advanced or metastatic EGFR-mutated NSCLC who received prior EGFR-directed therapy and platinum-based chemotherapy (FDA). This approval was based on a pooled efficacy analysis from two clinical trials: TROPION-Lung05, a multicenter, single-arm trial (NCT04484142) and TROPION-Lung01, a multicenter, open-label, randomized controlled trial (NCT04656652) (PMID:39250535, PMID:39761483). Among 114 patients meeting the labeled criteria, the confirmed overall response rate (ORR) was 45% (95% CI, 35%-54%) and median duration of response (DOR) was 6.5 months (95% CI, 4.2-8.4), as assessed by blinded independent central review using RECIST v1.1.

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TARGETED THERAPIES RECOMMENDED INDEPENDENT OF GENOMIC FINDINGS IN RELEVANT INDICATION exists#}}

The following targeted therapies are approved in the relevant indication independent of specific genomic findings. Approved indications for the listed therapies may have additional criteria of medical and treatment history and combination chemotherapy.

Cancer Type	Drugs	Status
Lung Non-Small Cell Carcinoma	Durvalumab	FDA Approval
Lung Non-Small Cell Carcinoma	Nivolumab	FDA Approval
Lung Non-Small Cell Carcinoma	Ipilimumab + Nivolumab	FDA Approval

Laboratory Director Joseph Michael Anderson, MD, FCAP
CLIA ID Number: 05D2200843 D TBC-LHI V1.0

Lucence Health Inc. 3520 West Bayshore Road, Palo Alto, CA 94303, USA
Tel: +1-(888)-LUCENCE (582-3623) Email: inquiry.us@lucence.com

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GLOSSARY OF TERMS AND ABBREVIATIONS

AACR	American Association for Cancer Research
Actionability	Actionability of a genomic finding is determined by the evidence of effective targeted therapy demonstrated in clinical trials and clinical/pre-clinical studies.
AMP	Association for Molecular Pathology
ASCO	American Society of Clinical Oncology
Biomarkers	Genomic findings that are not categorized as variants (SNVs, indels), fusions or copy number changes.
BTD	Breakthrough Therapy Designation
CAP	College of American Pathologists
ctDNA	Circulating tumor DNA
Chemotherapy	Cytotoxic drugs that stop the growth of fast-growing cells, both normal and tumor cells.
CI	Confidence Interval
Compelling Clinical Evidence	Evidence from multiple Clinical Studies and/or Case Reports predicting resistance to targeted therapies due to presence of Genomic Findings.
Copy Number Gain	Increased gene copy number present in the ctDNA. The copy number gain is reported as a relative fold-change in copy number, calculated as the detected copy number relative to a normal diploid copy number (2 copies). Relative copy number detected in circulation depends on the fraction of ctDNA that is of tumor origin (tumor fraction) and the degree of copy number gain in the tumor.
Copy Number Loss	Reduced gene copy number present in the ctDNA. The copy number loss is reported as a relative fold-change in copy number, calculated as the detected copy number relative to a normal diploid copy number (2 copies). Relative copy number detected in circulation depends on the fraction of ctDNA that is of tumor origin (tumor fraction).
COSMIC	Catalogue of Somatic Mutations In Cancer
CTC	Circulating tumor cells
dMMR	Deficient Mismatch Repair
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FDA Breakthrough Designation	FDA Breakthrough Designation is given to drugs with preliminary clinical evidence demonstrating substantial positive outcomes in the treatment of serious or life-threatening conditions over other available therapies.
Genomic Findings	Genomic Findings include mutations, copy number variations, fusions, genomic rearrangements and microsatellite instability detected by analyzing ctDNA.
GOF	Gain-of-Function
IASLC	International Association for the Study of Lung Cancer
LOF	Loss-of-Function

Microsatellite status	Microsatellite instability (MSI) is a condition of genetic instability in short nucleotide repeats (microsatellites) due to a deficiency in DNA mismatch repair (MMR) in the tumor. MSI is characterized by an excessive amount of short insertion or deletion mutations in the tumor genome.
MMR	Mismatch Repair
NCIt	National Cancer Institute thesaurus
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PFS	Progression Free Survival
PMID	PubMed IDentifier
Relevant Indication or Related	Relevant Indication is based on clinical diagnosis provided and is a disease term from the controlled vocabulary of disease terms from the National Cancer Institute thesaurus (NCIt), determined based on the most relevant match from clinical diagnosis provided. Related indication refers to a hierarchical subtype or supertype of the relevant indication defined by the controlled disease vocabulary defined at the National Cancer Institute thesaurus (NCIt). In cases where the specific disease is unknown or unclear, the NCIt disease term defaulted to for actionability determination is “Malignant Neoplasm”.
SNV	Single Nucleotide Variant
Somatic status	Somatic (not inherited) status of genomic findings is inferred primarily from the individual variant allele frequencies (VAF) and VAFs of genomic findings relative to one another, effect of variant on protein function and variant information from public databases such as Clinvar supporting an uncertain clinical significance in a germline context.
Targeted clinical trials	Clinical trials with specific genomic findings required as inclusion criteria.
Targeted therapy	Drugs targeting specific proteins/molecules in or on cancer cells.
Treatment-relevant genes	Genes that harbor clinically actionable alterations with FDA-approved targeted therapies, or genes that are included in the recommendations by professional oncology guidelines for molecular testing in the context of the relevant indication.
VAF	Variant Allele Frequency

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LIMITATIONS AND DISCLAIMERS

This report reflects the analysis of DNA from an extracted nucleic acid sample, and in very rare cases (for example, bone marrow transplant or recent blood transfusion) the analyzed DNA may not reflect the patient's genome, leading possibly to false negative and/or false positive results. Nucleic acid studies do not constitute a definitive test for the selected condition(s) in all individuals. This test is clinically validated for cerebrospinal fluid samples only. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. Test sensitivity may be altered based on factors such as excessive cell lysis before processing, sampling during treatment, tissue heterogeneity, and the relative yield of circulating nucleic acids from the sample. CSF specimens with elevated albumin and immunoglobulin G may also result in reduced assay sensitivity or assay failure. Sensitivity of this test has been determined for the test methodology for a set of variants which do not necessarily include those identified in this report. Sensitivity and specificity data for all variants reported are not available. Where reported allele frequencies fall below 0.1% or 0.75% depending on input for SNV or Indel, absolute number of variant reads supporting the call are considered, but specificity data is not available on this. Deletions or insertions involving more than 30 bp may not be reliably detected by the sequencing methodology. Although most of the intended targeted regions are sequenced in their entirety, some regions may be incompletely covered due to technical limitations. Therefore, absence of a detected variant in these regions and in regions not covered by this test does not exclude the presence of a pathogenic variant. Intronic variants and synonymous substitutions are not reported unless previously documented as clinically significant. Variants classified as benign or likely benign in ClinVar and/or variants with population allele frequency (in external or internal databases) of greater than 1% (non-founder mutations) are not reported but are available on request.

This test is not intended for, and cannot confirm germline status in any manner. Variants detected may be of tumor-derived somatic, germline, or non-tumor somatic origins, including mosaicism and clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations may be derived from CHIP include, but are not limited to: *ATM*, *JAK2*, *SF3B1*, *TP53*, and *U2AF1*. Clinical correlation is recommended. Genetic counseling may be considered if deemed appropriate clinically.

For cases where no genomic alterations are identified, the absence of CSF ctDNA alterations may correlate with low leptomeningeal disease involvement, or disease which is being effectively treated. It is also possible that there are genomic alterations in targets not included in the panel or others not detectable by this analysis due to inherent analytical limitations. Further clinical correlation is advised, with consideration of follow-up tissue and CSF testing.

This test should be one of many aspects used by the treating healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. Clinical diagnosis provided by the treating healthcare provider is used to determine Relevant Indication for determining appropriate clinical actionability / evidence and matching clinical trials, presentation of which may be adversely affected in cases of incomplete or incorrect diagnosis information provided. Any mention of pharmacologic agents, or their on-label or off-label use should not be considered as a recommendation or endorsement for therapeutic use. Approved indications for the listed therapies may have additional criteria of medical and treatment history and combination chemotherapy. Percentage map is for visualization purposes only and is not drawn to scale. Clinical correlation is advised. Past treatment or mutation history is not being considered for selection of clinical trials presented. Clinical correlation and suitability with specific trial's inclusion and exclusion criteria is advised. Drug and clinical trial information are obtained from curated databases including NCI thesaurus and ClinicalTrials.gov. Clinical trial curated database is updated with trials verified within the last month. Tiering of clinical actionability / evidence associated with a drug recommendation may be updated in source data, but not reflected as at the time of the report. For latest information, please refer to the FDA website and the respective source data websites for professional guidelines.

Lucence does not warrant that the data from such third party databases, websites, or guidelines are accurate, complete, or up to date and excludes all liability for any loss or damage howsoever arising as a result of any reliance on the accuracy of the data.

This report has been reviewed and approved by	Date and Time
 Joseph Michael Anderson, MD, FCAP Laboratory Director	May 04 2026, 1930 hrs (PDT)