KRAS — A Key Oncogenic Driver and Novel Investigational Target in NSCLC

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Oncology

Navigation Features

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Navigation Bar

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TABLE OF CONTENTS: To return to the table of contents

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This icon, located throughout the module, indicates that the associated text is hyperlinked and will take the user to additional content within the module when clicked

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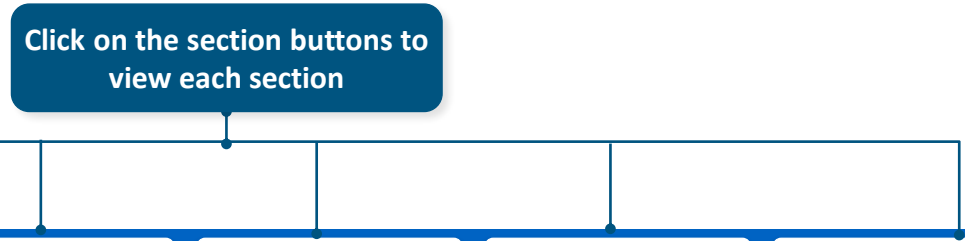

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Table of Contents

KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

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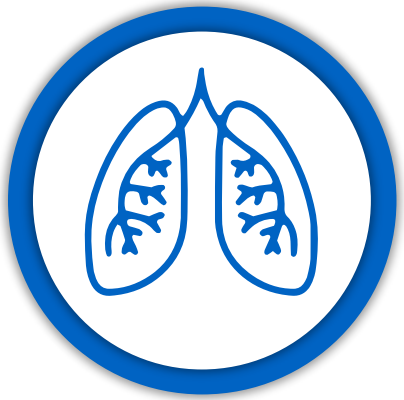
Lung Cancer Is the Leading Cause of Cancer Death and There Remains a Significant Need for New Therapies[1]

Lung Cancer Statistics

In the United States, it is estimated that there will be **230,000 new cases** and **140,000 deaths** from the disease in 2019[1]

Diagnosis



NSCLC accounts for **~85%** of all lung cancers with **~60%** of patients diagnosed at an advanced stage[2,3]

Treatment Outcomes

OS rates for patients with advanced NSCLC have been generally poor (5-year survival **~6%**).[4,*] Immunotherapy has improved **OS** in a subset of patients[5,6]

Biomarker Testing

Despite **biomarkers** serving as the foundation for precision medicine in patients with NSCLC, **molecular testing rates** are suboptimal[7-9]

*5-year relative survival in patients with advanced stage NSCLC from 2008-2014 in the US.[4]
NSCLC, non-small cell lung cancer; OS, overall survival.

1. National Cancer Institute. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_4. Accessed September 13, 2019. 2. National Cancer Institute. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed September 13, 2019. 3. American Cancer Society. https://www.cancer.org/cancer/lung-cancer.html. Accessed September 13, 2019. 4. National Cancer Institute. https://seer.cancer.gov/archive/csr/1975_2015/results_merged/topic_survival.pdf. Accessed September 13, 2019. 5. Garon EB, et al. *J Clin Oncol.* 2019;JCO1900934. 6. Antonia SJ, et al. *Lancet Oncol.* 2019;pii:S1470-2045(19)30407-3. 7. Ahmadzada T, et al. *J Clin Med.* 2018;7:153. 8. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. 9. Smeltzer M, et al. Presented at IASLC 2019 WCLC World Conference on Lung Cancer; September 7–10, 2019; Barcelona, Spain. Abstract MA21.03.

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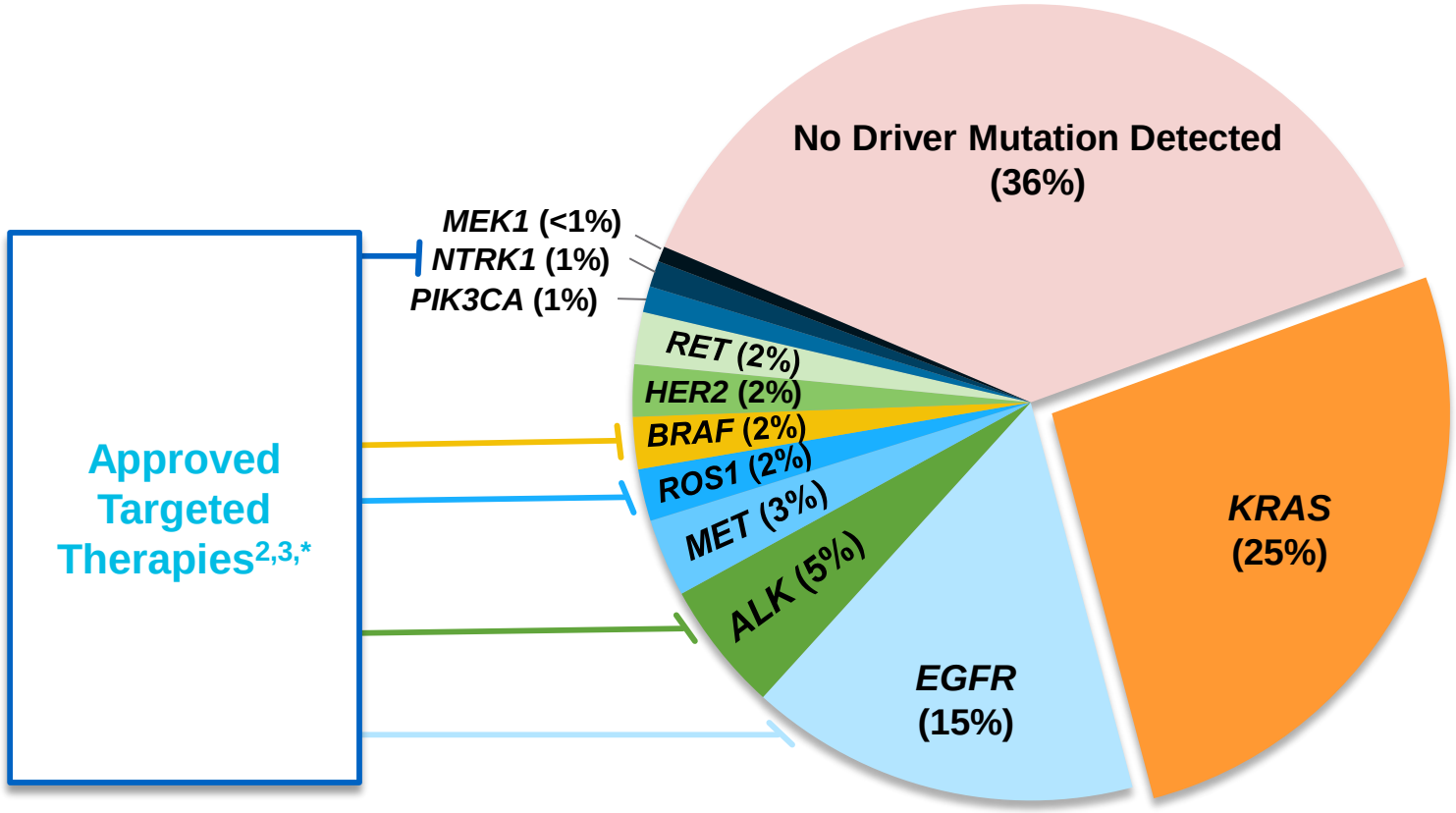
NSCLC Is Associated With Several Oncogenic Driver Mutations[1]

Prevalence of Driver Mutations in Lung Adenocarcinomas[2]



Targeted therapy is not currently available for patients with *KRAS* mutations[4]

*Currently approved therapies in NSCLC.
ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; HER2; human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma; MEK1, mitogen-activated protein kinase kinase 1; MET, mesenchymal-to-epithelial transition; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic tyrosine receptor kinase 1; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha polypeptide; RET, rearranged during transfection; ROS1, c-ros oncogene 1.

1. Skoulidis F, et al. *Nat Rev Cancer.* 2019;19:495-509. 2. Pakkala S, et al. *JCI Insight.* 2018;3:e120858. 3. Huang FW, et al. *Cell.* 2019;177:8. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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KRAS Is a Member of the *RAS* Gene Family[1]

The *RAS* gene family includes three isoforms, ***KRAS, NRAS, and HRAS***, which differ in frequency across cancer types[1]

86%

of *RAS*-driven cancers are caused by mutations in the *KRAS* isoform[1]

***KRAS* is an oncogenic driver that represents almost**

100%

of *RAS* mutations in lung adenocarcinoma[1]

KRAS is the most frequently mutated oncogene in human cancer[1,2]

HRAS, Harvey rat sarcoma; KRAS, Kirsten rat sarcoma; NRAS, neuroblastoma rat sarcoma; RAS, rat sarcoma.

1. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 2. Vogelstein B, et al. *Science.* 2013;339:1546-1558.

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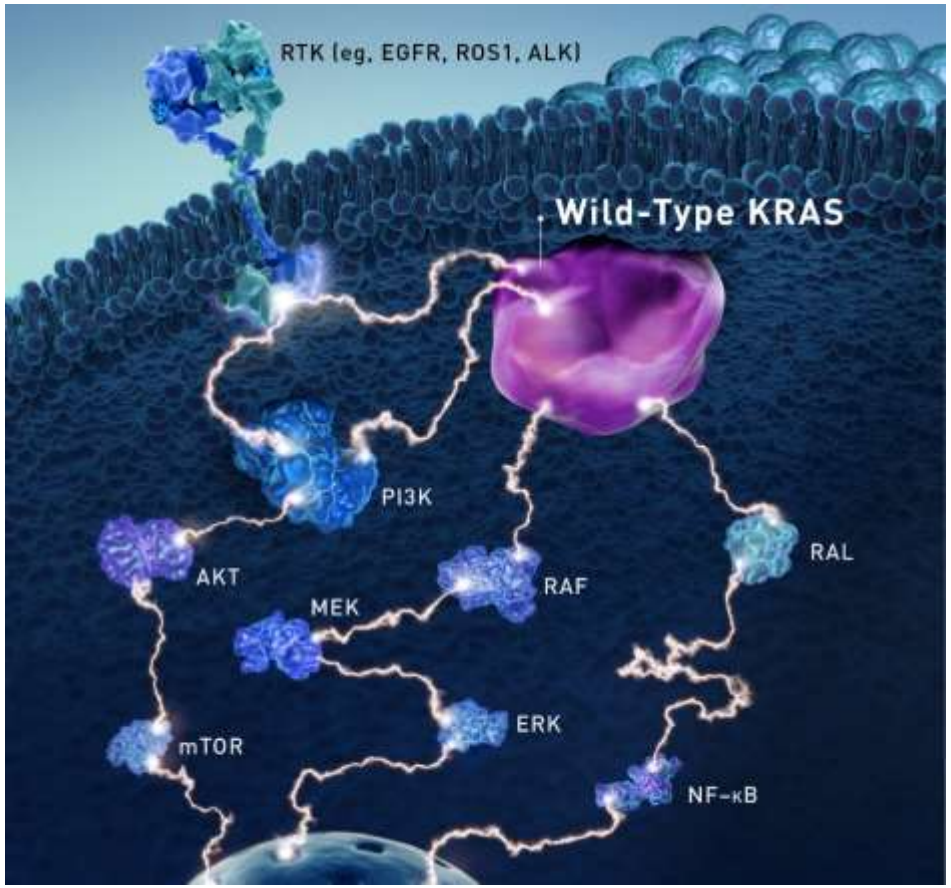
KRAS Is a Key Regulator of Cellular Proliferation and Differentiation[1-5]

- The *KRAS* gene encodes KRAS proteins, which are small GTPases that regulate signaling pathways responsible for cellular proliferation and differentiation[1-3]
- The KRAS protein cycles between a GTP-bound, active state and a GDP-bound, inactive state[1]
- In normal cells, KRAS serves as an on/off molecular switch to regulate downstream signaling pathways[3,6]



AKT, protein kinase B; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinase.

1. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. 2. Barbacid M. *Annu Rev Biochem*. 1987;56:779-827. 3. Simanshu DK, et al. *Cell*. 2017;170:17-33. 4. Neel NF, et al. *Genes Cancer*. 2011;2:275-287. 5. Ahmadzada T, et al. *J Clin Med*. 2018;7:pii:E153. 6. Ferrer I, et al. *Lung Cancer*. 2018;124:53-64.

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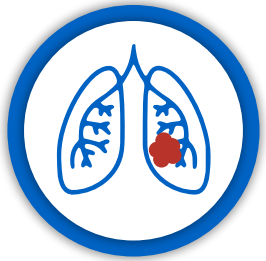
KRAS-Mutated NSCLC Tumors Are Associated With Molecular and Clinical Heterogeneity[1]

- *KRAS*-mutated NSCLC tumors frequently occur with co-mutations (*STK11/LKB1, TP53, CDKN2A/CDKN2B,* etc), which could impact the tumor microenvironment and oncogenic dependencies[1,2]



- *KRAS*-mutated tumors are typically adenocarcinomas[2]

- Approximately 9 out of 10 patients are former or current smokers[3,4]

CDKN2, cyclin dependent kinase inhibitor 2; KRAS, Kirsten rat sarcoma; LKB1, serine/threonine kinase 1; NSCLC, non-small cell lung cancer; STK11, serine/threonine kinase 11; TP53, tumor protein p53.

1. Skoulidis, F, et al. *Nat Rev Cancer.* 2019;19:495-509. 2. Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. 3. El Osta B, et al. *J Thorac Oncol*. 2019;14:876-889. 4. Renaud S, et al. *Br J Cancer.* 2016;115:346-353.

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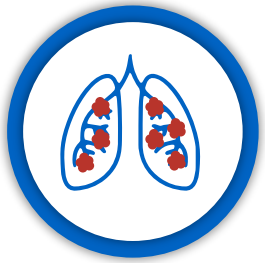
There Is an Unmet Need for KRAS-Targeted Therapies[1,2]

- *KRAS* mutations are often mutually exclusive from other predictive oncogenic mutations (eg, *EGFR, ALK,* and *ROS1*); patients with *KRAS*-mutated NSCLC are therefore unlikely to benefit from targeted therapies for these specific mutations[1-3]

- Only some patients with *KRAS*-mutated NSCLC achieve clinical benefit with currently available targeted therapies, chemotherapies, and immunotherapies[4-6]
  - In patients with lung cancer, overlap of *KRAS* mutations with *STK11/LKB1* has been associated with resistance to PD-1 blockade[7]



- *KRAS*-mutated NSCLC tumors have a high degree of intrinsic heterogeneity; therefore, not all patients may experience positive outcomes with current therapies[4-6,8]

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; LKB1, serine/threonine kinase 1; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; ROS1, c-ros oncogene 1; STK11, serine/threonine kinase 11.

1. Shea M, et al. *Ther Adv Respir Dis*. 2016;10:113-129. 2. Ahmadzada T, et al. *J Clin Med*. 2018;7:pii:E153. 3. Skoulidis F, et al. *Nat Rev Cancer*. 2019;19:495-509. 4. Jänne PA, et al. *Lancet Oncol*. 2013;14:38-47. 5. Jeanson A, et al. *J Thorac Oncol*. 2019;14:1095-1101. 6. Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. 7. Skoulidis F, et al. *Cancer Discov*. 2018;8:822-835. 8. Román M, et al. *Mol Cancer*. 2018;17:33.

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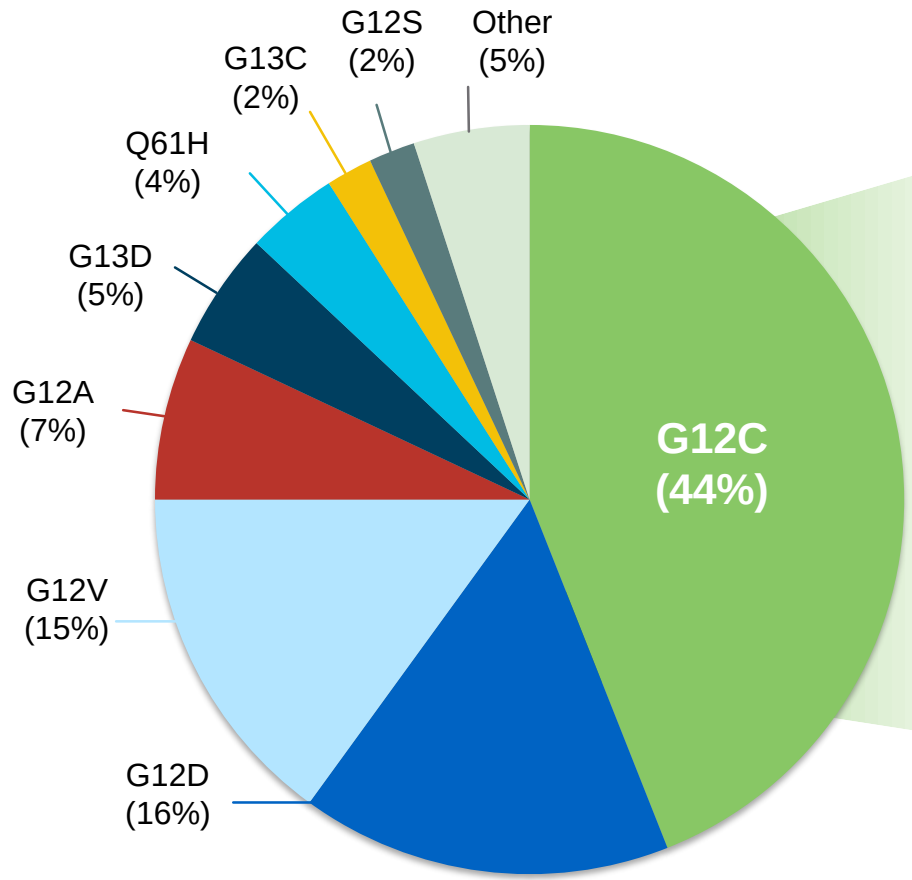
G12C Is the Most Common *KRAS* Mutation and Comprises Nearly Half of All *KRAS* Mutations in NSCLC[1,2]

Prevalence of *KRAS* Point Mutations[2]



Codon 12

Position where *KRAS* mutations are frequently seen[1]

13% (~1 in 8)

Patients in the US with NSCLC have the *KRAS G12C* driver mutation[3]

~23,000

New patients are diagnosed with *KRAS G12C* NSCLC annually in the US[4]

KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

1. El Osta B, et al. *J Thorac Oncol*. 2019;14:876-889. 2. Arbour KC, et al. *Clin Cancer Res*. 2018;24:334-340. 3. Biernacka A, et al. *Cancer Genet*. 2016;209:195-198. 4. Stephen AG, et al. *Cancer Cell*. 2014;25:272-281.

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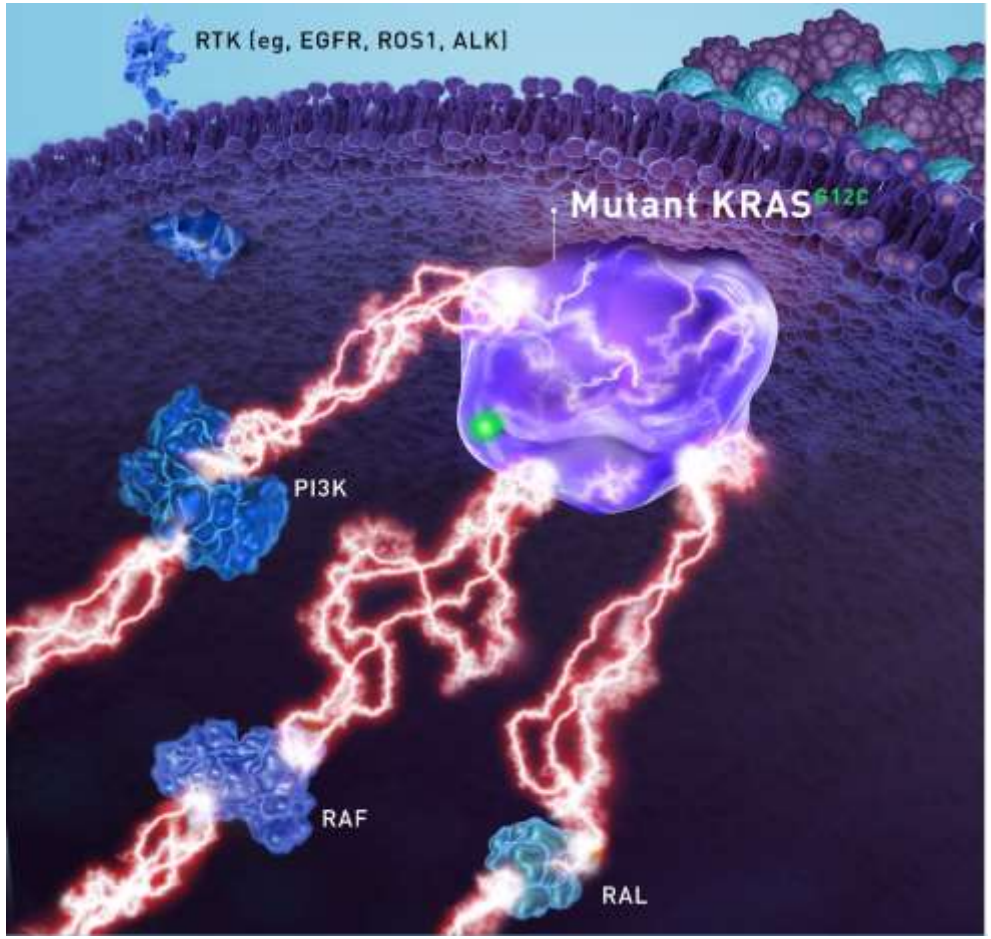
KRAS G12C Has Been Identified as an Oncogenic Driver of Tumorigenesis in NSCLC[1-5]

The *KRAS G12C* mutation favors the **active form** of KRAS mutant protein, supporting tumorigenesis[1,3]



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small lung cancer; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, ras-like; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinase.

1. Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720. 2. Simanshu DK, et al. *Cell.* 2017;170:17-33. 3. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 4. Neel NF, et al. *Genes Cancer*. 2011;2:275-287. 5. Ahmadzada T, et al. *J Clin Med*. 2018;7:pii:E153.

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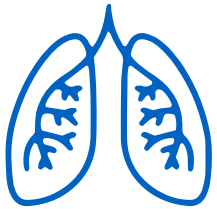
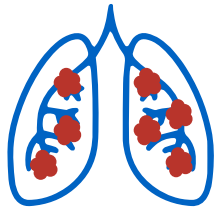
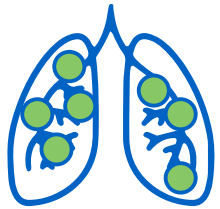
Retrospective Analyses Suggest That *KRAS G12C* Mutations May Be a Negative Prognostic Factor in Patients With NSCLC[1,2]

	 Wild-type *KRAS*	 Other *KRAS* Mutations	 *KRAS G12C*
2-Year OS Rates Following Surgery[1,*] **(All Stages)**	**80%** **(n=92)**	**~87%** **(n=50)**	**60%** **(n=35)**
Median OS Following 2L/3L Chemotherapy[2,†] **(Advanced-Stage NSCLC)**	**16.1 Months** **(n=90)**	**10.3 Months** **(n=24)**	**6.4 Months** **(n=15)**

* Retrospective analysis of outcomes for 179 patients with surgically resected NSCLC from the University of Michigan Health System between 1991 and 2007. Other KRAS mutations included G12D, G12V, G12A.[1] † Retrospective analysis of outcomes for 129 patients with advanced NSCLC treated with chemotherapy at the Department of Pneumology University Hospital between 2006 and 2015. Other KRAS mutations included A11P, G12A, G12D, G12R, G12S, G12V, G13C and G13D.[2]

2L/3L, second line/third line; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; OS, overall survival.

1. Nadal E, et al. *J Thorac Oncol*. 2014;9:1513-1522. 2. Svaton M, et al. *Anticancer Res*. 2016;36:1077-1082.

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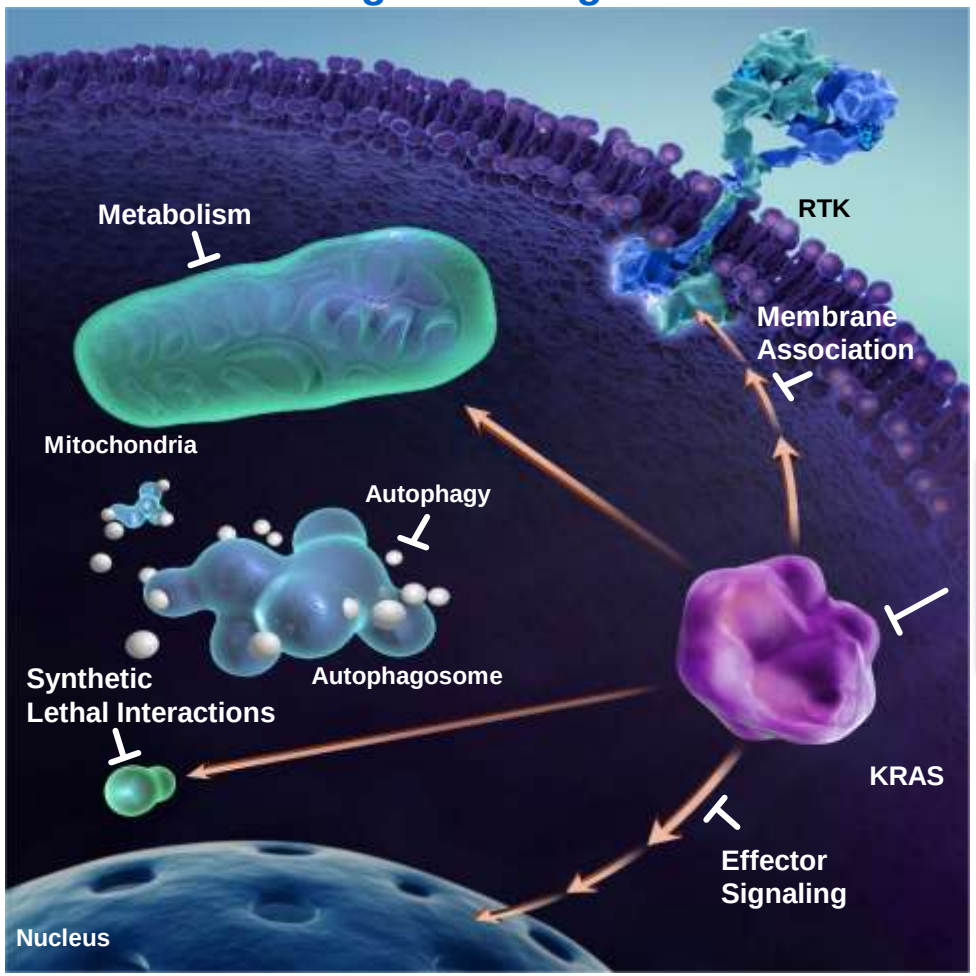
Despite Nearly Four Decades of Scientific Efforts, KRAS Has Not Been Successfully Targeted[1,2]

Strategies to Target KRAS[1,2]



Direct Inhibitors

Direct inhibition of KRAS has presented key challenges[1,2]

Lack of surface targets for binding[1]

High affinity for GTP, resulting in ineffective competitive inhibition[1,2]

Non-selective binding to wild-type KRAS limited approaches to targeting mutant KRAS[2]

GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; RTK, receptor tyrosine kinase.

1. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 2. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720.

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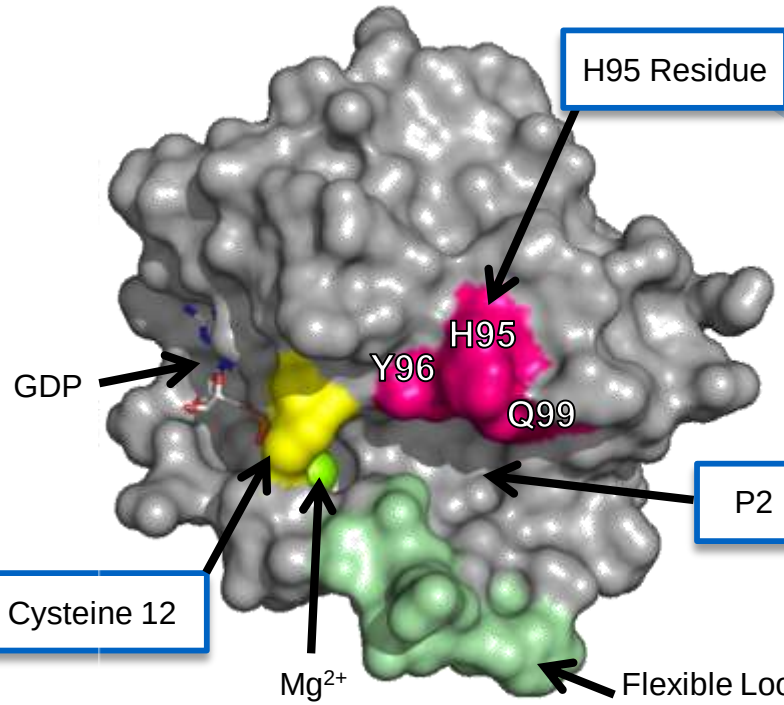
The G12C Mutation Creates a Narrow, Targetable Pocket on KRAS[1,2]



It's hypothesized that the KRAS-specific histidine 95 (H95) residue may provide an allosteric site to stabilize drug-protein interaction[3]

The mutant cysteine of $KRAS^{G12C}$ resides adjacent to a pocket (P2)[1,2]

The pocket (P2) is present in the inactive, GDP-bound form of KRAS[1,2]

Advances in understanding the structure of KRAS have prompted further investigations and may provide insights into the role of *KRAS* mutations in cancer development and maintenance[2]

GDP, guanosine diphosphate; KRAS, Kirsten rat sarcoma.

1. Saiki AY, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4484. 2. Lanman BA, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4455. 3. Bery N, et al. *Nat Commun*. 2019;10:2607.

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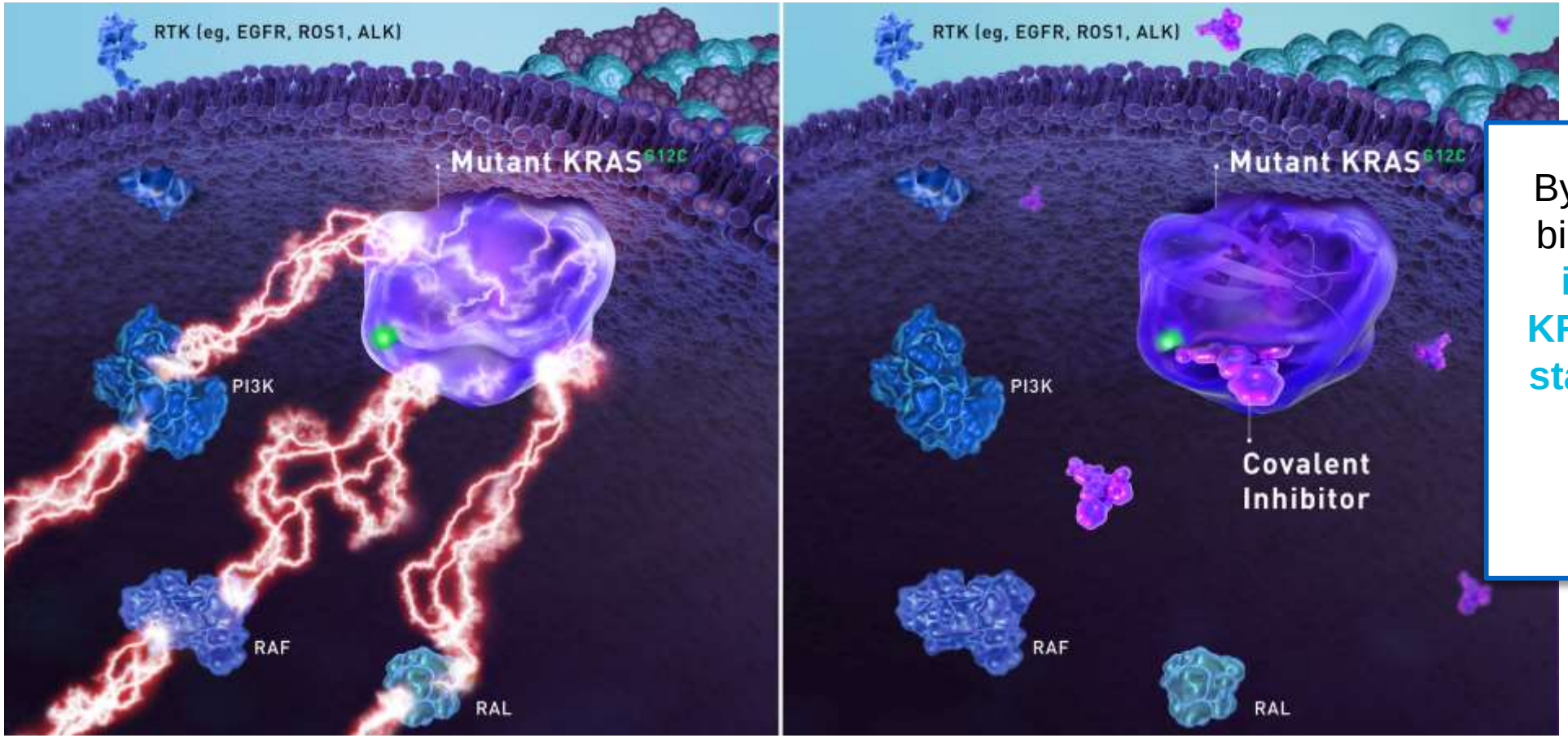
Inhibition of KRAS^{G12C} Represents an Important Therapeutic Approach in NSCLC Which Warrants Further Investigation[1-3]



By utilizing the KRAS^{G12C} binding pocket, **covalent inhibitors could lock KRAS^{G12C} in the inactive state**, blocking oncogenic signaling, without impacting wild-type KRAS signaling[1,3]

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinase.

1. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. 2. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 3. Lanman BA, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4455.

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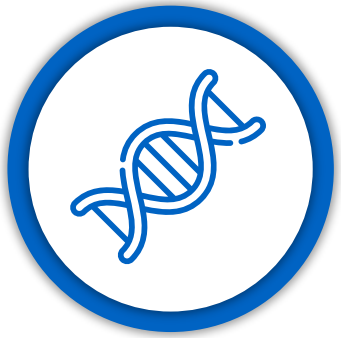
Biomarker Testing Is Critical[1,2]

Biomarker Identification



Provides information on patient outcomes and can help predict response to therapeutic interventions[3]

Targeted Therapy

May improve outcomes in patients with actionable biomarkers[4]

Diagnostics

Help facilitate and identify the right patients for the appropriate treatment[1,5,6]

1. Food and Drug Administration. https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics. Accessed August 27, 2019. 2. Li T, et al. *J Clin Oncol.* 2013;31:1039-1049. 3. FDA-NIH Biomarkers Working Group. https://www.ncbi.nlm.nih.gov/books/NBK402284/pdf/Bookshelf_NBK402284.pdf. Accessed August 31, 2019. 4. Kris MG, et al. *JAMA*. 2014;311:1998-2006. 5. Scheerens H, et al. *Clin Transl Sci.* 2017;10:84-92. 6. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-or-class-oncology. Accessed September 7, 2019.

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Biomarker Identification Provides Opportunities for Targeted Therapy in NSCLC[1,2]

The Role of Predictive and Emerging Biomarkers in NSCLC			
Predictive Biomarkers	Used to help predict response to therapeutic interventions[1]	*EGFR* mutations[3,4] *ALK* rearrangements[4] *ROS1* rearrangements[4] *NTRK* gene fusions[4]	Predicts response to targeted therapy with TKIs[3,5-7]
		BRAF point mutation[4]	Predicts response to combined BRAF and MEK inhibitors[6,7]
		PD-L1 expression levels[3]	Predicts response to immunotherapy[3]
Emerging Biomarkers	Under investigation as predictive biomarkers with the goal of identifying appropriate therapies for patients[1]	*KRAS* mutations[3] *RET* rearrangements[3,4] *MET* amplifications[3,4] *HER2* mutations[4] TMB[4]	Under investigation to facilitate appropriate therapies for patients[3]

KRAS mutations are prognostic for poor survival in NSCLC[8]

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated protein kinase; MET, hepatocyte growth factor; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden.

1. FDA-NIH Biomarkers Working Group. https://www.ncbi.nlm.nih.gov/books/NBK402284/pdf/Bookshelf_NBK402284.pdf. Accessed August 31, 2019. 2. Li T, et al. *J Clin Oncol.* 2013;31:1039-1049. 3. Thakur MK, et al. *Semin Respir Crit Care Med*. 2016;37(5):760-770. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 5. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. 6. National Cancer Institute. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_4. Accessed September 13, 2019. 7. Pakkala S, et al. *JCI Insight.* 2018;3:e120858. 8. Nadal E, et al. *J Thorac Oncol*. 2014;9:1513-1522.

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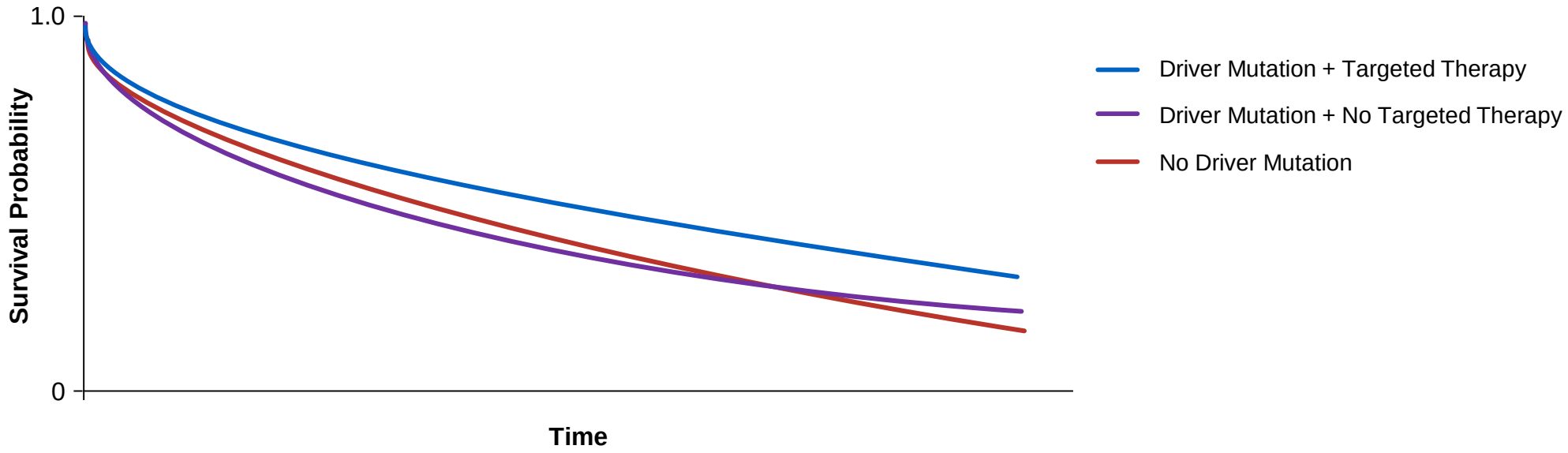
Targeted Therapeutic Interventions Based on Driver Mutations Can Improve Patient Outcomes[1,2]

Survival Trends for Driver Mutations and Targeted Therapy[1,*]



Biomarker testing and identification of driver mutations allow for targeted therapeutic interventions that lead to improved patient outcomes[1-3]

*This is hypothetical effect is based on data from a study of 1102 eligible patients with lung adenocarcinomas at 14 sites in the US.[1]

1. Kris MG, et al. *JAMA*. 2014;311:1998-2006. 2. Barlesi F, et al. *Lancet*. 2016;387:1415-1426. 3. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358.

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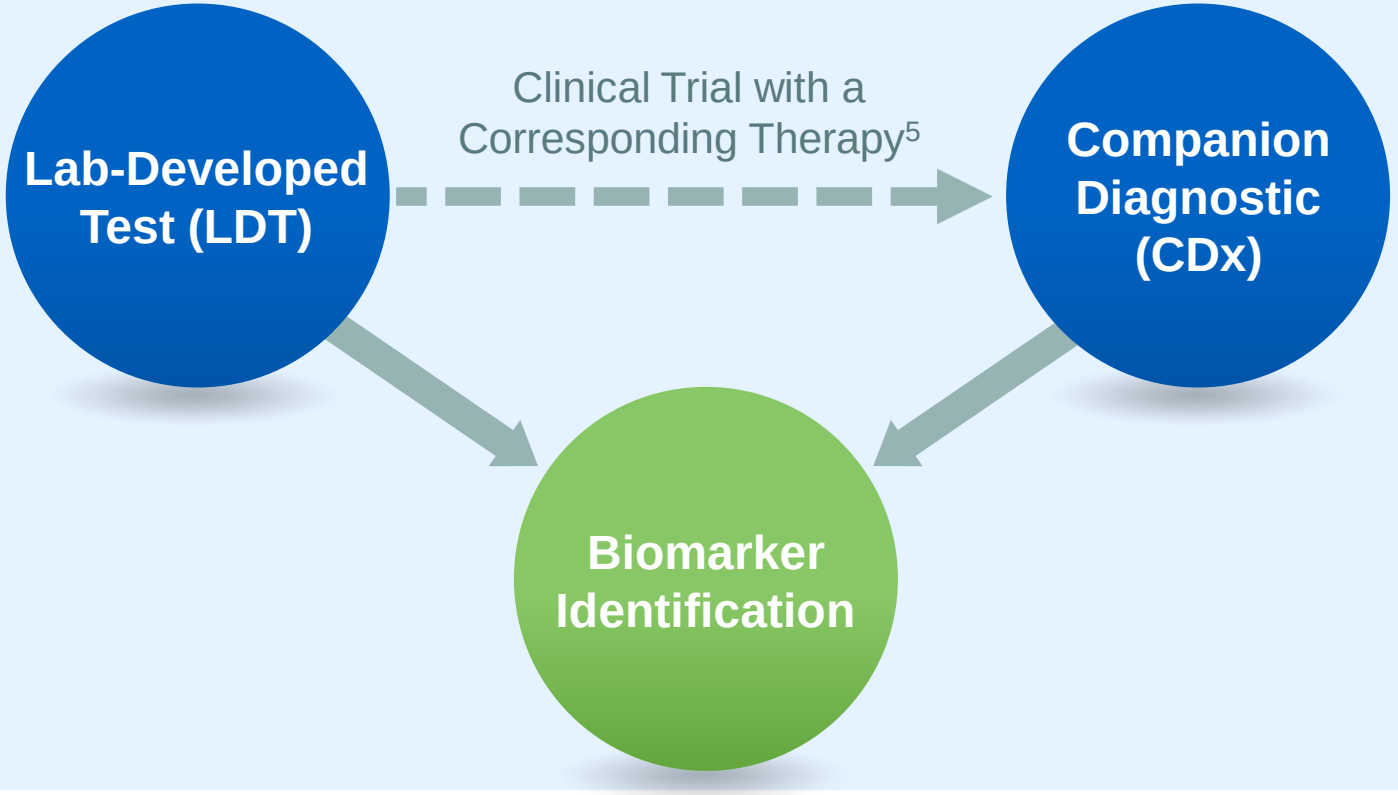
Lab-Developed Tests and Companion Diagnostics Assess Biomarkers to Identify Patients Appropriate for Therapy[1-5]

- In vitro diagnostic that is designed, manufactured, and used within a single lab[1]
- Regulated by CMS and validated by CLIA[6]



FDA-cleared diagnostic test that provides information essential for the safe and effective use of a corresponding therapy[2,4]

CLIA, Clinical Laboratory Improvement Amendments; CMS, Centers for Medicare and Medicaid Services; FDA, Food and Drug Administration.

1. Food and Drug Administration. https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests. Accessed September 7, 2019. 2. Food and Drug Administration. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed September 12, 2019. 3. Food and Drug Administration. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia. Accessed September 12, 2019. 4. Food and Drug Administration. https://www.fda.gov/media/81309/download. Accessed September 11, 2019. 5. Li T, et al. *J Clin Oncol.* 2013;31:1039-1049. 6. Centers for Medicare and Medicaid Services. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. Accessed September 17, 2019.

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Guideline Recommendations for Biomarker Testing in NSCLC Are Not Reflected in the Real World[1-6]

Predictive Biomarkers

Guidelines recommend testing of predictive biomarkers to select for personalized therapies

Emerging Biomarkers

Guidelines recommend testing of emerging biomarkers

Real-World Testing Rates

Many patients do not receive testing for guideline-recommended biomarkers

NSCLC, non-small cell lung cancer.

1. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. 2. Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. 3. Planchard D, et al. *Ann Oncol.* 2019;30:863-870. 4. Christian J, et al. *J Clin Oncol.* 2019;37:e20056. 5. Gutierrez ME, et al. *Clin Lung Cancer.* 2017;18:651-659. 6. Gierman HJ, et al. *J Clin Oncol.* 2019;37:1585.

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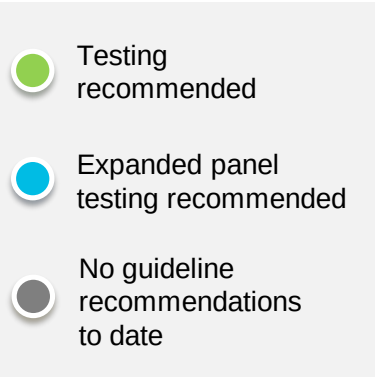
Guidelines Recommend Testing of Predictive Biomarkers to Select for Personalized Therapies[1-3]

PREDICTIVE BIOMARKERS	NCCN Guidelines[4]	CAP/IASLC/AMP Guidelines[1]	ASCO Guidelines[2,5]	ESMO/Pan-Asian Guidelines[3,6]
EGFR				
ALK				
ROS1				
BRAF				
PD-L1				
NTRK				



ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; BRAF, proto-oncogene B-Raf; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; IASLC, International Association for the Study of Lung Cancer; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; ROS1, c-ros oncogene 1.

1. Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. 2. Kalemkerian GP, et al. *J Clin Oncol*. 2018;36:911-919. 3. Planchard D, et al. *Ann Oncol*. 2019;30:863-870. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 5. Leighl NB, et al. *J Clin Oncol*. 2014;32:3673-3679. 6. Wu YL, et al. *Ann Oncol*. 2019;30:171-210.

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Many Guidelines Recommend Testing for Emerging Biomarkers as Part of an Expanded Panel or Single Gene Testing[1-3]

EMERGING/PROGNOSTIC BIOMARKERS	NCCN Guidelines[1]	CAP/IASLC/AMP Guidelines[2]	ASCO Guidelines[3]	ESMO/Pan-Asian Guidelines[4,5]
KRAS	●	◍	●	○
MET	●	●	●	○
RET	●	●	●	○
HER2	●	●	●	○
TMB	○	○	○	○

● Expanded panel testing recommended

◍ Single gene or expanded panel testing recommended

○ No guideline recommendations to date

AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ESMO, European Society for Medical Oncology; HER, human epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; MET, hepatocyte growth factor; NCCN, National Comprehensive Cancer Network; RET, rearranged during transfection; TMB, tumor mutational burden.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. 3. Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. 4. Wu YL, et al. *Ann Oncol.* 2019;30:171-210. 5. Planchard D, et al. *Ann Oncol.* 2019;30:863-870.

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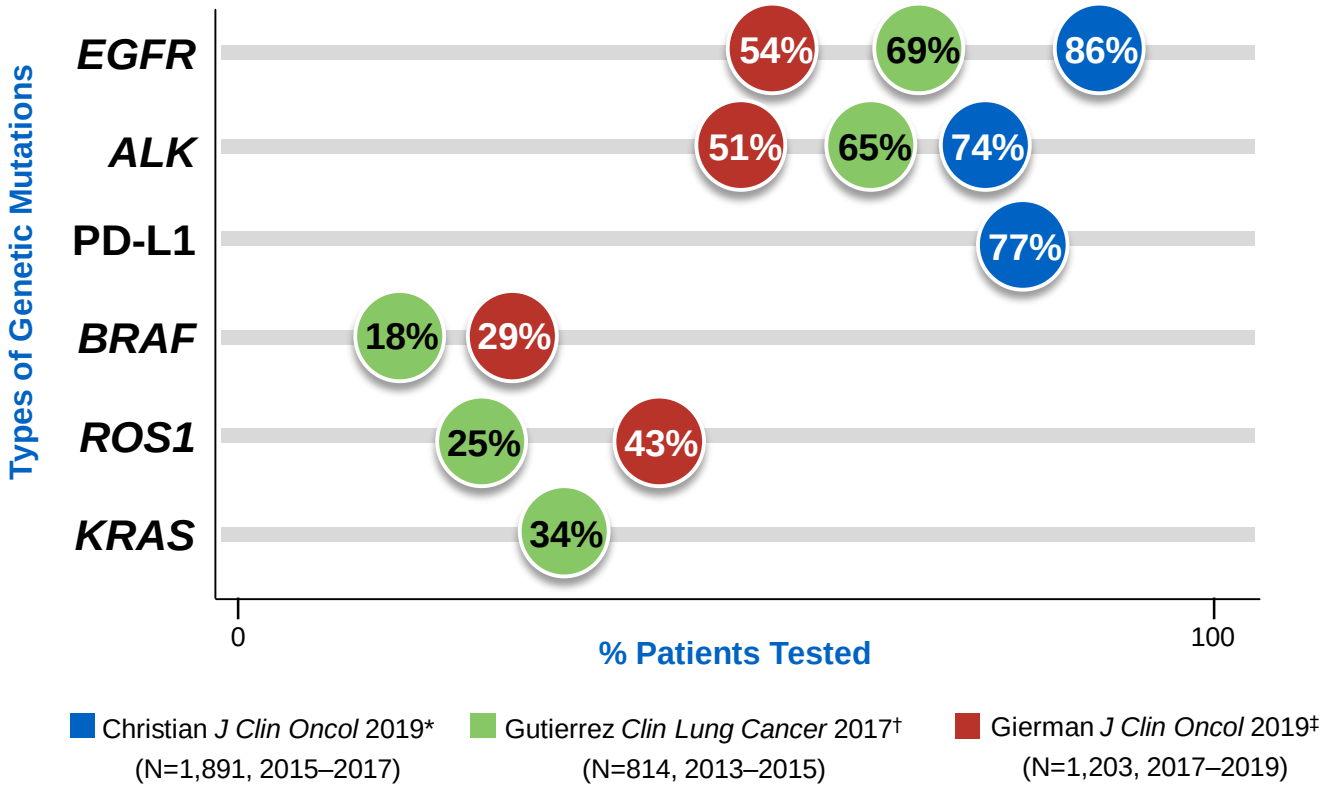
Many Patients Do Not Receive Testing for Guideline-Recommended Biomarkers[1-3]

US Testing Rates for NSCLC Biomarkers Vary[1-3]



Only 22% of Patients Received Testing for All Guideline Recommended Biomarkers *EGFR*, *ALK*, *ROS1*, and *BRAF* (N=1203)[3,‡]

55% of Patients With Targetable Mutations in *EGFR*, *ALK*, *ROS1*, or *BRAF* Did Not Receive Targeted Therapy (N=163)[3,‡]

*Retrospective analysis of biomarker testing from 2015–2017 in patients with NSCLC treated in a clinical setting.[1] †Retrospective study analyzing genomic testing patterns in patients with NSCLC from 2013–2015.[2] ‡Retrospective analysis of biomarker testing from 2017–2019 in patients with advanced NSCLC.[3]

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; ROS1, c-ros oncogene 1.

1. Christian J, et al. *J Clin Oncol.* 2019;37:e20056. 2. Gutierrez ME, et al. *Clin Lung Cancer.* 2017;18:651-659. 3. Gierman HJ, et al. *J Clin Oncol.* 2019;37:1585.

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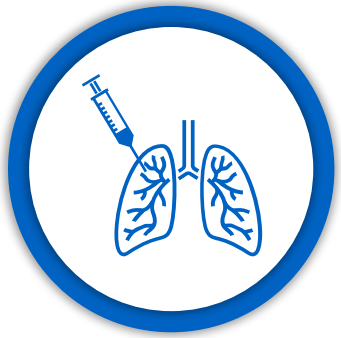
Considerations for Biomarker Testing and Analysis[1,2]

Sample Collection

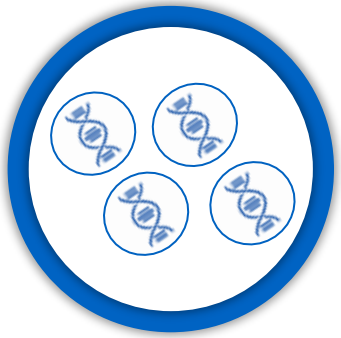


Tissue Biopsy[1]

Liquid Biopsy[3]

Testing Platforms

Single Gene[2]



Multigene[4]

Reporting Guidelines

Interpretation and Reporting[5]

1. Ofiara LM, et al. *Front Oncol.* 2014;4:253. 2. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. 3. Koessler T, et al. *Adv Clin Chem.* 2019;89:131-188. 4. Moorcraft SY, et al. *Crit Rev Oncol Hematol.* 2015;96:463-474. 5. Li MM, et al. *J Mol Diagn.* 2017;19:4-23.

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Considerations for Utilization and Interpretation of Biomarker Analysis[1]

Laboratory Requirements[1]

- Use of an accredited laboratory, with a minimum of CLIA accreditation

Testing Methodologies and Limitations[1,2]

- A number of different testing platforms are available (eg, NGS, PCR, Sanger, FISH, IHC) each with its own unique considerations and limitations
- Understand the spectrum of alterations tested or not tested by a particular assay

Specimen Acquisition and Management[1]

- Ensure sufficient tissue is procured during biopsy
- Techniques to maximize tissue for testing should be used when minimal tissue is available

Sample Analysis[1]

- Awareness of types of samples accepted by the testing laboratory
- Knowledge of whether sample collection is subject to pathology review and tumor enrichment prior to testing

CLIA, Clinical Laboratory Improvement Amendments; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.

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Genetic Alterations Can Be Detected Using Both Tissue and Liquid Biopsy Samples[1]

	Tissue Biopsy	Liquid Biopsy
Method	Gold standard; tissue extracted from primary tumor[1,2]	Blood sample containing cell free DNA[1,2]
Tumor heterogeneity	Limited to composition of tumor biopsies[1,2]	Captures tumor heterogeneity from primary tumors and metastases[1,2]
Sample collection	Invasive with possible complications[1]	Minimally invasive blood sample allows monitoring throughout disease[1,2]
Sample requirements	Sufficient tissue should be collected at diagnosis to optimize molecular testing[3]	Consider when insufficient tissue available or patient is unfit for invasive biopsy[4]
Sample integrity	DNA/RNA structural changes possible in FFPE samples[1]	Collection method may require fast turnaround to ensure sample integrity[4]

While tissue biopsy remains the gold standard, liquid biopsy may be used when insufficient tissue is available or based on patient's performance status[1,4]

FFPE, formalin-fixed paraffin-embedded.

1. Diaz LA Jr, et al. *J Clin Oncol*. 2014;32:579-586. 2. Mader S, et al. *Oncol Res Treat*. 2017;40:404-408. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. 4. Rolfo C, et al. *J Thorac Oncol.* 2018;13:1248-1268.

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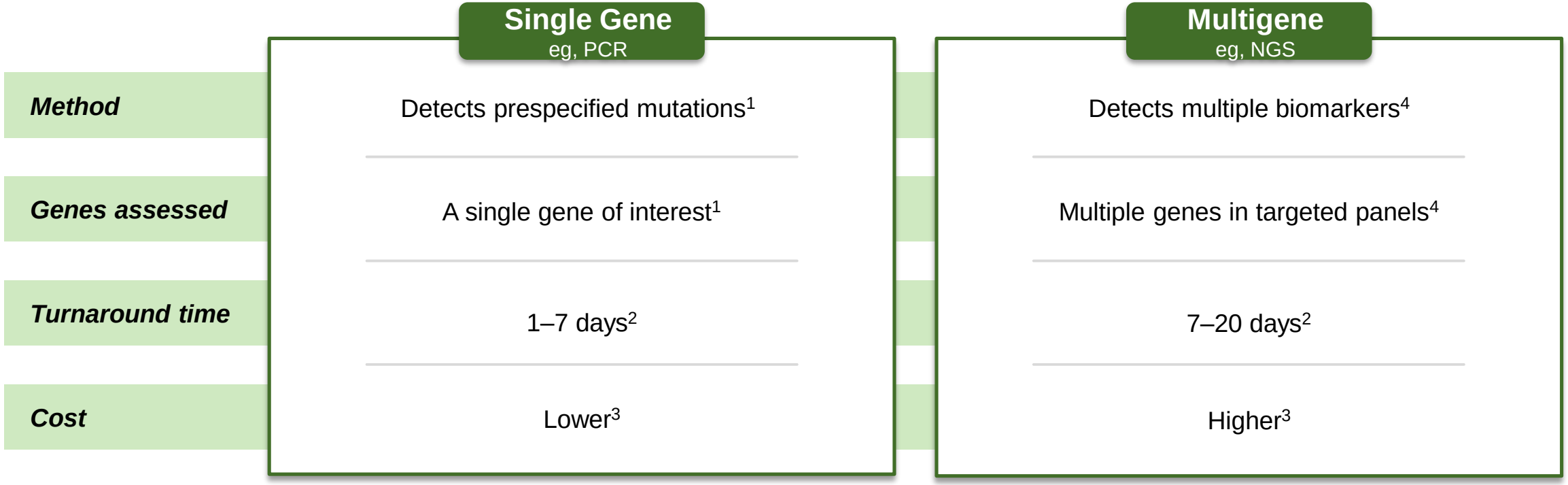
Considerations for Single-Gene Testing and Multigene Panels to Detect Genetic Alterations in Patients With NSCLC[1-4]



KRAS can be run as part of a multigene panel or as a single-gene test[5,6]

KRAS, Kirsten rat sarcoma; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

1. Rolfo C, et al. *J Thorac Oncol.* 2018;13:1248-1268. 2. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. 3. Moorcraft SY, et al. *Crit Rev Oncol Hematol*. 2015;96:463-474. 4. Rizzo JM, et al. *Cancer Prev Res (Phila)*. 2012;5:887-900. 5. Lindeman NI, et al. *J Thorac Oncol.* 2018;13:323-358. 6. Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919.

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Choice of Assay Depends on the Biomarker to Be Tested[1]

Single Gene | **Multigene Panel**

	IHC[2,3]	FISH[1,4-6]	PCR[1,4,7-9]	Sanger[1,4,7,8,10,11]	NGS[1,4,12]
Assessment	Protein expression levels	Gene rearrangements	Gene point mutations, insertions/deletions, rearrangements	Gene point mutations, insertions/deletions	Gene point mutations, insertions/deletions, copy number alterations, rearrangements
Turnaround time*	1–2 days	2–6 days	5–7 days	3–7 days	7–20 days
Biomarkers	PD-L1	*ALK, ROS1, RET*	*KRAS, EGFR, ALK, ROS1, BRAF, RET*	*KRAS, EGFR, ROS1, BRAF*	*KRAS, EGFR, ALK, ROS1, BRAF, MET, RET, HER2, TMB, NTRK*

*Turnaround time: business days between sample receipt and reporting of all results.[13]

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma; MET, hepatocyte growth factor; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase 1; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1; TMB, tumor mutational burden.

1. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. 2. Jain D, et al. *Cancer Cytopathol*. 2019;127:325-339. 3. Patel S, et al. *Hum Pathol*. 2012;43:1501-1505. 4. Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. 5. Savic S, et al. *Arch Pathol Lab Med*. 2016;140:1323-1330. 6. Illei PB, et al. *JCO Precis Oncol*. 2018;2:1-11. 7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed September 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 8. Benlloch S, et al. *PLoS One*. 2014;9:e89518. 9. LabCorp. https://www.labcorp.com/test-menu/24736/epidermal-growth-factor-receptor-egfr-gene-mutation-analysis-non%E2%88%92small-cell-lung-cancer-single-base-extension . Accessed September 19, 2019. 10. Moorcraft SY, et al. *Crit Rev Oncol Hematol*. 2015;96:463-474. 11. Scholl LM, et al. *J Thorac Oncol*. 2015;10:768-777. 12. Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342. 13. Leighl NB, et al. *J Clin Oncol*. 2014;32:3673-3679.

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Current Guideline* Recommendations Aim to Improve Consistency and Aid in Interpretation of Molecular Test Reports[1]

- Present critical information at the beginning
- Report negative findings
- Provide clinicopathologic context to inform clinical decisions such as functional, prognostic, or predictive significance
- Classify results on their level of clinical significance
- Present methodologic details at the end

*AMP/ASCO/CAP Guidelines.

AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.

Li MM, et al. *J Mol Diagn.* 2017;19:4-23.

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Summary

- NSCLC is associated with a variety of driver mutations, with *KRAS G12C* being the most common *KRAS* mutation, underscoring the need for effective therapies[1,2]

- Inhibitors of KRAS^{G12C} that block oncogenic signaling represent an important therapeutic approach in NSCLC, warranting further investigation[3-5]

- Clinical guidelines highly recommend biomarker testing to inform treatment decisions in NSCLC, yet many patients do not receive testing for guideline-recommended biomarkers[6-9]

KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

1. Skoulidis F, et al. *Nat Rev Cancer.* 2019;19:495-509. 2. Arbour KC, et al. *Clin Cancer Res.* 2018;24:334-340. 3. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 4. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. 5. Lanman BA, et al. Presented at: The American Association for Cancer Research; March 29–April 3, 2019; Atlanta, GA. Abstract 4455. 6. Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. 7. Kalemkerian GP, et al. *J Clin Oncol.* 2018;36:911-919. 8. Christian J, et al. *J Clin Oncol.* 2019;37:e20056. 9. Gutierrez ME, et al. *Clin Lung Cancer.* 2017;18:651-659. 10. Gierman HJ, et al. *J Clin Oncol.* 2019;37:1585.

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