

KRAS G12C—AN EMERGING BIOMARKER AND NOVEL INVESTIGATIONAL TARGET IN NON-SMALL CELL LUNG CANCER

Identification of genomic alterations is the foundation for precision medicine in NSCLC¹

KRAS G12C is the most prevalent emerging biomarker in NSCLC^{1,2}

KRAS G12C occurs in ~13% of patients with NSCLC, comparable to the prevalence of **EGFR** mutations^{1,2,*}

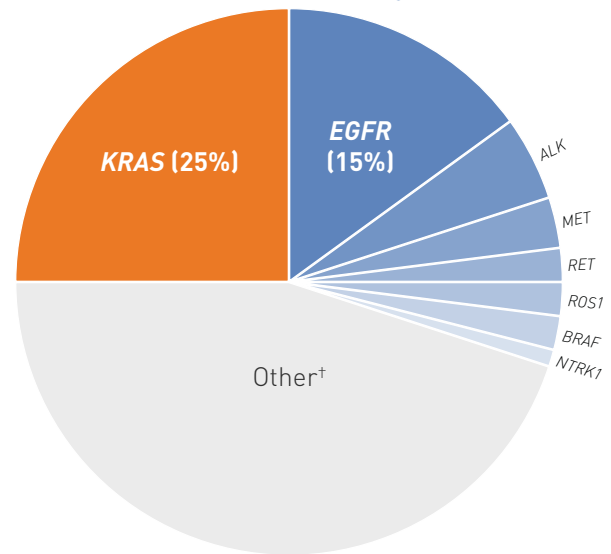
Each year in the US, ~25,000 patients who are newly diagnosed with NSCLC have the **KRAS G12C** mutation^{2,3}

Patients with the **KRAS G12C** mutation have poor survival outcomes consistent with the overall NSCLC population^{4,*}

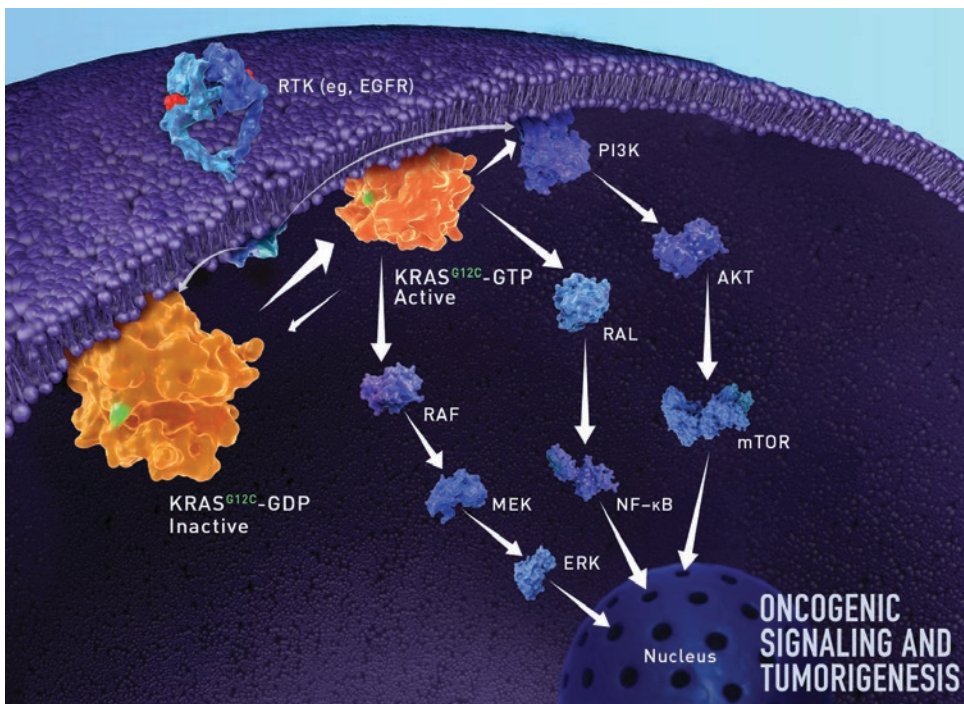
Up to 64% of patients with NSCLC may have identifiable driver mutations^{1,*}

*In patients with lung adenocarcinoma. **Other** includes *HER2*, *PIK3CA*, *MEK1*, and patients with no driver mutation detected, but does not include TMB or MSI-H!

Prevalence of driver mutations in lung adenocarcinoma¹



The **KRAS G12C** mutation drives cancer cell growth and survival⁵⁻⁹



The **KRAS G12C** mutation favors the active form of the KRAS mutant protein, driving tumorigenesis^{5,7}

- **KRAS G12C** is a single point mutation at codon 12 that causes the glycine to be substituted by a cysteine^{6,10,11}
- Investigating the structure of **KRAS G12C** reveals unique features of the mutant protein such as the P2 pocket and H95 residue¹²

Amgen is committed to investigating and understanding the role of **KRAS G12C** mutations in cancer development and maintenance

AKT, protein kinase B; ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; 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 kinase; MET, mesenchymal-to-epithelial transition; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic tyrosine receptor kinase 1; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; RET, rearranged during transfection; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinase.

Clinical guidelines recommend biomarker testing for all eligible patients at diagnosis of advanced NSCLC¹³⁻¹⁶

Biomarker testing at diagnosis can help inform the treatment journey^{13,14,17}

	Actionable Biomarkers							Emerging /Prognostic Biomarkers				
	EGFR	ALK	ROS1	BRAF	PD-L1	RET	NTRK	METex14	TMB	METamp	KRAS*	HER2
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines [®])	●	●	●	●	●	●	●	●	●	●	●	●
CAP/IASLC/AMP Guidelines	●	●	●	●	n/a	●	n/a	●	n/a	●	●	●

n/a, not applicable.

Expanded-panel testing recommended

Single-biomarker test or expanded-gene panel testing may be useful

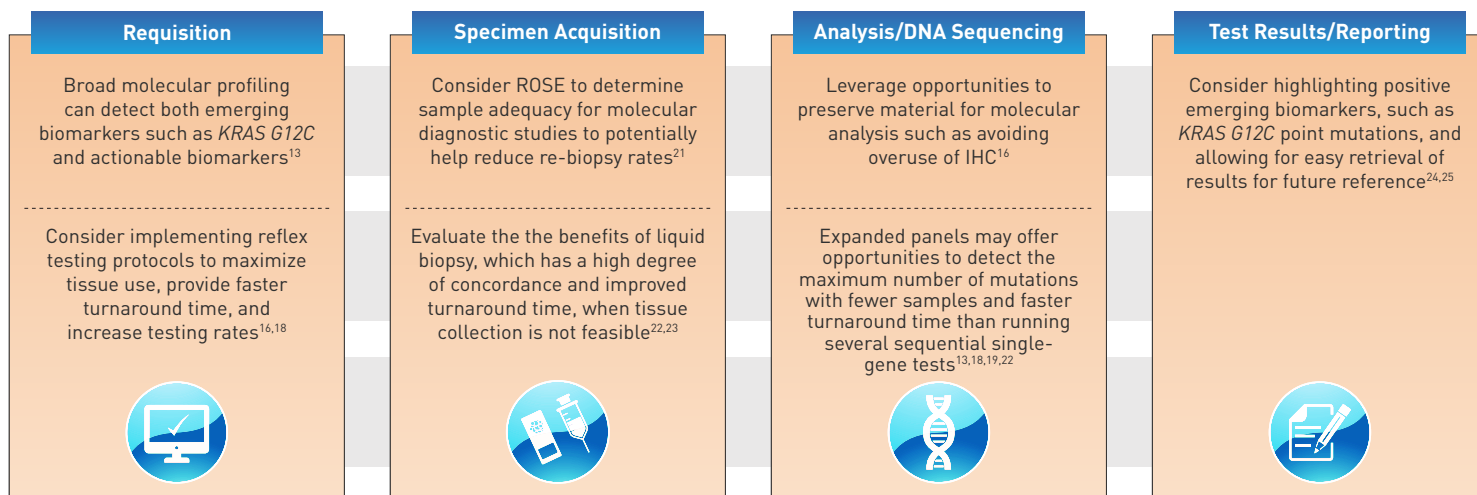
Single-biomarker test or expanded-gene panel testing recommended

*The NCCN Guidelines for NSCLC state that KRAS is a prognostic biomarker and also state that owing to the low probability of overlapping targetable alterations, the presence of a known activating mutation in KRAS identifies patients who are unlikely to benefit from further molecular testing.¹⁴

- **KRAS G12C** can be detected using established molecular testing platforms such as expanded panels (eg, NGS) or single-gene testing (eg, PCR)¹³
 - Many expanded panels already test for KRAS mutations, therefore **KRAS G12C** status may already be reported^{13,18}
- **KRAS G12C** can be detected using either tissue or liquid biopsy samples¹⁹
- **KRAS G12C** mutations are generally mutually exclusive from actionable biomarkers, such as EGFR, ALK, and ROS1; therefore, patients with KRAS G12C–mutated NSCLC may be ineligible for therapies targeting these mutations^{4,8}
- **KRAS G12C** mutations are truncal and persist during disease progression; therefore it is important to test in all NSCLC patients at diagnosis of advanced disease^{18,20}

Key considerations across the biomarker testing journey

Routine biomarker testing is a standard of care for advanced NSCLC^{13,16,18}



Learn more at [FindKRASG12C.com](https://www.findkrasg12c.com)

ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; BRAF, proto-oncogene B-Raf; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; METamp, mesenchymal-to-epithelial transition amplification; METex14, mesenchymal-to-epithelial transition exon 14; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1; ROSE, rapid on-site evaluation; TMB, tumor mutational burden.

References: 1. Pakkala S, et al. *JCI Insight*. 2018;3:e120858. 2. Data on file, Amgen; 2020. 3. American Cancer Society. <https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html>. Accessed August 4, 2020. 4. Aggarwal S, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. 5. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. 6. Simanshu DK, et al. *Cell*. 2017;170:17-33. 7. Neel NF, et al. *Genes Cancer*. 2011;2:275-287. 8. Ahmadzadeh T, et al. *J Clin Med*. 2018;7:153. 9. Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. 10. Cox AD, et al. *Nat Rev Drug Discov*. 2014;13:828-851. 11. Ihle NT, et al. *J Natl Cancer Inst*. 2012;104:228-239. 12. Canon J, et al. *Nature*. 2019;575:217-223. 13. Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. 14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines[®]] for Non-Small Cell Lung Cancer V8.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 22, 2020. 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. 15. Kalemkerian GP, et al. *J Clin Oncol*. 2018;36:911-919. 16. Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301. 17. Food and Drug Administration. <https://www.fda.gov>. Accessed August 25, 2020. 18. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. 19. Diaz LA Jr, et al. *J Clin Oncol*. 2014;32:579-586. 20. Thein KZ, et al. Presented at: The American Society of Clinical Oncology; June 2020; Virtual Meeting. Abstract 3547. 21. Ofiara LM, et al. *Front Oncol*. 2014;4:253. 22. Rolfo C, et al. *J Thorac Oncol*. 2018;13:1248-1268. 23. Leighl NB, et al. *Clin Cancer Res*. 2019;25:4691-4700. 24. Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342. 25. Li MM, et al. *J Mol Diagn*. 2017;19:4-23.