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 NSCLC[1]

KRAS G12C is the most prevalent emerging biomarker in NSCLC[1,2]

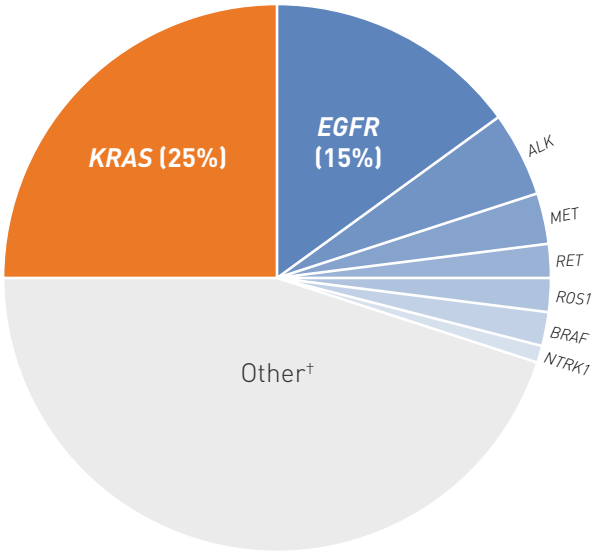
KRAS G12C **occurs in ~13% of patients with NSCLC, comparable to the prevalence of *EGFR* mutations[1,2,*]**

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,*]

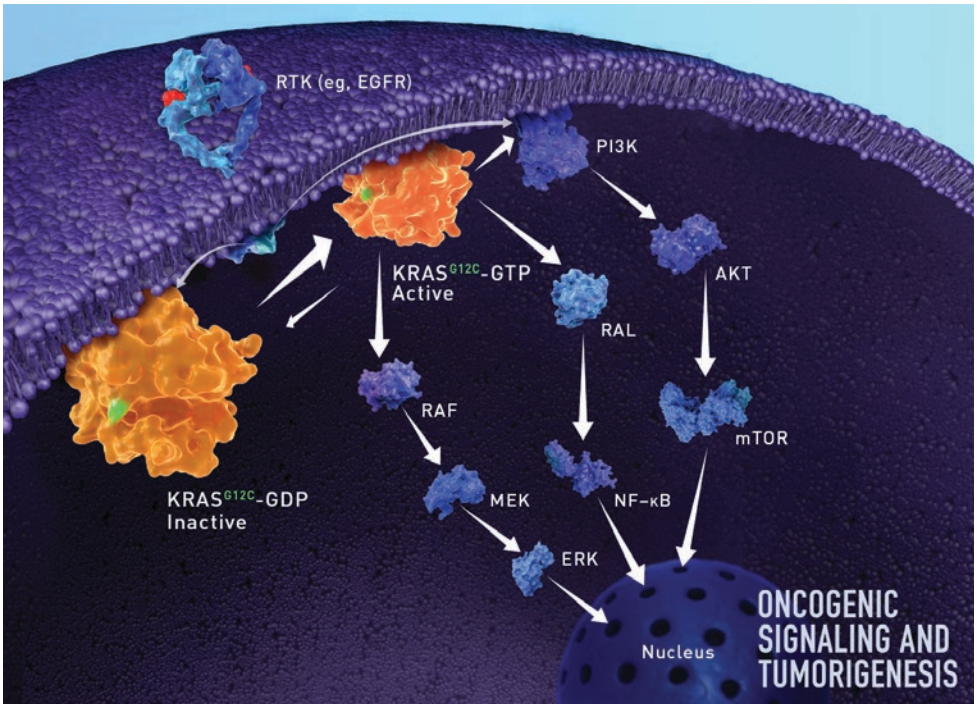
Up to **64%** of patients with NSCLC may have **identifiable driver mutations**[1,*]

Prevalence of driver mutations in lung adenocarcinoma[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.[1]

The *KRAS G12C* mutation drives cancer cell growth and survival[5-9]



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 residue[12]

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 NSCLC[13-16]

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*	*MET*ex14	TMB	*MET*amp	*KRAS**	*HER2*
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)	●	●	●	●	●	●	●	●	●	●	●	●
CAP/IASLC/AMP Guidelines	●	●	●	●	n/a	●	n/a	●	n/a	●	●	●

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

n/a, not applicable.

*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 samples[19]
- ***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]

Requisition

Broad molecular profiling can detect both emerging biomarkers such as *KRAS G12C* and actionable biomarkers[13]

Consider implementing reflex testing protocols to maximize tissue use, provide faster turnaround time, and increase testing rates[16,18]

Specimen Acquisition

Consider ROSE to determine sample adequacy for molecular diagnostic studies to potentially help reduce re-biopsy rates[21]

Evaluate the the benefits of liquid biopsy, which has a high degree of concordance and improved turnaround time, when tissue collection is not feasible[22,23]

Analysis/DNA Sequencing

Leverage opportunities to preserve material for molecular analysis such as avoiding overuse of IHC[16]

Expanded panels may offer opportunities to detect the maximum number of mutations with fewer samples and faster turnaround time than running several sequential single-gene tests[13,18,19,22]

Test Results/Reporting

Consider highlighting positive emerging biomarkers, such as *KRAS G12C* point mutations, and allowing for easy retrieval of results for future reference[24,25]

Learn more at 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.

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