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

KRAS G12C is a prevalent emerging molecular target in NSCLC[1]

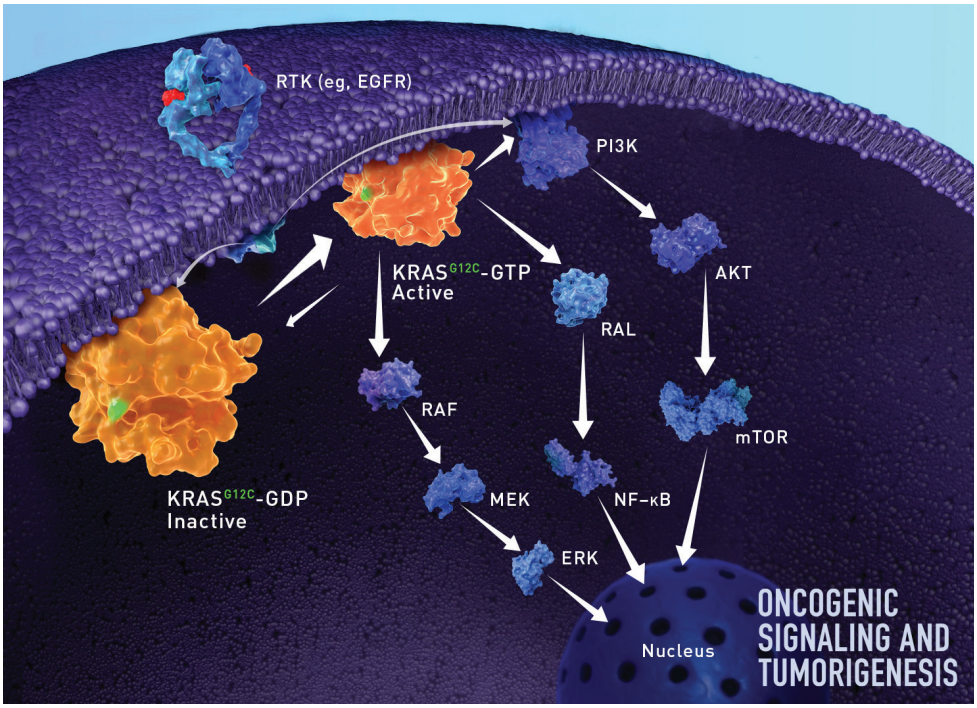
The prevalence of *KRAS G12C* mutations in NSCLC varies across regions/countries[1-4]

Prevalence Rates for Select Regions/Countries	
Region/Country	***KRAS G12C* Prevalence (%)**
1. Lebanon	18%
2. United States	13%*
3. Canada	13%†
4. Australia	11%
5. Europe	10%–15%‡
6. Brazil	8%
7. Morocco	7%
8. Asia	4%–5%§

KRAS G12C mutations can occur regardless of patient characteristics such as ethnicity, race, or smoking status[2,3,5]

*Excludes 2 histology categories: NSCLC (NOS) and squamous.[1]
†In nonsquamous NSCLC.[4]
‡Range depicts variability across European countries, including France, Germany, Greece, Hungary, Italy, the Netherlands, Russia, Sweden, and the UK.[2]
§Represents reported prevalence in Japan and the upper range of reported prevalence in China, South Korea, and India.[2,3]

The *KRAS G12C* mutation drives cancer cell growth and survival[6-9]



The *KRAS G12C* mutation favors the active form of the KRAS mutant protein, driving tumorigenesis[7,8]

- ***KRAS G12C*** is a single point mutation at codon 12 that substitutes the amino acid glycine for cysteine[10,11]
- Investigating the structure of **KRAS^{G12C}** revealed unique features of the mutant protein, such as the P2 pocket and H95 residue, which provide a potential binding site for covalent inhibitors[6]

AKT, protein kinase B; 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; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-like; RTK, receptor tyrosine kinase.

Clinical guidelines recommend biomarker testing for all eligible patients at diagnosis of advanced NSCLC[12-16]

Biomarker testing at diagnosis can help inform the treatment journey[12,13,15-17]

	Actionable Biomarkers								Emerging/Prognostic Biomarkers		
	EGFR	*ALK*	*ROS1*	*BRAF*	PD-L1	*RET*	*NTRK*	*MET*ex14	*MET*amp	*KRAS**	*HER2*
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)†	●	●	●	●	●	●	●	●	●	●	●
CAP/IASLC/AMP Guidelines	●	●	●	●	n/a	●	n/a	●	●	●	●
ESMO Guidelines	●	●	●	●	●	n/a	●	n/a	n/a	n/a	n/a
Pan-Asian Guidelines	●	●	●	●	●	n/a	n/a	n/a	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 addressed.

*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.[13]

†The NCCN Guidelines® for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.[13]

- ***KRAS G12C*** can be detected using established molecular testing platforms such as multigene panels (eg, NGS) or single-gene testing (eg, PCR)[12]
  - Most multigene panels already test for *KRAS* mutations; therefore, ***KRAS G12C*** status may already be reported[12,18,19]
- ***KRAS G12C*** can be detected using either tissue or liquid biopsy samples[20]
- ***KRAS G12C*** mutations are truncal in nature; therefore, mutational status may be unlikely to change over time in patients with NSCLC[18]

Key considerations across the biomarker testing journey

Routine biomarker testing is a standard of care for advanced NSCLC[12,19,21]

Specimen Acquisition

Consider **rapid on-site evaluation** (ROSE) to determine sample adequacy for molecular diagnostic studies to potentially help reduce rebiopsy rates[22]

Leverage opportunities to **preserve material for molecular analysis** such as avoiding overuse of IHC[21]

Genomic Profiling

Consider implementing **reflex testing** at histopathological diagnosis to maximize tissue use, provide faster turnaround time, and increase testing rates[19,21]

Broad molecular profiling can detect both actionable and emerging biomarkers, such as *KRAS G12C*[12]

Alternative Specimen/ DNA Sequencing

Consider **liquid biopsy**, which has a high degree of concordance (> 90%) with tissue biopsy and improved turnaround time, when tissue collection is not feasible[23,24]

Multigene 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[12,19,20,23]

Test Results/Reporting

Consider **highlighting positive emerging biomarkers**, such as *KRAS G12C* point mutations, and allowing for easy retrieval of results for future reference[25,26]

ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; BRAF, proto-oncogene B-Raf; CAP, College of American Pathologists; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; 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; 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.

References: 1. Data on file, Amgen; [1]; 2020. **2.** Data on file, Amgen; [2]; 2020. **3.** Data on file, Amgen; [3]; 2020. **4.** Data on file, Amgen; 2019. **5.** Aggarwal S, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. Abstract 1339P. **6.** Canon J, et al. *Nature*. 2019;575:217-223. **7.** Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720. **8.** Neel NF, et al. *Genes Cancer*. 2011;2:275-287. **9.** Ferrer I, et al. *Lung Cancer*. 2018;124:53-64. **10.** Kim D, et al. *Cell*. 2020;183:850-859. **11.** Ihle NT, et al. *J Natl Cancer Inst*. 2012;104:228-239. **12.** Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. **13.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer v.2.2021. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed December 16, 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. **14.** Kalemkerian GP, et al. *J Clin Oncol*. 2018;36:911-919. **15.** Planchard D, et al. *Ann Oncol*. 2018;29(suppl 4):iv192-iv237. Updated September 15, 2020. **16.** Wu Y-L, et al. *Ann Oncol*. 2019;30:171-210. **17.** OncologyPro. https://www.oncologypro.esmo.org. Accessed January 4, 2021. **18.** McGranahan N, et al. *Sci Transl Med*. 2015;7:283ra54. **19.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **20.** Diaz LA Jr, et al. *J Clin Oncol*. 2014;32:579-586. **21.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301. **22.** Ofiara LM, et al. *Front Oncol*. 2014;4:253. **23.** Rolfo C, et al. *J Thorac Oncol*. 2018;13:1248-1268. **24.** Leighl NB, et al. *Clin Cancer Res*. 2019;25:4691-4700. **25.** Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342. **26.** Li MM, et al. *J Mol Diagn*. 2017;19:4-23.

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