KRAS — A Key Oncogenic Driver and Novel Investigational Target in NSCLC
NSCLC is a heterogeneous disease with poor survival outcomes. KRAS is the most frequently mutated oncogene in NSCLC. The importance of oncogenic KRAS G12C in NSCLC has been recognized.

**Importance of Biomarker Testing**

Guideline recommendations and real-world testing.

**Approaches to Targeting KRAS G12C**

**Importance of Biomarker Testing**

**Summary**
NSCLC Is a Heterogeneous Disease With Poor Survival Outcomes
KRAS Is the Most Frequently Mutated Oncogene in NSCLC
Importance of Oncogenic KRAS G12C in NSCLC
Approaches to Targeting KRAS G12C
Importance of Biomarker Testing
Guideline Recommendations and Real-World Testing
Biomarker Testing and Analysis Considerations
Summary

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

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
**Lung Cancer Is the Leading Cause of Cancer Death and There Remains a Significant Need for New Therapies**

### 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.

### Diagnosis

NSCLC accounts for ~85% of all lung cancers with ~60% of patients diagnosed at an advanced stage.

### Treatment Outcomes

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

### Biomarker Testing

Despite biomarkers serving as the foundation for precision medicine in patients with NSCLC, molecular testing rates are suboptimal.

---

*5-year relative survival in patients with advanced stage NSCLC from 2008-2014 in the U.S.

NSCLC Is Associated With Several Oncogenic Driver Mutations

Prevalence of Driver Mutations in Lung Adenocarcinomas

Approved Targeted Therapies

No Driver Mutation Detected (36%)

KRAS (25%)

EGFR (15%)

ALK (5%)

MET (3%)

ROS1 (2%)

HER2 (2%)

BRAF (2%)

RET (2%)

PIK3CA (1%)

NTRK1 (1%)

MEK1 (<1%)

Targeted therapy is not currently available for patients with KRAS mutations

*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.

**KRAS Is a Member of the RAS Gene Family**

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

**86%**

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

**100%**

of RAS mutations in lung adenocarcinoma

**KRAS** is the most frequently mutated oncogene in human cancer

---

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


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
KRAS Is a Key Regulator of Cellular Proliferation and Differentiation

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

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.

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

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

- KRAS-mutated tumors are typically adenocarcinomas.

- Approximately 9 out of 10 patients are former or current smokers.
NSCLC is a heterogeneous disease with poor survival outcomes. KRAS is the most frequently mutated oncogene in NSCLC. KRAS mutations are often mutually exclusive from other predictive oncogenic mutations (e.g., EGFR, ALK, and ROS1); patients with KRAS-mutated NSCLC are therefore unlikely to benefit from targeted therapies for these specific mutations. Only some patients with KRAS-mutated NSCLC achieve clinical benefit with currently available targeted therapies, chemotherapy, and immunotherapies. In patients with lung cancer, overlap of KRAS mutations with STK11/LKB1 has been associated with resistance to PD-1 blockade. KRAS-mutated NSCLC tumors have a high degree of intrinsic heterogeneity; therefore, not all patients may experience positive outcomes with current therapies.
G12C Is the Most Common KRAS Mutation and Comprises Nearly Half of All KRAS Mutations in NSCLC\textsuperscript{1,2}

Prevalence of KRAS Point Mutations\textsuperscript{2}

- **G12C** (44%)
- **G12D** (16%)
- **G12V** (15%)
- **G12A** (7%)
- **G12D** (16%)
- **G12S** (2%)
- **G12S** (2%)
- **Q61H** (4%)
- **G13D** (5%)
- **G13C** (2%)
- **Other** (5%)

**Codon 12**

Position where KRAS mutations are frequently seen\textsuperscript{1}

13% (~1 in 8)

Patients in the US with NSCLC have the KRAS G12C driver mutation\textsuperscript{3}

~23,000

New patients are diagnosed with KRAS G12C NSCLC annually in the US\textsuperscript{4}

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

**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.

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
Retrospective Analyses Suggest That \textit{KRAS G12C} Mutations May Be a Negative Prognostic Factor in Patients With NSCLC\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Wild-type KRAS</th>
<th>Other KRAS Mutations</th>
<th>KRAS G12C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2-Year OS Rates Following Surgery</strong>\textsuperscript{1,*} (All Stages)</td>
<td><strong>80%</strong> (n=92)</td>
<td><strong>~87%</strong> (n=50)</td>
</tr>
<tr>
<td><strong>Median OS Following 2L/3L Chemotherapy</strong>\textsuperscript{2,†} (Advanced-Stage NSCLC)</td>
<td><strong>16.1 Months</strong> (n=90)</td>
<td><strong>10.3 Months</strong> (n=24)</td>
</tr>
</tbody>
</table>

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

Despite Nearly Four Decades of Scientific Efforts, KRAS Has Not Been Successfully Targeted\textsuperscript{1,2}

Direct Inhibitors

Direct inhibition of KRAS has presented key challenges\textsuperscript{1,2}

- Lack of surface targets for binding\textsuperscript{1}
- High affinity for GTP, resulting in ineffective competitive inhibition\textsuperscript{1,2}
- Non-selective binding to wild-type KRAS limited approaches to targeting mutant KRAS\textsuperscript{2}

GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; RTK, receptor tyrosine kinase.
The G12C Mutation Creates a Narrow, Targetable Pocket on KRAS\textsuperscript{1,2}

The mutant cysteine of KRAS\textsuperscript{G12C} resides adjacent to a pocket (P2)\textsuperscript{1,2}

It’s hypothesized that the KRAS-specific histidine 95 (H95) residue may provide an allosteric site to stabilize drug-protein interaction\textsuperscript{3}

The pocket (P2) is present in the inactive, GDP-bound form of KRAS\textsuperscript{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\textsuperscript{2}

GDP, guanosine diphosphate; KRAS, Kirsten rat sarcoma.


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
Inhibition of KRAS\textsuperscript{G12C} Represents an Important Therapeutic Approach in NSCLC Which Warrants Further Investigation\textsuperscript{1-3}

By utilizing the KRAS\textsuperscript{G12C} binding pocket, covalent inhibitors could lock KRAS\textsuperscript{G12C} in the inactive state, blocking oncogenic signaling, without impacting wild-type KRAS signaling\textsuperscript{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.

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\(^1,5,6\)

---


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
**Biomarker Identification Provides Opportunities for Targeted Therapy in NSCLC**

1. **NSCLC is a Heterogenous Disease With Poor Survival Outcomes**
   - KRAS is the Most Frequently Mutated Oncogene in NSCLC
   - Importance of Oncogenic KRAS G12C in NSCLC

2. **Approaches to Targeting KRAS G12C**
   - Importance of Biomarker Testing
   - Guideline Recommendations and Real-World Testing
   - Biomarker Testing
   - Summary

### The Role of Predictive and Emerging Biomarkers in NSCLC

<table>
<thead>
<tr>
<th>Predictive Biomarkers</th>
<th>Used to help predict response to therapeutic interventions¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutations³,⁴</strong></td>
<td>Predicts response to targeted therapy with TKIs³,⁵,⁷</td>
</tr>
<tr>
<td><strong>ALK rearrangements⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ROS1 rearrangements⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NTRK gene fusions⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF point mutation⁴</strong></td>
<td>Predicts response to combined BRAF and MEK inhibitors⁶,⁷</td>
</tr>
<tr>
<td><strong>PD-L1 expression levels³</strong></td>
<td>Predicts response to immunotherapy³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emerging Biomarkers</th>
<th>Under investigation as predictive biomarkers with the goal of identifying appropriate therapies for patients¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS mutations³</strong></td>
<td>Under investigation to facilitate appropriate therapies for patients³</td>
</tr>
<tr>
<td><strong>RET rearrangements³,⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MET amplifications³,⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 mutations⁴</strong></td>
<td></td>
</tr>
<tr>
<td><strong>TMB⁴</strong></td>
<td></td>
</tr>
</tbody>
</table>

**KRAS mutations are prognostic for poor survival in NSCLC⁸**


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
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\\)
NSCLC is a heterogeneous disease with poor survival outcomes.

KRAS is the most frequently mutated oncogene in NSCLC.

Importance of Oncogenic KRAS G12C in NSCLC

Approaches to Targeting KRAS<sup>G12C</sup> and Other KRAS Mutations

Importance of Biomarker Testing

Guideline Recommendations and Real-World Testing

Biomarker Testing

Summary

Lab-Developed Tests and Companion Diagnostics Assess Biomarkers to Identify Patients Appropriate for Therapy<sup>1-5</sup>

- In vitro diagnostic that is designed, manufactured, and used within a single lab<sup>1</sup>
- Regulated by CMS and validated by CLIA<sup>6</sup>

Clinical Trial with a Corresponding Therapy<sup>5</sup>

FDA-cleared diagnostic test that provides information essential for the safe and effective use of a corresponding therapy<sup>2,4</sup>

Biomarker Identification

Lab-Developed Test (LDT)

Companion Diagnostic (CDx)

Guideline Recommendations for Biomarker Testing in NSCLC Are Not Reflected in the Real World¹⁻⁶

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.

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
NSCLC Is a Heterogenous Disease With Poor Survival Outcomes

KRAS Is the Most Frequently Mutated Oncogene in NSCLC

Importance of Oncogenic KRAS G12C in NSCLC

Approaches to Targeting KRAS<sup>G12C</sup>

Importance of Biomarker Testing

Guideline Recommendations and Real-World Testing

Biomarker Testing

Summary

---

### Guidelines Recommend Testing of Predictive Biomarkers to Select for Personalized Therapies<sup>1-3</sup>

<table>
<thead>
<tr>
<th>PREDICTIVE BIOMARKERS</th>
<th>NCCN Guidelines&lt;sup&gt;4&lt;/sup&gt;</th>
<th>CAP/IASLC/AMP Guidelines&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ASCO Guidelines&lt;sup&gt;2,5&lt;/sup&gt;</th>
<th>ESMO/Pan-Asian Guidelines&lt;sup&gt;3,6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>ALK</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>ROS1</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>BRAF</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>PD-L1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTRK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Testing recommended**

**Expanded panel testing recommended**

**No guideline recommendations to date**

---

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.
Many Guidelines Recommend Testing for Emerging Biomarkers as Part of an Expanded Panel or Single Gene Testing\textsuperscript{1-3}

<table>
<thead>
<tr>
<th>EMERGING/PROGNOSTIC BIOMARKERS</th>
<th>NCCN Guidelines\textsuperscript{1}</th>
<th>CAP/IASLC/AMP Guidelines\textsuperscript{2}</th>
<th>ASCO Guidelines\textsuperscript{3}</th>
<th>ESMO/Pan-Asian Guidelines\textsuperscript{4,5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel or expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="No guideline recommendations to date" /></td>
</tr>
<tr>
<td>MET</td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel or expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="No guideline recommendations to date" /></td>
</tr>
<tr>
<td>RET</td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel or expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="No guideline recommendations to date" /></td>
</tr>
<tr>
<td>HER2</td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel or expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="No guideline recommendations to date" /></td>
</tr>
<tr>
<td>TMB</td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel or expanded panel testing recommended" /></td>
<td><img src="image" alt="Expanded panel testing recommended" /></td>
<td><img src="image" alt="No guideline recommendations to date" /></td>
</tr>
</tbody>
</table>

1. \textsuperscript{1} Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\textsuperscript{®}) for Non-Small Cell Lung Cancer. v.7.2019. © National Comprehensive Cancer Network, Inc. All rights reserved.
2. 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.

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.

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.

**Many Patients Do Not Receive Testing for Guideline-Recommended Biomarkers**

US Testing Rates for NSCLC Biomarkers Vary

- **EGFR**
  - 54% (Christian J Clin Oncol 2019*)
  - 69% (Gutierrez Clin Lung Cancer 2017†)
  - 86% (Gierman J Clin Oncol 2019‡)

- **ALK**
  - 51% (Christian J Clin Oncol 2019*)
  - 65% (Gutierrez Clin Lung Cancer 2017†)
  - 74% (Gierman J Clin Oncol 2019‡)

- **PD-L1**
  - 77% (Gierman J Clin Oncol 2019‡)

- **BRAF**
  - 18% (Christian J Clin Oncol 2019*)
  - 29% (Gutierrez Clin Lung Cancer 2017†)

- **ROS1**
  - 25% (Christian J Clin Oncol 2019*)
  - 43% (Gutierrez Clin Lung Cancer 2017†)

- **KRAS**
  - 34% (Christian J Clin Oncol 2019*)


**Only 22% of Patients Received Testing for All Guideline Recommended Biomarkers EGFR, ALK, ROS1, and BRAF (N=1203)⁴**

55% of Patients With Targetable Mutations in EGFR, ALK, ROS1, or BRAF Did Not Receive Targeted Therapy (N=163)⁴

---

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
Considerations for Biomarker Testing and Analysis¹,²

Sample Collection

- Tissue Biopsy¹
- Liquid Biopsy³

Testing Platforms

- Single Gene²
- Multigene⁴

Reporting Guidelines

- Interpretation and Reporting⁵


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
Considerations for Utilization and Interpretation of Biomarker Analysis

- Use of an accredited laboratory, with a minimum of CLIA accreditation
- A number of different testing platforms are available (e.g., 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
- Ensure sufficient tissue is procured during biopsy
- Techniques to maximize tissue for testing should be used when minimal tissue is available
- 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.

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

<table>
<thead>
<tr>
<th>Tissue Biopsy</th>
<th>Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tumor heterogeneity</strong></td>
<td>Blood sample containing cell free DNA</td>
</tr>
<tr>
<td><strong>Sample collection</strong></td>
<td>Captures tumor heterogeneity from primary tumors and metastases</td>
</tr>
<tr>
<td><strong>Sample requirements</strong></td>
<td>Minimally invasive blood sample allows monitoring throughout disease</td>
</tr>
<tr>
<td><strong>Sample integrity</strong></td>
<td>Collection method may require fast turnaround to ensure sample integrity</td>
</tr>
</tbody>
</table>

While tissue biopsy remains the gold standard, liquid biopsy may be used when insufficient tissue is available or based on patient’s performance status.

**Gold standard; tissue extracted from primary tumor**

**Limited to composition of tumor biopsies**

**Invasive with possible complications**

**Sufficient tissue should be collected at diagnosis to optimize molecular testing**

**DNA/RNA structural changes possible in FFPE samples**

**Blood sample containing cell free DNA**

**Captures tumor heterogeneity from primary tumors and metastases**

**Minimally invasive blood sample allows monitoring throughout disease**

**Consider when insufficient tissue available or patient is unfit for invasive biopsy**

**Collection method may require fast turnaround to ensure sample integrity**

---

FFPE, formalin-fixed paraffin-embedded.


Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
Considerations for Single-Gene Testing and Multigene Panels to Detect Genetic Alterations in Patients With NSCLC\(^1-^4\)

<table>
<thead>
<tr>
<th>Method</th>
<th>Single Gene (e.g., PCR)</th>
<th>Multigene (e.g., NGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detects</td>
<td>Detects prespecified mutations(^1)</td>
<td>Detects multiple biomarkers(^4)</td>
</tr>
<tr>
<td>Genes assessed</td>
<td>A single gene of interest(^1)</td>
<td>Multiple genes in targeted panels(^4)</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1–7 days(^2)</td>
<td>7–20 days(^2)</td>
</tr>
<tr>
<td>Cost</td>
<td>Lower(^3)</td>
<td>Higher(^3)</td>
</tr>
</tbody>
</table>

**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.

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
NSCLC is a heterogeneous disease with poor survival outcomes. KRAS is the most frequently mutated oncogene in NSCLC. Approaches to targeting KRAS<sup>1</sup> include importance of biomarker testing and guideline recommendations and real-world testing.  

**Choice of Assay Depends on the Biomarker to Be Tested**

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Assessment</th>
<th>Turnaround Time*</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Gene</td>
<td>Protein expression levels</td>
<td>1–2 days</td>
<td>PD-L1, ALK, ROS1, RET, KRAS, EGFR, ALK, ROS1, BRAF, RET</td>
</tr>
<tr>
<td>Single Gene</td>
<td>Gene rearrangements</td>
<td>2–6 days</td>
<td>ALK, ROS1, RET</td>
</tr>
<tr>
<td>Single Gene</td>
<td>Gene point mutations, insertions/deletions, rearrangements</td>
<td>5–7 days</td>
<td>KRAS, EGFR, ALK, ROS1, BRAF, RET</td>
</tr>
<tr>
<td>Single Gene</td>
<td>Gene point mutations, insertions/deletions</td>
<td>3–7 days</td>
<td>KRAS, EGFR, ROS1, BRAF</td>
</tr>
<tr>
<td>Multigene Panel</td>
<td>Gene point mutations, insertions/deletions, copy number alterations, rearrangements</td>
<td>7–20 days</td>
<td>KRAS, EGFR, ALK, ROS1, BRAF, MET, RET, HER2, TMB, NTRK</td>
</tr>
</tbody>
</table>

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

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

---

**5**Reference with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) 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.

---

**6**Biomarker Testing.  

Do not copy or distribute. © 2019 Amgen Inc. All rights reserved.
NSCLC is a Heterogenous Disease With Poor Survival Outcomes

KRAS is the Most Frequently Mutated Oncogene in NSCLC

Importance of Oncogenic KRAS G12C in NSCLC

Approaches to Targeting KRAS G12C

Importance of Biomarker Testing

Guideline Recommendations and Real-World Testing

Biomarker Testing Summary

Current Guideline* Recommendations Aim to Improve Consistency and Aid in Interpretation of Molecular Test Reports¹

- 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.
NSCLC is associated with a variety of driver mutations, with KRAS G12C being the most common KRAS mutation, underscoring the need for effective therapies\textsuperscript{1,2}

Inhibitors of KRAS\textsuperscript{G12C} that block oncogenic signaling represent an important therapeutic approach in NSCLC, warranting further investigation\textsuperscript{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\textsuperscript{6-9}

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