The Evolving Biomarker Landscape in Advanced NSCLC

AMGEN
Oncology

Objectives

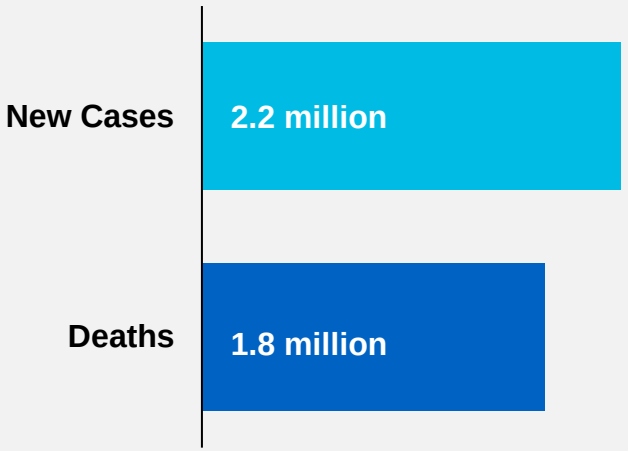
1. Review the heterogeneity of NSCLC and the evolving biomarker landscape
2. Describe the characteristics of patients with NSCLC tumors
3. Outline considerations for biomarker testing in NSCLC

NSCLC, non-small cell lung cancer.

AMGEN Oncology

Lung Cancer Is the Leading Cause of Cancer Death Worldwide

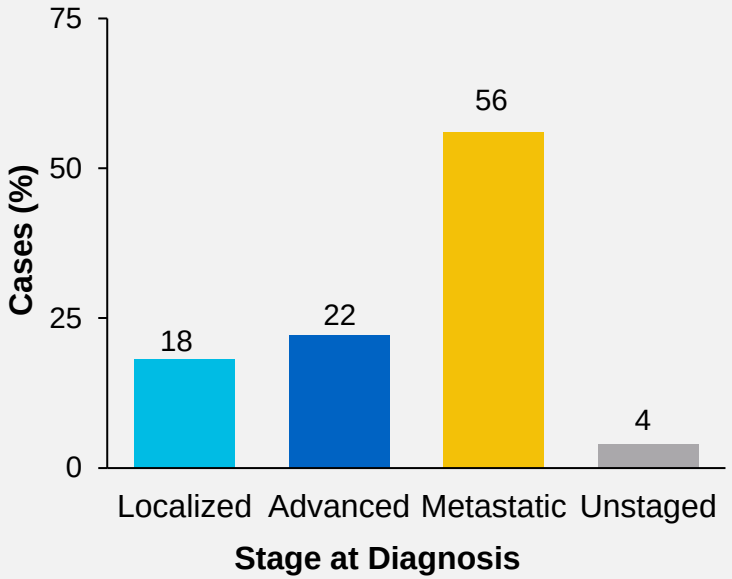
Global Statistics



Number of Estimated Lung Cancer Cases (2020)

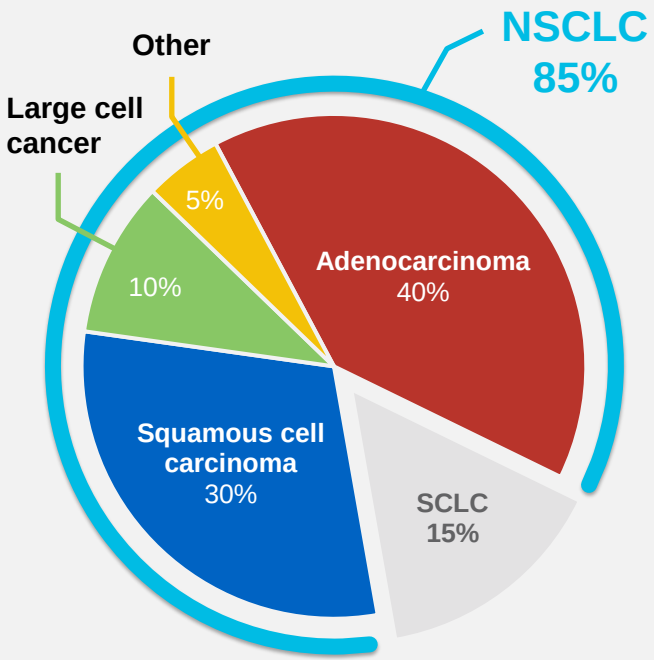
Lung cancer accounts for more deaths than colon, breast, and prostate cancers combined [1]

Late Diagnosis



Most patients with lung cancer (78%) are diagnosed with advanced or metastatic disease [2,*]

Subtypes



NSCLC accounts for 85% of lung cancer cases [3]

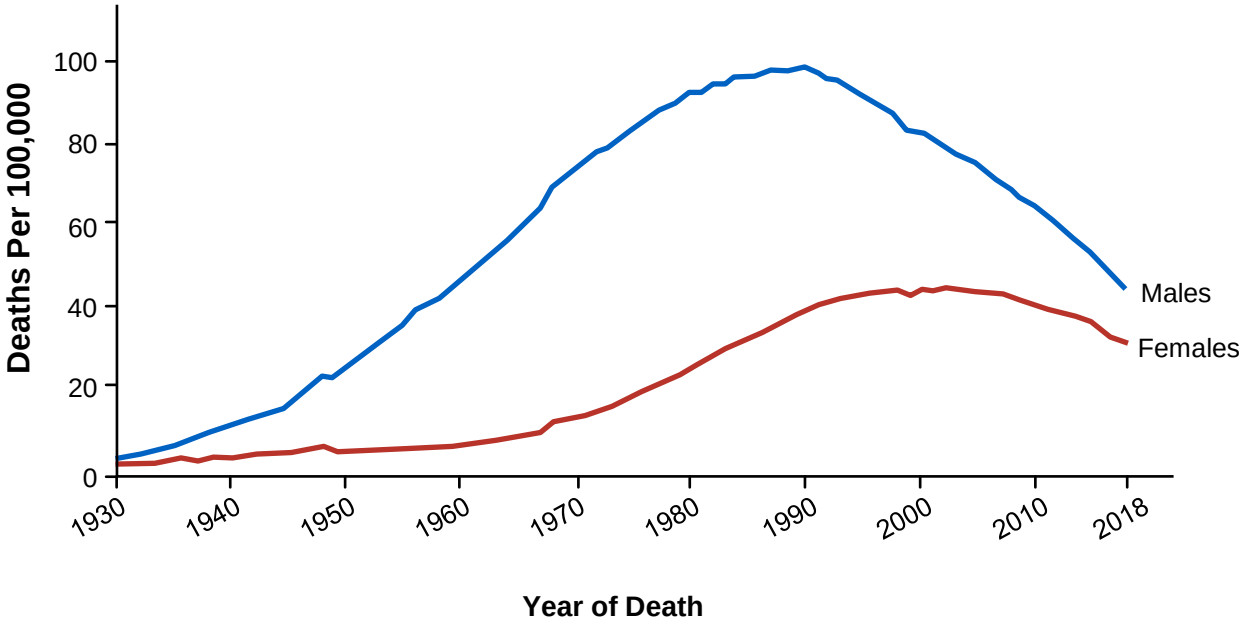
*Patients diagnosed with regional or distant stage at diagnosis. [2]
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

1. Sung H, et al. *CA Cancer Clin*. 2021;71:209-249. **2.** National Cancer Institute. www.seer.cancer.gov. Accessed June 16, 2021. **3.** Duma N, et al. *Mayo Clin Proc.* 2019;94:1623-1640.

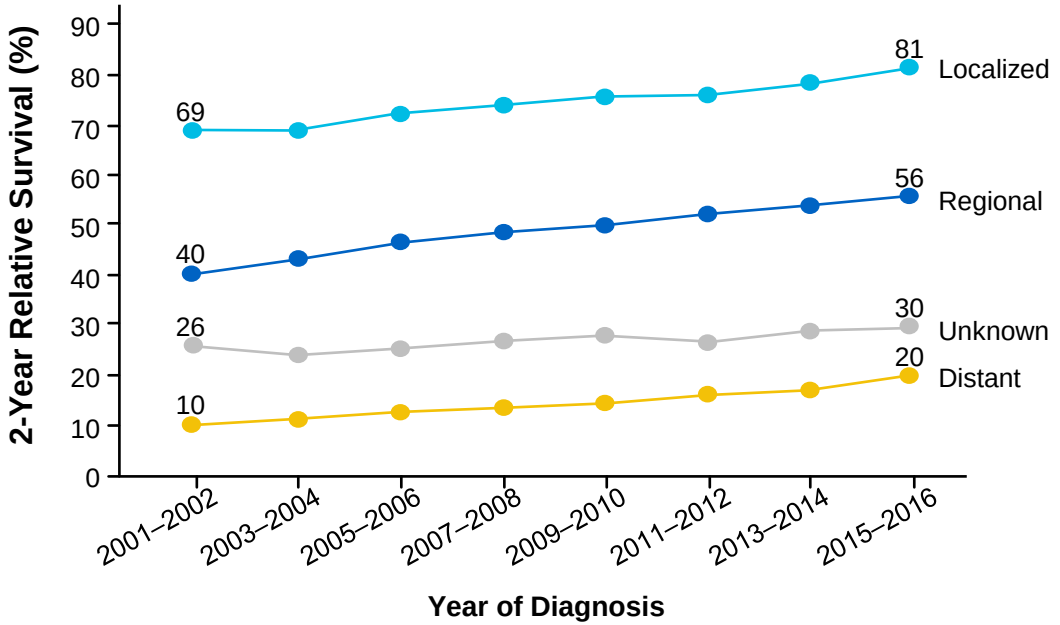
AMGEN Oncology

Survival Outcomes Are Improving for NSCLC Due In Part to Personalized Medicine [1,2]

Trends in Mortality By Sex in Patients With Lung and Bronchus Cancer (US, 1930–2018) [1,*]



2-Year Survival By Year of NSCLC Diagnosis (US) [1,†]



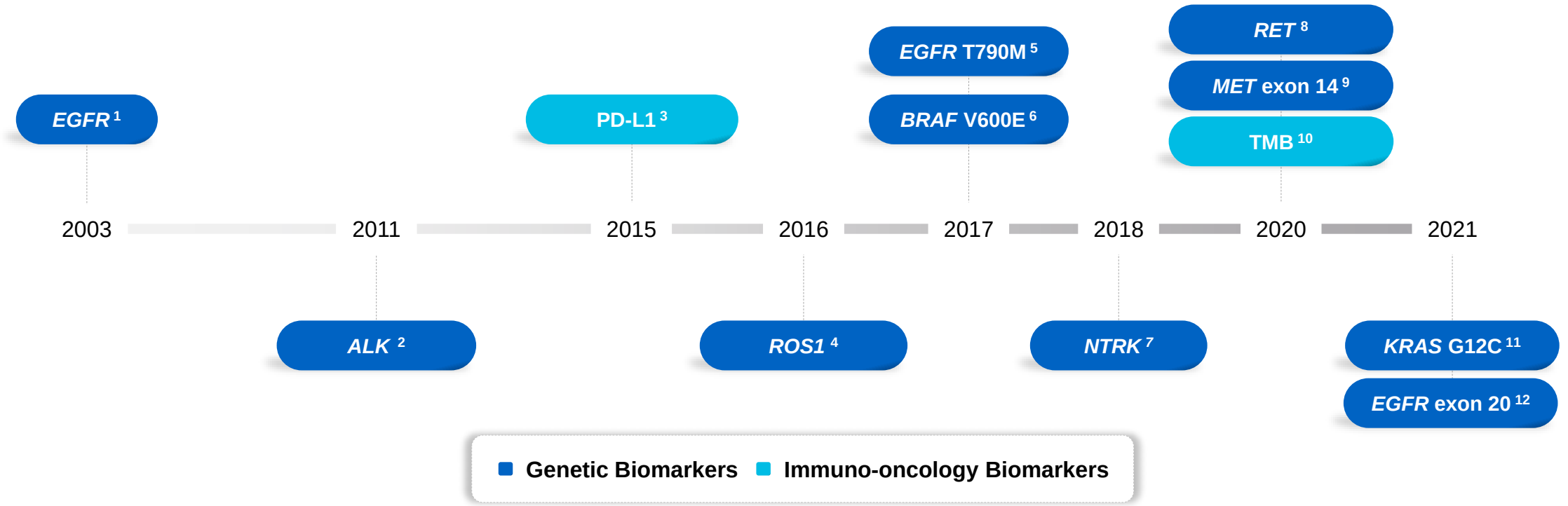
Smoking cessation and novel therapies have contributed to a decline in mortality in NSCLC

*Rates are age adjusted to the 2000 US standard population. [1] †Results based on patients diagnosed during 2001 to 2016, all followed through 2017. [1]
NSCLC, non-small cell lung cancer.

1. Siegel RL, et al. *CA Cancer J Clin.* 2021;71:7-33. **2.** Nadler E, et al. *Clin Lung Cancer.* 2018;19:360-370.

AMGEN Oncology

There Are an Increasing Number of Actionable Biomarkers in NSCLC



Identification of biomarkers allows for selection of personalized therapies in patients with NSCLC [13]

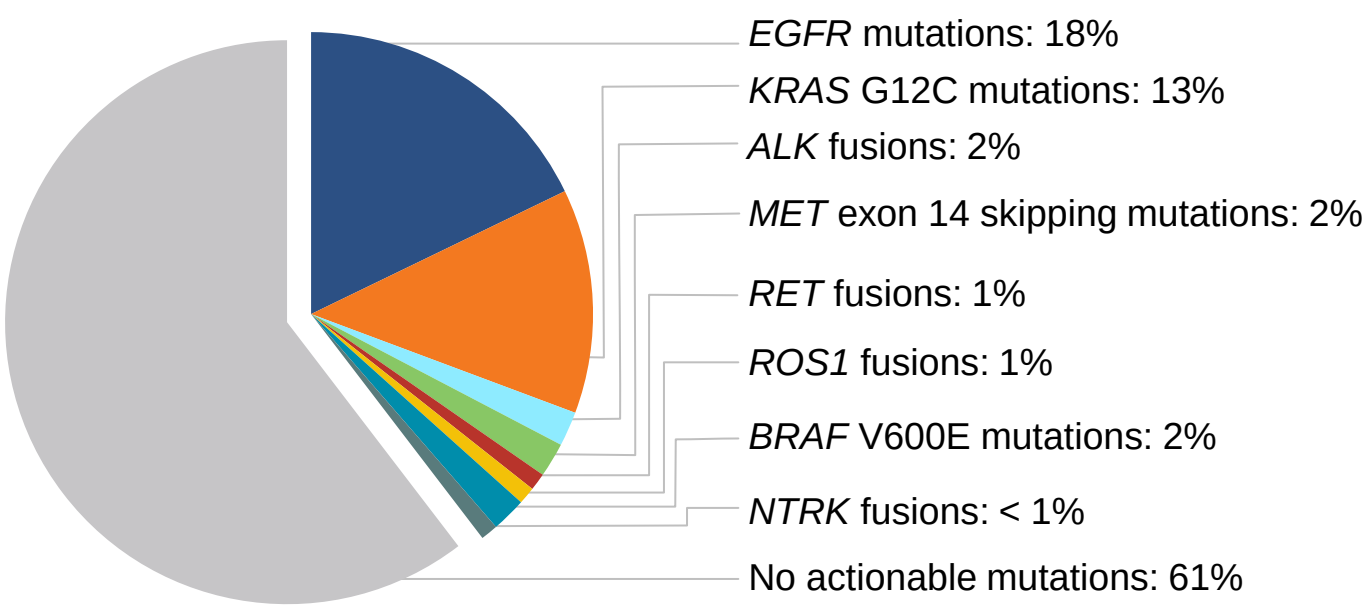
ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1; TMB, tumor mutational burden.

1. Pakkala S, et al. *JCI Insight.* 2018;3:e120858. **2.** American Society of Clinical Oncology. www.asco.org. Accessed June 16, 2021. **3.** National Institutes of Health. www.cancer.gov. Accessed June 16, 2021. **4.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **5.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **6.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **7.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **8.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **9.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **10.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **11.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **12.** Food and Drug Administration. www.fda.gov. Accessed June 16, 2021. **13.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.

AMGEN Oncology

Actionable Oncogenic Drivers Are Found in ~ 40% of Patients With Non-Squamous NSCLC

Prevalence of Actionable Oncogenic Drivers in Non-Squamous NSCLC [1,*,†]



EGFR and *KRAS* G12C mutations are the most prevalent genetic biomarkers in non-squamous NSCLC [1]

~ 1 in 3 patients with non-squamous NSCLC will have either an *EGFR* or *KRAS* G12C mutation [1]

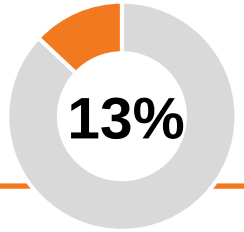
*From a 2020 analysis of patients with NSCLC in the AACR Genie database (v8.0, N=14,485) and prevalence of *KRAS* G12C mutations or alterations with an annotation of FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication in patients with non-squamous NSCLC. [1] †*EGFR* prevalence does not include exon 20 insertions, which can be found in ~ 2% of the overall NSCLC population. [1,2]

AACR, American Association for Cancer Research; ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; ROS1, c-ros oncogene 1.

1. Data on file, Amgen; 2020. **2.** Reiss JW, et al. *J Thorac Oncol.* 2018;13:1560-1568.

AMGEN Oncology

KRAS G12C Is One of the Most Common Genetic Biomarkers in Patients With NSCLC



1 in 8 patients (13%) with non-squamous NSCLC have a *KRAS* G12C mutation [1]

	KRAS G12C–Mutated NSCLC		All NSCLC
	AACR Genie [2,*] (n=416)	Flatiron [3,‡] (n=743)	Flatiron [3,‡] (N=7,069)
Median age at diagnosis, years	68 †	68	68
Female gender, %	64	61	50
Current/former smoker, %	97	97	82
Non-squamous NSCLC, %	88	91	76
Distant metastases at diagnosis, %	NR	86	84
***STK11* Co-mutation, %**	24	22	12
***KEAP1* Co-mutation, %**	10	7	6

While patients with *KRAS* G12C–mutated NSCLC tend to be ever-smokers and have non-squamous histology, all eligible patients should undergo comprehensive biomarker testing [4]

*****Data from an analysis of the AACR Project GENIE Database that included 416 patients with *KRAS* G12C–mutated NSCLC, of which 270 (65%) were diagnosed in 2015 or later. [2] †Median age at advanced diagnosis. [2] ‡Data from an analysis of the Flatiron Health-Foundation Medicine Clinico-Genomic Database of 7,069 patients diagnosed with NSCLC between 2011 and 2019, with at least 6 months of follow-up, of which 743 patients had the *KRAS* G12C mutation. [3]

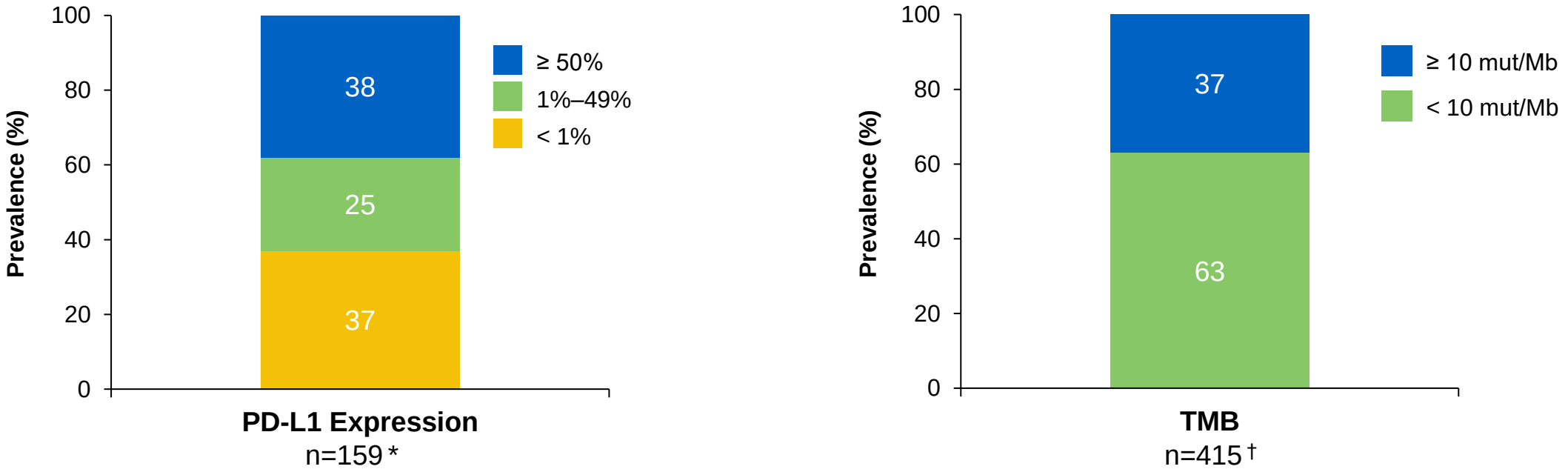
AACR, American Association for Cancer Research; KEAP1, kelch-like ECH-associated protein 1; KRAS, Kirsten rat sarcoma; NR, not reported; NSCLC, non-small cell lung cancer; STK11, serine/threonine kinase 11.

1. Data on file, Amgen; 2020. **2.** Ricciuti B, et al. Presented at: American Association for Cancer Research; April 2021. Virtual Congress. Abstract 102. **3.** Spira AI, et al. *Lung Cancer.* 2021. doi:10/1016/j.lungcan.2021.05.026. **4.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.

AMGEN Oncology

KRAS G12C–Mutated NSCLC Tumors Are Heterogeneous With Varying Levels of PD-L1 Expression and TMB

PD-L1 Expression Levels and TMB in Patients With *KRAS* G12C–Mutated NSCLC



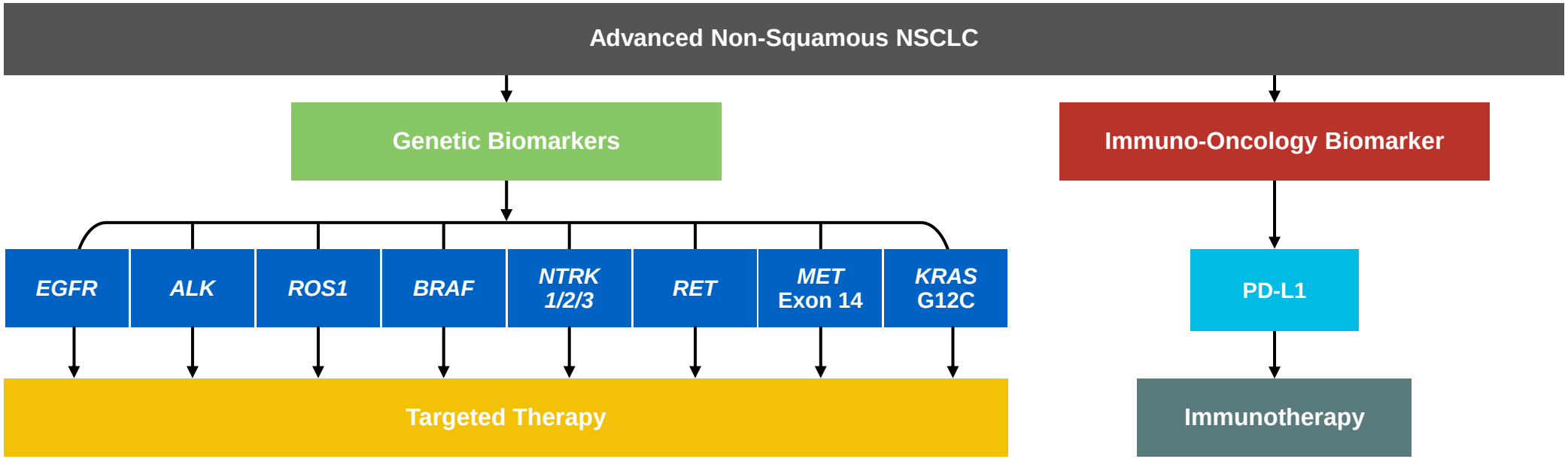
The majority of patients with the *KRAS* G12C mutation have moderate or low PD-L1 expression and 1 in 3 patients have high TMB

*PD-L1 expression was assessed on the same NSCLC specimen used to determine *KRAS* G12C mutation positivity. †TMB was available in 99% of cases.
KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TMB, tumor mutational burden.
Ricciuti B, et al. Presented at: American Association for Cancer Research; April 2021. Virtual Congress. Abstract 102.

AMGEN Oncology

Guidelines Recommend Biomarker Testing in All Eligible Patients With Advanced Non-Squamous NSCLC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC *,†



*The NCCN Clinical Practice Guidelines in Oncology (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 or commercial laboratories. †The NCCN Guidelines® for NSCLC recommend broad molecular testing to identify rare driver variants for which targeted therapies may be available to ensure patients receive the most appropriate treatment.

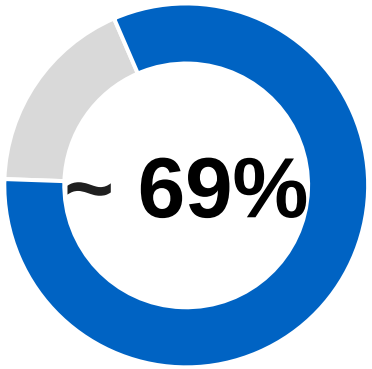
ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; NCCN, National Comprehensive Cancer Network® (NCCN®); NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; RET, rearranged during transfection; ROS1, c-ros oncogene 1.

AMGEN Oncology

Guideline-Recommended Biomarker Testing Results in Improved Patient Outcomes

Adherence * to Guideline-Recommended Biomarker Testing †

N=28,784
Adherent: n=19,787 (68.7%)
Non-Adherent: n=8,997 (31.3%)



~ 2/3 of patients received a recommended biomarker test for any biomarker †

Risk of Mortality in Patients Adherent * vs Non-Adherent to Biomarker Testing †

HR: 0.89 ‡

(95% CI: 0.86–0.92; *P* < 0.01)

Adherence to National Comprehensive Cancer Network® (NCCN®)-recommended biomarker testing was associated with lower risk of mortality

*Testing adherence consisted of patients with evidence of testing for any biomarker, including *EGFR, ALK, BRAF, KRAS, ROS1,* or PD-L1 between 14 days prior to and 90 days after diagnosis of advanced NSCLC. †A retrospective study evaluating the association between adherence to the NCCN Guidelines and clinical outcomes in 28,784 patients diagnosed with advanced NSCLC from the Flatiron Health database between January 2011 and July 2019. ‡Multivariable analysis was adjusted for age at diagnosis of advanced NSCLC, sex, smoking status, and stage at initial diagnosis of NSCLC.

ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; KRAS, Kirsten rat sarcoma; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; ROS1, c-ros oncogene 1.

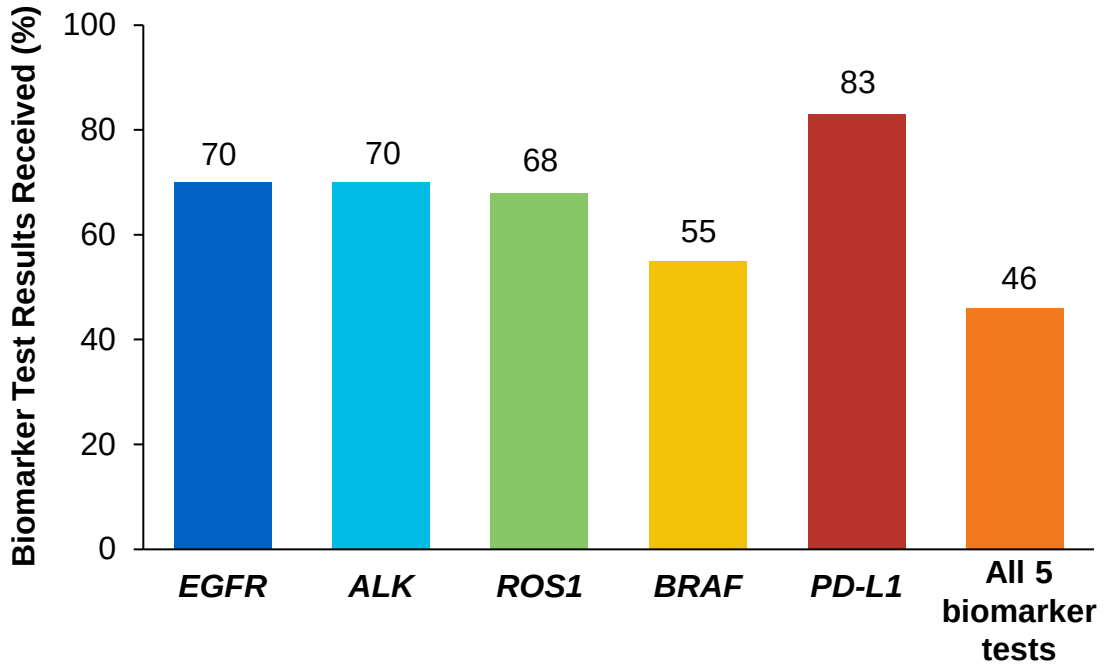
John A, et al. *Adv Ther.* 2021;38:1552-1566.

AMGEN Oncology

Despite Guideline Recommendations for Biomarker Testing, Rates Can Be Improved, Particularly in the Community Setting

MYLUNG Consortium™ Analysis of EMRs of Patients With Metastatic NSCLC From US Oncology Network Community Practices (2018–2020) [1,*]

Real-world data showed that individual testing rates for biomarkers were suboptimal among 3,474 patients initiating 1L systemic therapy



Less than 50% of patients with metastatic NSCLC in the community setting received testing for all 5 biomarkers [2]

*A retrospective, observational study assessing real-world biomarker testing patterns in patients with metastatic NSCLC from community oncology practices within The US Oncology Network between 2018–2020.

1L, first line; ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; EMR, electronic medical record; MYLUNG, Molecularly Informed Lung Cancer Treatment in a Community Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; ROS1, c-ros oncogene 1.

1. Robert NJ, et al. Presented at: The American Society of Clinical Oncology; June 4–8, 2021; Virtual Meeting. Abstract 102. **2.** Gierman HJ, et al. Presented at: The American Society of Clinical Oncology; May 31–June 4, 2019; Chicago, IL. Abstract 1585.

AMGEN Oncology

There Remains an Even Greater Need to Increase Broad Biomarker Testing Among Racial and Ethnic Minority Groups in the US

- Race is generally underreported in cancer studies (eg, lung, breast, and prostate cancers) compared with demographics, such as age and sex [1]
- Overall, there is low awareness and knowledge of genetic testing for cancer among African American, Hispanic, and Asian American minority groups [2]

Flatiron Health EMR-Derived Data Analysis of Patients With Advanced/Metastatic NSCLC From US Sites of Care (2017–2020) [3,*]

Biomarker Testing	Overall (N=14,768)			Non-Squamous (n=10,333)		
	White (n=9,793)	Black/AA (n=1,288)	*P* Value †	White (n=6,705)	Black/AA (n=922)	*P* Value †
Ever Tested	76.4%	73.6%	0.03	85.0%	82.9%	0.09
Ever NGS Tested	50.1%	39.8%	< 0.0001	54.7%	43.8%	< 0.0001

In a recent analysis, Black/AA patients had lower rates of testing with NGS assays compared with White patients, even in patients with non-squamous histology, where testing rates are higher

*A retrospective cohort study of patients with advanced/metastatic NSCLC (N=14,768) from ~ 800 sites of care identified via the Flatiron Electronic Health Record Database between 2017–2020. [1] †For comparison of White vs Black patients. [1]
AA, African American; EMR, electronic medical record; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer
1. Nugent A, et al. *Genet Med.* 2019;21:2676-2680. **2.** Hann KEJ, et al. *BMC Public Health.* 2017;17:503. **3.** Bruno DS, et al. Presented at: The American Society of Clinical Oncology; June 4–8, 2021; Virtual Meeting. Abstract 9005.

AMGEN Oncology

Biomarker Testing in NSCLC Is Associated With Challenges

In an IASLC Survey, HCPs in the US/Canada Reported Multiple Barriers That Impact Biomarker Testing Rates in NSCLC [1,*]

Cost and coverage challenges are the most frequently reported barriers to biomarker testing [1,2]

Varying **turnaround time** to obtaining molecular test results, with HCPs typically reporting ≥ 10-day turnaround [1]

Challenges associated with inadequate **quantity or quality** of tumor tissue were reported by 85% and 57% of HCPs, respectively [1]

Awareness of rapidly evolving guidelines and **reporting, interpreting, and accessing molecular test results** [1,2]

*HCPs include oncologists, pulmonologists, thoracic surgeons, pathologists, and nonclinical scientists or others. [1]

HCP, healthcare provider; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer.

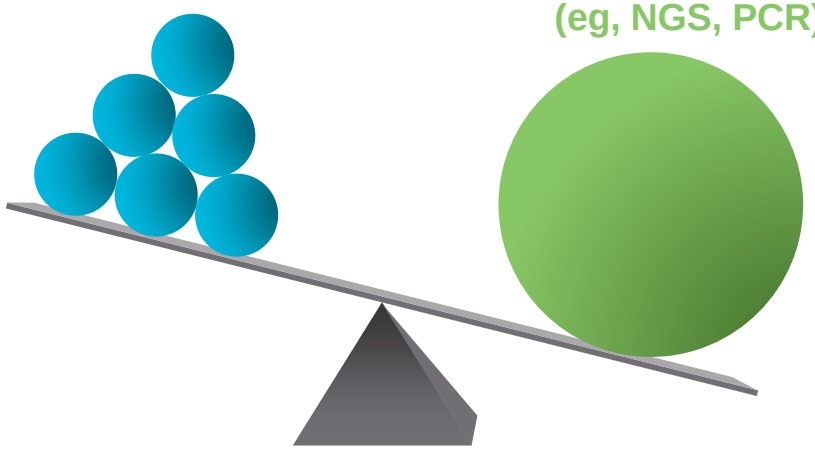
1. Smeltzer MP, et al. *J Thorac Oncol*. 2020;15:1434-1448. **2.** Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342.

AMGEN Oncology

Biomarkers Can Be Detected With Established Molecular Testing Platforms

Guidelines recommend broad biomarker testing which allows for simultaneous detection of many actionable and emerging biomarkers [1]

Molecular alterations can be detected by single-gene, multiplex, or broad testing [1]



Benefits offered by broad biomarker testing [2]

- **Able to test for all actionable and emerging biomarkers simultaneously, potentially saving time and costs [2]**
- **Minimizes amount of tissue required for biomarker testing [2]**
- **Can help direct patients to appropriate clinical trials [2]**

While upfront broad testing may prove more cost effective and provide timely results, multiplex and single-gene testing may be useful in certain clinical circumstances [1]

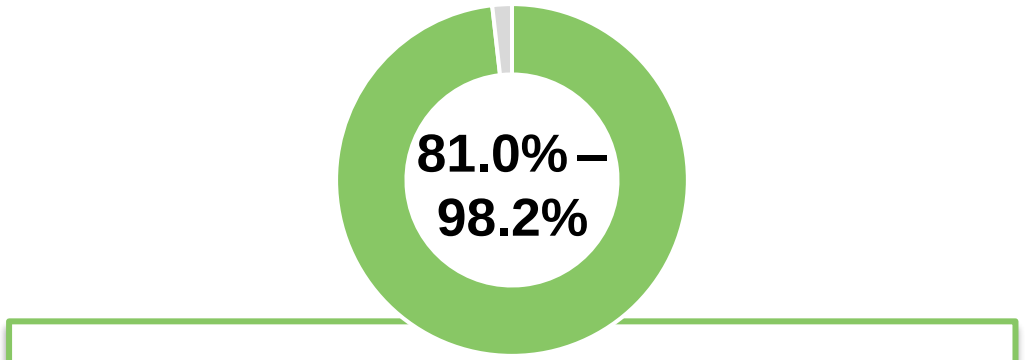
NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

1. Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542. **2.** Colomer R, et al. *EClinicalMedicine*. 2020;25:100487.

AMGEN
Oncology

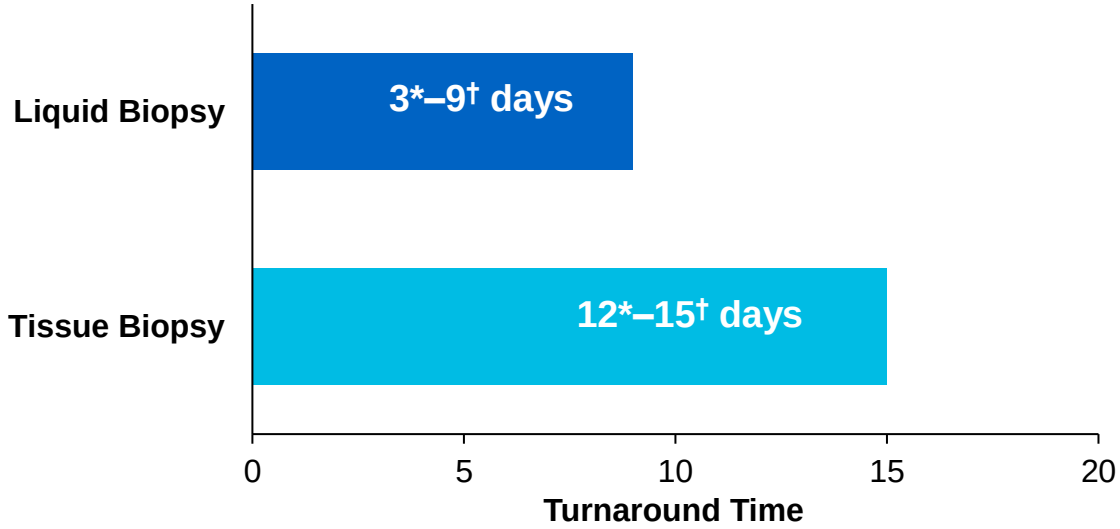
Liquid Biopsy Can Also Address Certain Challenges Associated With Biomarker Testing

Liquid biopsy is a minimally invasive procedure that may be an option when tumor tissue is inadequate for analysis [1]



concordance between tissue and liquid-based testing [2]

Liquid Biopsy Results in Faster Median Turnaround Time Than Tissue-Based Testing [2,3]



While tissue biopsy remains the gold standard in NSCLC, liquid biopsy demonstrates a high degree of concordance [2]

*Turnaround time for plasma genotyping was measured in business days from the date of blood draw until reporting of results to the study investigator. [3] †Turnaround time was defined as the number of days between test order date and the retrieval of test results. [2]

NSCLC, non-small cell lung cancer.

1. Rolfo C, et al. *J Thorac Oncol.* 2021;13:1248-1268. **2.** Leighl NB, et al. *Clin Cancer Res*. 2019;25:4691-4700. **3.** Sacher AG, et al. *JAMA Oncol.* 2016;2:1014-1022.

AMGEN Oncology

An MDT Can Also Help Establish Some Best Practices for Biomarker Testing

MDTs often develop standardized practices for reporting and documenting molecular test results [1]

Reporting Test Results

- A template can help guide ordering of biomarkers [1]
- A set location for reports can allow for easier access by providers [1]
  - Some reports may be retrieved via fax, email, or directly from the EMR

Documenting Test Results

- Consider the use of uniform nomenclature for biomarker status [2,3]
  - For example, some reports may present *KRAS* G12C results as 12Cys or Gly12Cys (GGT → TGT)
- Record patients' biomarker status in their chart for future reference [1]

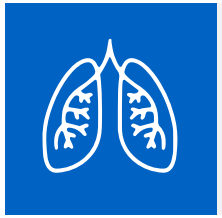
Continued Education

- Consider multidisciplinary tumor boards to educate on recent approvals and evolving guidelines [1,4]
- Provides your MDT with the knowledge to utilize biomarker testing results efficiently/appropriately [5]

EMR, electronic medical record; KRAS, Kirsten rat sarcoma; MDT, multidisciplinary team.

1. Kim ES, et al. *J Thorac Oncol.* 2019;14:338-342. **2.** Li MM, et al. *J Molec Diagn*. 2017;19:4-23. **3.** Sholl LM, et al. www.documents.cap.org. Accessed June 16, 2021. **4.** van der Velden DL, et al. *Ann Oncol*. 2017;28:3070-3075. **5.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301.

Summary



NSCLC is a heterogeneous disease with multiple actionable biomarkers that inform personalized treatment plans [1]

Regardless of patient characteristics, biomarker testing should be conducted in all eligible patients with advanced NSCLC [2]

Opportunities remain to improve biomarker testing rates to ensure no patient who potentially has a targetable mutation is left behind [2]

NSCLC, non-small cell lung cancer.

1. Skoulidis F, et al. *Nat Rev Cancer.* 2019;19:495-509. **2.** Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:531-542.

AMGEN Oncology