MIDWEST HEALTH INITIATIVE

Biomarkers to Inform Lung Cancer Treatment:

Understanding Access and Utilization in Missouri

To accompany a recent **report** on lung cancer screening and diagnosis trends in Missouri, the Midwest Health Initiative (MHI) undertook quantitative and qualitative analysis to:

1. Evaluate employer and commercial health plan coverage of biomarker testing to inform lung cancer treatment for Missourians.
2. Assess trends in biomarker testing utilization among commercially-insured Missourians diagnosed with lung cancer.

Though "biomarker testing" can refer to a wide range of measurements, this report focuses on **biomarker testing, or molecular profiling, of tumor cells to determine treatment options for patients diagnosed with cancer.**

Key Findings:

1. In the past two decades, **discoveries in cancer genomics have revolutionized cancer treatment,** causing a shift from the traditional "one-size-fits-all" model to a precision medicine model, informed by biomarker testing of tumor cells.

2. A rapidly evolving medical practice like biomarker testing needs an established authority that physicians and other health care decision makers within the field can look to for up-to-date, reliable guidelines.

3. **The National Comprehensive Cancer Network® (NCCN®) provides regularly updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**, which provide comprehensive cancer care recommendations, including those for biomarker testing, that serve as the recognized authority regarding cancer management.

4. **Coverage is not a barrier to biomarker testing for non-small cell lung cancer for commercially-insured Missourians.** None of the employers or five major state health plans evaluated classified any NCCN-recommended biomarker tests as investigational or experimental services to be excluded from coverage. **The health plans classified all NCCN-recommended biomarker tests as medically necessary.**

5. Biomarker utilization by commercially-insured Missourians diagnosed with lung cancer increased from 2018 to 2019, but sharply declined in 2020 and 2021, decreasing by more than 50%, possibly due to the pandemic. Utilization rates were mostly consistent across the state, all between 4.5% and 7%, with the exception of St. Joseph, with 10.8%.

I. Project Overview

Biomarker testing, or molecular profiling, of tumor cells is a rapidly evolving field and a key part of precision medicine in oncology.

Interested in the language that health plans and employers are using to discuss testing coverage in their plan documents and whether a lack of coverage is a barrier to testing for commercially-insured Missourians, MHI obtained and analyzed eight summary plan documents (SPDs) from employer plan sponsors and publicly available clinical guidelines and policies from five of the state's major commercial health plans.

To investigate trends in biomarker utilization among individuals diagnosed with lung cancer in Missouri, MHI utilized its commercial claims data set, comprised of medical and pharmacy claims representing care received by more than two million people across Missouri and its bordering metropolitan areas.

II. Biomarker Testing for Cancer Treatment

Precision Medicine in Cancer

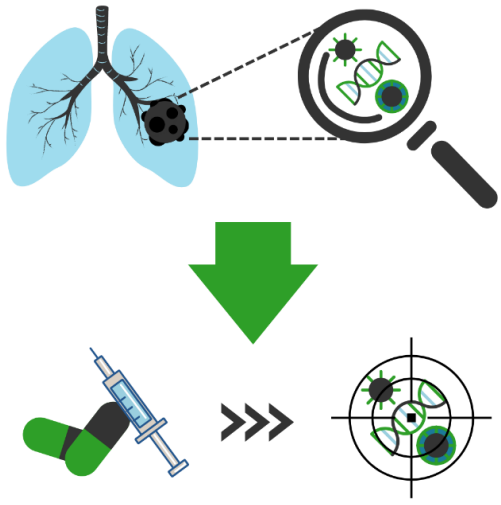
Since the completion of the Human Genome Project in 2003, discoveries in cancer genomics have revolutionized oncology treatment.[1] A better understanding of the genetic mutations and molecular pathways that contribute to the progression of cancer has led to the development of "targeted therapies" that aim to specifically inhibit pathways unique to cancerous cells. These discoveries have also led to a shift in oncology from a "one-size-fits-all" treatment model- traditionally consisting of surgery, chemotherapy, and/or radiation- to a precision medicine, or personalized medicine, model that can tailor treatment to fit the characteristics of a specific patient's cancer cells. This is informed by the use of biomarker testing, also called molecular testing or tumor profiling.

What is Biomarker Testing?

In general, biomarkers are a broad category of characteristics that are able to be objectively measured in an individual to provide information about their biological conditions.[2] Examples range from temperature and blood pressure to genetic mutations and protein levels.[3]

In oncology, various biomarker tests can be used to predict an individual's risk of cancer, detect the presence of cancer cells, or predict treatment outcomes.[4] Biomarker tests to inform treatment entail studying a patient's tumor cells to characterize their genetic mutations, protein expression, and tissue environment, allowing clinicians to identify potential treatments to target their tumor's specific molecular pathways.[5]

Figure 1. Biomarkers for Targeted Cancer Treatment



Navigating Biomarkers in Oncology

In a cutting-edge field with continuous discoveries and new treatment development, it is essential to have a recognized authority providing up-to-date standards and recommendations for cancer care. The National Comprehensive Cancer Network® (NCCN®) is an alliance of 33 leading cancer centers in the U.S. that provides tools and guidelines for health care decision makers.[6] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) serve as the recognized industry standard guidelines for cancer management and provide comprehensive cancer care recommendations, including those for biomarker testing to inform treatment. These guidelines are used by clinicians, health plans, patients, payers, and others to make evidence-based care and coverage decisions.

Biomarker Testing and Targeted Treatment in Lung Cancer

Non-small cell lung cancer (NSCLC), which accounts for about 80 to 85% of lung cancer incidences, is one of the types of cancer for which biomarker tumor testing is most routinely utilized.[7,8] Though lung cancer remains the leading cause of cancer death, mortality has declined in the past decade, likely in part due to advancements in immunotherapy and targeted treatments informed by tumor testing.[9] For certain patients with NSCLC, NCCN Guidelines® version 3.2023 recommend: (1) genetic profiling of tumor cells for analysis of nine genes with known mutations associated with responsiveness to certain lung cancer treatments and (2) immunohistochemistry testing for elevated levels of PD-L1, a protein expressed by some tumor cells that suppresses nearby immune cells' ability to target the cancer (Table 1).[10] When appropriate, it is recommended that genetic profiling be conducted through broad, panel-based tests (tests that examine multiple genes). Based on results from these molecular analyses, targeted treatments may be prescribed that are associated with responsiveness to certain biomarker indications.

Table 1. NSCLC Tumor Biomarkers and Associated Treatment

Type	Biomarker	Associated Treatment[11, 12]
Genetic mutations/ alterations	**EGFR**	EGFR tyrosine kinase inhibitor (TKI)
	ALK	ALK TKI
	ROS1	ROS1 TKI
	RET	RET TKI
	ERBB2/HER2	HER2 antibody drug-conjugate
	NTRK	TRK inhibitor
	MET	MET TKI
	BRAF	BRAF inhibitor + MEK inhibitor
	KRAS	KRAS GC12 inhibitor
Elevated protein levels	**PD-L1**	Immune checkpoint inhibitor

Biomarker Testing Is Not for Everyone

Not all cancer patients will benefit from biomarker testing, and it is especially important in cancer treatment that patients receive optimal care as quickly as possible. Clinicians' decisions to utilize biomarker testing are guided by complex algorithms which consider a multitude of factors regarding the individual patient and tumor. For NSCLC, these factors include the clinical stage of the cancer, histology of the tumor cells, previous or in-progress cancer treatment, and smoking history.

III. Biomarker Coverage and Utilization in Missouri

Coverage Not a Barrier to Biomarker Testing

MHI examined eight employer summary plan documents (SPDs) to identify any gaps in coverage that may serve as barriers to biomarker testing for commercially-insured Missourians. These documents typically provide a high-level overview of covered services, as well as lists of any excluded or non-covered services; biomarker tests are more specific than what is generally discussed in SPDs, and though no employers mention them explicitly, they likely fall under the broader categories of "genetic" or "diagnostic" testing, depending on how the plan sponsor defines them.

Seven of the eight employer SPDs listed coverage for "genetic testing," with some requiring the testing to be determined to be medically necessary by a genetic counselor and others stating that the testing results would need to directly impact treatment. **All employers listed "diagnostic testing" as a covered service. No employers listed biomarker testing as an excluded or non-covered service.**

Interpretation of employers' coverage guidelines and determination of whether a specific service meets their criteria for medical necessity generally falls to their health plan administrators. Thus, in order to evaluate coverage for NCCN-recommended lung cancer biomarker testing, MHI also analyzed clinical guidelines and medical policies from Missouri's five major commercial health plans. **As of April 20, 2023, all investigated health plans classified both multigene panel tests covering the recommended genetic biomarkers and tests evaluating PD-L1 levels to be medically necessary for NSCLC (Table 2). Coverage is not a barrier to biomarker testing for lung cancer treatment for commercially-insured Missourians.**

Table 2. Health Plan Classification of Tumor Biomarkers Tests for NSCLC

Health Plan	Multigene panel*	PD-L1
A	*Medically Necessary*	*Medically Necessary*
B	*Medically Necessary*	*Medically Necessary*
C	*Medically Necessary*	*Medically Necessary*
D	*Medically Necessary*	*Medically Necessary*
E	*Medically Necessary*	*Medically Necessary*

**Multigene panel testing (up to 50 genes) including all nine genetic biomarkers recommended by the NCCN.*

Opportunity for Employers

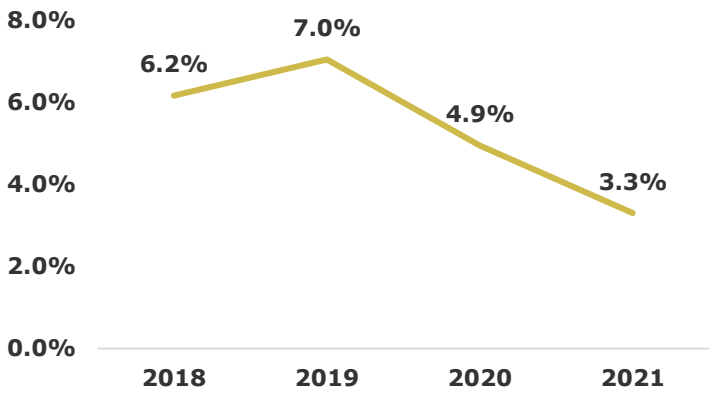
As this field continues to evolve and new tests and treatment options are discovered, employers may benefit by adding biomarker coverage information to their plan descriptions. Similarly to how SPDs often state coverage for all preventive services with an "A" or "B" grade recommendation from the U.S. Preventive Service Task Force, rather than listing them all, simply referencing NCCN Guidelines may be beneficial. Stating coverage for all biomarker tests recommended by the NCCN to inform cancer treatment would prevent the need for SPDs to delve into the complexities of which biomarker tests are covered and would ensure that coverage is consistent with the most recent NCCN Guidelines.

Lung Cancer Biomarker Test Utilization in Missouri

MHI also examined biomarker utilization from 2018 to 2021 among individuals who received a lung cancer diagnosis.

MHI found the average annual biomarker utilization rate among patients diagnosed with lung cancer from 2018 to 2021 to be 5.4%. Utilization increased from 2018 to 2019, but sharply declined in 2020 and 2021, decreasing by more than 50%. This decline may be associated with the COVID-19 pandemic, or with a decrease in the proportion of lung cancer diagnoses that were NSCLC and met the required criteria for biomarker testing.

Figure 2. Biomarker Testing Utilization Among Patients Diagnosed with Lung Cancer, 2018-2021

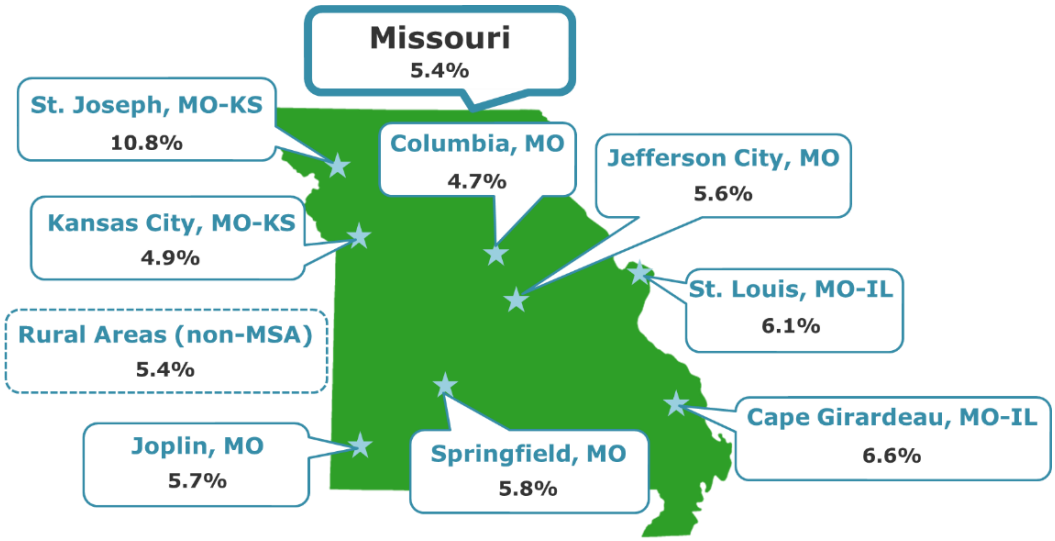


It is important to note again that **biomarker testing is only recommended for certain patients with NSCLC**, dependent on a wide variety of clinical factors. **Therefore, it is not clear what would be an ideal utilization rate among lung cancer patients.** Further analysis of biomarker testing utilization in future years and within specific subtypes of lung cancer may provide clearer, more actionable insights.

Regional Variation

Taking a closer look at Missouri's metropolitan statistical areas (MSAs), MHI found somewhat consistent average annual rates of utilization across the state, all between 4.5 and 7%, with the exception of St. Joseph, with 10.8%.

Figure 3. Average Annual Biomarker Testing Utilization Rate Among Patients Diagnosed with Lung Cancer by Missouri MSA, 2018-2021



IV. Conclusion & Policy Considerations

Biomarker testing to inform cancer treatment is a rapidly evolving, cutting-edge field essential to providing evidence-based, precision treatment for eligible cancer patients. It is crucial to have a recognized authority for physicians and other health care decision makers to look to for up-to-date, reliable treatment guidelines in order to ensure that cancer patients are able to get to the care that is right for them as quickly as possible. **The NCCN's frequently updated, comprehensive Clinical Practice Guidelines in Oncology serve as this key resource.**

In addition to having a trusted central information source, employer and health plan policies establishing coverage for all NCCN-recommended biomarker tests are necessary to ensure quick and equitable patient access to the latest, most effective treatment options. **While coverage is not currently a barrier to biomarker tests for commercially-insured Missourians, there is an opportunity for employers to clarify biomarker coverage for their employees and prevent future coverage gaps that may emerge as technologies advance; explicitly stating coverage in their plan documents for biomarker tests recommended by NCCN Guidelines would make certain that members are covered and ensure that coverage is always consistent with the most recent NCCN Guidelines.** This may prevent any uncertainties about coverage due to new Guideline updates that have not yet been added to employer or health plan policies, which could complicate or delay the approval process, costing cancer patients time they do not have.

Biomarker utilization among commercially-insured Missourians diagnosed with lung cancer increased from 2018 to 2019, but declined during the COVID-19 pandemic, measured at 3.3% in 2021. Because of the variety of complex factors that contribute to physicians' decisions to utilize biomarker testing for any one specific patient, it is difficult to evaluate these utilization rates. Without knowing the proportion of patients diagnosed with lung cancer that were appropriate candidates for biomarker testing, the discernible insights are limited. Future analysis of biomarker utilization among patients with more specific subtypes of cancer could provide valuable information in identifying geographical variation or determining whether there are any non-coverage barriers to biomarker testing.

Further utilization research, along with exploration of other key factors, such as average cost of tests, types of biomarker tests most commonly offered, and access to testing facilities across various geographies, could also contribute to a clearer and more accurate picture of the landscape of this new, rapidly evolving field. Given these remaining areas to be investigated and the consistent commercial coverage of biomarker tests, there is no current need for policy intervention regarding biomarker testing in Missouri. Further, the ever-changing nature of oncology treatment standards would make it very difficult for legislation to stay up-to-date, and a deep level of clinical understanding is needed to navigate the complex and highly nuanced practice of cancer management. These decisions should be left with physicians and medical experts.

About the Midwest Health Initiative

The Midwest Health Initiative (MHI) brings together those who provide, pay for, and use health care to share knowledge and develop solutions for the problems that vex our region's health care system. As a Missouri nonprofit health improvement collaborative, MHI is dedicated to generating data insights that support multi-stakeholder collaboration for higher quality, more affordable health care. A belief in the power of information and collaboration to transform health care is the common thread that binds MHI's multi-stakeholder leaders and partners.

The MHI Data Set

In addition to its common table, MHI stewards the region's largest commercial claims data set, which includes medical and pharmacy claims, as well as enrollment and provider files, representing care received by more than two million people across Missouri and the metropolitan areas along its borders.

MHI's unique data asset can help our community learn about the health of its residents and the care provided. It also assists physicians, hospitals, and other health care providers in better understanding the care received by their patients.

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References

1. Krzyszczyk P, Acevedo A, Davidoff EJ, et al. The Growing Role of Precision and Personalized Medicine for Cancer Treatment. *Technology (Singap World Sci).* 2018;6(3-4):79-100. doi:10.1142/S2339547818300020
2. Center for Drug Evaluation and Research. About Biomarkers and Qualification. U.S. Food and Drug Administration. https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification. Published July 7, 2021. Accessed March 1, 2023.
3. McBride B. Examples of Biomarkers and Biomarker Data Analysis. Fios Genomics. https://www.fiosgenomics.com/examples-of-biomarkers-and-biomarker-data-analysis/. Published December 13, 2022. Accessed March 1, 2023.
4. Sarhadi VK, Armengol G. Molecular Biomarkers in Cancer. *Biomolecules*. 2022; 12(8):1021. https://doi.org/10.3390/biom12081021
5. What to Know About Biomarker Testing for Lung Cancer: An Expert Q&A. Cancer.Net. https://www.cancer.net/blog/2022-06/what-know-about-biomarker-testing-lung-cancer-expert-qa. Published June 9, 2022. Accessed November 9, 2022.
6. Referenced with permission from the National Comprehensive Cancer Network, Inc. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed March 27, 2023. To view the most recent and complete version of the recommendations, go online to NCCN.org.
7. Biomarker testing for cancer treatment. National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/types/biomarker-testing-cancer-treatment. Published December 14, 2021. Accessed March 1, 2023.
8. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *New England Journal of Medicine.* 2020;383(7):640-649. doi:10.1056/nejmoa1916623
9. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed April 20, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.
10. PD-L1, PD1, TMB and Lung Cancer. American Lung Association. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/biomarker-testing/pdl1-pd1-tmb. Published 2023. Accessed March 1, 2023.
11. Lung Cancer Biomarker Testing. American Lung Association. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/biomarker-testing. Published November 16, 2021. Accessed November 14, 2022.
12. Jaber N. Enhertu Marks First Targeted Therapy for HER2-Mutant Lung Cancer. National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-lung-cancer-enhertu-her2. Published September 13, 2022. Accessed March 1, 2023.

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