Executive Summary

For oncology biomarkers, commercial payers uniformly cover companion diagnostics because clinical utility is established as a component of FDA review (there is typically a therapeutic agent that is approved in parallel). For other biomarkers that are not FDA reviewed, commercial payers rely upon NCCN guidelines, Technology Assessment organizations, and peer-reviewed published evidence. Often, evidence of clinical utility is the determinant of coverage.

Payers are generally skeptical that panels meet the clinical utility threshold. Depending on the tumor type, the number of recognized biomarkers with clinical utility may number fewer than five. It is difficult, therefore, to justify coverage of a panel with 50 or more genes. Consequently, payers may consider the entire test to be experimental and investigational (E&I) if all genes on the panel do not have established utility. Others will cover the test but negotiate payment only for those medically necessary biomarkers.

NSCLC has an adequate number of actionable biomarkers for payers to consider coverage of NGS panels. Neither breast cancer nor colon cancer have an adequate number of biomarkers with established utility to warrant coverage of panels. Payers will likely modify their policies as the number of actionable biomarkers increases, but they will do this in a tumor specific fashion. If tumor site agnostic biomarkers are identified, this equation could change, leading to broader coverage.

Most payers, aside from Medicare, do not recognize biomarker testing to identify clinical trial candidates as providing clinical utility. Although commercial payers are required by the ACA to provide coverage for clinical trials, they do not feel this extends to "screening" for somatic mutations. Many biomarker driven trials are industry sponsored and these do not meet the statutory definition of a clinical trial that must be covered by the ACA. Further, patients are not technically enrolled until they are biomarker positive. To date, clear evidence that panel testing succeeds in trial enrollment is lacking.

The current coding infrastructure does not differentiate between targeted and comprehensive NGS panels. The CPT codes for NGS describe either a 50 gene panel or a 51+ gene panel. Some diagnostics manufacturers have obtained Proprietary Laboratory Analyses (PLA) codes to uniquely identify their proprietary NGS panels. There is a paucity of targeted NGS panels that are FDA approved, including FoundationOne CDx, Oncomine Dx Target Test, and the Praxis Extended RAS Panel.

At the current time, commercial payer policies are unchanged as a result of the NCD on NGS. This was in line with our expectation that commercial payers would continue to cover (or not) NGS panels based on evidence of clinical utility in tumor site specific analytes of interest. Companion diagnostics will continue to enjoy broad coverage, as the results are profoundly impactful on coverage policy of the associated therapeutic agent.

Non-Small Cell Lung Cancer (NSCLC)

Key Takeaways

Most payers cover and pay for select individual biomarkers, but even these biomarkers are not consistent across plans. Generally, EGFR, ALK, and ROS1 are covered; some payers also cover BRAF and/or KRAS. Emerging biomarkers, like HER2, RET, and MET, are covered by even fewer payers.

Payers are increasingly adopting tissue-based multi-gene panels in NSCLC as a mechanism to realize value and efficiencies. There seems to be growing recognition by payers of sequential testing of

individual biomarkers is not practical when patients have limited tissue available and the results of these tests can inform urgent treatment decisions. The increasing number of individual actionable analytes in NSCLC is leading to a consideration of coverage for a panel as the most expeditious and potentially most cost-effective approach.

Clinical Guidelines

NCCN Guidelines (Version 6.2018)[1] currently support biomarker testing of EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF mutations. To conserve tissue, NCCN recommends broad molecular profiling using a validated test to assess the aforementioned biomarkers, at a minimum. The guidelines also note the availability of an FDA-approved companion diagnostic NGS test, no doubt the FoundationOne CDx test, that simultaneously tests for these biomarkers. The guidelines identify the following emerging biomarkers: HER2 mutations, RET rearrangements, and MET mutations.

Gene	NCCN Category 1 or 2A Recommended Therapeuti
ALK	crizotinib, ceritinib, and alectinib
EGFR	afatinib, erlotinib hydrochloride, and gefitinib
ROS 1	crizotinib
KRAS	Avoid TKI
BRAF	dabrafenib and vemurafib
MET	crizotinib

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors[2] represents a 2018 evaluation by the College for American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP). This joint guideline recommends multiplexed genetic sequencing panels (e.g., NGS testing) over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1. When NGS is performed, several other genes are also recommended – BRAF, ERBB2, MET, RET, and KRAS

ASCO Guideline. Molecular Testing Guideline for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors[3] supports testing for EGFR, ALK, BRAF, and ROS1. New for 2018 are recommendations for standalone ROS1 testing with additional confirmation testing in all patients with advanced lung adenocarcinoma, and RET, ERBB2 (HER2), KRAS, and MET testing as part of larger panels. ASCO also recommends standalone BRAF testing in patients with advanced lung adenocarcinoma. The guideline also supports multiplexed genetic sequencing panels are preferred where available over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, BRAF, and ROS1.

[1] https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
[2] https://www.amp.org/clinical-practice/practice-guidelines/updated-molecular-testing-guideline-for-the-selection-of-lung-cancer-patients-for-treatment-with-targeted-tyrosine-kinase-inhibitors/
[3] http://ascopubs.org/doi/full/10.1200/JCO.2017.76.7293

National Commercial Payers

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers	ALK, EGFR, KRAS, RET, ROS Targeted solid organ genomic sequencing panel (50 genes) VeriStrat	10/01/2018	81235, 81275, 8127 0022U, 81445 81538
Anthem	Molecular Profiling and Proteogenomic Testing for the Evaluation of Malignant Tumors	EXaCT-1 Whole Exome Sequencing (Clinical Genomics) FoundationOne CDx (Foundation Medicine) Molecular Intelligence Service/Target Now (Caris) GeneKey (GeneKey Corp.) GeneTrails Solid Tumor Panel (Knight Diagnostic Labs) MSK-IMPACT (Memorial Sloan Kettering Cancer Center) OncInsights (Intervention Insights) OmniSeq Advance (OmniSeq) OnkoMatch (GenPath Diagnostics) SmartGenomics (PathGroup)	07/26/2018	81445, 81455, 81479, 81599, 0037U, 0048U
	EGFR Testing	EGFR activating mutations (TKI therapy) EGFR T790M mutation ctDNA test	07/26/2018	81235
	BRAF Mutation Analysis	V600E mutation	07/26/2018	81210, 81406
	Analysis of KRAS Status	KRAS activating mutations (anti-EGFR monoclonal antibody therapy)	07/26/2018	81275, 81276, 8147
Cigna	Tumor Profiling, Gene Expression Assays and Molecular Diagnostic Testing for Hematology/ Oncology Indications	ALK rearrangements BRAF (targeted mutation analysis or sequencing) EGFR Mutation Testing HER2 (ERBB2) Mutation Testing KRAS Mutation Testing MET Amplification RET Gene Rearrangements ROS Gene Rearrangements Guardant360 Oncomine Dx Target Test VeriStrat	6/15/2018	81210, 81235, 81275, 81276, 81404, 81405, 81406, 0022U, 81538

Humana	Genetic Testing for Diagnosis and Monitoring of Cancer and Molecular Profiling	Non-covers all NGS-based cancer profiling tests	2/22/2018	81445, 81455, 0048U (Non-covered)
	Pharmacogenomics and Companion Diagnostics	ALK, EGFR, ROS1 Serum proteomic testing	6/26/2018	81235 81538
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions	Targeted solid organ genomic sequencing panels (50 genes)	7/1/2018	81445

Regional Commercial Payers

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
BCBSA	Molecular Analysis for Targeted Therapy for NSCLC	EGFR, ALK, BRAF, ROS1 (CV) KRAS, HER2, RET, MET (NCD-Non-Covered)	March 2018	
	Tumor/Genetic Markers	Non-covers expanded cancer molecular panels	08/23/2018	81445, 81455
BCBSMA	Expanded Molecular Panel Testing of Cancers	Covers tumor panel testing services. PA required for commercial managed care beneficiaries	07/01/2016	81445, 81455
Dean Health Insurance	Genetic Testing for Somatic Tumor Markers	Medically necessary hematology-oncology multigene panels	06/20/2018	81445
Highmark	Genetic Testing by Multigene Panels	Covers medically necessary multigene panels	October 2017	81445, 81455

	Tumor Marker Testing Solid Tumors	EGFR, ALK Multi-gene panel when specific criteria met	March 2018	81235, 81401, 81479 81445, 81455
Horizon BCBSNJ	Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies	NGS testing for patients with NCSCLC	11/14/2017	81445, 81455
Independence	Genetic Testing	Oncomine Dx Target Test		0022U (Covered) 81445, 81455 (Non-Covered)
	Pharmacogenetic Testing to Determine Drug Sensitivity	EGFR, KRAS	11/22/2017	81235, 81275, 81403
Priority Health	Multi-marker tumor panels	NGS testing for patients newly diagnosed with stage IV NSCLC	11/12/2016	81455 (Covered) 81445 (Non-Covered)
	Genetics: Counseling, Testing, Screening	Prior authorization (PA) is obtained, if applicable	May 2018	81210, 81235, 81275 81276, 81400-81408, 81445, 81455, 81479, 81599

Integrated Health Delivery Networks

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Geisinger Health Plan	Molecular Testing	Independent assessment		
	Pharmacogenetic Testing	EGFR for Gilotrif ALK for Xalkori PDL1 for Keytruda	September 2016	
Kaiser Permanente	Genetic Panels using NGS	Non-covers NGS genetic panels	8/29/2018	81445, 81455

UPMC	Genetic Testing – Lung Cancer	ALK, EGFR, ROS1, BRAF KRAS (Medicare only)	June 2018	81210, 81235 81275, 81276

Local Medicare Administrative Contractors (MACs)

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
CGS/WPS	MolDX: NSCLC, Comprehensive Genomic Profile Testing	Comprehensive somatic genomic profiling on tumor tissu only for NSCLC	*Superseded by NCD	81445, 81455
NGS	Genomic Sequenc Analysis Panels in the Treatment of NSCLC	Genomic Sequential Analysis Panel represented by CPT 81445	02/03/2016	81445
	DRAFT Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasm	Genomic Sequential Analysis Panel represented by CPT 81445	Draft policy under comment period: 10/17/18-11/30/18	81445, 0048U
Novitas	Biomarkers for Oncology	EGFR, KRAS, BRAF Oncomine DX Target Test LungSeq	10/04/2018	81235, 81275, 81276 0022U 81445

Colorectal Cancer (CRC)

Key Takeaways

All payers cover select individual biomarkers in CRC, and these biomarkers are fairly consistent across plans. Generally, NRAS, KRAS, and occasionally BRAF are considered medically necessary. Few payers consider MSI testing.

With rare exceptions, payers consider tissue-based multi-gene panels in CRC to be experimental and investigational. The relative lack of actionable targets makes it difficult to establish clinical utility of a panel.

Clinical Guidelines

NCCN Guidelines (Version 3.2018) support biomarker testing of KRAS, NRAS, and BRAF mutations in patients with metastatic CRC. Microsatellite instability (MSI) or mismatch repair (MMR) testing is also supported. The guidelines specifically note that testing for MSI may be accomplished with a validated NGS panel, especially in patients with metastatic disease who require genotyping of RAS and BRAF.

The guidelines review several multigene panels for prognosis and recurrence, including Oncotype DX Colon, ColoPrint, and ColDx. The panels states that there is insufficient data to recommend the use of multigene assay panels to determine adjuvant therapy in colon cancer patients.

Gene	NCCN Category
KRAS/NRAS exon 2, codons 12/13	2A
KRAS/NRAS exon 3, codons 59/61	2A
KRAS/NRAS exon 4, codons 117/14	2A
BRAF V600E	2A
MSI	2A

European Society for Medical Oncology (ESMO)[4] (2016) support biomarker testing of RAS, BRAF, and MSI in patients with metastatic CRC.

> RAS testing should be carried out on all patients at the time of diagnosis of mCRC. RAS testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab. RAS analysis should include at least KRAS exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and NRAS exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117)
>
> Tumor BRAF mutation status should be assessed alongside the assessment of tumor RAS mutational status for prognostic assessment (and/or potential selection for clinical trials).
>
> MSI testing in the metastatic disease setting can assist clinicians in genetic counselling. MSI testing has strong predictive value for the use of immune checkpoint inhibitors in the treatment of patients with mCRC.

[4] https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Management-of-Patients-with-Metastatic-Colorectal-Cancer

Combined guideline from the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO (Version 2017[5])

1. Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)

    Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate

2a. BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification

    Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

2b. BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome

    Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

3. Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification

    Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low.

[5] http://ascopubs.org/doi/full/10.1200/JCO.2016.71.9807

National Commercial Payers

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers	KRAS, NRAS, BRAF tumor tissue genotyping MLH1, MSH2, MSH6 for colorectal cancer in persons under age 50; and all persons with Stage II colon cancer	10/01/2018	81275, 81276, 81311, 81210, 81292, 81293, 81294
Anthem	Molecular Profiling	EXaCT-1 Whole Exome Sequencing (Clinical Genomics) FoundationOne CDx (Foundation Medicine) Molecular Intelligence Service/Target Now (Caris) GeneKey (GeneKey Corp.) GeneTrails Solid Tumor Panel (Knight Diagnostic Labs) MSK-IMPACT (Memorial Sloan Kettering Cancer Center) OncInsights (Intervention Insights) OmniSeq Advance (OmniSeq) OnkoMatch (GenPath Diagnostics) SmartGenomics (PathGroup)	07/26/2018	81445, 81455, 81479, 81599, 0037U, 0048U
	Gene Expression Profiling for Colorectal Cancer	Non-covers gene expression profiling to manage CRC	05/03/2018	81525
Cigna	Tumor Profiling, Gene Expression Assays and Molecular Diagnostic Testing for Hematology/Oncology Indications	KRAS NRAS BRAF	6/15/2018	81275, 81276 81311 81210
Humana	Genetic Testing and Molecular Profiling	Non-covers all NGS-based cancer profiling tests	2/22/2018	81445, 81455, 0048U(Non-covered)
	Pharmacogenomics and Companion Diagnostics	KRAS, NRAS	6/26/2018	81275, 81276 81311
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis,	Non-covers multi-gene panels for CRC	7/1/2018	81445, 81455 (Non-covered)

	and Treatment Decisions			

Regional Commercial Payers

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
BCBSA	KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer	KRAS NRAS BRAF	09/2018	81275, 81276 81311 81210
	Tumor/Genetic Markers	Non-covers expanded cancer molecular panels	08/23/2018	81445, 81455
BCBSMA	Expanded Molecular Panel Testing of Cancers	Covers tumor panel testing services. PA required for commercial managed care beneficiaries	07/01/2016	81445, 81455
Dean Health Insurance	Genetic Testing for Somatic Tumor Markers	Medically necessary hematology-oncology multi-gene panels	06/20/2018	81445
Highmark	Genetic Testing by Multigene Panels	Medically necessary multi-gene panels	October 2017	81445, 81455
	Tumor Marker Testing Solid Tumors	BRAF, KRAS, NRAS Multi-gene panel when specific criteria met	March 2018	81210, 81275, 81311, 81445, 81455
Horizon BCBSNJ	Expanded Molecular Panel Testing	Non-covers expanded NGS testing for CRC	11/14/2017	81445, 81455 (non-covered)
	KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer	KRAS NRAS BRAF	08/14/2018	81275, 81276 81311 81210
Independence	Genetic Testing	Non-covers expanded cancer molecular panels		81445, 81455 (Non-Covered)

	Pharmacogenetic Testing to Determine Drug Sensitivity	KRAS, BRAF	11/22/2017	81275, 81403, 81210
Priority Health	Multi-marker tumor panels	NGS testing for x Patients newly diagnosed with selected stage IV rare or uncommon solid tumors for whom very limited or no systemic treatment exists in clinical care guidelines and/or pathways. x Patients newly diagnosed with selected Stage I solid tumor types having poor prognosis, very limited benefit from standard of care chemotherapies and a high prevalence of actionable genomic alterations. x Patients with stage IV solid tumors who have exhausted the established guideline-driven systemic therapy and requisite molecular testing but who desire further treatment.	11/12/2016	81455 (Covered) 81445 (Non-Covered)
	Genetics Counseling, Testing, Screening	Prior authorization (PA) is obtained, if applicable	May 2018	81210, 81275, 81276, 81311, 81400-81408, 81445, 81455, 81479, 81599

Integrated Health Delivery Networks

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Geisinger Health Plan	Oncotype Dx Multi-gene Expression Assay for Predicting Recurrence in Colon Cancer	Oncotype DX Colon	July 2017	81525

	Pharmacogenetic Testing	KRAS for Erbitux and/or vectibix EGFR for Erbitux	September 2016	
Kaiser Permanente	Genetic Panels using NGS	Non-covers NGS genetic panels	8/29/2018	81445, 81455
UPMC	Genetic Testing – Colorectal Cancer Treatment	BRAF, KRAS, NRAS, MSI MLH1, SEPT9, hereditary colon cancer panel, Oncotype colon	January 2018	81210, 81275, 81276, 81301, 81311 81288, 81327, 81435, 81436, 81479, 81525

Local Medicare Administrative Contractors (MACs)

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
NGS	Molecular Pathology Procedures	KRAS, NRAS, BRAF, MSI	02/03/2016	81275, 81276, 81311, 81210, 81301
	Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasm	Genomic Sequential Analysis Panel represented by CPT 81445	Draft policy under comment period: 10/17/18-11/30/18	81445, 0048U
Novitas	Biomarkers for Oncology	KRAS (12/13) KRAS codon 61, 146 NRAS BRAF MSI by PCR MLH1 promoter hypermethylation Oncotype Colon Sept9 ColonSeq	10/04/2018	81275 81276 81311 81210 81301 81292, 81293, 81294 81525 81327 81445

MolDX	NRAS Genetic Testing	KRAS, NRAS, BRAF	02/26/2018	81275, 81276, 81311, 81210
WPS	Comprehensive Genomic Profiling to Guide Treatment in Patients with mCRC	Comprehensive somatic genomic profiling on tumor tissu only for mCRC	*Superseded by NCD	81445, 81455

Breast Cancer

KeyTakeaways

Biomarkersindicated in breast cancer, including ER, PR, and HER2, are detected by methodologies other than NGS. Immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH) primarily used for these types of analyses. Worth noting for Medicare payment, both IHC and FISH are paid on the Physician Fee Schedule (PFS) as compared to NGS, which is paid on the Clinical Laboratory Fee Schedule (CLFS).

Clinical Guidelines

NCCN Guidelines (Version 2.2018) support biomarker testing of ER, PR, and HER2. The guidelines state that the use of DNA microarray technologies to characterize breast cancer has allowed for development of classifications of breast cancer by gene expression profile. Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling. In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and overall survival.

2016 ASCO Evidence-Based Guideline[6] on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, Prosigna, Breast Cancer Index, and Mammaprint (updated for 2017) in specific subgroups of breast cancer. No biomarker except for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was found to guide choices of specific treatment regimens. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

ASCO considers the conclusions on prognostic and predictive biomarkers in early-stage invasive breast cancer to be limited by the lack of prospective confirmatory studies; findings of sufficient clinical utility; and, in many cases, a lack of data on clinical validity and reproducibility of assays. The expert panel awaits the completion and publication of several randomized trials to establish the clinical utility of some of these assays. Extensive research is needed to validate some of the biomarker candidates described and to identify promising new biomarkers.

[6] http://ascopubs.org/doi/full/10.1200/JOP.2017.024646

National Commercial Payers

Payer	Medical Policy	Covered Biomarkers/Tests	Date of Last Review	CPT Codes
Aetna	Tumor Markers	Breast Cancer Index, EndoPredict, Prosigna, Mammapr Oncotype DX Breast	10/01/2018	81599, 81520, 81521, 81519
Anthem	Gene Expression Profiling for Managing Breast Cancer Treatment	Oncotype DX Breast, EndoPredict, Prosigna, Breast Cancer Index(BCI)	07/26/2018	81519, 81520, 81599 (EndoPredict or BCI)
Cigna	Tumor Profiling, Gene Expression Assays ar Molecular Diagnostic Testing for Hematology/Oncology Indications	ER, PR by IHC HER2 by IHC, FISH Mammaprint Oncotype DX Breast Prosigna	6/15/2018	88360 88377 81521 81519 81520
Humana	Pharmacogenomics and Companion Diagnostics	HER2 by IHC, FISH BRCA CDx	6/26/2018	88360, 88377
UHC	Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions	Breast Cancer Index, EndoPredict, Prosigna, Mammapr Oncotype DX Breast	7/1/2018	81599, 81520, 81521, 81519

Primary Research: Payer Opinions on Current Role of NGS Panels in Determining Optimal Therapy for Solid Tumors

To better capture the most current thinking about the role of NGS panel testing in cancer care and to contextualize current coverage policy, ADVI interviewed eight managed care medical directors. The respondents were informed of the general nature of this project but were blinded to its sponsors. The medical directors selected are influential subject matter experts in cancer care and, although not primary decision makers in every case, have significant influence in their health plan's medical policy. Of the eight medical directors, four work for large national health plans, two work for large BCBS plans, one works for a market dominant not for profit health plan, and one works for a benefit management organization.

The medical directors were asked four questions, and their responses are summarized below:

1. Do you believe NGS panels have a role in the management of advanced malignancies? Lung cancer? Colon cancer? Breast cancer?
2. Has the CMS NCD changed your thinking in any way?
3. What is holding the field back?
4. Should payers support NGS as a tool to identify patients for enrollment in clinical trials?

Do you believe NGS panels have a role in the management of advanced malignancies? Lung cancer? Colon cancer? Breast cancer?

In general, the respondents believe NGS panels have a limited role in the management of patients with advanced solid tumors. All respondents agreed that NSCLC is a disease where NGS panels have a role because of the number of actionable analytes and the issue of tissue adequacy using other methods of mutation detection. This response was tempered by their view that most panels have many analytes that are not actionable. There was absolutely no support for panels with more than 50 genes, and none of the respondents believed there was a role for NGS panels in either colorectal or breast cancer. The general absence of actionable analytes in these tumor types was uniformly identified as the reason NGS panels are not valuable – analyzing one or two mutations can be done by more conventional methods.

Has the CMS NCD changed your thinking in any way?

Except for the impact of the NCD on coverage for Medicare Advantage beneficiaries, the answer was unanimously no. Some respondents acknowledged that the NCD has prompted their health plans to review existing medical policies, but not change them.

What is holding the field back?

Responses generally fell into two categories. The most common response was the absence of clinical utility, i.e. an inadequate number of actionable mutations. The second response, which is related, was evidence of appropriate use of test results in clinical decision making (i.e. good discipline in prescribing targeted therapies in circumstances where efficacy has been established as opposed to prescribing based on out of context mutations because a therapy exists). Also, there was a general consensus that developing a 'use case' for alternative payment models and value-based care could be helpful (e.g. cost

effectiveness of testing. One respondent commented that the hype around the uses of this approach was counterproductive and detrimental to meaningful dialogue.

Should payers support NGS as a tool to identify patients for enrollment in clinical trials?

Respondents were supportive of the use of NGS panels to identify potential candidates for clinical trials, with some caveats. They expressed concern that the number of clinical trials widely available is somewhat limited. Nonetheless, given the clinical circumstances where conventional treatment options were often futile, enrollment in these trials may offer the best option. Respondents questioned whether their respective organizations should pay for comprehensive panels, given the potential for inappropriate use of the information (e.g. divert patients from trials to unproven therapies). They acknowledged the precedent they would set in doing so – paying for screening before enrollment in a clinical trial. Because the costs of the experimental treatment would largely be borne by the study sponsor, and because of the ACA mandate for payers to support clinical trials, the respondents were generally receptive to this idea. Several respondents also favored the idea that coverage of testing for trial eligibility could trigger a mandatory review of goals of therapy and an honest assessment of likelihood of clinical benefit.

Key Takeaways

In primary research, influential medical directors are skeptical of the benefits of NGS panel testing being broadly used in the treatment of cancer patients, except for NSCLC. This is due to the lack of clinical utility, which is a direct result of the absence of actionable mutations in these panels, particularly those with more than 50 genes. It is extremely unlikely that NGS panels with 50+ genes will enjoy broad coverage in the near term, perhaps only for NSCLC. In NSCLC, payers acknowledge the value of NGS panels; the increasing number of actionable mutations combined with the challenges of tissue adequacy for multiple sequential tests will lead to more uniform coverage of NGS panels in NSCLC.

Identification of patients for enrollment in clinical trials of targeted therapies is potentially a path forward for coverage of NGS panels. However, widespread availability of such studies and practical considerations regarding which panels optimally fulfill this function and how they should be reimbursed remain challenges.

Appendix A: CPT Codes – Non-Small Cell Lung Cancer

CPT Code	Descriptor	2018 Rate
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)	$175.40
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)	$324.58
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)	$193.25
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)	$193.25
81406	Molecular pathology procedure, Level 7 (eg, analysis of 2-51 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as following]: BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence	$282.88
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5 or 50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	$597.91
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	$2,919.60
81479	Unlisted molecular pathology procedure	
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival VeriStrat; Biodesix, Inc.	$2,871.00
81599	Unlisted multianalyte assay with algorithmic analysis	
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider Oncomine Dx Target Test, Thermo Fisher Scientific	
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationOne CDx; Foundation Medicine, Inc.	$3,500.00

0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) MSK-IMPACT; Memorial Sloan Kettering Cancer Center	

Appendix B: CPT Codes – Colorectal Cancer

CPT Code	Descriptor	2018 Rate
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)	$175.40
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) ge analysis; variants in exon 2 (eg, codons 12 and 13)	$193.25
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis, additional variant(s) (eg, codon 61, codon 146)	$193.25
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, heredit non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis	$675.40
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, heredit non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants	$331.00
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	$202.40
81301	Microsatellite instability analysis (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed	$357.48
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)	$295.79
81327	SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis	
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5 to 50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	$597.91
81455	Targeted genomic sequence analysis panel, solid organ or hematolymp neoplasm, DNA analysis, and RNA analysis when performed, 51 or grea genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, E IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PD PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	$2,919.60
81479	Unlisted molecular pathology procedure	
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score Oncotype DX Colon Cancer Assay, Genomic Health	$3,116.00
81599	Unlisted multianalyte assay with algorithmic analysis	
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analy 324 genes, interrogation for sequence variants, gene copy number	$3,500.00

	amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationOne CDx; Foundation Medicine, Inc.	
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) MSK-IMPACT; Memorial Sloan Kettering Cancer Center	

Appendix C: CPT Codes – Breast Cancer

CPT Code	Descriptor	2018 Rate
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin fixed paraffin-embedded tissue, algorithm reported as recurrence score Oncotype DX, Genomic Health	$3,873.00
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a recurrence risk score Prosigna Breast Cancer Assay, NanoString Technologies, Inc	$3,099.02
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis MammaPrint, Agendia, Inc.	$3,873.00
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual	$136.44
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology	$148.32
88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen, each multiplex probe stain procedure	$417.60

(ACS CAN) is making cancer a top priority for public o cials and candidates at the federal, state and local lev - els. ACS CAN empowers advocates across the country to make their voices heard and in uence evidence-based public policy change as well as legislative and regulatory solutions that will reduce the cancer burden. As the American Cancer Society's nonpro t, nonpartisan advocacy a liate, ACS CAN is critical to the ght for a world without cancer. For more information, visit www. ghtcancer.org.

About LUNGevity Foundation

LUNGevity is the nation's leading lung cancer organization investing in lifesaving, translational research and providing support services and education for patients and caregivers. LUNGevity's goals are three-fold: (1) accelerate research to patients, (2) empower patients to be active participants in their treatment decisions, and (3) remove barriers that patients face in accessing the right treatments.

LUNGevity Foundation is rmly committed to making an immediate impact on increasing quality of life and survivorship of people with lung cancer by accelerating research into early detection and more e ective treatments, as well as by providing community, support, and education for all those a ected by the disease. LUNGevity's comprehensive resources include a medically vetted website with the latest information on all aspects of the disease, a toll-free HELPLine in partnership with CancerCare®, a unique Lung Cancer Navigator app, peer-to-peer mentoring for patients and caregivers (LUNGevity LifeLine), and survivorship conferences. LUNGevity also helps patients nd and navigate clinical trials through our Clinical Trial Finder tool, a Clinical Trial Ambassador program, and participation with EmergingMed.

Our vision is a world where no one dies of lung cancer. For more information about LUNGevity Foundation, a four-star Charity Navigator organization, please visit www. LUNGevity.org.