Comprehensive Genomic Profiling and Genetic Testing for Solid Tumors

INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Related Documents

Please refer to CMS website for the most current applicable CMS Online Manual System (IOMs)/National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/ Transmittals.

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
NCD	Next Generation Sequencing (NGS)	90.2		
LCD LCA	Lab: Special Histochemical Stains and Immunohistochemical Stains MolDX: MGMT Promoter Methylation Analysis MolDX: Molecular Diagnostic Tests (MDT) MolDX: Next-Generation Sequencing for Solid Tumors MolDX: NRAS Genetic Testing Billing and Coding: MolDX: know error®	L36805 L37001 L36807 L38158 L36797 A55172	J5, J8 - Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
LCD LCA	Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms Molecular Pathology Procedures Billing and Coding: Molecular Pathology Procedures Response to Comments: Molecular Pathology Procedures	L37810 L35000 A56199 A59383	J6, JK - National Government Services, Inc.	CT, IL, ME, MA, MN, NH, NY, RI, VT, WI
LCD LCA	MolDX: MGMT Promoter Methylation Analysis MolDX: Molecular Diagnostic Tests (MDT) MolDx: Next-Generation Sequencing for Solid Tumors MolDX: NRAS Genetic Testing	L36113 L36021 L38067 L35442	J15 - CGS Administrators, LLC	KY, OH

	Billing and Coding: MolDX: know error®	A54273		
LCD LCA	Lab: Special Histochemical Stains and Immunohistochemical Stains MolDX: MGMT Promoter Methylation Analysis MolDX: Molecular Diagnostic Tests (MDT) MolDX: Next-Generation Sequencing for Solid Tumors MolDX: NRAS Genetic Testing Billing and Coding: MolDX: know error®	L36351 L36188 L35160 L38119 L36335 A55274	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
LCD LCA	Lab: Special Histochemical Stains and Immunohistochemical Stains MolDX: MGMT Promoter Methylation Analysis MolDX: Molecular Diagnostic Tests (MDT) MolDX: Next-Generation Sequencing for Solid Tumors MolDX: NRAS Genetic Testing Billing and Coding: MolDX: Know error®	L36353 L36192 L36256 L38121 L36339 A55275	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
LCD LCA	Biomarkers for Oncology Biomarkers Overview Billing and Coding: Molecular Pathology and Genetic Testing	L35396 L35062 A58917	JH, JL - Novitas Solutions, Inc.	AR, CO, DE, LA, MD, MS, NJ, NM, OK, PA, TX, D.C.
	Lab: Special Histochemical Stains and Immunohistochemical Stains	L35922		

LCD LCA	MolDX: MGMT Promoter Methylation Analysis MolDX: Molecular Diagnostic Tests (MDT) MolDX: Next-Generation Sequencing for Solid Tumors MolDX: NRAS Genetic Testing Billing and Coding: MolDX: know error®	L35974 L35025 L38045 L35073 A53554	JJ, JM - Palmetto GBA	AL, GA, NC, SC, TN, VA, WV
LCD	Molecular Pathology Procedures	L34519	JN - First Coast Service Options, Inc. (Part A/B MAC)	FL, PR, U.S. VI

Description

Comprehensive genomic profiling (CGP) (also referred to as comprehensive molecular profiling) is a type of somatic (tumor) test that involves a combination of laboratory methodologies to detect genetic alterations and the simultaneous evaluation of large numbers (hundreds to thousands) of biomarkers in tumor tissue to aid in the management of advanced solid tumors, including guiding treatment decisions as well as determination of clinical trial eligibility. Techniques can vary from test to test and may include next-generation sequencing (NGS), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) and often provides information on tumor mutational burden (TMB), microsatellite instability (MSI) and homologous recombination deficiency (HRD). Examples include **Altera Tumor Genomic Profiling, Guardant360, NeoGenomics Solid Tumor NGS Fusion Panel** and **TissueNext**.

Some CGP tests analyze both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). **NeoTYPE DNA & RNA – Lung** is an NGS profiling test that detects single nucleotide variants, insertions/deletions, copy number variants, and/or RNA fusions in a total of 50 genes (44 genes analyzed by DNA and 19 by RNA), plus MSI and TMB. **Tempus xT** is another example of a CGP somatic test performed for the management of advanced cancer. Previously Tempus xT conducted sequencing for both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) within a single panel. However, a new test, **Tempus xR**, is now available as an independent assay dedicated solely to RNA sequencing. This means that Tempus xT focuses on DNA analysis while Tempus xR specializes in RNA analysis, and they are no longer combined into one test.

Single gene testing can be utilized to diagnose and monitor cancer including, but may not be limited to, cholangiocarcinoma, gallbladder cancer, gastrointestinal stromal tumor, glioblastoma, melanoma and thyroid cancer. This type of testing is indicated for an individual who exhibits disease symptoms and may be necessary to diagnose or rule out suspected cancer.

DNA Specimen Provenance Assignment (DSPA) Testing (eg, know error System) is a molecular diagnostic test intended for the protection and control of tissue samples to purportedly decrease the incidence of diagnostic mistakes due to the misidentification, specimen transposition or cell contamination of samples, also known as specimen provenance complications (SPCs). Breast and prostate tissues are most often tested but other tissue types, such as bone marrow, may also be examined.

Coverage Determination

iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS "reasonable and necessary" criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary's specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the MolDX program and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare's reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

Comprehensive Genomic Profiling for Solid Tumors
Comprehensive genomic profiling (CGP) for solid tumors will be considered medically reasonable and necessary when the following requirements are met:[44]

- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program; **AND**
- The test is ordered by a treating physician; **AND**
- **ALL** of the following:
    - Cancer that has returned (recurrent or relapsed), cancer that does not respond to treatment (refractory), cancer that has spread from original site to another part of the body (metastatic) or advanced stages III or IV cancer; **AND**

- Individual has not been previously tested using the same comprehensive genomic profiling test for the same primary diagnosis; **AND**

- Decision to seek further cancer treatment (eg, therapeutic chemotherapy)

Criteria for Single Gene Testing

***IDH1* (81120) and/or *IDH2* (81121) gene analysis** will be considered medically reasonable and necessary for the following indications:

- Cholangiocarcinoma that is locally advanced, metastatic or unresectable disease **(*IDH1* only)**;[71] **OR**
- Gallbladder cancer that is metastatic or unresectable disease **(*IDH1* only)**;[71] **OR**
- Glioblastoma[15]

***KIT* (*c-KIT*) gene analysis** will be considered medically reasonable and necessary to guide therapeutic decision making[43] when for the following indications:

- Gastrointestinal stromal tumor (GIST) (81272);[15] **OR**
- Melanoma, metastatic or unresectable (81272)[15]

***MGMT* promoter methylation testing** (81287) will be considered medically reasonable and necessary to guide therapeutic decision making[43] for the following indications:

- Glioblastoma;[15] **OR**
- Neuroendocrine tumors[15]

***NRAS* gene analysis** (81311) will be considered medically reasonable and necessary for the following indications:

- Metastatic colorectal cancer when needed to determine if a Medicare covered therapy is a reasonable option given the individual's specific clinical presentation;[15,37,38,39,40,41] **OR**

- Metastatic melanoma;[15] **OR**

- Thyroid carcinoma[15]

***PDGFRA* gene analysis** (81314) will be considered medically reasonable and necessary to guide therapeutic decision making[43] when an individual presents with a mass known or clinically suspected to be GIST.[13]

***TERT* gene analysis** (81345) will be considered medically reasonable and necessary for glioblastoma.[13,15]

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage
The following tests may not be considered a benefit (statutory exclusion):

- Tests performed to measure the quality of a process, including DNA Specimen Provenance Assignment (DSPA) testing to decrease specimen provenance complications (SPC) (eg, know error System) (81265)[7,8,9,10,11,12]

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law;[88] **OR**

- Tests that confirm a diagnosis or known information;[88] **OR**

- Tests to determine risk for developing a disease or condition;[88] **OR**

- Tests performed to measure the quality of a process;[88] **OR**

- Tests without diagnosis specific indications;[88] **OR**

- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial[88]

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following items will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the MolDX Program

- *TERT* mutation testing for melanoma

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

The following items will not be considered medically reasonable and necessary:

- CGP RNA sequencing as a stand-alone test without MolDX approval (eg, Tempus xR)

A review of the current medical literature shows that there is no evidence to determine that this service is standard medical treatment. There is an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of this service in clinical management.

Summary of Evidence

Tempus xR
Tempus xR is now offered as a stand-alone test, separate from Tempus xT. In the past, Tempus xT sequenced both RNA and DNA in a single panel but now Tempus xR focuses solely on RNA and Tempus xT is dedicated to DNA analysis. Most CGP tests typically analyze both DNA and RNA in a single panel and there is insufficient evidence for RNA-only CGP. The validity of analysis, its clinical relevance and utility are yet to be established in published, peer-reviewed medical literature.

TERT Mutation Testing for Melanoma
A systematic review and meta-analysis investigation the connection between somatic mutations in the *TERT* gene promoter and melanoma survival revealed limited yet suggestive evidence of an adverse impact of *TERT* mutations on the survival of an individual diagnosed with melanoma. The authors gathered data from 19 independent studies and found that individuals with *TERT*-mutated melanoma had a significantly worse overall survival compared to wild-type mutations.[58]

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)	
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)	

81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)	
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)	
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis	
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)	
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)	
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)	
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis	
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis	

81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	
81479	Unlisted molecular pathology procedure	
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 or absence of variants and associated therapy(ies) to consider	
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	
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)	
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association	
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue	
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden	

0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations	
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden	
0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden	
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice- site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Change Summary

- 01/01/2024 New Policy.