Pharmacogenomics and Companion Diagnostics

Medicare Advantage Medical Coverage Policy

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Disclaimer
The Coverage Summaries are reviewed by the iCare Medicare Utilization Management Committee. Policies in this document may be modified by a member’s coverage document. Clinical policy is not intended to preempt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. References to CPT® codes or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee of claims payment. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from iCare.

Related Medicare Advantage Medical/Pharmacy Coverage Policies

Comprehensive Genomic Profiling for Solid Tumors
Genetic Testing
Genetic Testing for Diagnosis and Monitoring of Cancer
Testing for Hereditary Breast Ovarian Pancreatic and Prostate Cancer
Liquid Biopsy
Pharmacogenomics Testing

Related Documents

Please refer to CMS website for the most current applicable National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.
<table>
<thead>
<tr>
<th>Type</th>
<th>Title</th>
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<th>Jurisdiction Medicare Administrative Contractors (MACs)</th>
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<tr>
<td>NCD</td>
<td>Next Generation Sequencing (NGS)</td>
<td>90.2</td>
<td>J5 - Wisconsin Physicians Service Insurance Corporation</td>
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<td>LCD</td>
<td>Molecular Pathology Procedures</td>
<td>L35000</td>
<td>J6 - National Government Services, Inc. (Part A/B MAC)</td>
<td>IL, MN, WI</td>
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<td>LCD</td>
<td>MolDX: Pharmacogenomics Testing</td>
<td>L38435</td>
<td>J8 - Wisconsin Physicians Service Insurance Corporation</td>
<td>IN, MI</td>
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<td>LCD</td>
<td>MolDX: Pharmacogenomics Testing</td>
<td>L38394</td>
<td>J15 - CGS Administrators, LLC (Part A/B MAC)</td>
<td>KY, OH</td>
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<td>LCD</td>
<td>MolDX: Pharmacogenomics Testing Billing and Coding: MolDX: Germline testing for use of PARP inhibitors</td>
<td>L38335, A55294</td>
<td>JF - Noridian Healthcare Solutions, LLC</td>
<td>AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY</td>
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<td>Pharmacogenomics Testing Biomarkers for Oncology</td>
<td>L39063, L35396</td>
<td>JH - Novitas Solutions, Inc. (Part A/B MAC)</td>
<td>AR, CO, NM, OK, TX, LA, MS</td>
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<td>LCD</td>
<td>MolDX: Pharmacogenomics Testing</td>
<td>L38294</td>
<td>JJ - Palmetto GBA (Part A/B MAC)</td>
<td>AL, GA, TN</td>
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<td>Molecular Pathology Procedures</td>
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<td>JK - National Government Services, Inc. (Part A/B MAC)</td>
<td>CT, NY, ME, MA, NH, RI, VT</td>
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<td>JL - Novitas Solutions, Inc. (Part A/B MAC)</td>
<td>DE, D.C., MD, NJ, PA</td>
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<td>L38294</td>
<td>JM - Palmetto GBA (Part A/B MAC)</td>
<td>NC, SC, VA, WV</td>
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Description

Pharmacogenomics and companion diagnostics tests are laboratory studies that use an individual’s unique genetic makeup to help determine response to a specific medication. Companion diagnostics differ from pharmacogenomics testing because they are co-developed with a specific drug to help evaluate response or nonresponse to the drug. Companion diagnostics are often approved by the US Food & Drug Administration (FDA) corresponding with a specific pharmacotherapy. Both types of tests are used to guide management for several cancers such as non-small cell lung cancer (NSCLC), breast and colorectal cancer (CRC). Techniques can vary from test to test include, but may not be limited to, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) and next-generation sequencing (NGS).

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene). Panels often include medically actionable genes but may also include those with unclear medical management.

Coverage Determination

iCare follows the CMS requirement that only allows coverage and payment for services that are reasonable and necessary for the diagnosis or 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:

Somatic (Acquired) Cancer
Pharmacogenomics and companion diagnostic testing (including single gene, multi-gene panels, and combinatorial tests) in somatic (acquired) cancer will be considered medically reasonable and necessary when all the following requirements are met:

- Testing services are performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician; AND

- Individual is diagnosed with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; AND

- Individual has not been previously tested with the same test using NGS or other methodology for the same cancer genetic content; AND

- Decided to seek further cancer treatment (eg, therapeutic chemotherapy); AND

- The diagnostic laboratory test using NGS or other methodology (eg, FISH, IHC) must have:
  - FDA approval or clearance as a companion in vitro diagnostic; AND
  - FDA approved or cleared indication for use in that patient’s cancer; AND
  - Results provided to the treating physician for management of the patient using a report template to specify treatment options

Germline (Inherited) Cancer
Pharmacogenomics and companion diagnostic testing (including single gene, multi-gene panels, and combinatorial tests) in germline (inherited) cancer (eg, MyChoice CDx [0172U]) when all of the following criteria are met:

- Testing services are performed in a CLIA certified laboratory, when ordered by a treating physician; AND

- Individual is diagnosed with ovarian (including fallopian tube, primary peritoneal cancer) or breast cancer; AND

- Clinical indication for germline testing for hereditary breast or ovarian cancer (per National Comprehensive Cancer Network [NCCN] guidelines); AND

- Risk factor for germline breast or ovarian cancer; AND

- Individual has not been previously tested with the same germline test using NGS or other methodology for the same germline genetic content
• The diagnostic laboratory test using NGS or other methodology (eg, FISH, IHC) must have all of the following:
  
  o FDA approval or clearance; **AND**
  
  o Results provided to the treating physician for management of the individual using a report template to specify treatment options

*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**


The following services/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](https://www.accessmedicare.gov/moldx-program/

• Repeat genetic testing utilizing the same tissue sample for the same content

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

Screening services such as presymptomatic genetic tests and services used to detect and undiagnosed diseased or disease predisposition are not a Medicare benefit and are not covered.

The following test types are examples of testing services that may not be considered a benefit (statutory excluded) and denied as Medicare Excluded tests:

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

• Tests that confirm a diagnosis or known information; **OR**

• Tests to determine risk for developing a disease or condition; **OR**

• Tests performed to measure the quality of a process; **OR**
• Tests without diagnosis specific indications; 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

**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.

<table>
<thead>
<tr>
<th>CPT® Code(s)</th>
<th>Description</th>
<th>Comments</th>
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<tr>
<td>81191</td>
<td>NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis</td>
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<tr>
<td>81192</td>
<td>NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis</td>
<td></td>
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<td>81193</td>
<td>NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis</td>
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<tr>
<td>81194</td>
<td>NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis</td>
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<tr>
<td>81232</td>
<td>DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)</td>
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<td>81233</td>
<td>BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)</td>
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<td>81236</td>
<td>EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence</td>
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<tr>
<td>81237</td>
<td>EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)</td>
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<td>81275</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)</td>
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<tr>
<td>81276</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)</td>
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<tr>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
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<tr>
<td>81309</td>
<td>PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)</td>
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<td>81320</td>
<td>PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)</td>
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<tr>
<td>81346</td>
<td>TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)</td>
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<td>81381</td>
<td>HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each</td>
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**MOLECULAR PATHOLOGY PROCEDURE LEVEL 1**

**MOLECULAR PATHOLOGY PROCEDURE LEVEL 2**

**MOLECULAR PATHOLOGY PROCEDURE LEVEL 4**

**MOLECULAR PATHOLOGY PROCEDURE LEVEL 5**

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<td>81400</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 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</td>
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<td>81401</td>
<td>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, FLT3, 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</td>
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<td>81447</td>
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<td>84999</td>
<td>Unlisted chemistry procedure</td>
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<td>88341</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)</td>
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<tr>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure</td>
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<tr>
<td>88360</td>
<td>Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual</td>
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<td>0037U</td>
<td>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</td>
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<tr>
<td>0111U</td>
<td>Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue</td>
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<td>0154U</td>
<td>Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C&gt;T], p.S249C [c.746C&gt;G], p.G370C [c.1108G&gt;T], p.Y373C [c.1118A&gt;G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status</td>
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<td>0172U</td>
<td>Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score</td>
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<td>0177U</td>
<td>Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status</td>
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<tr>
<td>0249U</td>
<td>Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report</td>
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<td>0332U</td>
<td>Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint–inhibitor therapy</td>
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**CPT® Category III Code(s)**

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**References**


180. US Food & Drug Administration (FDA). Full prescribing information: Lorbrena (lorlatinib).

181. US Food & Drug Administration (FDA). Full prescribing information: Lumakras (sotorasib).

182. US Food & Drug Administration (FDA). Full prescribing information: Lynparza (olaparib).

183. US Food & Drug Administration (FDA). Full prescribing information: Lytgobi (futibatinib).


185. US Food & Drug Administration (FDA). Full prescribing information: Opdivo (nivolumab).

186. US Food & Drug Administration (FDA). Full prescribing information: Paraplatin (carboplatin).


188. US Food & Drug Administration (FDA). Full prescribing information: Piqray (alpelisib).

189. US Food & Drug Administration (FDA). Full prescribing information: Platinol (cisplatin).

190. US Food & Drug Administration (FDA). Full prescribing information: Retevmo (selpercatinib).

191. US Food & Drug Administration (FDA). Full prescribing information: Rozlytrek (entrectinib).


194. US Food & Drug Administration (FDA). Full prescribing information: Tecentriq (atezolizumab).

196. US Food & Drug Administration (FDA). Full prescribing information: Truseltiq (infigratinib). 

197. US Food & Drug Administration (FDA). Full prescribing information: Vectibix (panitumumab). 


199. US Food & Drug Administration (FDA). Full prescribing information: Xalkori (crizotinib). 


201. US Food & Drug Administration (FDA). Full prescribing information: Zejula (niraparib). 


205. US Food & Drug Administration (FDA). Premarket approval. FoundationOne CDx. 


209. US Food & Drug Administration (FDA). Premarket approval. PD-L1 IHC 22C3 PharmDx. 

211. US Food & Drug Administration (FDA). Premarket approval. Therascreen FGFR RGQ PCR Kit. 

212. US Food & Drug Administration (FDA). Premarket approval. Therascreen KRAS RGQ PCR Kit. 

213. US Food & Drug Administration (FDA). Premarket approval. Therascreen PIK3CA RGQ PCR Kit. 

214. US Food & Drug Administration (FDA). Premarket approval. Ventana ALK (D5F3) CDx assay – P140025. 


218. US Food & Drug Administration (FDA). Premarket approval. Vysis ALK Break Apart Fish Probe Kit. 


Change Summary

- Click or tap to enter a date. New Policy.