MEDICAL POLICY	Next Generation Sequencing for Cancer (All Lines of Business Except Medicare)
Effective Date: 1/1/2023  1/1/2023 Medical Officer Date	Medical Policy Number: 352 Medical Policy Committee Approved Date: 8/2022; 11/2022

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business except Medicare (*unless otherwise directed by a Medicare medical policy. Note that investigational services are considered "**not medically necessary**" for Medicare members.)*

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- All relevant CPT/HCPCS codes billed

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POLICY CRITERIA

Note: This policy does not address circulating tumor cell/cell-free DNA testing.

I. Multi-gene or next generation sequencing (NGS) panels may be considered **medically necessary** in members with somatic cancer when all of the following criteria are met (A.-F.):

   A. Member has **one** of the following conditions (1.-2.):
      1. Recurrent, relapsed, metastatic, or advanced (stage III or IV) solid tumor; **or**
      2. Risk assessment using broad molecular testing has been validated by the National Comprehensive Cancer Network (NCCN) guidelines as a category 1 or 2A recommendation for the member's cancer type (see Policy Guidelines section for utilizing NCCN guidelines); **and**
   B. **One or more** of the following is true (1.-2.):
      1. Genomic biomarker-linked therapies have been approved by the Food and Drug Administration (FDA) for the specific cancer/disease site; **or**
      2. Treatment is being considered for which there are specific genomic biomarker-based contraindications or exclusions; **and**
   C. Member has not been previously tested with a multi-gene panel on the same tumor sample for the same indication; **and**
   D. Results of testing will directly impact clinical decision making, including both of the following clinical notes (1.-2.):
      1. Reason (indication) for performing test, including tumor type; **and**
      2. How results from current test request will impact clinical decision making; **and**
   E. Testing is being conducted in a Clinical Laboratory Improvement Amendments (CLIA)-certified lab; **and**
   F. Documentation states that member has decided to seek further cancer treatment.

II. Repeat testing may be considered **medically necessary** in the event of tumor progression after initial response to a targeted therapy with a known genetic-driven resistance mechanism.

III. Testing of multiple concurrent tumors may be considered **medically necessary** when there is clinical documentation of separate, synchronous tumors or clinical presentation supports the potential for two independent primary tumors.

IV. Multi-gene panels/NGS panels to assess mismatch repair deficiency status (dMMR),

microsatellite instability-high status (MSI-H), and/or tumor mutational burden (TMB) may be considered **medically necessary** in members with advanced or metastatic solid tumors who are candidates for immunotherapy.

V. Multi-gene panels/NGS panels are considered **not medically necessary and not covered** when criteria above are not met.

Link to Policy Summary

POLICY GUIDELINES

Examples of next generation sequencing (NGS) panels include but are not limited to:

- Cancer MI Tumor Seek
- FoundationOne CDx
- ProvSeq 523/Providence Personalized Medicine Panel- Solid Tumor

Resources

- National Comprehensive Cancer Network (NCCN) guidelines can be accessed on website at: https://www.nccn.org/guidelines/category_1

- The internal resource for NCCN Guidelines is linked here.

BILLING GUIDELINES

Some, but not all, panel tests may have a specific CPT or HCPCS code assigned (81410-81471). When no specific CPT or HCPCS code exists for the panel, the provider is required to bill using an unlisted code. It is not appropriate for the provider to bill any of the tests/genes in a panel separately as if they were performed individually. See Coding Policy 30.0, Laboratory Panel Billing, for more information.

CPT/HCPCS CODES

All Lines of Business Except Medicare

Prior Authorization Required

Code	Description	Related Panel
0022U	Targeted genomic sequence analysis panel, cholangiocarcinoma and non-small cell lung neoplasia, DNA and RNA analysis, 1-23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider	Oncomine Dx Target Test, *Life Technologies Corporation*

0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffinembedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number	Guardant360 TissueNext™, *Guardant Health, Inc*.
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.*
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)	Memorial Sloan Kettering- Integrated Mutational Profiling of Actionable Cancer Targets (MSK-IMPACT), *Memorial Sloan Kettering*
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities	CNGnome, PerkinElmer Genomics
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	MI Tumor Seek, *Caris Life Sciences*
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	Oncotype MAP Pan Cancer Tissue Test, *Genomic Health, Inc.*
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	PGDx Elio Tissue Complete, *Personal Genome Diagnostics*
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid	Versiti aHUS Genetic Evaluation, *Versiti Diagnostic Laboratories*
0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid	Versiti Autosomal Dominant Thrombocytopenia

		Panel, *Versiti Diagnostic Laboratories*
0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid	Versiti Coagulation Disorder Panel, *Versiti Diagnostic Laboratories*
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive	Versiti Comprehensive Bleeding Disorder Panel, *Versiti Diagnostic Laboratories*
0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid	Versiti Fibrinolytic Disorder Panel, *Versiti Diagnostic Laboratories*
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid	Comprehensive Platelet Disorder Panel, *Versiti Diagnostic Laboratories*
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid	Versiti Inherited Thrombocytopenia Panel, *Versiti Diagnostic Laboratories*
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid	Versiti Platelet Function Disorder Panel, *Versiti Diagnostic Laboratories*
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid	Versiti Thrombosis Panel, *Versiti Diagnostic Laboratories*
0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)	PancreasSeq Genomic Classifier, *UPMC*
81445	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	
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, 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	
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	
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; 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	
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy, then **prior-authorization is required.**		
81479	Unlisted Molecular Pathology	

DESCRIPTION

Multi-gene panel testing

Multi-gene panel testing refers to a laboratory test in which many genes are studies in a sample of tissue. In patients with cancer, multi-gene panels detect mutations and alterations in a broad selection of genes that may help plan treatment or predict prognosis.

Next-Generation Sequencing (NGS)

Next generation sequencing (NGS), also known as massively parallel or deep sequencing, refers to a technology for determining the sequence of DNA or RNA to study genetic variations associated with disease or other biological phenomena.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of multi-gene testing for cancer. Below is a summary of the available evidence identified through July 2022.

In 2022, Hayes published a report on comprehensive molecular profiling tests for solid tumors intended to be used as a broad molecular profiling tool to assigned matched therapy.[1] The report reviewed abstracts of studies addressing comprehensive molecular profiling (CMP) test with > 50 genes, excluding CMP via liquid biopsy and targeted testing.

Based on a review of included abstracts, there appears to be some support—as indicated by the number of abstracts identified (12)—with regard to CMP tests for the intended use as a broad molecular profiling tool (assessing DNA or RNA variants in > 50 genes) to identify biomarkers present in solid tumor tissue and then assign matched therapy specific to those biomarkers (may include FDA-approved or off-label use), and reported outcomes of treatment and compared with patients who did not receive matched targeted treatment based on the results of the CMP test. This conclusion reflects:

- A moderate number of abstracts were identified that met inclusion criteria, though some of the abstracts are likely to have patient overlap or represent multiple publications from a single clinical trial.
- Abstracts reported the use of CMP testing for broad molecular profiling to guide treatment and impact patient outcomes (clinical utility).
- No abstracts within the search time frame (approximately 5 years) had a randomized controlled trial (RCT) design; however, 1 earlier RCT and 1 in progress trial were identified. Findings from these studies should be interpreted with caution. In general, these studies evaluated patients who underwent CMP and compared outcomes between those who received matched therapies based on the findings and those who did not receive matched therapies. Of note, patients who did not receive matched therapies may have had fewer treatment options or other disease-related factors that could complicate any conclusions drawn from this comparison.

CLINICAL PRACTICE GUIDELINES

American Society of Clinical Oncology

In 2022, ASCO published a provisional clinical opinion on Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer.[2] The publication recommended the following guidelines:

- "PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

- PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

- PCO 1.3. If the genomic sequencing results are used to inform clinical care, such testing must be performed in an appropriately certified laboratory (strength of recommendation: strong).

- PCO 1.4. Clinical decision making should incorporate (1) the known or predicted impact of a specific genomic alteration on protein expression or function and (2) clinical data on the efficacy of targeting that genomic alteration with a particular agent (strength of recommendation: strong)

- PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel–based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

- PCO 2.2. When TMB [tumor mutational burden] may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

- PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate)."[2]

National Comprehensive Cancer Network (NCCN)

NCCN Clinical Practice Guidelines in Oncology are used to determine the medical necessity of NGS testing for cancer. For each request, the most up to date NCCN guideline will be reviewed.[3]

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to

determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Circulating Tumor Cell and DNA Assays for Cancer Management (All Lines of Business Except Medicare)
- Genetic and Molecular Testing (All Lines of Business Except Medicare)
- Genetic Counseling (All Lines of Business Except Medicare)
- Next Generation Sequencing for Minimal Residual Disease Detection (All Lines of Business Except Medicare)

REFERENCES

1. Hayes. Comprehensive Molecular Profiling Test(s) for Solid Tumors Intended to be Used as Broad Molecular Profiling Tool to Assigned Matched Therapy. Published Jan 11, 2022. https://evidence.hayesinc.com/report/pmi.pancancer5125. Accessed 7/13/2022.
2. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *Journal of Clinical Oncology.* 2022;40(11):1231-1258. https://ascopubs.org/doi/abs/10.1200/JCO.21.02767
3. National Comprehensive Cancer Network. NCCN Guideline. Treatment by cancer type. . https://www.nccn.org/guidelines/category_1. Accessed