Next Generation Sequencing for Cancer

MEDICAL POLICY NUMBER: 352

Effective Date: 1/1/2024

Last Review Date: 11/2023

Next Annual Review: 5/2024

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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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.

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

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial**   ☒ **Medicaid/OHP***   ☐ **Medicare****

<u>*Medicaid/OHP Members</u>

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.

<u>**Medicare Members</u>

This <u>*Company*</u> policy may be applied to Medicare Plan members only when directed by a separate <u>*Medicare*</u> policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE 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.

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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** when criteria above are not met.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Circulating Tumor Cell and DNA Assays for Cancer Management, MP122
- Next Generation Sequencing for Minimal Residual Disease Detection, MP110
- Genetic and Molecular Testing, MP215
- Genetic Counseling , MP316

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

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

RESOURCES

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.

BACKGROUNDS

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.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

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]

BILLING GUIDELINES AND CODING

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.

CODES*		
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	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 22 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 60 genes and duplication/deletion of PLAU, 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 62 genes and duplication/deletion of PLAU, 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

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		Panel, *Versiti Diagnostic Laboratories*
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 40 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid	Versiti Platelet Function Disorder Panel, *Versiti Diagnostic Laboratories*
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 14 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*
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	Oncomap Xtra, *Genomic Health*
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	Solid Tumor Expanded Panel, *Quest Diagnostics*
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, splicesite variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score	Strata Select. *Strata Oncology Inc*
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	
81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis	
81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	

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81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, 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	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	
81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability	
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability	
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	
81479	Unlisted Molecular Pathology	

*Coding Notes:
- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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 4/20/2023.
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 4/20/2023.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Q2 2023 Code set update
7/2023	Q3 2023 Code set update
8/2023	Annual update. Added CPT 0329U
10/2023	Q4 Code set update. Revised code descriptions
1/2024	Q1 2024 code set update. 3 new codes and 4 code description revisions.