Geisinger Health Plan Policies and Procedure Manual

Policy: MP360

Section: Medical Policy

Subject: Minimal Residual Disease NGS Testing

Applicable line of business:

Commercial	**x**	**Medicaid**	**x**
Medicare	**x**	**ACA**	**x**
CHIP	**x**		

I. Policy: Minimal Residual Disease NGS Testing

II. Purpose/Objective:

To provide a policy of coverage regarding Minimal Residual Disease NGS Testing

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment
Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:
Minimal Residual Disease (MRD) refers to a subclinical measure of cancer burden that remains during and following treatment. MRD status is a reliable indicator of clinical outcome and response to therapy such as drug resistance. Results can be used for risk stratification and to guide treatment options when used in conjunction with other clinical and molecular data in multiple malignancy types. MRD detection can identify patients at risk of recurrence earlier and is a practical addition to disease monitoring, following intervention.

MRD testing is recommended at a regular intervals over a specific time period. MRD testing often requires two types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline (solid and/or liquid) tumor signature as defined by the test methodology. This is followed by a series of assays run on a minimally invasive specimen (i.e., liquid biopsy or bone marrow aspirate) to detect the presence or recurrence of tumor based on the measured biomarkers, expression, or other analytes over various timepoints. This series of assays comprises a single test when the patient is known to have cancer.

Signatera (Natera) 0340U

The Signatera test is personalized and tumor-informed, tailored to fit the unique signature of clonal mutations found in that individual's tumor. Signatera is offered for bladder, breast, colorectal, lung, melanoma, ovarian, and malignancies of unknown origin. This test can be performed as a standalone test, or as a tumor-informed test.

INDICATIONS:

Colorectal Cancer:

- Stage II-IV and oligometastatic colorectal cancer (CRC) in the adjuvant and recurrence monitoring setting

Breast Cancer:

- Stage II-IV breast cancer in the neoadjuvant setting, regardless of subtype
- Stage IIb and higher breast cancer in the adjuvant and recurrence monitoring settings

Muscle invasive bladder cancer (MIBC):

- in the adjuvant and recurrence monitoring settings

Ovarian / Fallopian Tube / Peritoneal Cancer:

- Stage II-IV in the adjuvant and recurrence monitoring settings

Any Solid Tumor:

- For monitoring of response to immune-checkpoint inhibitor (ICI) therapy

ClonoSeq 0364U

INDICATIONS:

MRD testing (e.g., clonoSEQ) is considered to be medically necessary when performed in members with:

Multiple myeloma:
- During surveillance after response to primary treatment
- After each treatment phase (e.g. after induction therapy, high-dose therapy/autologous stem-cell transplantation, consolidation, and maintenance)

Acute myeloid leukemia:
- At completion of initial induction therapy
- Prior to allogeneic transplantation
- Periodic retesting guided by the regimen used

Acute lymphoblastic leukemia:
- At completion of initial induction therapy
- Periodic retesting guided by the regimen used
- Serial monitoring in members with molecular relapse or persistent low-level disease burden

Chronic lymphocytic leukemia or small lymphocytic lymphoma
- After completion of treatment
- For consideration of therapy with lenalidomide for high-risk patients after first-line therapy

Guardant Reveal

INDICATIONS:
MRD testing (ctDNA Guardant Reveal) is a tissue-free test. It is considered to be medically necessary when performed in members with:

Breast Cancer
- Stage I, II, or III breast cancer
- Recurrence monitoring after curative-intent procedure

Colorectal Cancer
- Stage II and III colorectal cancer
- Recurrence monitoring after curative-intent treatment procedure

Lung Cancer
- Stage II and III lung cancer

This test is not yet validated in other tumor types.

For the Medicare and Medicaid Business Segments
Although there is no National Coverage Determination issued for this service, CMS directives may allow MRD testing to be considered for coverage when used to predict risk of recurrence risk in members with personal history of cancer where treatment intent is curative.

Effective 12/26/2021 Palmetto GBA established a formal coverage policy for all Medicare patients. This local carrier determination is applicable nationally. Please refer to policy numbers L38779 and A58376 on Centers for Medicare & Medicaid Services website. Coverage criteria under the policy have been met for (1) the diagnosis of disease progression, recurrence, or relapse for colon cancer and (2) monitoring of response to immune-checkpoint inhibitor therapy for any solid tumor.

Coverage of ClonoSeq (baseline assay and multiple follow-up assays) is indicated for Acute lymphoblastic leukemia (ALL), Multiple myeloma (MM), and Chronic lymphocytic leukemia (CLL). Since Adaptive Biotechnologies is located in Seattle Washington, Noridian Healthcare Solutions, LLC policy A58997 applies.

NavDx Test 0356U
Per MolDx policy L38779, the NavDx test is considered to be medically necessary for the surveillance of recurrence in members with a personal history of documented HPV-driven oropharyngeal cancer, who presently have no evidence of disease, starting three months following completion of any regimen of curative intent therapy, with a frequency of:

- not more often than every three months for the first 24 months thereafter,
- not more often than every six months for the next 36 months thereafter,
- not more often than annually thereafter until if and when a positive test result is detected.

EXCLUSIONS:
The use of MRD NGS tests not specified in this policy will be considered **experimental, investigational or unproven** and therefore, **NOT COVERED**.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:
Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

CODING ASSOCIATED WITH:
The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov ***or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

81479 Unlisted molecular pathology procedure
81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (EG, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or MRNA expression levels, if performed *{ClonoSeq}*
81445 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; DNA analysis or combined DNA and RNA analysis.
0306U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD
0307U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
0340U Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate *{Signatera™}*
0364U Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate *{clonoSeq}*
0356U Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence.*{NavDx}*
0470U Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma *{HPV-SEQ Test}*
0502U Human papillomavirus (HPV), E6/E7 markers for high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), cervical cells, branched-chain capture hybridization, reported as negative or positive for high risk for HPV

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:
National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology Acute Lymphoblastic Leukemia v2.2024

National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology Hairy Cell Leukemia v1.2025

National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V1.2025

National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology Hodgkin Lymphoma v4.2024

National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology Multiple Myeloma v1.2025

National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology Colon Cancer v5.2024

Thompson PA, Srivastava J, Peterson C, et al. Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. Blood. 2019; 134(22):1951-1959

Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood. 2018; 132(23):2456-2464

Wood, B., Wu, D., Crossley, B., Dai, Y., Williamson, et al Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood, 2018;131(12), 1350-1359.

Luskin, M. R., Murakami, M. A., Manalis, S. R., & Weinstock, D. M. Targeting minimal residual disease: a path to cure? Nat Rev Cancer, 2018;18(4), 255-263.

Medina, A., Puig, N., Flores-Montero, J., et al Comparison of next-generation sequencing (NGS) and next-generation flow (NGF) for minimal residual disease (MRD) assessment in multiple myeloma. Blood Cancer J, 2020; 10(10), 108.

Del Giudice, I., Raponi, S., Della Starza, I., De Propris, et al Minimal Residual Disease in Chronic Lymphocytic Leukemia: A New Goal? Front Oncol, 2019;9, 689.

Carlson, J. J., Eckert, B., & Zimmerman, M. Cost-effectiveness of next-generation sequencing minimal residual disease testing during maintenance treatment for multiple myeloma. Journal of Clinical Oncology, 2019; 37(15_suppl), e19529-e19529

Bai, Y., Orfao, A., & Chim, C. S. Molecular detection of minimal residual disease in multiple myeloma. Br J Haematol, 2018;181(1), 11-26. d

Goicoechea, I., Puig, N., Cedena, M. T., Burgos, L., et al. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. Blood, 2021;137(1), 49-60.

Ching T, Duncan ME, Newman-Eerkes T, McWhorter MME, Tracy JM, Steen et al Analytical evaluation of the clonoSEQ Assay for establishing measurable (minimal) residual disease in acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma. BMC Cancer, 2020;20(1):612.

Monter A, Nomdedéu JF. ClonoSEQ assay for the detection of lymphoid malignancies. Expert Rev Mol Diagn, 2019;19(7):571–578.

Balagopal V, Hantel A, Kadri S, et al. Measurable residual disease monitoring for patients with acute myeloid leukemia following hematopoietic cell transplantation using error corrected hybrid capture next generation sequencing. PLoS One. 2019;14(10):e0224097.

MolDX: ClonoSEQ® Assay for Assessment of Minimal Residual Disease (MRD) in Patients with Specific Lymphoid Malignancies (A56307). Local coverage article.

MolDX: Minimal Residual Disease Testing for Colorectal Cancer L38290, L38779

Loupakis F, Sharma S, Derouazi M, et al. Detection of molecular residual disease using personalized circulating tumor DNA assay in patients with colorectal cancer undergoing resection of metastases. JCO Precis Oncol. 2021;5:PO.21.00101

Parikh AR, Van Seventer EE, et al. Minimal residual disease detection using a plasma-only circulating tumor DNA assay in colorectal cancer patients. Clin Cancer Res. 2021 doi:10.1158/1078-0432.CCR-21-0410

Geisinger Health Plan Technology Assessment Committee, NavDx Testing, Sept. 2023 (15 references)

Zhu L, Xu R, Yang L, et al. Minimal residual disease (MRD) detection in solid tumors using circulating tumor DNA: a systematic review. Front Genet. 2023 Aug 10;14:1172108. PMID: 37636270.

Abbosh C., Birkbak N. J., Swanton C. (2018). Early stage NSCLC: challenges to implementing ctDNA-based screening and MRD detection. Nat. Rev. Clin. Oncol. 15 (9), 577–586. PMID: 29968853.

Coakley M, Villacampa G, Sritharan P, et al. Comparison of Circulating Tumor DNA Assays for Molecular Residual Disease Detection in Early-Stage Triple-Negative Breast Cancer. Clin Cancer Res. 2024 Feb 16;30(4):895-903. doi: 10.1158/1078-0432.CCR-23-2326. PMID: 38078899; PMCID: PMC10870111

This policy will be revised as necessary and reviewed no less than annually**.**

Devised: 6/22

Revised: 6/23 (add indication); 12/23 (add NavDx for Medicare); 12/24 (add indications)

Reviewed:

CMS UM Oversight Committee Approval: 12/23, 02/25