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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Somatic Tumor Testing

Proprietary

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Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Use of an FDA-approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues

- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Somatic Tumor Testing

Clinical Indications

General Requirements

The genomic testing must have established analytical and clinical validity and be performed in an appropriately certified laboratory.

Repeated testing of the same individual for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing of the same tumor site with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same individual and the same tumor by different providers over a short period of time

Definitions

- **Transcriptome** – The complete set of RNA molecules expressed in a cell, tissue, or organism at a particular time. This includes all forms of RNA, such as messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), and non-coding RNAs. ***Whole transcriptome analysis*** is the study of the complete set of RNA transcripts present in a cell or tissue at a specific point in time.
- **RNA Gene Expression Profiling** – RNA gene expression profiling refers to a technique that analyzes mRNA levels (gene activity) to determine which genes are upregulated or downregulated in a cell or tissue, such as in a tumor sample.
- **RNA Fusion** – RNA fusion refers to the occurrence of hybrid RNA molecules formed from two previously separate genes due to structural alterations in the genome, such as translocations or other rearrangements. These fusions can result in abnormal proteins often associated with cancer and other diseases, driving oncogenesis or altered cellular functions. ***RNA fusion analysis*** aids in diagnosing specific cancers and understanding their molecular drivers.

Somatic Testing of Solid Tumors

General Criteria

If cancer-site specific criteria (e.g., breast cancer, colorectal cancer, prostate cancer, etc.) are described in this guideline, apply those criteria prior to use of the General Criteria.

The use of an FDA-approved companion diagnostic test or an appropriately validated lab developed test (LDT) performed in a certified laboratory may be considered **medically necessary** when the following criteria are met.

Somatic Genomic Testing (Solid tumor biomarker testing)

Somatic genomic testing is considered **medically necessary** in individuals with cancer when **ALL** the following criteria are met:

- Clinical decision making incorporates the known or predicted impact of a specific genomic alteration on protein expression or function and published clinical data on the efficacy of targeting that genomic alteration with a particular agent
- The genetic test is reasonably targeted in scope and has established clinical utility such that a positive or negative result will meaningfully impact the clinical management of the individual and will likely result in improvement in net health outcomes (i.e., the health benefits of the interventions outweigh any medical or psychological harmful effects of the testing intervention)
- When the clinical utility is based on potential impact on clinical management based on genomic biomarker-linked therapies, one or more of these additional criteria must also be met:
    - The genomic biomarker-linked therapies are approved by the US Food and Drug Administration (FDA) or recommended by NCCN as a Category 2A for the individual's specific cancer scenario and such therapies are being considered in the near term
    - Treatment is being considered for which there are specific genomic biomarker-based contraindications or exclusions related to cancer treatment being considered in the near term aligned with the FDA label or NCCN 2A recommendations
    - Treatment is being considered for which the member's health plan has a drug-specific policy requiring additional, appropriately focused genetic biomarker testing otherwise not specified by the FDA label or NCCN 2A recommendation

Rationale

Nearly every malignancy will have somatic pathogenic variant/likely pathogenic (P/LP) variants that have been described, although most known P/LP variants do not have clinical management implications. While various common conditions are covered by specific guideline criteria for somatic testing of tumors, it is not feasible to establish criteria for every clinical scenario in oncology and hematology. The general criteria for somatic testing (above) apply to malignancy when more specific criteria may or may not be available.

Metastatic or Advanced Cancer (Tissue-Agnostic Testing)

Tissue-agnostic testing for patients with advanced solid tumors

Multigene panel testing is considered **medically necessary** when **ALL** the following are true:

- The individual has a metastatic or advanced solid tumor and adequate performance status for cancer treatment
- There are no satisfactory tumor-specific standard therapies available
- Tumor testing falls into **one or more** of the following categories:
    - Mismatch-repair (MMR) deficiency
        - MLH1, MSH2, MSH6, PMS2 or EPCAM genes by PCR or NGS testing
        - Microsatellite testing (MSI) and/or dMMR testing
        - MLH-1 promoter methylation and/or BRAF V600E testing with nuclear expression loss of MLH1 and PMS2 by immunohistochemistry
    - Tumor mutational burden (TMB) testing as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb)
    - NTRK1/2/3 and RET fusion testing
    - BRAF V600E testing
    - FGFR1/2/3 fusions or pathogenic/likely pathogenic (P/LP) variants

Rationale

Traditionally, oncologists have based therapy selections and prognoses on the site of origin and histology of tumors. In specific cases, biomarkers have been integrated, such as immunohistochemistry (IHC) for HER2 and estrogen/progesterone receptor status in breast cancer More recently, genomic characterization has become vital, especially for advanced diseases, guiding treatment decisions through large-scale sequencing studies like The Cancer Genome Atlas and the International Cancer Genome Consortium, which have outlined genomic landscapes and identified driver alterations in 20–30 solid tumor types.

Comprehensive next-generation sequencing (NGS) testing reveals a broad range of potentially actionable genomic alterations in 40%-94% of patients with advanced cancer.[1] However, the practical application has its challenges, with only 10%-25% of patients actually receiving sequencing-informed therapy. The primary randomized trial on NGS-based therapy for advanced cancer did not show improvement in progression-free survival with molecularly matched therapy (but the field remains hopeful about the effectiveness of this strategy based on ongoing advances and descriptive data about changes in drug treatment in practice based on NGS testing.[2, 3] However, in an evaluation by authors from the National Cancer Institute regarding the rigor of the peer-reviewed literature cited in the National Coverage Determination Memorandum for the FoundationOneCDx, 113 studies were reviewed and significant gaps were found and described in the supporting evidence for broad comprehensive genomic profiling use in patients with solid tumors.[4] These authors concluded that rigorous studies that assess clinical utility would better inform the approval process for novel diagnostic tests.

Current standards prioritize somatic testing for specific tumor scenarios, driven by effectively treatable alterations.[5] The FDA has approved tissue-agnostic indications in cases where treatments have failed, including pembrolizumab for microsatellite instability (MSI) or high tumor mutational burden (TMB), larotrectinib, entrectinib, or repotrectnib for NTRK fusions, selpercatinib for RET fusions, and dabrafenib plus trametinib for BRAF V600E, and fam-trastuzumab deruxtecan for HER2-positive solid tumors.

Microsatellite Instability

Microsatellite Instability (MSI), caused by defects in the DNA mismatch repair (MMR) system, is marked by high frameshift pathogenic variants in microsatellite DNA. While 80% of MSI instances are sporadic due to MLH1 promoter hypermethylation, germline P/LP variants in MMR genes can also cause hereditary Lynch syndrome.[5] Studies have demonstrated that MMR deficiency is reliably diagnosed using either polymerase chain reaction (PCR) for MSI or immunohistochemistry (IHC) for MMR protein expression, with concordance rates typically between 90% and 98%.[6] MMR deficiency occurs in roughly 4% of adult cancers.

High Tumor Mutational Burden

Tumor Mutational Burden (TMB) measures the total mutations per megabase in tumor DNA, crucial for personalized therapy. The FDA approved pembrolizumab for TMB ≥10 mutations/Mb in 2020. Balancing TMB evaluation is complex, as tests like the FoundationOneCDx and MSK-IMPACT use different metrics and bioinformatics methods, complicating equivalence across tests.[7, 8]

The predictive value of TMB for response to immune-checkpoint inhibitors is only proven for certain histologies and even for these, sensitivity and specificity for the prediction of benefit are limited.[9] The tumor-agnostic FDA approval was contentious due to arbitrary TMB cut-offs, lacking clear survival benefits and questioning cost efficiency versus alternatives.[10, 11] The impact of the sequencing strategy, bioinformatics pipeline, spatial heterogeneity and temporal heterogeneity are important in TMB measurement. Differences in the sequencing platform pipelines are significant also, which makes TMB estimation not easily reproducible across assays.[9, 12] Prospective studies are necessary to establish consistent predictive utility for TMB across therapies.

NTRK Fusion Genes

NTRK fusions occur mainly in rare adult and pediatric cancers but are significant when found in common cancers. Though rare (e.g., 0.27% of patients tested), notable activity has been observed with larotrectinib and entrectinib in NTRK fusion-positive tumors.[13]

Testing methods for NTRK, including IHC, FISH, and NGS, vary in specificity, and the selection depends on tumor type and assay requirements. Yet, given the rarity of NTRK fusions, broad testing yields low benefit.[14]

Tumor-Agnostic Therapies

RET fusion, identified in some lung and thyroid cancers, led to the accelerated approval of selpercatinib. Trials like LIBRETTO-001 demonstrated objective responses in various cancer types, revealing potential despite rare occurrence.[15]

Dabrafenib with trametinib was approved in 2022 for BRAF V600E pathogenic variants, specifically excluding colorectal cancers due to resistance. This approval stemmed from findings in trials like BRF117019 and NCI-MATCH.[5]

Recent Advances and FDA Approvals

Recent studies underscore significant shifts toward tumor-agnostic testing. The European Society for Medical Oncology (ESMO) guidelines now recommend genomic testing for FGFR1/2/3 fusions and pathogenic variants[16], supported by evidence from the RAGNAR study.[17] These guidelines emphasize standardized genomic test reporting, including clinical actionability, essential for implementing precision oncology across various cancer settings.

The FDA has recently approved several tissue-agnostic therapies, highlighting a trend toward genetic alteration-based treatment. Notable approvals include:

- Repotrectinib (AUGTYRO®) for NTRK gene fusions (2024)
- Selpercatinib (Retevmo®) for RET fusions in pediatric populations (2024)
- Fam-trastuzumab deruxtecan (Enhertu®) for HER2-positive solid tumors (2024)

These approvals reflect the increasing use of tumor-agnostic therapies in clinical practice and their potential to inform treatment pathways in diverse cancer types.

Conclusion

The approach to cancer treatment continues to evolve with tumor-agnostic therapies, urging a shift from traditional, location-based therapies to those informed by genetic alterations. Significant challenges remain in addressing the additional barriers to its wider implications including efforts to improve process efficiencies, clinician genomic literacy, and decision-making support.[18] In this regard, the concept of molecular tumor boards and their potential structure, role, and ongoing evaluation is a topic of growing interest.[19] The ESMO Scale of Clinical Actionability of Molecular Targets (ESCAT) classifies NTRK fusion, high TMB, and MSI typically as tier IC, highlighting the need for evidence of clinical benefit despite the rarity of prospective trials.[5] ESMO has recently proposed use of the ESMO Tumour-Agnostic Classifier (ETAC) as a rubric to define minimum requirements to screen for tumor-agnostic potential as part of drug development. This involves robust preclinical, mechanistic evidence associated with prospective clinical evidence from phase I-II trials demonstrating an objective response in at least one out of five patients (ORR ≥ 20%) in two-thirds of the investigated tumor types (and in at least four tumor types) with at least five evaluable patients per tumor type in the setting of refractory disease.[20] As tumor-agnostic therapies evolve, prospective research remains crucial to validate these biomarkers comprehensively, and further research is essential to maximize the clinical utility of treating patients with targeted therapy based on this tumor-agnostic approach.

Cancer-specific Criteria

Bladder Cancer (Urothelial Carcinoma, including the Upper Tract)

Gene expression profiling tests as a technique for urothelial cancer management and surveillance are considered **not medically necessary** for all indications.

For multianalyte assays used for screening and diagnosis (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven urothelial carcinoma of the bladder or upper urinary tract.
- The individual has not had prior MSI or dMMR testing

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing for FGFR P/LP variants is considered **medically necessary** for individuals with urothelial tumors of the bladder or upper urinary tract when **ALL** the following criteria are met:

- The individual has biopsy-proven urothelial malignancy
- The urothelial malignancy is locally advanced (stage IIIB), recurrent, or metastatic (stage IV)
- The individual is a potential candidate for an FDA-approved (or NCCN 2A) targeted therapy prescribed on the basis of this testing

- The individual has not had prior FGFR testing in the locally advanced, recurrent, or metastatic setting

Note: Tumor agnostic genetic testing indications may also apply depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Bladder cancers exhibit significant biological diversity and can be classified into “molecular subtypes” based on expression profiling.[21, 22] More than 90% of muscle-invasive bladder cancers can be categorized as either luminal or basal-squamous subtypes. While various subtypes, including the Lund Taxonomy are associated with distinct clinical behaviors, histologies, and molecular alterations, their clinical utility remains unproven, and their use in bladder cancer management is currently not recommended.[23, 24] Guidelines from the American Urological Association (AUA), European Association of Urology (EUA), the Society of Urological Oncology (SUO), and the NCCN [25] continue to not support genetic testing for risk stratification or management guidance in non-muscle invasive bladder cancer (NMIBC).[26, 27] Driven by the low sensitivity of urine cytology in low grade tumours, numerous urinary tests have been developed, None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up for the purpose of avoiding cystoscopy.[27]

FGFR3 Alterations and Associated Therapies

Oncogenic alterations in FGFR3 are observed in approximately 15% of muscle-invasive bladder cancers. The luminal subtype specifically shows enrichment of FGFR3 P/LP variants and overexpression.[24] FGFR P/LP variants are seen more frequently in upper tract urothelial cancers (≈30%) compared to bladder cancers (≈14%).[28]

The FDA has approved erdafitinib for adult patients with locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations. The approval is for tumors that have shown progression on or after at least one line of prior systemic therapy. Additionally, enfortumab vedotin in combination with pembrolizumab is now approved for patients with locally advanced or metastatic urothelial cancer who are eligible (or ineligible) for cisplatin-containing chemotherapy, integrating immune-checkpoint inhibitor routinely into initial therapy for advanced disease and reducing the role of tumor-agnostic testing to identify candidate for immune-checkpoint inhibitors.

Guidelines and Emerging Therapies

Updated European Association of Urology (EAU) guidelines emphasize the role of genetic testing for therapeutic guidance in advanced-stage patients after platinum-based therapy.[29] Nivolumab combined with cisplatin and gemcitabine has also received FDA approval for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma..

In bladder cancer-related clinical practices, NECTIN4 amplifications are being explored as genomic predictors of response to the antibody-drug conjugate enfortumab vedotin in metastatic urothelial carcinoma, although more prospective evaluations are necessary before they are clinically implemented.[30]

Conclusion

The status of FGFR3 and other genetic alterations remains a significant focus area for therapeutic research and development in bladder cancer. Ongoing studies and trials are crucial for transforming these genomic insights into clinically actionable strategies, with the current guidelines recommending targeted therapy only under specific conditions post-platinum chemotherapy.

Brain Cancer (Malignant Glioma)

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with malignant gliomas of the brain when **ALL** the following criteria are met:

- The individual has biopsy-proven, primary malignant glioma of the brain
- Genetic testing includes at least the following:
    - BRAF V600E
    - IDH1 and IDH2
- The individual has not had prior testing for these genes

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven, malignant glioma of the brain
- The individual is under age 50 years and IDH wild type
- The individual has not had prior MSI or dMMR testing

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Most primary brain tumors in adults originate from glial cells. In the United States, the average annual age-adjusted incidence rate for all glial tumors is 5.95 per 100,000 people, with glioblastoma being the most common type, occurring at a rate of 3.23 per 100,000 people.[31] The World Health Organization released the fifth edition of the Classification of Tumors of the Central Nervous System in 2021. This classification integrates advancements in understanding the molecular pathogenesis of brain tumors alongside histopathology. The former category of adult-type diffuse gliomas has been refined into three types: astrocytoma with isocitrate dehydrogenase (IDH) pathogenic variant; oligodendroglioma with IDH pathogenic variant and 1p/19q co-deletion; and glioblastoma that is IDH wild type.[32] These modifications, driven by the IDH pathogenic variant status, restrict the diagnosis of glioblastoma to tumors that are IDH wild type.[33] This updated classification significantly impacts patient prognosis, management, and the design and execution of clinical trials.[31]

The strategy for molecular testing in malignant gliomas is influenced by the specific tumor entity, the patient's clinical status, and available treatment options, including clinical trials. Next-generation sequencing (NGS) panels are favored over immunohistochemistry for identifying pathogenic variants due to their efficiency in providing diagnostic, prognostic, and predictive information. In a large real-world study comparing sample sufficiency and post-sequencing success rate shows that CNS tumors have similarly high tissue biopsy reporting success rates as with other solid tumors, but far less success with liquid biopsy.[34] The frequency of various molecular aberrations by disease subtype and the ESMO Scale for Actionability of Molecular Targets (ESCAT) classification is summarized in the European Association of Neuro-Oncology (EANO) guidelines.[31] Testing for IDH1 and IDH2 pathogenic variants is crucial as it differentiates tumors' prognostic paths: IDH wild-type tumors typically show poorer outcomes.[33] Additionally, MGMT hypermethylation is a positive predictor of chemotherapy response.

Mismatch repair deficiency (MMRD), though rare in low-grade gliomas, is identified in 3.7% to 12.4% of high-grade gliomas and is often seen in younger patients under 50 with IDH wild-type tumors.[35, 36] Germline factors, often related to Lynch syndrome, account for most primary MMRD gliomas, which underscores the importance of genetic testing for accurate diagnosis and appropriate management strategies.[36]

The BRAF V600E pathogenic variant is an emerging predictive biomarker in pediatric gliomas, with promising preliminary results for its role in high-grade types as well. In adults, it serves as a criterion for clinical trial eligibility.

The INDIGO trial showed that an oral IDH inhibitor could significantly improve progression-free survival in adults.[37] However, despite regulatory approvals for NTRK fusion inhibitors and pembrolizumab for specific CNS tumors, the evidence of clinical benefit remains modest.[31, 38]

Breast Cancer

Localized breast cancer; early adjuvant setting

Gene expression profiling is considered **medically necessary** to guide adjuvant therapy* treatment-decision making for individuals with localized breast cancer using Oncotype DX®, MammaPrint®, EndoPredict®, Prosigna® Breast Cancer Prognostic Gene Signature Assay when **ALL** the following criteria are met:

- Surgery has been performed, and a full pathological evaluation of the specimen has been completed
- Histology is invasive ductal, lobular, mixed, or metaplastic
- Receptor status is estrogen receptor positive (ER+), progesterone receptor positive (PR+), or both; AND HER2-negative

- Lymph node status is node-negative (pN0) or axillary lymph node micro-metastasis (pN1mi) less than or equal to 2 mm
- Tumor features include **ANY** of the following:
    - Tumor size greater than 1.0 cm and less than or equal to 5.0 cm
    - Tumor size 0.6–1.0 cm and moderately (histologic grade 2) or poorly-differentiated (histologic grade 3)
    - Tumor size 0.6–1.0 cm and well-differentiated (histologic grade 1) with **EITHER** of the following:
        - angiolymphatic invasion
        - high nuclear grade (nuclear grade 3)
- Chemotherapy is being considered by the individual and their provider
- No other breast cancer gene expression profiling assay has been conducted for this tumor (this includes testing on any metastatic foci or on other sites when the tumor is multifocal)

Gene expression profiling is considered **not medically necessary** to guide adjuvant therapy treatment decision-making for individuals with ductal carcinoma in situ (DCIS) when DCIS is the sole breast cancer histology.

Gene expression profiling with the Oncotype DX or MammaPrint is considered **medically necessary** for postmenopausal females and adult males (referring to the sex assigned at birth) with 1 to 3 positive axillary lymph nodes (pN1a, pN1b or pN1c) when **ALL** the following criteria are met:

- Surgery has been performed, and a full pathological evaluation of the specimen has been completed
- Histology is ductal, lobular, mixed, or metaplastic
- Receptor status is estrogen receptor positive (ER+), progesterone receptor positive (PR+), or both; **AND** HER2-negative
- Chemotherapy is being considered by the individual and their provider
- No other breast cancer gene expression profiling assay has been conducted for this tumor (including testing on any metastatic foci or on other sites when the tumor is multifocal)

Localized breast cancer; extended adjuvant setting

Gene expression profiling using the Breast Cancer Index® (BCI™) is considered **medically necessary** to assist with extended adjuvant therapy treatment-decision making for individuals with localized breast cancer when **ALL** the following criteria are met:

- Receptor status is estrogen receptor positive (ER+), progesterone receptor positive (PR+), or both; AND HER2-negative
- The individual is premenopausal at the time of the extended adjuvant decision-making
- The individual has not been treated with ovarian suppression, an aromatase inhibitor, a CDK 4/6 inhibitor, or a PARP inhibitor

Metastatic and/or locally advanced breast cancer**

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing for P/LP variants of PIK3CA, AKT1, PTEN, and ESR1 is considered **medically necessary** for postmenopausal females and adult males when **ALL** the following criteria are met:

- The individual has ER-positive and HER2-negative metastatic breast cancer

- The individual is a candidate for treatment per FDA label (or NCCN 2A) with alpelisib, capivasertib plus fulvestrant, or inavolisib with palbociclib and fulvestrant **AND/OR** the individual is a candidate for treatment per FDA label (or NCCN 2A) with elacestrant
- The individual has not had prior tissue-based testing for the targeted gene(s) of interest in the metastatic setting

Notes

**Adjuvant therapy refers to treatments early in the trajectory of treatment for localized breast cancer (e.g., within 12 weeks of surgery) to reduce risk of breast cancer recurrence; this is distinct from extended-adjuvant therapy decision-making that takes places years after initiation of adjuvant treatment and involves a decision about the duration of treatment.*

***Locally advanced breast cancer refers to AJCC stages IIIA, IIIB, or IIIC disease or stage IIB disease considered inoperable and requiring systemic therapy.*

Genetic Liquid Biopsy guideline criteria may apply; see Carelon Guidelines for Genetic Liquid Biopsy in the Management of Cancer and Cancer Surveillance. Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Initial Adjuvant Therapy for Breast Cancer

Breast tumors are routinely assessed using immunohistochemical staining to detect the presence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression. This information is crucial for guiding hormonal and HER2-targeted therapies. Breast cancer affects individuals across various gender identities, though most treatment data originate from studies involving individuals assigned female at birth.

Characterizing the gene expression profile for invasive breast cancer helps stratify recurrence risk. For more than one-third of females with breast cancer in the U.S., multigene expression assays are used to evaluate the benefit of adjuvant chemotherapy in early-stage cases. In the ASCO 2016 biomarker guideline for early breast cancer, the Breast Cancer Index was among the tests with a moderate strength of recommendation for use in node-negative, estrogen receptor positive early breast cancer.[39] A prominent test that emerged since 2016 is Oncotype DX, a 21-gene assay validated in lymph node-negative early breast cancer through the TAILORx trial, which included 10,273 females. The RXPonder trial further established its use for node-positive early breast cancer in a cohort of 5,083 females.[40] The MammaPrint assay, evaluated in the MINDACT trial with 6,693 females presenting with node-negative or 1–3 node-positive early-stage breast cancer, primarily ER-positive, is employed similarly.[41, 42] The 2022 ASCO guidelines categorize use based on lymph node status, age, menopausal status, and HER2 receptor status. Oncotype DX is strongly recommended for node-negative females irrespective of age or menopausal status (based on the TailorX trial), and postmenopausal females with 1–3 positive nodes (based on the RXPonder trial).[43]

MammaPrint is strongly recommended for node-negative or node-positive (1–3 positive nodes) patients over 50. Newer tests like EndoPredict and Prosigna receive moderate recommendations.[43] For early-stage adjuvant treatment decisions, the Breast Cancer Index is not commonly in use. There is currently no established role for emerging biomarkers such as PD-L1, circulating tumor cells, or tumor-infiltrating lymphocytes. In addition, there is no established role for gene expression profile testing to guide treatment of non-invasive breast cancer like ductal carcinoma in situ (DCIS).[44]

Extended Adjuvant Therapy for Breast Cancer

The risk of recurrence for hormone receptor-positive breast cancer never goes away; it can recur post-5 years of adjuvant endocrine therapy.[45] Extended hormonal therapy consideration is backed by trials like MA17, ABCSG, aTToM, ATLAS, IDEAL, and NSABP-B42, along with newer AERAS trial data demonstrating improved disease-free survival with extended anastrozole.[46] ASCO guidelines suggest extended therapy offers modest added benefits with challenges of increased toxicity.[43, 47] Decision-making includes risk of recurrence, treatment tolerability, and patient preference, with considerations including psychological and financial impacts.[48, 49] The role of genomic testing in predicting extended adjuvant therapy benefits requires further prospective studies.[50]

The Breast Cancer Index (BCI) test has been proposed as a tool to guide decision-making about extended adjuvant hormonal therapy in patients with hormone receptor-positive (HR+) early-stage breast cancer. However, recent evaluations and

guideline updates reflect significant concerns about its clinical utility, prompting a reassessment of whether BCI should be deemed medically necessary for this purpose. The BCI test relies heavily on data from retrospective analyses. Studies by Noordhoek et al.[51] and Bartlett et al.[52, 53] evaluated data from the previously conducted IDEAL and aTToM trials, respectively, and described treatment to biomarker interactions to explore the value of the BCI for predicting endocrine therapy benefits. The Noordhoek study was positive, although only 53% of the eligible patients had BCI testing. The Bartlett study was negative in the overall population, but the node-positive subset was explored and emphasized as positive. The B-42 trial, presented at ASCO 2021 and finally published in 2024 by Mamounas [54], failed to confirm the predictive performance of BCI, casting doubt on the reliability of previous findings. Likewise, a similar study focused on the utility of the 70-gene Mammaprint assay for this same use as a predictor of benefit from extended adjuvant therapy was conducted from a sample of 1886 patients who were treated in the context of the B-42 trial and this study was also negative.[55] Overall, the role of genomic testing as a predictor of benefit for use of extended adjuvant therapy remains to be established in prospective studies [56], results of prospective-retrospective studies have been inconsistent, and it has not yet been integrated into multiple trials for extended adjuvant therapies. In 2024, the NCCN acknowledged limitations of the BCI data in a footnote but still considers this testing to be NCCN 2A. ASCO guidelines[43] acknowledge the BCI but similarly acknowledge with the same strength of evidence and strength of recommendation a free online calculator called the CTS5 [57] to help guide clinicians in shared decision-making for postmenopausal patients in the extended adjuvant setting.

The Breast Cancer Index has also been recently explored in a cohort of premenopausal women. The study was designed as a prospective-retrospective translational investigation utilizing tumor tissue samples from 1687 premenopausal women involved in the Suppression of Ovarian Function Trial (SOFT). Contrary to the study's hypothesis, patients with BCI-low tumors derived significant benefit from ovarian suppression therapy, while those with BCI-high tumors did not. This finding diverges from prior research where BCI-high tumors seem to suggest greater benefit from extended endocrine therapy in postmenopausal populations. The biological mechanisms underlying this discrepancy remain unclear, and the findings require validation in larger, independent cohorts to confirm the predictive and prognostic utility of BCI in this specific population.[58]

Metastatic Breast Cancer

The ESMO Translational Research and Precision Medicine Working Group developed the ESCAT system classifying molecular aberrations for clinical actionability.[59] For metastatic breast cancer, routine use of broad NGS testing is not recommended, though HER2 amplifications, BRCA1/2 and PIK3CA P/LP variants fall under tier IA of actionability.[60, 61]

The PI3K-AKT and mTOR pathways are among the most commonly activated pathways in breast cancer, whose crucial role in the pathogenesis of this tumor type has spurred major efforts to target this pathway.[62] Alpelisib targets the PIK3CA-mutated, ER-positive/HER2-negative metastatic breast cancer, approved following the Solar-1 trial.[63] In genotype-driven therapy, elacestrant is approved based on phase III Emerald Trial for patients with ER-positive/HER2-negative advanced breast cancer with certain ESR1 pathogenic variants.[64] Additionally, olaparib is a standard treatment for those with BRCA P/LP variants as per the OlympiaAD trial.[65]

Most recently, the FDA approved capivasertib with fulvestrant for HR-positive, HER2-negative breast cancer with PIK3CA/AKT1/PTEN alterations [66, 67], and also inavolisib with palbociclib and fulvestrant for similar patients with PIK3CA P/LP variants.[68] The 2023 ASCO guidelines recommend evaluating P/LP variants like ESR1, PIK3CA, or inactivation of PTEN in progression samples.[69] A rapid update of these ASCO guidelines in 2024 emphasized the recommendation for use of multiple lines of endocrine treatment, frequently paired with targeted agents, with choices informed by prior treatments and by routine testing for activating P/LP variants in ESR1, PIK3CA, or AKT1 or inactivation of PTEN. The guideline states for both PIK3CA and ESR1 that testing should be on blood OR tissue. Also noted was that combining endocrine therapy with the AKT pathway inhibitor capivasertib is appropriate for tumors harboring PIK3CA or AKT1 P/LP variants or PTEN inactivation while endocrine therapy combined with the PI3 kinase inhibitor alpelisib is an option for tumors harboring PIK3CA P/LP variants, but not AKT1 P/LP variants.

Most kinase fusion targets are in development, but NTRK inhibitors are approved. Other biomarkers, such as FGFR1/FGFR2, NFI, and tumor signatures, are currently in clinical trials, while agents for HER2, BRCA P/LP variants, and PALB2 P/LP variants show promise but limited evidence.[70, 71]

Cholangiocarcinoma (Biliary Tract Cancers)

Tissue-based somatic tumor testing for P/LP variants in individuals with cholangiocarcinoma is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven cholangiocarcinoma
- The cholangiocarcinoma is locally advanced, unresectable, or metastatic
- The panel testing to include analysis of the following genes: IDH1, FGFR, HER2/ERBB2, and BRAF

- The individual is a potential candidate for targeted therapy that is FDA approved (or NCCN 2A), prescribed on the basis of the panel test results
- The individual has not had prior somatic tumor testing for IDH1, FGFR, HER2/ERBB2, and BRAF in the metastatic setting

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Biliary tract cancer encompasses a spectrum of invasive adenocarcinomas, including cholangiocarcinoma (arising in the intrahepatic, perihilar, or distal biliary tree) as well as gallbladder carcinoma. Distinct patient subgroups with driver P/LP variants suitable for targeted therapy have been identified. These subgroups generally demonstrate mutually exclusive genetic alterations, often corresponding to the tumor's anatomical subsite.[72] Common molecular alterations in biliary tract malignancy include P/LP variants in IDH1 (seen in 13% of intrahepatic cholangiocarcinoma cases), FGFR pathway P/LP variants particularly FGFR2 (found in 20% of intrahepatic cholangiocarcinoma cases), HER2 overexpression/amplification (up to 20% in gallbladder and extra-hepatic cholangiocarcinoma) HER2/ERBB2 P/LP variants, and BRAF V600E (present in 5% of intrahepatic cholangiocarcinoma cases). It is now standard practice to conduct molecular profiling for cholangiocarcinoma patients, especially those with intrahepatic variants, to identify these potential therapeutic targets.[61, 73]

Unfortunately, patients with FGFR2 fusions or IDH1 P/LP variants often experience intrinsic resistance to targeted therapies, or the responses are short-lived due to acquired resistance.[74] Rare P/LP variants in NTRK or MMR deficiency may also occur, offering additional avenues for targeted agent use.[75] KRAS G12D pathogenic variants are uncommon in biliary tract cancers and targeted treatments are considered ESCAT I-C. The negative prognostic association is limited to intrahepatic cholangiocarcinomas.[76]

Most patients are diagnosed with advanced disease. In such cases, chemotherapy with cisplatin and gemcitabine, followed by secondary chemotherapy, remains the foundational treatment in the absence of targetable P/LP variants. Deficits in genes involved in the homologous recombination and DNA damage response have been found not to confer higher sensitivity to platinum agents and this testing is not indicated.[77] In adult patients with unresectable locally advanced or metastatic hepatocellular cholangiocarcinoma featuring IDH1 P/LP variants—identified through an FDA-approved test—ivosidenib is a viable FDA-approved treatment following 1 to 2 prior lines of systemic therapy for advanced disease.[78]

For patients harboring FGFR2 fusions or rearrangements, Phase II single-arm registrational trials of FGFR inhibitors have demonstrated an overall response rate between 23% and 42%, with a median progression-free survival spanning 7 to 9 months. FGFR inhibitors including pemigatinib and infigratinib show potential in this context. Similarly, there is observed efficacy in treating patients with BRAF V600E pathogenic variants using dabrafenib plus trametinib, as well as entrectinib for those with NTRK inhibitors. While HER2-directed therapies show less convincing efficacy in chemo-refractory patients, trastuzumab combined with pertuzumab is recommended by the NCCN as a subsequent-line therapy option for certain biliary tract cancers with disease progression. This recommendation stems from a multicenter, open-label, phase 2a study where nine out of 39 patients achieved a partial response (objective response rate of 23%), despite ten patients experiencing serious treatment-emergent adverse events.[79]

Colorectal Cancer

Gene expression profiling tests as a technique for colorectal cancer management and surveillance are considered **not medically necessary** for all indications.

For multianalyte assays used for screening and diagnosis (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Universal testing for all patients with newly diagnosed localized or metastatic colorectal cancer

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the colon or rectum
- The individual has not had prior MSI or dMMR testing

Localized colorectal cancer

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with localized (stage II-III) colorectal cancer when **BOTH** of the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the colon or rectum
- Includes **ANY** or **ALL** of the following, with no prior testing
    - MSI testing by PCR
    - BRAF V600E
    - KRAS
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)

See the Carelon Guidelines for Hereditary Cancer Testing for further details regarding indications for germline MMR testing.

Metastatic colorectal cancer

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with recurrent or metastatic colorectal cancer and may be performed on the primary tumor or a metastatic site when **ALL** the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the colon or rectum
- Assessment includes **ANY** or **ALL** of the following:
    - POLE
    - POLD P/LP variants
    - Extended RAS testing (KRAS and NRAS exons 2,3, and 4)
    - BRAF V600E
    - HER2 amplification testing
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)
- There has been no prior testing for these molecular aberrations

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

For multianalyte assays used for prognostication (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Rationale

Colorectal cancer (CRC) presents significant challenges, with 20% of patients diagnosed with metastatic CRC and 40% experiencing recurrence after initially successful treatment of localized disease.[80] Among localized CRC patients, about 15% exhibit deficiencies in DNA mismatch repair (MMR) proteins, with approximately one-quarter of these cases attributed to Lynch syndrome. Further, around 90% to 95% of CRC in Lynch syndrome patients exhibit microsatellite instability (MSI).[81, 82]

In the context of early-stage CRC, particularly stage II, MMR status is a crucial prognostic and predictive biomarker. Deficient MMR (dMMR) is linked to better prognostic outcomes but a reduced response to fluorouracil treatment.[83] Recent advancements highlight the efficacy of neoadjuvant immunotherapy in early stage dMMR CRC, which demonstrates high response rates and a favorable safety profile, reinforcing the imperative of dMMR testing in all newly diagnosed CRC cases.[84, 85]

In metastatic CRC, about 5% of tumors are MMR-deficient or MSI-high (MSI-H), making these tumors suitable candidates for immunotherapy.[80] Thus, it is essential to conduct MMR deficiency testing through immunohistochemistry or determine MSI-H status through polymerase chain reaction to screen for Lynch syndrome and refine therapeutic decision-making in both localized and metastatic CRC.

The standard of care in metastatic CRC has evolved since 2015 to include extended RAS testing.[86] Specific P/LP variants in RAS genes, particularly in exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) of KRAS and NRAS, serve as markers of resistance to epidermal growth factor receptor (EGFR)-targeting monoclonal antibodies such as cetuximab and panitumumab. Consequently, these treatments are recommended for patients with RAS wild-type tumors only.[87] The European Society for Medical Oncology (ESMO) guidelines address molecular testing for various biomarkers in colorectal cancer treatment.[61] In the ESMO guideline, note that HER2 testing is graded on the ESMO Scale of Clinical Actionability of Molecular Targets (ESCAT) at IIB and POLE testing is also ESCAT IIB. POLD1 P/LP variants are rare in colorectal cancer and routine testing is not recommended by ESMO, although guidelines from the National Comprehensive Cancer Network (NCCN) recommend POLE/POLD1 testing for recurrent or metastatic CRC patients.[88] While HER2-targeted therapies show promise, their activity is primarily observed in RAS and BRAF wild-type patients.[89] In an analysis of data from the CALGB/SWOG 80405 trial, HER2 expression was prognostic and predictive in CALGB/SWOG 80405, suggesting that HER2 tumor expression may inform treatment selection for patients with low HER2 favoring bevacizumab- versus cetuximab-based therapies.[90] Although NTRK gene fusions are rare, their prevalence is higher in MMR-deficient tumors, occurring in approximately 0.35% of CRC cases.

BRAF V600E pathogenic variants, present in approximately 5%-10% of metastatic CRC cases, contribute to continuous BRAF kinase activity and sustained MAPK pathway signaling. These P/LP variants correlate with specific demographic and tumor characteristics, often resulting in reduced response to standard chemotherapy.[91] In this context, the BEACON study demonstrated the efficacy of BRAF and MEK inhibitor combination therapy (encorafenib plus cetuximab) in improving survival outcomes compared to standard chemotherapy.[91]

While some studies suggest prognostic value in BRAF and KRAS testing for stage II-III localized CRC, the NCCN guidelines indicate insufficient data to support their routine use for estimating recurrence risk or informing adjuvant therapy decisions.[88]

The current ESCAT level for KRAS G12D testing in advanced colorectal cancer is Tier III. This classification indicates that its actionability is not yet fully established for routine clinical decision-making in this context. In a pooled analysis of the TRIBE trials, KRAS G12D pathogenic variants were present in 16% of patients, but no prognostic difference was evident between KRASG12D mut and other RAS mutant patients overall.[92]

Recent FDA approvals have further expanded therapeutic options in colorectal cancer. For example, tucatinib combined with trastuzumab has been approved for patients with unresectable, HER2-positive, RAS wild-type metastatic CRC, post-chemotherapy progression, as evidenced by the MOUNTAINEER trial.[93] In KRAS G12C mutated colorectal cancer, the FDA has approved use of sotarasib with panitumumab and also approved use of adagrasib with cetuximab for patients who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.[94, 95] The FDA also granted accelerated approval to encorafenib with cetuximab and mFOLFOX6 for patients with metastatic colorectal cancer with a BRAF V600E pathogenic variant.[96]

Endometrial Carcinoma

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven endometrial carcinoma
- The individual has not had prior MSI or dMMR testing

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with endometrial carcinoma and may be performed on the primary tumor or a metastatic site when **ALL** the following criteria are met:

- The individual has biopsy-proven endometrial carcinoma
- Assessment includes the following, as applicable:
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)
    - POLE gene testing (NGS)

    - P53 gene testing (NGS)
- There has been no prior testing for these molecular aberrations

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details. Additionally, for MLH1 germline testing for Lynch Syndrome, please refer to the Carelon Guidelines for Hereditary Cancer Testing.

Rationale

The standard approach to somatic genetic testing for individuals with endometrial carcinoma is focused on identifying both therapeutic targets and hereditary cancer risks. FDA approved companion diagnostics are used to select patients with deficient mismatch repair (dMMR) and microsatellite instability-high (MSI-H) solid tumors, respectively, for treatment with pembrolizumab. The initial approval was based on results from KEYNOTE-158, a multicenter, non-randomized, open-label, multi-cohort trial, assessing individuals with unresectable or metastatic MSI-H or dMMR endometrial carcinoma over two cohorts. Patients received pembrolizumab at a dosage of 200 mg intravenously every three weeks until the onset of unacceptable toxicity or documented disease progression. The trial reported an objective response rate of 48% with and a median progression-free survival of 13.1 months.

These findings demonstrated significant antitumor activity and improved survival outcomes for individuals with MSI-H/dMMR endometrial cancers receiving pembrolizumab.[97] Dostarlimab-gxly and durvalumab are other immune checkpoint inhibitors that now have FDA indications in treating dMMR endometrial carcinoma.

In the context of Lynch syndrome, the absence of immunohistochemical (IHC) nuclear expression of MLH1 can be attributed to either Lynch syndrome or methylation of the MLH1 promoter region, common in sporadic MSI carcinoma. IHC loss of nuclear expression in MHL1 and PMS2 should prompt further MLH1 methylation studies. Presence of MLH1 methylation typically indicates a sporadic tumor rather than a germline P/LP variant, potentially negating the need for further germline testing. Conversely, absence of MLH1 methylation suggests Lynch syndrome, necessitating germline testing for MLH1. The loss of nuclear expression of MSH2 and MSH6, MSH6 alone, or PMS2 alone is associated with a high probability of Lynch syndrome, suggesting a need for genetic counseling.[98]

Beyond MMR genes, somatic tumor testing may include analysis of other genes commonly mutated in endometrial cancer, such as PTEN, PIK3CA, TP53, POLE, and POLD1. Molecular subgroups, such as ultramutated DNA polymerase epsilon (POLE-mut) and p53 (p53abn) variants, have been recognized following their identification in the Cancer Genome Atlas (TCGA) study, correlating with favorable and poor prognoses, respectively.[99] Subsequent studies have investigated the relation between these variants and histologic features and their clinical utility. For instance, data from the PORTEC-1, PORTEC-2, and PORTEC-3 trials underscore the significance of molecular-risk subsets (POLE-mutated, dMMR, p53 abnormal, and no specific molecular profile) in guiding treatment decisions.[100, 101] The Gynecological Cancer InterGroup has outlined consensus recommendations for clinical research in endometrial carcinoma and has stressed that patient selection for targeted therapy should be based on validated biomarker assays and that the role of ctDNA as a predictive or prognostic biomarker remains under investigation.[102]

Ongoing trials, such as the PORTEC-4a randomized phase III study, are examining the impact of molecular-risk profiling-directed standard and individualized adjuvant treatment in high-intermediate-risk endometrial cancer. However, results are pending.[103] Earlier results from the PORTEC-3 trial indicated a beneficial recurrence-free survival rate over five years for patients with pathogenic p53 variants receiving chemotherapy versus radiotherapy alone (59% vs. 36%) in high-risk endometrial cancer.[104] Reflecting advancements in this area, routine testing for these molecular subgroups is now incorporated into nationally recognized guidelines.[105]

Melanoma

Prognostic testing in melanoma

Gene expression profiling of indeterminate melanocytic skin lesions or of established cutaneous, mucosal, or uveal melanoma for prognostication is considered **not medically necessary**.

For multianalyte assays used for screening and diagnosis (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Somatic tumor testing in advanced melanoma

Tissue-based somatic tumor testing for the **BRAF V600E** pathogenic variant by validated PCR or NGS methods for individuals with resectable or unresectable high-risk stage IIC, stage III or stage IV cutaneous melanoma is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven cutaneous malignant melanoma
- Prior testing has not been performed

Additional testing in high-risk stage II-IV cutaneous melanoma or mucosal melanoma

Tissue-based somatic tumor testing (50 genes or fewer) for individuals with resectable or unresectable high-risk stage IIC, stage III or stage IV melanoma or mucosal melanoma is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven malignant melanoma
- Prior testing has not been performed
- Testing includes **ANY** or **ALL** the following:
    - KIT variant testing
    - NRAS variant testing
    - Additional BRAF variant testing

Additional somatic tumor testing in metastatic uveal melanoma

Testing of individuals with **metastatic uveal melanoma** for **HLA-A*0201** is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven uveal melanoma and evidence of metastatic disease
- Prior testing for HLA-A*0201 has not been performed
- The individual is a candidate for treatment with tebentafusp

**Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.*

Rationale

Diagnosis of Indeterminate Melanocytic Lesions

Light microscopic evaluation by a trained pathologist is capable of providing an accurate diagnosis for the majority of melanocytic lesions. However, a small subset of these lesions resists appropriate classification using conventional light microscopy alone, complicating the prediction of clinical behavior and treatment recommendations.[106] Ancillary tests such as comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) have been developed to assist in diagnosing these ambiguous melanocytic proliferations. While sometimes employed, the correlation between chromosomal abnormalities and clinical outcomes remains unclear.[106]

Prognostic Classification of Localized Cutaneous Melanoma

Clinicopathologic features such as Breslow thickness, ulceration, and tumor-infiltrating lymphocytes are reliably associated with melanoma outcomes for localized disease, making pathologic prognostication quite robust.[107] ESMO clinical practice guidelines for cutaneous melanoma indicate that molecular testing for actionable P/LP variants should be considered in clinical stage IIB-IIC [V, C] but not for stage I or IIA disease [V, D].[108] In an international multicenter analysis of potential predictors of recurrence-free and melanoma specific survival after sentinel lymph node biopsy, 4071 patients were evaluated in a prediction model development cohort and 4822 in a validation cohort, and potential predictors evaluated included sex, age, presence of ulceration, primary tumor location, histological subtype, Breslow thickness, sentinel node status, number of sentinel nodes removed, maximum diameter of the largest sentinel node metastasis, and Dewar classification.[109] The resulting prediction model and nomogram did not include any molecular genetic information and accurately predicted patient-specific risk probabilities for 5-year recurrence-free and melanoma-specific survival, improving personalized risk stratification beyond the AJCC staging system.[110]

Use of gene expression profiling (GEP) for categorizing localized (stage I and II) cutaneous melanoma based on metastatic risk, has been explored to guide decisions such as sentinel lymph node biopsy and surveillance intensity. GEP tests typically classify the tumor into prognostic categories, such as class 1 vs. class 2, rather than providing specific survival predictions.[107] A meta-analysis of a 31-gene GEP test analyzing three studies plus data from an additional cohort of 211 patients reported recurrence-free and distant metastasis-free survival rates of 91.4% and 94.1% for Class 1A, and 43.6% and 55.5% for Class 2B patients.[111] However, the methodology of this analysis was criticized for lacking a pre-specified protocol and failing to adjust for confounders or assess bias comprehensively.[112] Clinical utility of GEP classifiers is still uncertain, and smaller absolute risk differences were found between the 31-gene tested cohort and unmatched cohorts.[113] These tests should be evaluated alongside traditional phenotypic models and simple outcome algorithms.[114] Of note, the NCCN guidelines for cutaneous melanoma[115] describes a risk classification and suggests systemic imaging based on the scheme. There are no references to support this general rubric or to illustrate the importance of any single risk bullet (such as GEP profiling) in implementing this algorithm. Meanwhile, further research is ongoing. For example, the NivoMela trial (NCT04309409) is enrolling with resected stage IIA-C and uses a prognostic gene expression signature to limit treatment to a subgroup of patients that is at a higher risk of relapse. Only patients with a positive gene expression score are randomized to treatment with either 12 months of nivolumab or observation, while patients with a negative score are only under clinical observation.[116] The role of ctDNA testing for measurable residual disease (MRD) is also under evaluation. The DETECTION Study (NCT04901988) is following 1050 patients with resected Stage IIB/IIC melanoma with regular ctDNA assessment. Patients positive for ctDNA are randomized to either continue (blinded) clinical follow-up and standard of care treatment if they develop metastatic disease, or (unblinded) treatment at the time of molecular recurrence with single agent nivolumab. This study addresses whether recurrence can be detected earlier with ctDNA monitoring than with standard clinical follow-up, and whether early treatment of molecular recurrence with immunotherapy results in a survival benefit.[116]

Prognostic Classification of Uveal Melanoma

Uveal melanoma carries a 30%-50% risk of metastasis within five years, mostly to the liver.[117] Metastatic risk has historically been predicted by tumor morphologic and pathologic features such as thickness, diameter, and location, among others.[118] Monosomy 3 and additional copies of 8q have been linked to poor survival.[117]

The 15-gene expression profile test DecisionDX-UM® predicts metastatic risk based on tumor biology and may aid in surveillance program decisions.[119] Another test by Impact Genetics Inc. assesses chromosomal changes and sequences certain genes.[118] However, no survival benefit has been documented for early detection of asymptomatic disease, leaving surveillance recommendations uncertain.[117] In the COOG2.1 prospective multicenter study of 1577 patients, the integrated 15-GEP/PRAME classifier was shown to be as a superior prognostic tool for metastatic risk in uveal melanoma (UM) compared to the 15-GEP alone. However, the 15-GEP is not a current standard of care.[120] While the integrated classifier may be seen as a tool to enhance prognostic precision, it does not directly inform treatment decisions (i.e. it is not a predictive biomarker) and there is currently no evidence that identifying high-risk patients using this tool leads to improved outcomes, particularly as effective adjuvant therapies for uveal melanoma are still lacking. These data are being used for adjuvant clinical trial stratification. Overall, decisions should consider the patient's emotional well-being, potential for treatment of minimal metastatic disease, and trial eligibility.[121] Surveillance decisions involve consideration of clinical variables such as tumor characteristics (size and location) in conjunction with personal preferences and genetic data.[118]

Somatic Tumor Testing for Resectable or Unresectable Stage III or Stage IV Melanoma

Many melanomas exhibit P/LP variants in MAPK pathway genes like BRAF, NRAS, or NF1, with BRAF pathogenic variants present in 40%-60% of cases.[122] More than 90% of BRAF P/LP variants are V600E, followed by V600K. BRAF status is crucial for predicting therapeutic response in advanced melanoma, and BRAF V600E testing is the standard in resectable or unresectable stage III or IV melanoma.[108, 123]

Other frequently mutated genes vary by melanoma subtype, with CDKN2A, NRAS, and TP53 common in cutaneous melanoma, and NRAS, NF1, and KIT common in acral melanoma.[123] The clinical utility of large panel NGS testing to ascertain TMB status to guide the choice between dual ICI therapy and singe agent ICI therapy is unknown. Prospective biomarker-driven research is needed to explore this further.[124]

Metastatic uveal melanoma testing for HLA-A*0201 assists in identifying patients for treatment with tebentafusp, which improved survival in trials.[125] NRAS P/LP variants correlate with poor prognosis, and certain therapies have shown activity in BRAF and NRAS-mutant melanomas.[126, 127] KIT P/LP variants, found in mucosal and acral melanoma subtypes, respond to specific inhibitors, though their exceptionality warrants only optional testing.[128]

Non-Small Cell Lung Cancer

Gene expression profiling tests as a technique for non-small cell lung cancer (NSCLC) cancer management and surveillance are considered **not medically necessary** for all indications.

For multianalyte assays used for screening and detection (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Localized (stage IB-IIIA) NSCLC

Tissue-based somatic testing is considered **medically necessary** to identify EGFR and/or ALK pathogenic variant in individuals with localized NSCLC when **BOTH** of the following criteria are met:

- Biopsy-proven, stage IB-IIIA NSCLC
- Test results will determine candidacy for treatment with targeted agents used per FDA label (or NCCN 2A)

Advanced NSCLC

Tissue-based NGS panel testing is considered **medically necessary** to identify P/LP variants in individuals with stage IIIB, IIIC, or IV (metastatic) NSCLC when **ALL** the following criteria are met:

- Biopsy-proven NSCLC
- The multigene NGS panel testing contains, at minimum*, testing of appropriate molecular aberrations (P/LP variant, rearrangements, fusions, or amplifications) in **ALL** the following genes: EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS, MET exon 14 skipping, NTRK, and RET
- The multigene NGS panel contains NRG1 for fusion analysis if use of zenocutuzumab-zbco therapy is being considered
- The individual has not had prior tissue-based NGS testing in the metastatic setting, unless **BOTH** of the following are met:
    - There is evidence of disease progression while on EGFR-targeted therapy
- Tissue biopsy of a progressing lesion is being used for additional testing

Notes:

**Testing may be more focused if other techniques (such as IHC or FISH) are simultaneously (or previously) used for specific genes listed in the criteria that are also not included on the multigene panel.*

Tumor-agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

For multianalyte assays used for prognostication (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Rationale

Metastatic non-small cell lung cancer (NSCLC) has traditionally been classified by histology and treated with cytotoxic chemotherapy. However, over the past decade, there has been substantial progress in understanding the disease's biology and its oncogenic driver P/LP variants. Modern NSCLC treatment is now characterized by molecularly defined subsets, which are actionable with targeted therapies and immune checkpoint inhibitors. It is estimated that 35%–50% of patients with advanced non-squamous NSCLC harbor a targetable alteration [129, 130], and selecting patients based on predictive biomarkers is associated with improved outcomes. ASCO guidelines show no role for tumor mutational burden (TMB) testing or other molecular testing other than PD-L1 immunohistochemistry testing regarding NSCLC patients who do not have actionable molecular aberrations.[131, 132]

Molecular testing for sensitizing EGFR P/LP variants, BRAF V600E, and rearrangements in ALK and ROS1 has long been the standard-of-care for patients with advanced NSCLC, as is testing for the EGFR T790M pathogenic variant upon resistance to first- or second-generation EGFR tyrosine kinase inhibitors.[133] A second wave of specific molecular alterations worthy of routine testing emerged including ERBB2 (HER2), KRAS, RET, MET, and NTRK genes.[133, 134] This expansion made multiplexed genetic sequencing panels preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, BRAF, and ROS1. Retrospective studies have indicated that timely reporting of NGS testing results is important to guide treatment in the first line setting.[135, 136] Multiple additional targeted therapies have been approved in the past 2 years

for treating metastatic NSCLC, including tepotinib for patients with MET exon 14 skipping alterations [137], repotrectinib for ROS1-positive NSCLC [138], encorafenib with binimetinib for BRAF V600E pathogenic variant -positive NSCLC [139], pralsetinib for RET fusion-positive NSCLC [140], and amivantamab-vmjw with carboplatin and pemetrexed for EGFR exon 20 insertion pathogenic variants [141], ensartinib for ALK-positive NSCLC, and zenocutuzumab-zbco for NSCLC with NRG1 gene fusions.[142]

Insertions in exon 20 are the third most common type of EGFR pathogenic variant, representing up to 12% of all EGFR-mutated NSCLC cases. While the Papillon study [143], utilized standard tissue biopsy and CLIA-certified lab testing, Guardant 360 liquid testing also supported its FDA PMA application. Thus, tissue testing remains a standard approach for exon 20 insertions and an acceptable method for selecting patients for amivantamab plus chemotherapy. The newly approved targeted agents are included in updated guidelines for oncogene-addicted metastatic NSCLC from ESMO [144] and the ASCO living guideline for stage IV NSCLC with driver alterations.

In contrast to metastatic non-squamous NSCLC, managing early-stage non-squamous NSCLC does not involve routine testing for oncogenic driver P/LP variants. However, patients with stage Ib to IIIA NSCLC considered for FDA-approved adjuvant therapy with either osimertinib (an oral targeted EGFR inhibitor) or alectinib (an oral targeted ALK inhibitor). For adjuvant use of osimertinib, patients should be tested for EGFR exon 19 deletions or L858R point pathogenic variants s, based on the ADAURA study, which showed significant improvement in disease-free survival.[145] More recent data indicate that adjuvant osimertinib for patients with resected stage Ib-IIIA NSCLC is associated with clinically significant improvements in overall survival.[146] In addition, the FDA approved alectinib for adjuvant treatment following tumor resection in patients with anaplastic lymphoma kinase (ALK)-positive NSCLC based on the randomized, open-label ALINA trial.[147] Eligible patients were required to have resectable Stage IB (tumors ≥ 4 cm) to IIIA NSCLC.

Testing for EGFR P/LP variants using tissue specimens can be performed before or during surgery. Preclinical and retrospective clinical data support hypothesis testing of biomarker-driven treatment strategies in earlier stages of NSCLC, with ongoing prospective clinical trials.[148] While neoadjuvant treatment targeting EGFR P/LP variants is being explored, it has not yet proven effective, with recent data showing major pathological response rates of 15%, which are below expected thresholds.[149, 150]

A specific subset of patients with pure squamous cell histology may benefit from molecular testing. ESMO recommends such testing only in exceptional cases, such as patients under 50, never smokers, or those who quit smoking more than 15 years ago.[144]

Ovarian Cancer (Epithelial)

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing to determine HRD status by testing for P/LP variants of BRCA1, BRCA2 with concomitant evaluation for genomic instability is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven locally advanced (stage III), metastatic (stage IV), or recurrent epithelial ovarian cancer
- The individual has not had prior testing that establishes the presence of actionable germline or somatic P/LP variants in BRCA1 or BRCA2 genes or eligibility for PARP-inhibitor treatment based on HRD status
- The individual is a candidate for treatment with a PARP inhibitor per FDA label (or NCCN 2A)

Germline testing for P/LP variants is considered **medically necessary** for all individuals with epithelial ovarian carcinoma. *See Hereditary Cancer Testing guideline for further details.*

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

The approval of PARP inhibitors marked a significant advancement in the treatment of ovarian cancer. Initially, in 2014, the FDA approved olaparib for patients with germline mBRCA-associated recurrent ovarian cancer. Nevertheless, recent clinical trials have shown that mBRCA's role as a predictive biomarker is less crucial than previously thought.[151] These trials indicated that PARP inhibitor efficacy extends to patients without germline mBRCA P/LP variants, with alternative predictors like somatic BRCA P/LP variants and homologous recombination deficiency (HRD) being significant. In 2016, the FDA's approval of rucaparib expanded PARP inhibitor therapy eligibility to include patients with ovarian cancer linked to somatic BRCA P/LP

variants. The ARIEL3 trial demonstrated that rucaparib significantly extends progression-free survival in patients with platinum-sensitive ovarian cancer who responded to platinum-based chemotherapy.[152] The trial also introduced the prospective validation of a tumor-based NGS HRD test assay, highlighting that rucaparib benefits were not exclusively driven by patients with BRCA-mutant tumors.[153] In April 2018, the FDA approved rucaparib alongside a diagnostic test for simultaneously determining BRCA and HRD status in tumor samples.

ESGO-ESMO-ESP guidelines for ovarian cancer emphasize tumor NGS testing for patients with high grade ovarian carcinoma combined with evaluating HRD status using clinically validated genomic instability tests.[61, 154] ASCO guidelines also recommend testing for those with progressive disease on neoadjuvant chemotherapy if they have not already been tested.[155] The Society of Gynecologic Oncology (SGO) notes that one acceptable approach to testing is to pursue somatic testing at the time of diagnosis for patients whose germline testing was negative for actionable germline findings, while simultaneous germline and somatic testing is also considered acceptable.[156] Although detecting P/LP variants in non-BRCA homologous recombination genes, such as ATM, BARD1, BRIP1, among others, is not compulsory, these genes are often part of extensive panels in HRD tests.

There are ongoing developments in test methodologies, including targeted gene capture assays for calculating a genome-wide loss of heterozygosity (LOH) score, particularly for high-grade non-clear cell ovarian carcinoma. These assays have rarely shown strong predictive correlations with treatment outcomes.[157] The Geneva test, which utilizes the Oncoscan FFPE Assay Kit alongside Large-scale State Transitions (LST) counts, is promising but not yet FDA-approved.[158] Recent data regarding assays for genomic instability assessment (such as CytoSNP, AmoyDX, Illumina TSO500 HRD, OncoScan, NOGGO GISv1, and QIAseq HRD panel) not only show a high concordance with each other but also in correlation with Myriad myChoice. Thus, almost all of these assays are promising in regard to being able to effectively assess HRD-associated genomic instability in the clinical setting.[159]

The FDA's accelerated approval of mirvetuximab soravtansine-gynx on November of 2022 (and full approval in March of 2024) for folate receptor alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer further expanded treatment options; however, FRα testing is outside the scope of these guidelines, due to it being an immunohistochemical rather than a genomic test.[160]

Pancreatic Adenocarcinoma

Germline testing for P/LP variants is considered **medically necessary** for all individuals with pancreatic adenocarcinoma. *See Hereditary Cancer Testing guideline for further details.*

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven pancreatic adenocarcinoma
- The individual has not had prior MSI or dMMR testing

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven locally advanced (stage III), metastatic (stage IV), or recurrent pancreatic adenocarcinoma
- The NGS panel includes BRCA1, BRCA2, PALB2, KRAS, and NRG1 as applicable
- The individual has not had prior tissue-based NGS testing in the locally advanced, metastatic, or recurrent setting

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Up to 10% of individuals diagnosed with pancreatic adenocarcinoma have a pathogenic germline alteration. Those with BRCA1 or BRCA2 P/LP variants, or microsatellite instability (MSI) resulting from germline or somatic P/LP variants in DNA

mismatch repair (MMR) genes, may benefit particularly from platinum-based therapies or PARP inhibitors.[161] Consequently, it is recommended that individuals with newly diagnosed pancreatic cancer, irrespective of the stage, undergo multidisciplinary evaluation and management, along with germline testing and integrated supportive care.[162]

The potential for PARP inhibition as targeted therapy in BRCA-mutated pancreatic cancer was initially supported by the 2019 POLO trial. This study randomized 154 patients with metastatic pancreatic adenocarcinoma and germline BRCA P/LP variants to maintenance olaparib versus a placebo following 16 weeks of first-line platinum-based chemotherapy.[163] Results revealed a statistically significant improvement in progression-free survival for olaparib (median 7.4 vs. 3.8 months; hazard ratio 0.53). However, more recent data demonstrate no significant improvements in overall survival, nor in quality of life.[164] Due to these outcomes and certain concerns regarding the POLO trial's design[165], enthusiasm for using olaparib as a maintenance therapy has waned.

Current clinical practice guidelines, including those from the European Society for Medical Oncology (ESMO and the National Comprehensive Cancer Network (NCCN, recommend somatic tumor testing for BRCA and KRAS pathogenic variants, as well as NTRK fusions, particularly in the context of advanced pancreatic cancer. These guidelines highlight the significance of such testing in guiding treatment decisions. In addition, the FDA granted accelerated approval to zenocutuzumab-zbco (Bizengri) for adults with advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy. Efficacy was evaluated in the eNRGy study, a multicenter, open-label, multicohort trial that enrolled 30 adults with advanced or metastatic NRG1 fusion-positive pancreatic adenocarcinoma who had disease progression following standard of care treatment.[142]

Prostate Cancer

Localized prostate cancer

Gene expression profiling and genomic biomarker tests as a technique for prostate cancer management and surveillance are considered **not medically necessary** for all indications.

For multianalyte assays used for screening and detection (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Metastatic prostate cancer

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the prostate
- The individual has not had prior MSI or dMMR testing

Tissue-based NGS panel testing is considered **medically necessary** to identify P/LP variants in individuals with metastatic prostate cancer when **ALL** the following criteria are met:

- The individual has biopsy-proven castrate sensitive metastatic adenocarcinoma of the prostate (mCSPC) with high burden of disease* or castrate resistant metastatic adenocarcinoma of the prostate (mCRPC)
- The individual is a current or likely future candidate for **ONE** of the following therapies:
    - PARP inhibitor (olaparib, rucaparib, or another PARP inhibitor FDA approved or per NCCN 2A use in this setting)
    - PD-1 inhibitor (pembrolizumab or another checkpoint inhibitor FDA approved or per NCCN 2A for use in this setting)
- The NGS panel includes BRCA2, BRCA1, and may also include other genes encoding molecules involved in homologous recombination DNA damage repair (DDR), such as ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L
- The individual has not had prior tissue-based NGS testing in the metastatic setting

Germline testing for P/LP variants is considered **medically necessary** for all individuals with metastatic prostate adenocarcinoma. *See Hereditary Cancer Testing guideline for further details.*

**High burden of disease is defined per the STAMPEDE trial as the presence of visceral metastases or 4 or more bone metastases.*

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.

Rationale

Localized Prostate Cancer

Prostate cancer is usually suspected on the basis of a digital rectal exam (DRE) and/or an elevated prostate-specific antigen (PSA) test. Definitive diagnosis depends on histopathologic verification. Abnormal DRE is an indication for biopsy, but as an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound.[166] The histologic grading system for prostate cancer drives nearly all management decisions in localized prostate cancer, with Gleason score 6 being nearly universally indolent up to Gleason score 10 which is almost certainly lethal in the long run.[167] The decision to proceed with a further staging workup is guided by which treatment options are available, taking into account the patient's preference and comorbidity. There are currently 10 or more pretreatment risk stratification tools for use in prostate cancer care, all of which use clinical and/or imaging factors without incorporating somatic genetic test information. The most commonly used are the D'Amico-derived systems (NCCN, NICE, GUROC, EAU, AUA) which involve categorization into 5 ordinal categories of risk: very low, low, intermediate, high, or very high. The Memorial Sloan Kettering nomogram, Cancer of the Prostate Risk score, and the Cambridge Prognostic Group are other systems and these perform slightly better in predicting prostate cancer death.[168] Prognostic approaches are sometimes explored using other, surrogate endpoints such as time to radiographic progression assessed by blinded independent central review, development of distant metastases, risk of adverse pathology during active surveillance, and others. Ultimately, management decisions for localized prostate cancer are typically made after appropriate options have been discussed with a multidisciplinary team (including urologists, radiation oncologists, medical oncologists, pathologists, and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered in shared decision-making with the patient.

Numerous molecular biomarkers, particularly tissue-based genomic biomarker tests, have been developed to improve risk stratification and patient management. One of the unique challenges for use of these biomarkers is the complex spatial heterogeneity of prostate cancer.[169] While few of these genomic panels have undergone extensive validation, there are several commercially available tests (Oncotype DX prostate, Prolaris, Decipher, and ProMark) that have been shown in retrospective analyses to provide additional information beyond standard clinical models in prognostication or patient selection for therapy.[170, 171] Given the absence of prospective clinical trial data, NCCN and ASCO guidelines do not recommend routine ordering of any molecular tests to guide decision-making in localized prostate cancer regarding the role of active surveillance or the use of post-prostatectomy adjuvant versus salvage radiation therapy. The ASCO guideline on molecular biomarkers in localized prostate cancer emphasizes that there is a paucity of prospective studies assessing the short and long-term outcomes of patients when these biomarkers are integrated into clinical decision-making.[170] These guidelines acknowledge that, based on lower level evidence and expert consensus, some specific molecular profiling biomarkers may be considered in specific situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. The most common settings where such testing is sometimes considered on that basis is with low or favorable intermediate risk localized prostate cancer in men with life expectancy over 10 years. One limitation of the data regarding use of these tumor tissue-based genomic biomarker tests for active surveillance is that the tests were all developed in cohorts of patients who had already undergone primary treatment and were higher clinical risk than those typically considered for active surveillance.[172] Overall, it remains uncertain what prognostic endpoints should be prioritized and what magnitude of association with those prognostic endpoints are important. Nevertheless, in recent years, there has been more than 10-fold increase in tissue-based genomic biomarker testing related to prostate cancer with striking regional variability.[173] Practice patterns also vary widely within regions.[174] Issues surrounding clinician education and awareness of these assays (also referred to as "relationships with industry") may have contributed to this rising pattern of use.[172] The relative accuracy of these biomarker tests compared to other standard tests is unknown.[174] Also, while prospective trials are ongoing, the impact on key clinical outcomes (survival, quality of life, or need for treatment) attributable to use any of these tissue-based genomic biomarker tests (in any specific setting) is also uncertain.[172]

Metastatic Prostate Cancer

Patients with metastatic prostate cancer have multiple treatment options with varied mechanisms of action beyond androgen deprivation therapy alone. Such options include androgen-receptor-targeted agents, taxane-based chemotherapies, bone-targeted radiopharmaceutical radium-223, and biomarker-driven therapy with the immune-checkpoint inhibitor pembrolizumab (for those with mismatch-repair deficiency (dMMR) or microsatellite instability (MSI)) and the PARP inhibitors olaparib and rucaparib (for those with homologous-recombination gene deficiency). Olaparib was approved by the FDA on May 31, 2023, for adult patients with deleterious or suspected deleterious BRCA-mutated metastatic castration-resistant prostate cancer

(mCRPC), as determined by an FDA-approved companion diagnostic test. Such tests include BRCAnalysis CDX, Foundation One CDX, and Foundation One Liquid CDX. This was based on data from the PROpel trial, which showed that significant clinical benefit for Olaparib + abiraterone was restricted to the subset of patients with BRCA P/LP variants.[175] Practice patterns vary in terms of the sequencing of therapies for both castrate-sensitive and castrate-resistant patients, and also variation in responses between patients with any given therapy.

The prevalence of recurrent genomic alternations varies across various prostate cancer clinical scenarios and also by published cohort. Common aberrations are typically not actionable and involve the androgen receptor (observed in >50% of cases); TP53 (in >40% of cases); genes encoding components of the PI3K pathway, such as PTEN (in 45% of cases); loss of RB1, which encodes the tumor suppressor Rb (in ~20% of cases); and others.[176] ESCAT level I molecular aberrations are those that the match of an alteration and a drug has been validated in clinical trials and should drive treatment decision in daily practice.[16] In this category, BRCA2, BRCA1, ATM and other genes encoding molecules involved in homologous recombination DNA damage repair ([DDR], such as PALB2, FANCA, RAD51D, CHEK2, and CDK12) are found in 20%-25% of cases and may prompt consideration of PARP inhibitors. Moreover, roughly 3%–5% of prostate cancers harbor evidence of DNA mismatch-repair deficiency (dMMR), hyper-mutation or increased microsatellite instability which may prompt consideration of PD-1 inhibitors.[176] The ESMO Precision Medicine working group recommends multigene NGS panel testing in metastatic prostate cancer to assess for ESCAT level 1 alterations.[16] Commercially available prostate-cancer specific NGS panels include 11-14 genes.[177] A metastatic biopsy for histologic and molecular evaluation is the standard of care and preferred over ctDNA testing, which can produce false positive biomarker signals due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP). It is noteworthy that MSI-H status and HRD are generally mutually exclusive phenomena across cancer types, but may rarely co-occur, especially in prostate cancer. Most BRCA P/LP variants coexisting with microsatellite instability are likely bystander events that may not result in sensitivity to poly (ADP-ribose) polymerase inhibitors.[178]

The pivotal clinical trials of PARP inhibitors in metastatic castrate resistant prostate cancer are the phase III Profound trial (for olaparib) and the phase II Triton2 trial (for rucaparib). In the Profound trial[179, 180], there was a randomization to olaparib versus enzalutamide or abiraterone for patients who had either BRCA1, BRCA2, or ATM P/LP variants (cohort A) or alterations in any of 12 other HRD genes (cohort B). The statistically significant benefit in progression free survival (7.4 months vs 3.6 months, HR 0.34) and overall survival (19.1 vs 14.7 months, HR 0.69) was limited to the cohort A patients. The phase II TRITON2 study of rucaparib included patients with mCRPC and deleterious BRCA or non-BRCA DNA damage-repair gene alterations treated after 1-2 lines of next-generation androgen-receptor directed therapy and 1 prior taxane-based regimen. In the BRCA mutated patients, the overall response rate was 43.5%[181], and for those with non-BRCA DNA damage-repair alterations the responses were much lower for PALB2, FANCA, BRIP1 and RAD51B and non-existent for ATM, CDK12, and CHEK2.[182] Subsequent studies include TRITON3, which showed that testing for BRCA P/LP variants and treating castrate-resistant patients who had progressed on a second-generation androgen receptor pathway inhibitor (ARPI) have median imaging-based PFS improvements of slightly less than 5 months, supporting the value of BRCA testing in castrate-resistant prostate cancer.[183] The ongoing phase III MAGNITUDE trial has thus far shown improved radiographic progression-free survival in patients with BRCA 1/2-altered mCRPC when treated with niraparib plus abiraterone acetate with prednisone.[184]

Sarcoma (including soft tissue sarcoma, bone sarcoma, gastrointestinal stromal tumor, uterine sarcoma)

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual has biopsy or resection-proven sarcoma
- The individual has not had prior MSI or dMMR testing

Targeted (i.e., 50 or fewer genes) tissue-based somatic tumor testing by PCR or NGS* is considered **medically necessary** for individuals when **ANY** of the following criteria are met:

- The individual has biopsy or resection proven sarcoma **or** a soft tissue neoplasm where molecular testing will establish the diagnosis
- The individual is a potential candidate for an FDA-approved targeted therapy or ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) level I gene alteration associated with drug therapy
- The individual is a candidate for **ONE or more** of the following therapies:
    - FDA-approved kinase inhibitor (entrectinib, larotrectinib) approved for use with *NTRK1, NTRK2*, and *NTRK3* fusions without a known acquired resistance P/LP variant

  - FDA-approved kinase inhibitor (selpercatinib) for adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options
  - FDA-approved kinase inhibitor (avapritinib) with *PDGFRA (D842V)* pathogenic variants for GIST
- The individual has not had prior testing for the same indication

SARCOMA SPECIFIC TESTING: Whole blood

SYNOVIAL SARCOMA: Whole blood DNA HLA-A locus sequencing for eligible alleles: HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles and exclusion alleles: HLA-A*02:05 and its P-group alleles in adults with unresectable or metastatic synovial sarcoma is considered **medically necessary** when **ALL** the following criteria are met:

- The individual is a candidate for FDA-approved autologous T-cell immunotherapy (afamitresgene autoleucel) indicated for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy

AND

- The tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices

Table 1 lists genomic alterations recognized as either diagnostic, level 1 ESCAT changes associated with therapy (ESMO Scale for Clinical Actionability of molecular Targets), or Level 2A tests recommended in NCCN sarcoma guidelines. This list is a representative sample of some of the most common genomic alterations in sarcomas for which somatic molecular testing is medically necessary for diagnosis and/or treatment. Diagnostic targeted molecular or NGS panel testing for specific sarcoma types is listed below. The list is not exhaustive, and all listed genes are not required to be included in an NGS test panel.

Table 1

Specific Sarcoma Types	Gene(s)
Sarcoma, not otherwise specified	
Sarcoma, not otherwise specified	NTRK1,2,3, RET, FGFR1/2/3, BRAF-V600E
Sarcoma subtypes	
Alveolar rhabdomyosarcoma	FOX01, FOX04, PAX3, PAX7, AFX
Alveolar soft parts sarcoma	ASPSCR1, TFE3
Chondrosarcoma	IDH1, IDH2
Clear cell sarcoma	ATF1, CREB1, EWSR1
Congenital/infantile fibrosarcoma	ETV6, NTRK3
Dedifferentiated liposarcoma	CDK4, GLI1, HMGA2, MDM2, SAS, TSPAN31
Dermatofibrosarcoma protuberans (DFSP)	COL1A1, PDGFB
Desmoplastic small round cell tumor (DSRCT)	EWSR1, WT1
Embryonal rhabdomyosarcoma	MYOD1, BCOR, FBXW7, FGFR4, HRAS, KRAS, NF1, NRAS, PIK3CA, TP53, DICER1
Epithelioid sarcoma	INI1/SMARCB1

Specific Sarcoma Types	Gene(s)
Extraskeletal myxoid chondrosarcoma	EWSR1, NR3A3, TAF15, TCF12, TFG
Ewing sarcoma/peripheral neuroectodermal tumor (ES/PNET)	ERG, ETV1, ETV4, EWSR1, FEV, FLI1, FUS, PATZ1, ZSG
Gastrointestinal stromal tumor (GIST)	KIT, PDGFRA, SDHB, BRAF, NF1, FGFR1, NTRK1, NTRK2, NTRK3, SDHB
Giant cell tumor of bone	H3F3A
Low grade fibromyxoid sarcoma	CREB3L1, CREB3L2, FUS
Leiomyosarcoma: see uterine sarcoma	Leiomyosarcoma: see uterine sarcoma
Malignant peripheral nerve sheath tumor (MPNST)	CDKN2A, EED, NF1, SUZ12
Mesenchymal chondrosarcoma	HEY1, NCOA2
Myxoid/round cell liposarcoma	DDIT3, EWSR1, FUS
NTRK-rearranged spindle cell neoplasm	NTRK1, NTRK2, NTRK3
Osteosarcoma	MDM2 amplification with differential of parosteal osteosarcoma
Round cell sarcoma	BCOR, CCNB3, CIC, DUX4
Synovia sarcoma	SS18, SSX1, SSX2, SSX4
Uterine sarcoma	NTRK1, NTRK2, NTRK3, PLAG1, ATRX, BRCA2, BAP1, PTEN, RB1, TP53, BRD8, EPC1, EPC2, EZHIP, JAZF1, MBTD1, MEAF6, PHF1, SUZ12, BCOR, NUTM2A, NUTM2B, YWHAE, ZC3H7B, SMARCA4, ESR1, GREB1, NC0A1, NCOA2, NCOA3, CDK4, CDK2A, CDKN2C, DICER1, FGFR2, KMT2C, MDM2, MYBL1, TERT, FAM22, DAXX, PDGFRB
Well-differentiated liposarcoma/atypical lipomatous tumor	CDK4, GLI1, HMGA2, MDM2, SAS, TSPAN31
Other soft tissue neoplasms	
Angiomatoid fibrous histiocytoma	ATF1, CREB1, EWSR1, FUS
Chordoma	INI1/SMARCB1
Desmoid fibromatosis (DF)	CTNNB1, APC
Epithelioid hemangioendothelioma	CAMTA1, TFE3, WWTR1, YAP1
Extrarenal rhabdoid tumor	SMARCB1
Inflammatory myofibroblastic tumor	ALK, ATIC, CARS1, CLTC, ETV6, NTRK3, RANBP2, ROS1, TFG, TPM3, TPM4, IGFBP5, RANBP2, RRBP1, THBS1, TIMP3
Perivascular epithelioid cell neoplasm (PEComa)	TSC1, TSC2, TFE3, RAD51B, HTR4, ST3GAL1
Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumor	CSF1
Solitary fibrous tumor	NAB2, STAT6

Notes:

Tumor agnostic genetic testing indications may also apply depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would

apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the *Tissue-Agnostic Testing* guideline for details.

Gene expression profiling tests as a technique for sarcoma management and surveillance are considered **not medically necessary** for all indications.

For multianalyte assays used for screening and diagnosis (often combined with algorithmic analyses), see the Carelon Guidelines for *Predictive and Prognostic Polygenic Testing*.

Rationale

Somatic genetic testing has become a fundamental component in the diagnosis of sarcomas, a heterogeneous group of malignancies arising from mesenchymal tissues. Traditional diagnostic methods often face challenges due to the overlap in histological and immunophenotypic characteristics of these tumors. These challenges can be effectively addressed by analyzing tumor-specific P/LP variants, gene fusions, or rearrangements. Such analyses play a crucial role in enhancing diagnostic accuracy and can lead to the reclassification of sarcomas in a significant number of cases.[185] Furthermore, genetic alterations with prognostic or therapeutic implications are increasingly utilized by multidisciplinary teams in specialized sarcoma centers to guide management decisions.[186]

Despite its potential, somatic genetic testing does present technical challenges. Many sarcomas do not exhibit pathognomonic genetic alterations, and issues such as low tumor purity or heterogeneity within samples may result in false-negative outcomes. Therefore, it is essential to integrate somatic genomic data with histopathology, immunohistochemistry, cytogenetics, and clinical findings to develop a comprehensive diagnostic perspective.[185]

The expansion of the ESMO Precision Medicine Working Group's guidelines in 2024 includes sarcomas with ESCAT Tier 1 molecular targets for next-generation sequencing, reflecting a move toward more personalized medicine approaches.[61] Tumor-agnostic biomarkers such as *NTRK* fusions and *BRAF-V600E* pathogenic variants are acceptable for use in sarcomas, thereby broadening the scope of molecular testing. Specifically, for advanced gastrointestinal stromal tumors [61], evaluating *KIT* and *PDGFRA* genes is recommended due to their significant diagnostic and therapeutic implications.[187] Additionally, specific gene alterations such as *ALK* in inflammatory myofibroblastic tumors and *INI1/SMARCB1* in epithelioid sarcoma support individualized patient management.[186] Molecular testing is particularly beneficial when the pathologic diagnosis remains uncertain or when the sarcoma exhibits a specific molecular alteration.[59] The NCCN endorses molecular genetic testing as a valuable ancillary technology in diagnosing and treating soft tissue sarcoma, bone sarcoma, gastrointestinal stromal tumor, and uterine sarcomas.[188-191] Genetic alterations in relevant genes within various soft tissue tumors have an evidence level of 2A.

Multiple tumor-agnostic biomarkers, including *NTRK1,2,3* fusions, *RET* and *FGFR1/2/3* fusions or P/LP variants, *BRAF-V600E* pathogenic variants, MSI-H, and high tumor mutation burden (TMB-H) are validated for use in sarcomas without specific type designation. The ESMO guidelines recommend performing multigene NGS to evaluate fusions in advanced cancers, particularly where tumor-agnostic therapies are applicable.[61]

The efficacy of somatic genetic testing is further supported by retrospective studies, such as those conducted by Fujii, which highlight the utility of comprehensive genomic profiling in advanced gastrointestinal stromal tumors.[192] The classification and diversity of sarcomas, as emphasized in WHO guidelines, underscore the vital necessity of integrating histopathologic and molecular features for accurate diagnosis. Additionally, the challenges associated with conducting clinical studies on ultra-rare sarcomas underscore the necessity for innovative research methods and collaboration across regulatory and industry bodies.[193]

Finally, there is growing interest in the potential role of epigenetic biomarkers in sarcoma. A study by Brockman et al. examined the epigenetic profiles of CpG islands in types such as MPNST, osteosarcoma, rhabdomyosarcoma, and synovial sarcoma, identifying differential methylation among these entities.[194] Future research is required to assess the clinical utility of CpG island methylation concerning tumor progression, metastatic potential, and the prognostic and predictive capabilities of molecular signatures. Current studies indicate no clinical utility for CpG methylation markers.

Thyroid Cancer

Testing of indeterminate thyroid nodules (ITN)

Use of next-generation gene expression classifier testing from fine needle aspirate sampling of a thyroid nodule is considered **medically necessary** when **ALL** the following criteria are met:

- There has been no prior testing of the same thyroid nodule
- Initial cytopathology is reported as **ANY** of the following (Bethesda III or IV) categories:

  - Atypia of undetermined significance (AUS)
  - Follicular neoplasm (FN)
- The ITN is ≤4 cm
- **ONE** of the following gene expression classifiers may be used when performed as a stand-alone classifier test:
  - ThyGeNEXT/ThyraMIR multiplatform test
  - ThyroSeq Genomic Classifier
  - Afirma GSC

Somatic genetic testing of thyroid malignancy

Tissue-based somatic tumor testing (50 genes or fewer) is considered **medically necessary** for individuals with advanced thyroid carcinoma that is not amenable to radioactive iodine therapy when the following criteria* are met:

- The individual has biopsy proven unresectable, locally advanced, recurrent, or metastatic thyroid carcinoma or anaplastic thyroid carcinoma (any stage)
- The testing includes assessment for P/LP variants of BRAF V600E and RET
- The individual is considered a potential candidate for FDA-approved oral targeted therapy based on the results of this testing

**See additional guidelines concerning tissue-agnostic somatic testing or hereditary cancer risk testing depending on the clinical scenario.*

Rationale

Molecular Testing of Indeterminate Thyroid Nodules

Thyroid nodules are prevalent in the general population, with 4%-7% having palpable nodules and up to 30% detectable through ultrasound.[195] Indeterminate thyroid nodules (ITNs) present a clinical challenge, as they are frequently discovered but typically benign, often not necessitating treatment. The care goal is to balance reducing overtreatment with identifying and treating nodules that pose a threat due to potential malignancy. Most thyroid cancer patients have a low recurrence risk (<5%), and even lower cancer-related mortality risk.[196] Consequently, recent studies have investigated treatment de-escalation, including active surveillance.[197]

The current standard for evaluating a thyroid nodule encompasses fine-needle aspiration for cytopathology. The American Thyroid Association (ATA) updated its ITN guidelines in 2015, recommending surgery for benign nodules over four centimeters, exhibiting local compressive symptoms, or those clinically suspicious.[198] For suspicious nodules, the 2023 Bethesda System for Reporting Thyroid Cytopathology 3rd edition is recommended by the ATA.[199] This system includes six classifications: I)Nondiagnostic; II) Benign; III) Atypia of undetermined significance (AUS); IV) Follicular neoplasm (FN); V) Suspicious for malignancy (SUSP); and VI Malignant.[199] Molecular testing a adjunct aims to refine risk stratification , particularly for Bethesda III and IV nodules, which have malignancy rates of 6%-18% and 10%-40%, respectively.[200]

Significant advancements include third-generation DNA and RNA sequencing tests like ThyroSeq v3 and machine learning-based classifiers like Afirma GSC. These tests enhance classification by detecting genomic alterations.[201] Additionally, a multiplatform test combines a mutation panel (ThyGenX) with a microRNA risk classifier (ThyraMIR) for high negative and positive predictive values in ITNs.[202, 203] However, molecular testing is viewed as an adjunct, and no single test has been universally accepted for clinical utility across all indeterminate cases.[204] A 2023 clinical practice guideline from the European Thyroid Association provides a detailed overview of the standard care for thyroid nodule management. It underscores the importance of molecular testing, particularly for Bethesda III and IV nodules.[205] In parallel, the clinical utility and risk-based management approach for indeterminate thyroid nodules, especially in relation to molecular testing for Bethesda III/IV categories, are highlighted in a Lancet review by Chen et al.[206]

Various contemporary studies, including a large, blinded, multicenter study of ThyroSeq v3, have evaluated the efficacy of these tests. The study found that ThyroSeq v3 did not reach the ATA threshold for a "rule-in" test due to its low positive predictive value (PPV). However, it demonstrated significant value as a "rule-out" test, with a high negative predictive value (NPV) of 97% when cancer prevalence was 28%.[207] A systematic review and meta-analysis of gene expression classifier

studies indicated that the published validation cohorts were not representative of the populations where these tests are applied. This discrepancy, particularly the variations in cancer prevalence rates, affects the test's negative predictive value.[208]

Overall, several molecular classifiers show analytical and clinical validity in evaluating indeterminate thyroid nodules (ITNs). However, these findings are often limited by diagnostic review bias, verification bias, and study design limitations.[209] Some approaches involve combining a molecular classifier with additional somatic testing to identify molecular variants and fusions.[210] These bundled testing methodologies have not yet established clinical utility, as their net clinical benefit requires comprehensive evaluation.[211] The prevalence of thyroid cancer in these nodules varies significantly across studies and sites.[208, 212] Thus, clinicians need to be aware of their local cancer prevalence when applying these test results. Additionally, careful consideration is required when using these tests, especially when surgery is indicated based on cytology, nodule size [213-216], sonographic pattern[217], or if surgery is contraindicated for various reasons.[212]

Special attention is given to ITNs with Hürthle cells, which are thyroid follicular-derived epithelial cells with oncocytic cytology. Accurate classification of these nodules is challenging via fine-needle aspiration. Third-generation molecular classifiers have been explored for this subset; however, patients with advanced oncocytomas of the thyroid generally have a poor prognosis, whereas those with minimally invasive disease present with a favorable prognosis.[218] Most of these lesions are low-risk or lack molecular alterations and are typically benign on follow-up. Unfortunately, no singular molecular alteration distinctly defines cytologically indeterminate Hürthle cell lesions, and current molecular testing does not definitively guide conservative management.[219] Efforts continue to improve the classification accuracy of these nodules[220], yet the reliability of the current molecular tests remains insufficient for informing surgical management.

Unresectable, Advanced, and Anaplastic Thyroid Cancer

The ESMO recommendations for NGS testing for patients with advanced thyroid cancers are fasted on RET aberrations for medullary thyroid cancer (which occur in over 60% of cases) and BRAF V600E pathogenic variants which occur in 10%-15% of anaplastic thyroid cancers [61] and for which specific treatment algorithms have emerged.[221] For advanced anaplastic thyroid cancer, regardless of stage, the NCCN recommends molecular testing due to its aggressive progression.[222] Strong genotype–phenotype associations exist with specific RET pathogenic variants, which can help predict the clinical aggressiveness of medullary thyroid cancer.[223] Regarding treatment of advanced or metastatic medullary thyroid cancer (MTC), the FDA granted traditional approval in September 2024 to selpercatinib for adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET pathogenic variant based on the LIBRETTO-531 study.[224] NTRK gene fusions, present in approximately 1.9% of thyroid carcinoma cases, respond favorably to NTRK inhibitors.[225]

Unknown Primary Site Cancer

Gene expression profiling and somatic genetic testing for individuals to predict the site of tumor origin (i.e., non-agnostic tissue testing) of cancer of unknown primary are considered **not medically necessary**.

For multianalyte assays used for prognostication (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

***Note**: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue-Agnostic Testing guideline for details.*

Rationale

Cancer of unknown primary (CUP), also known as occult primary cancers, refers to a heterogeneous group of cancers where, even after a comprehensive array of clinic, laboratory, pathology, and imaging investigations, the tissue of origin remains unidentified. Due to advances in immunohistochemistry and modern imaging techniques, the incidence of CUP has decreased significantly from approximately 3%–5% in the 1990s to 1%–2% currently.[226]

CUP is categorized into four histological types: adenocarcinoma of good-to-moderate differentiation (50%), poorly undifferentiated adenocarcinomas (30%), squamous cell carcinoma (15%), and undifferentiated neoplasms (5%).[227] Most patients present with disseminated and incurable disease, often affecting the liver and lungs. Patients with nodal, pleural, or peritoneal disease generally experience longer survival (14 to 16 months) compared to those with visceral metastases (6 to 9 months).[228] Rare presentations, such as bone-predominant or lymph node-only CUP, exhibit different survival rates and necessitate unique risk stratification and treatment approaches.[229] The ESMO guidelines distinguish the poor risk subset of patients as those who do not have one of the specific, recognized patterns of disease that drives specific treatment.[230] Historically, poor risk CUP constitute about 80% of cases and this has been treated as a distinct cancer, with phase 2 trial response rates between 25% and 35%, and survival rates disappointingly low ranging from 6 to 16 months.

Various tissue of origin (TOO) classifiers have been developed using diverse molecular methods, including targeted DNA sequencing, whole exome and genome sequencing, RNA, and methylation profiling.[231] These classifiers can distinguish between 18 and 35 cancer types, although their efficacy varies across subtypes of common and uncommon cancers. Performance differences also exist when applied to untreated versus treated metastatic cancers.[231] Despite advancements in diagnostics, these have not yet translated to clinical utility or survival benefits; no significant difference has been observed in outcomes between empirical and molecularly guided treatments.[227] A prospective trial involving 158 CUP patients demonstrated that genomic profiling led to treatment recommendation changes in only 2.5% of cases.[232]

More recently, two prospective trials have been conducted that showed signals of small magnitude but statistically significant progression-free survival improvements using a molecularly guided strategy. This has garnered some enthusiasm from some editorialists.[233, 234] First, a large phase 2, prospective, randomized, open label trial called the CUPISCO study was designed to inform a molecularly guided treatment strategy to improve outcomes over standard platinum-based chemotherapy in patients with newly diagnosed, unfavorable, non-squamous CUP.[235] The aim of the trial was to compare the efficacy and safety of molecularly guided therapy (MGT) versus standard platinum-based chemotherapy in these patients. Treatment options for patients in the MGT group were defined by the investigator with advice from a virtual molecular tumor board, which included the treating investigator, a referent pathologist, a referent oncologist, and, when required, a genomics expert from Foundation Medicine. In this unusual study design, per protocol, the primary analysis of PFS was based on the intention-to-treat population to evaluate the efficacy of patients randomized to molecularly-guided therapy versus patients randomized to platinum chemotherapy in patients with CUP whose response to 3 cycles of platinum induction chemotherapy was a complete or partial response or stable disease (which was 76% of the population). Overall, 72% of patients in the MGT group did not have an actionable target and were treated per protocol with continued chemotherapy plus atezolizumab in the absence of any molecular guidance. This study design obscures the impact of the genomic profiling aspect of the study. Even with the biases in the study design, the magnitude of benefit noted in the CUPISCO study regarding the progression free survival endpoint was less than 2 months (ESMO magnitude of clinical benefit grade 1). Another randomized trial, FUDAN CUP-001, is a single center study of 182 patients enrolled in China, compared site-specific therapy directed by a 90-gene expression assay compared to empirical chemotherapy, found a similarly low signal of benefit (3 months difference in progression-free survival but short follow-up with few patients at risk by 12 months).[236] While there remains some hope and enthusiasm regarding MGT versus standard empirical chemotherapy, and even speculations about a future shift toward broader tumor-site agnostic approaches to all management of advanced cancer [237], shortcomings in the design of these trials and the low magnitude of benefit in only the surrogate endpoint of progression free survival make it unclear whether this strategy moves the needle for well-recognized patient-centered endpoints. Meanwhile, attempts to establish benefit of this type of approach in retrospective datasets confirm the limitations of the strategy. A retrospective study of 578 tumor samples identified the most common molecular aberrations: KRAS (35%), CDKN2A (15%), TP53 (15%), and ERBB2 (12%) were seldom actionable.[238] Furthermore, in a single center retrospective study from Italy, over a period of more than 6 years, only 44 consecutive patients had CUP, 33 of whom had molecular testing.[239] Of the 33 patients tested, 8 had actionable findings and 2 received targeted therapy to match the genomic alterations. Outcomes were generally poor with median progression-free survival of the cohort of under 4 months with median OS of nearly 19 months. Overall, while the feasibility of molecular profiling is established, its routine clinical utility in CUP diagnosis and treatment remains uncertain against standard approaches, which selectively incorporate genomic profiling after initial evaluation.

The National Comprehensive Cancer Network (NCCN) guidelines focus on immunohistochemical testing for CUP over genomic profiling.[240] Similarly, the European Society for Medical Oncology (ESMO) does not recommend gene expression profiling-based site-directed therapy [61, 241, 242], but tumor-agnostic testing approaches are recommended, essentially treating unfavorable CUP as a condition for which effective standard therapies do not exist. Nomograms based on clinicopathological factors have been developed, providing robust personalized prognostication for decision-making and patient stratification in clinical trials.[243]

Somatic Testing of Hematologic Malignancies

General Criteria

If hematologic malignancy specific criteria (e.g., acute myelogenous leukemia, chronic myeloid leukemia, multiple myeloma, etc.) are described in this guideline, apply those blood cancer criteria prior to use of the General Criteria.

Somatic Genomic Testing (blood cancer biomarker testing)

Somatic genomic testing is considered **medically necessary** in individuals with cancer when **ALL** the following criteria are met:

- Clinical decision making incorporates the known or predicted impact of a specific genomic alteration on protein expression or function and published clinical data on the efficacy of targeting that genomic alteration with a particular agent
- The genetic test is reasonably targeted in scope and has established clinical utility such that a positive or negative result will meaningfully impact the clinical management of the individual and will likely result in improvement in net health outcomes (i.e., the health benefits of the interventions outweigh any medical or psychological harmful effects of the testing intervention)
- When the clinical utility is based on potential impact on clinical management based on genomic biomarker-linked therapies, one or more of these additional criteria must also be met:
    - The genomic biomarker-linked therapies are approved by the US Food and Drug Administration (FDA) or recommended by NCCN as a Category 2A for the individual's specific cancer scenario and such therapies are being considered in the near term
    - Treatment is being considered for which there are specific genomic biomarker-based contraindications or exclusions related to cancer treatment being considered in the near term aligned with the FDA label or NCCN 2A recommendations
    - Treatment is being considered for which the member's health plan has a drug-specific policy requiring additional, appropriately focused genetic biomarker testing otherwise not specified by the FDA label or NCCN 2A recommendation

Blood Cancer-specific Criteria

Acute Lymphoblastic Leukemia and Pediatric B-cell Precursor Lymphoblastic Lymphoma

Initial Diagnosis

Tissue- (**OR** bone marrow-) based (**OR** alternatively, peripheral blood if morphologically detectable circulating blasts) somatic genetic testing (50 or fewer genes) is considered **medically necessary** for children or adults with acute lymphoblastic leukemia (ALL) or pediatric B-cell precursor lymphoblastic lymphoma (BCP-LBL) when **BOTH** of the following criteria are met:

- Testing is for the purpose of establishing the diagnosis, to stratify risk, or to identify actionable therapeutic targets
- A multigene panel contains genes that are identified with B-ALL, T-ALL or BCP-LBL, such as ABL1, ABL2, CRLF2, CSF1R, FLT3, FGFR, NTRK, LYN, PTK2Br, IL7R, JAK1, JAK2, JAK3, ETV6, RUNX1, TCF3, TCF4, PBX1, DUX4, PAX5, KMT2A, HLF, ZNF384, MEF2D, ZNF384, MYC, PDGFRB, SH2B3, TP53, IKZF1, NUTM1, MEF2D, ZNF384, RAS, PTEN, NOTCH1, and FBXW7

Measurable Residual Disease (MRD)

The use of NGS testing on bone marrow specimen is considered **medically necessary** in children or adults with ALL to measure minimal residual disease (MRD) at the end of initial treatment induction and end of initial consolidation and at similar defined points over the course of sequential therapies.

BCR-ABL kinase domain point pathogenic variant analysis is considered **medically necessary** in the evaluation of individuals with BCR-ABL (Philadelphia chromosome) positive ALL to evaluate treated individuals who manifest suboptimal response to initial tyrosine kinase inhibitor therapy or loss of response to tyrosine kinase inhibitor therapy.

PCR testing for BCR-ABL1 quantification on bone marrow specimen is considered **medically necessary** in the monitoring of Philadelphia chromosome-positive ALL.

Rationale

Acute lymphoblastic leukemia (ALL) exhibits a bimodal age distribution, first peaking at around 5 years of age and again near 50 years. ALL can originate from B-cell precursor or T-cell lineage. In the United States, it is the most prevalent cancer among children and the leading cause of cancer-related mortality before age 20.[244] The cure rate for pediatric ALL surpasses 80%, while the adult cure rate ranges from 30% to 40%.[245] Genetic risk factors, such as Down's syndrome, are linked to increased ALL susceptibility, though most patients lack any known inherited risk factors.

High-throughput genomic studies have revealed that childhood ALL genomes harbor an average of 10 to 20 non-silent coding P/LP variants at diagnosis, typically doubling at relapse. P/LP variants commonly involve transcriptional regulation, cell-cycle control, the TP53-retinoblastoma tumor-suppressor pathway, and major signaling pathways, including Ras, phosphatidylinositol 3-kinase, and JAK-STAT, as well as nucleoside metabolism and epigenetic modifications.[244] Adult ALL exhibits more prevalent P/LP variants in genes such as IKZF1, MLL2, and JAK3 compared to pediatric cases but fewer PTPN11 alterations.[246] However, the precise role of these genetic and epigenetic changes in leukemogenesis, drug resistance, and leukemic clone evolution remains an ongoing investigation.[246]

Quantification of measurable/minimal residual disease (MRD) through polymerase chain reaction (PCR), flow cytometry, or next-generation sequencing (NGS) has become a cornerstone in prognostic evaluation. Children with MRD levels of 0.01% or higher at induction therapy's end and beyond face a 3 to 5 times greater risk of treatment failure and death than those with lower MRD levels.[244] MRD testing's prognostic value is demonstrated across multiple studies, confirming its significance in diverse pediatric and adult ALL subsets, therapies, methods, and disease subtypes. This was underscored by a meta-analysis of 39 publications encompassing over 13,000 patients.[247]

Challenges with MRD testing include the potential for sanctuary sites within the body to conceal leukemic cells undetectable by conventional methods, and technical difficulties may yield inaccurate results. Standardized MRD determination techniques are limited outside specialized centers.[247] A clinical trial exploring intensified therapy for patients with elevated MRD levels indicated a non-significant survival improvement but highlighted its potential for patient selection in clinical trials.[248] MRD monitoring is now integral to trials by organizations such as the St. Jude Consortium and Children's Oncology Group and is considered essential in consensus guidelines.[249] Recent studies further validate MRD testing's role in risk stratification for B-cell precursor ALL [250], young adult T-cell ALL [251], and mixed cohort ALL patients on investigational protocols. [252] Timing of MRD assessment aligns with National Comprehensive Cancer Network (NCCN) guidelines, most notably upon completion of initial induction, and at the end of consolidation.[253]

New insights into genetic alterations underscore the variability in ALL outcomes. For instance, the presence of TP53 and IKZF1 alterations in adults with KMT2A-rearranged B-cell precursor ALL significantly influences prognosis and guides therapeutic stratification.[250] Similarly, combining TAL1 lesions with MYC and RAS P/LP variants in T-ALL patients has been found to identify those likely to fail conventional therapy, suggesting a need for alternative treatment strategies.[251]

Acute Myelogenous Leukemia

Initial Diagnosis

Tissue-based (**OR** alternatively, peripheral blood if morphologically detectable circulating blasts) somatic genetic testing (50 or fewer genes) is considered **medically necessary** for individuals with acute myelogenous leukemia (AML) when **BOTH** of the following criteria are met:

- Testing is for the purpose of establishing the diagnosis, to stratify risk, or to identify actionable therapeutic targets

- A multigene panel contains genes that are identified with AML, such as FLT3 (including FLT3-ITD), IDH1, IDH2, NPM1, CBFB, MYH1, CEBPA, MLLT3, KMT2A, DEK, NUP214, KAT6A, CREBBP, GATA2, EVI1, DDX41, TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and ZRSR2

Measurable Residual Disease (MRD)

The use of multigene panel NGS testing on peripheral blood or bone marrow specimens is considered **not medically necessary** in individuals with AML to measure minimal residual disease (MRD).

The use of focused testing of peripheral blood or bone marrow using RT-qPCR is considered **medically necessary** when used at appropriate defined points over the course of therapy, such as at the end of initial treatment induction, at the end of initial consolidation, or at the completion of other sequential therapies, to measure minimal residual disease (MRD) in individuals with AML involving **ONE** of the following disease molecular subtypes:

- Acute promyelocytic leukemia (APL)
- NPM1
- Core binding factor
- Internal tandem duplication of FLT3 (FLT3-ITD)

Rationale

Acute myelogenous leukemia (AML) is characterized by the proliferation of clonal, abnormally differentiated hematopoietic cells infiltrating the bone marrow, blood, and other tissues. At diagnosis, AML often exhibits clonal heterogeneity, and relapse typically involves a pre-existing or closely related clone.[254] The dynamic clonal evolution patterns during relapse likely contribute to therapy resistance.[255] For adults under 60, intensive leukemia treatment results in a cure rate of approximately 40%.[255] However, AML primarily affects older adults, with a median diagnosis age of 68 and a significantly worse prognosis in this group, yielding a cure rate near 10%.[256]

The 2022 World Health Organization (WHO) Classification of Tumours emphasizes genetic abnormalities over differentiation in defining AML subtypes, including fusions and rearrangements such as PML::RARA, RUNX1::RUNX1T1CBFB::MYH11, DEK::NUP214, RBM15::MRTFA, BCR:ABL1, and P/LP variants in genes like NPM1 or CEBPA.[257] Genomic evaluations provide a higher diagnostic yield than traditional cytogenetic analyses.[258]

The European LeukemiaNet (ELN) 2022 guidelines offer the leading consensus for AML risk stratification, recommending the screening of gene P/LP variants linked to diagnosis and actionable therapeutic targets, including FLT3, IDH1, IDH2, NPM1, CEBPA, and TP53, among others.[259] The field remains rapidly evolving, with additional genes under investigation.[260]

Recent studies expand our understanding of therapy-related AML (t-AML). Normal karyotype t-AML (NK-t-AML), compared to *de novo* AML, presents with distinct clinicopathologic and molecular features, influencing survival outcomes. Patients with NK-t-AML show significantly shorter overall and relapse-free survival and a distinct genetic P/LP variant pattern compared to *de novo* AML cases.[261]

Measurable residual disease (MRD) detection methods such as PCR, flow cytometry, and next-generation sequencing (NGS) have prognostic implications across various AML subsets.[262, 263] For instance, persistence of FLT3-ITD or NPM1 variants before stem cell transplant is linked to higher relapse rates and lower survival.[264] While multiparametric flow cytometry remains the gold standard for most AML subsets, specific subtypes like acute promyelocytic leukemia or NPM1 associated AML might benefit from NGS testing. MRD detection is a factor in tailored therapeutic approaches, although its clinical utility requires further validation.[265]

B-cell Lymphomas

The use of focused multigene panel NGS testing (20 genes or fewer) on bone marrow specimens is **medically necessary** when **ALL** the following criteria are met:

- Individuals have high-grade B-cell lymphoma or diffuse large B-cell lymphoma (DLBCL)
- Testing is for the purpose of establishing the diagnosis, to stratify risk, or to identify actionable therapeutic targets

The use of multigene panel NGS testing on peripheral blood or bone marrow specimens is considered **not medically necessary** for individuals with B-cell lymphomas for the purpose of evaluating minimal residual disease (MRD).

Rationale

Somatic genetic testing has become a cornerstone in the diagnosis, classification, and management of B-cell lymphomas. The diagnostic process for B-cell lymphomas routinely incorporates a combination of morphological evaluation and a series of genetic studies. Immunophenotyping and cytogenetic assays remain integral to accurately classifying the subtypes of B-cell lymphomas.[266] Initial diagnostic studies often deploy a broad panel of antibodies, subsequently refined based on morphological findings. This approach facilitates the efficient use of genetic studies, which are increasingly essential in the differential diagnosis of B-cell lymphomas.

Fluorescence In Situ Hybridization (FISH) is a pivotal technique for detecting specific chromosomal translocations and inversions associated with high-risk P/LP variants such as *TP53* and *MYD88*. It is particularly valuable for characterizing subtypes like high-grade B-cell lymphomas, which are defined by MYC, BCL2, and BCL6 rearrangements.[267] FISH aids in differentiating between aggressive forms requiring intensive therapy and more indolent variants. NGS panels enable the identification of actionable P/LP variants, thereby informing the selection of suitable FDA-approved targeted therapies, such as BTK, BCL2, and EZH2 inhibitors.

Challenges in Clinical Application

The application of whole-exome and RNA sequencing has unveiled several genetic subtypes, such as those classified under the LymphGen and LymphPlex algorithms. These subtypes exhibit distinct genetic signatures and therapeutic implications, but the clinical utility of these algorithms compared to standard approaches has not yet been addressed.[268]

Despite the potential benefits, the integration of somatic genetic testing into routine practice is fraught with challenges. Overall, routine NGS panel testing is not universally indicated across all B-cell lymphomas due to varying clinical utility.[267] The clinical relevance of some genetic subtypes remains under debate, primarily due to a paucity of prospective studies corroborating improved outcomes with therapy intensification based on genomic findings.[269] Approximately 40% of DLBCL cases still defy classification into established genetic subtypes, underscoring the need for further research and refinement of existing algorithms.[268] Another significant hurdle is the accessibility. While NGS and other molecular diagnostic techniques provide valuable insights, their widespread implementation is often limited by financial and logistical constraints, particularly in smaller medical centers.

Genetic Subtypes and Targeted Therapy

Recent advances in genomic classification have expanded our understanding of the heterogeneous nature of B-cell lymphomas. Diffuse Large B-cell Lymphoma (DLBCL), the most common subtype, exemplifies the complex genomic diversity within B-cell lymphomas. Classification into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes is critical, as it influences treatment decisions. For instance, cases with MYD88 P/LP variants and BCL2/MYC double-expression (termed "double hit" lymphomas) demand aggressive treatment strategies due to their poor prognosis.[270] Subtypes like the MCD and BN2 also highlight unique oncogenic pathways and prognostic factors. Such genetic classifications are being explored for stratifying patients and recommending personalized therapies. Chimeric antigen receptor (CAR) T-cell therapies and novel inhibitors targeting dysregulated oncogenic pathways offer promising therapeutic options for those with high-risk genetic profiles.[267]

Future Directions

To bridge the gap between theoretical potential and clinical practice, future research must focus on validating the prognostic and therapeutic significance of identified genetic subtypes through large-scale clinical trials. There is also a pressing need for the development of cost-effective and scalable genomic testing platforms that can be readily adopted in diverse healthcare settings. Moreover, the field should aim to establish standardized guidelines for the deployment of somatic genetic testing in B-cell lymphomas. Evidence-based protocols will help streamline diagnostic workflows and reduce variability in clinical management, ensuring that genetic insights translate into tangible patient outcomes.

Chronic Lymphocytic Leukemia

Bone marrow tissue-based **OR** peripheral blood somatic genetic testing using a focused multigene panel NGS testing (20 genes or fewer) is **medically necessary** when **ALL** the following criteria are met:

- Individuals have been diagnosed with chronic lymphocytic leukemia (CLL)
- Testing is for the purpose of initial risk stratification and treatment selection

- A multigene panel includes testing of TP53, SF3B1, NOTCH1, BIRC3, and ATM

The use of multigene panel NGS testing on peripheral blood or bone marrow specimens is considered **not medically necessary** in individuals with CLL for initial workup or to measure minimal residual disease (MRD).

Rationale

Chronic lymphocytic leukemia (CLL) is a common type of leukemia that predominantly affects older adults, characterized by the accumulation of small, mature-appearing lymphocytes in the blood and lymphoid tissues. Advances in understanding the genetic landscape of CLL have led to the development of somatic genetic testing as a tool for prognosis and personalized treatment strategies. The molecular assessment of CLL typically starts with flow cytometry to determine the clonality of B cells, which is crucial before pursuing further molecular testing. Flow cytometry of blood samples is essential for the initial diagnosis of CLL/SLL, helping to distinguish between these and other potential hematological disorders.[271] After confirming diagnosis, genetic testing is employed to identify P/LP variants and chromosomal abnormalities that can inform prognosis and guide treatment.

Genetic Abnormalities and Testing Approaches

Somatic genetic testing in CLL focuses on identifying specific genetic markers associated with disease progression and treatment response. Fluorescence in situ hybridization (FISH) is a common tool employed to detect chromosomal abnormalities such as del(13q), del(11q), del(17p), and trisomy 12. These abnormalities have significant prognostic implications. For instance, del(13q) is generally associated with a favorable prognosis, whereas del(11q) and del(17p) indicate a more aggressive disease course and poor response to conventional therapies.[272, 273]

P/LP variants in the TP53 gene and the immunoglobulin heavy chain variable region (IGHV) are also critical. In particular, unmutated IGHV status correlates with worse prognosis. Accordingly, NCCN guidelines recommend testing for TP53 P/LP variants and assessing IGHV P/LP variant status as standard practice.[271] The detection of these genetic features helps stratify patients into different risk categories, thereby guiding treatment decisions and clinical trial eligibility.

Minimal Residual Disease and its Assessment

The evaluation of minimal residual disease (MRD) is an emerging facet in CLL management, offering insights into disease progression and relapse risk. MRD testing can be conducted using techniques such as multicolor flow cytometry, PCR, and next-generation sequencing (NGS). Although MRD assessment is recognized for its theoretical benefits, such as predicting progression-free survival (PFS), its routine use in clinical practice outside of clinical trials remains limited due to challenges in methodological standardization and clinical utility validation.[274, 275]

Clinical trials have demonstrated a strong association between undetectable MRD status and favorable clinical outcomes, such as extended PFS. However, the current consensus, as reflected in the consensus recommendations and NCCN guidelines, suggests that MRD assessment should primarily be used as a research tool rather than a standard clinical practice, except to inform clinical trial endpoints.[271, 276]

Targeted Therapy and MRD-Guided Treatment

The treatment paradigm for CLL is shifting from traditional chemoimmunotherapy to targeted therapies, such as Bruton tyrosine kinase (BTK) inhibitors and BCL2 inhibitors. Genetic testing results directly influence treatment decisions, especially concerning the use of these agents, which may offer more favorable outcomes in patients with certain genetic profiles.[273]

Recent studies, such as the FLAIR trial, have explored the use of combination therapy (ibrutinib and venetoclax) guided by MRD status. The trial demonstrated the efficacy of MRD-directed therapy in improving PFS, particularly in patients with unmutated IGHV status, although this did not translate into substantial changes in current guideline recommendations due to the limited benefit observed in those with mutated IGHV status.[277]

Future Directions

While somatic genetic testing has provided significant advancements in the characterization and treatment of CLL, challenges remain. Standardization of testing methodologies, particularly for MRD, is critical to ensure consistency and reliability across clinical settings. Moreover, the integration of novel genetic insights into clinical practice requires ongoing research and robust clinical trial data to define the clinical utility of their use and define their roles in treatment algorithms.

Chronic Myeloid Leukemia

Focused bone marrow tissue-based **OR** peripheral blood somatic genetic testing is considered **medically necessary** for establishing the diagnosis of suspected chronic myelogenous leukemia (CML) when the following criterion is met:

- PCR or FISH testing includes the evaluation of the BCR-ABL1 fusion gene

BCR-ABL kinase domain point P/LP variant analysis is considered **medically necessary** in the monitoring of CML in the following circumstance:

- Evaluation of individuals with CML to evaluate treated individuals who manifest suboptimal response to tyrosine kinase inhibitor therapy indicated by **ANY** of the following:
    - Lack of a partial hematologic or cytogenetic response at 3 months or greater after treatment onset
    - Less than a complete hematologic and cytogenetic response at 12 months
    - Disease progression to accelerated or blast phase

Measurable Residual Disease (MRD) testing

PCR testing for BCR-ABL1 quantification is considered **medically necessary** for response assessment every 3 months during active treatment with tyrosine kinase inhibitor therapy.

PCR testing for BCR-ABL1 quantification is considered **medically necessary** for monitoring patients who have undergone discontinuation of tyrosine kinase inhibitor therapy with assessment not more frequent than the following schedule: monthly for the first 6 months after discontinuation, bimonthly for months 7 to 12, and every 3 months thereafter.

Rationale

See *combined rationale for CML and other myeloproliferative neoplasms*.

Myeloproliferative Neoplasms

Bone marrow tissue-based **OR** peripheral blood somatic genetic testing (50 or fewer genes) is considered **medically necessary** for initial evaluation of suspected myeloproliferative neoplasms (MPN) (e.g., essential thrombocytosis, polycythemia vera, chronic neutrophilic leukemia, and primary myelofibrosis) when **BOTH** of the following criteria are met:

- PCR, FISH, or NGS testing is targeting applicable JAK2, CALR, CSF3R, and MPL genes for diagnostic workup and (if applicable) a focused set of additional genes for initial risk stratification in the event that a specific myeloproliferative neoplasm is diagnosed
- **ONE** of the following clinical scenarios (for MPNs other than primary or secondary myelofibrosis):
    - Hemoglobin ≥16.5 g/dL in male and hemoglobin ≥16.0 g/dL in female
    - Hematocrit greater than 49% in male and hematocrit greater than 48% in female
    - Platelet count ≥450 X 10^9/L
    - Leukocytosis (white blood cell) ≥11 X 10^9/L

Rationale

Chronic myeloid leukemia (CML) and other myeloproliferative neoplasms (MPNs) commonly present with elevated peripheral blood counts, such as leukocytosis, thrombocytosis, and polycythemia. These hematopoietic stem-cell disorders are characterized by the abnormal proliferation of mature bone marrow cell lineages, potentially leading to marrow fibrosis and acute leukemia over time.[278] CML results from the BCR-ABL1 fusion gene, a consequence of the t(9;22)(q34;q11) translocation, which produces proteins with increased tyrosine kinase activity.[279]

Patients suspected of having CML or MPNs undergo detailed hematological analyses, including peripheral blood smear examination and BCR-ABL1 testing. Absence of the BCR-ABL1 translocation and dysplasia prompts further molecular evaluation for JAK2, CALR, CSF3R, and MPL P/LP variants, alongside bone marrow evaluation, to achieve an accurate diagnosis.[280] While these genetic variants indicate a hematopoietic stem cell disorder, they are not singularly definitive for any specific disease.[278] Distinction between MPN types integrates peripheral blood, molecular, and bone marrow morphologic findings because none alone provide adequate diagnostic specificity.[278] For example, diagnostic criteria of essential thrombocythemia includes 4 major criteria: (1) thrombocytosis (platelet count ≥450 × 10^9 /L), (2) bone marrow examination that shows megakaryocyte proliferation of mature forms, (3) exclusion of other myeloid neoplasms, and (4) a driver variant in JAK2, CALR, or MPL.[281]

BCR-ABL1 must be confirmed cytogenetically and through multiplex RT-PCR to diagnose CML. Baseline quantitative RT-PCR and P/LP variant analysis for BCR-ABL1 are not typically required for initial decision-making.[279] Targeted therapy using tyrosine kinase inhibitors (TKIs), such as imatinib, has markedly improved the prognosis, with 10-year overall survival rates reaching 80%-90%.[282] The goal of TKI therapy is achieving stable molecular remission, permitting the possibility of treatment-free remission.[283] Treatment monitoring now relies heavily on quantitative PCR to measure BCR-ABL1 transcript levels according to the International Scale, with remission, warning, and treatment failure thresholds well-established.[284]

TKI resistance can occur in 10%-15% of patients, with P/LP variants contributing in about one-third of chronic phase cases and two-thirds of accelerated or blast phases.[285] Over 100 kinase domain P/LP variants have been identified as affecting TKI binding. Next-generation sequencing (NGS) provides a more comprehensive assessment of BCR-ABL1 P/LP variants compared to standard Sanger sequencing and is the recommended technology for assessing TKI resistance P/LP variants in patients not responding adequately to treatment.[285]

Myelodysplastic Syndrome

Somatic testing (i.e., 50 or fewer genes) of bone marrow tissue **OR** peripheral blood is considered **medically necessary** for individuals with clinically diagnosed or suspected myelodysplastic syndrome when **BOTH** of the following criteria are met:

- Testing is for the purpose of establishing the diagnosis, to stratify risk, or to identify actionable therapeutic targets
- A multigene panel contains genes that are identified with MDS, such as ASXL1, DNMT3A, EZH2, NRAS, RUNX1, SF3B1, SETBP1, SRSF2, STAG2, TET2, TP53, U2AF1, ZRSR2, and UBA1

Rationale

Myelodysplastic syndromes (MDS) are clonal hematopoietic neoplasms characterized by cytopenias and morphologic dysplasia. While MDS primarily affects older adults, with a median age of onset of 70 years, it can occur in younger individuals as well.[286] MDS can progress to acute myeloid leukemia (AML) through clonal selection, with varying transformation patterns depending on the MDS subtype and the driving genetic P/LP variants. In subtypes associated with lower transformation risk, treatment focuses on alleviating anemia and other cytopenias. Conversely, high-risk MDS management emphasizes delaying disease progression and extending survival. Although allogeneic stem cell transplantation is a potentially curative option, its applicability is limited due to the older age of most patients.[287] The Molecular International Prognostic Scoring System (IPSS-M) considers P/LP variants in 31 specific genes with emphasis on high-risk P/LP variants such as TP53, KMT2A, and FLT3 (TKK or ITD alterations) as well as P/LP variant burden and key co-P/LP variants and cytogenetic abnormalities. In retrospective data, there is evidence to support the clinical relevance of including genomic features into the hematopoietic stem cell transplantation decision making process in patients with MDS.[288]

This update introduces genetically defined disease subtypes instead of grouping based on risk features like blast percentage, ring sideroblasts, and number of dysplastic lineages. Common somatic P/LP variants in MDS with an incidence of 5% or higher include ASXL1, DNMT3A, EZH2, NRAS, RUNX1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, and ZRSR2. Investigators have used 3233 representative samples from patients with MDS from the cohort built to develop the International Prognostic Scoring System Molecular (IPSS-M) to identify molecular subgroups of MDS associated with distinct clinical phenotypes and disease courses.[289]

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, caused by somatic P/LP variants in UBA1, presents as a distinct form of myelodysplastic syndrome. Its clinical presentation and progression differentiate it from classical MDS, underscoring the importance of UBA1 testing.[290, 291]

To address the heterogeneity in the clinical course and outcomes of MDS, the International Prognostic Scoring System–Revised (IPSS-R), was developed. This tool plays a crucial role in risk stratification, clinical trial design, and treatment recommendations.[292] More recently, the integration of molecular data into prognostication has led to the validation of the IPSS-

Molecular (IPSS-M) model.[293, 294] Multivariable analysis has identified TP53, FLT3, and KMT2A (MLL) P/LP variants as predictors of poor outcomes, whereas SF3B1 P/LP variants correlate with favorable prognoses. Furthermore, P/LP variants in ASXL1, BCOR, EZH2, NRAS, RUNX1, STAG2, and U2AF1 are significantly associated with adverse risk for several key outcomes. The IPSS-M model also informs the selection of candidates for hematopoietic stem cell transplantation.[295]

Multiple Myeloma

Gene expression profile tests

Gene expression profile tests for diagnostic evaluation, risk stratification, or management of multiple myeloma are considered **not medically necessary**.

For multianalyte assays used for prognostication (often combined with algorithmic analyses), see the Carelon Guidelines for Predictive and Prognostic Polygenic Testing.

Measurable Residual Disease (MRD) testing

The use of NGS testing of tumor DNA from bone marrow specimens to detect or quantify minimal residual disease (MRD) in individuals with myeloma is considered **medically necessary** under **EITHER** of the following circumstances:

- MRD testing used prior to initiating new treatment intended to induce myeloma remission
- MRD testing used to assess depth of response after a cycle of treatment intended to induce myeloma remission

Rationale

Multiple myeloma represents a significant hematological malignancy, being the second most prevalent and accounting for about 2% of cancer deaths in the United States. The disease often progresses from a premalignant stage known as monoclonal gammopathy of undetermined significance (MGUS), with progression rates largely influenced by cytogenetic findings.[296] Diagnosis typically requires the identification of clonal plasma cells within the bone marrow or through a biopsy-proven bone or extramedullary plasmacytoma. Most patients present with symptoms due to organ involvement such as hypercalcemia, renal insufficiency, anemia, and bone lesions, although some diagnoses occur through abnormal blood or urine tests.[297]

Recognizing multiple myeloma as a collection of heterogeneous diseases is crucial due to its diverse cytogenetic, molecular, and proliferative characteristics. Effective risk stratification is essential for prognostication and to guide treatment strategies, incorporating cytogenetic profiling with disease stage and other prognostic factors.[296] The Revised International Staging System (R-ISS), validated since 2015, and more recent models like the Mayo Additive Staging System and the mSMART risk stratification method, provide structured frameworks for this stratification.[298, 299]

Advancements in therapeutic approaches have yielded high complete response rates, propelling the development of new response categories focused on minimal residual disease (MRD) detection using sophisticated techniques like flow cytometry and next-generation sequencing (NGS). While bone marrow testing remains the evidence-based standard, peripheral blood-based MRD evaluations currently lack adequate sensitivity.[300] Despite ongoing research into circulating tumor cells, appropriate clinical cut-off levels remain undetermined.[301, 302] Bone marrow assessment defines MRD negativity as the absence of tumor plasma cells within 1,000,000 bone marrow cells, a key indicator of favorable progression-free and overall survival outcomes.[303] Endorsement of routine MRD testing is supported by guidelines from the American Society, Cancer Care Ontario, the European Society of Medical Oncology, and the European Hematology Association.[297, 304]

The ASCO guidelines strongly recommend utilizing the International Myeloma Working Group criteria to measure response quality and depth after each therapy cycle aimed at remission induction.[304] The potential to guide treatment adjustments during maintenance therapy based on MRD status is being explored, although ASCO advised against altering maintenance therapy based on these parameters due to insufficient supporting evidence.[305] More recently, in a systematic review and meta-analysis, MRD-negativity at 12 months was associated with reduced risk of progression. Also, the treatment effect on MRD was correlated with the treatment effect on progression-free survival (PFS).[306] The authors concluded that MRD-negativity is reasonably likely to eventually demonstrate a treatment effect on PFS. Similarly, in a large prospective study conducted by the Blood and Marrow Transplant Clinical Trials Network from the National Heart, Lung, and Blood Institute, MRD was assessed through next-generation multiparameter flow cytometry (MFC). These data demonstrate that regardless of the type of treatment, the achievement of MRD negativity is most relevant for the outcome of myeloma patients.[307] In this small field of myeloma, the use of MRD has become widely accepted, particularly as a test to evaluate new therapeutics.

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
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)
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

Code	May Be Medically Necessary When Criteria are Met
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
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)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81301	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
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
81307	*PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81309	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)
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
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)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)

Code	May Be Medically Necessary When Criteria are Met
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
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
81450	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; DNA analysis or combined DNA and RNA analysis
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
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 procedure
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score (Endopredict)
81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis - MAAA Breast Cancer Metastasis RNA Sequencing
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)
81599	Unlisted multianalyte assay with algorithmic analysis

Code	May Be Medically Necessary When Criteria are Met
0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
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 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
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or nondetection of FLT3 mutation and indication for or against the use of midostaurin
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
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
0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
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)
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
0111U	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
0154U	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>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3- kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status
0172U	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
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
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
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
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
0364U	clonoSEQ® Assay, Adaptive Biotechnologies: 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. The test analyzes a blood or bone marrow specimen from a hematolymphoid (blood/lymph) cancer patient using next generation sequencing (NGS) to track the levels of specific (clonal) DNA sequences related to the cancer. Repeating the test allows clinicians to determine whether the patient has remaining cancer cells, called minimal residual disease (MRD), during and after treatment.
0414U	Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker

Code	May Be Medically Necessary When Criteria are Met
0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s)
0471U	Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalin-fixed paraffin-embedded (FFPE), predictive, identification of detected mutations
0473U	Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), **648** genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden
0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
0481U	IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (eg, central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions)
0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffin-embedded (FFPE) tissue, next-generation sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection
0523U	Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change
0538U	Oncology (solid tumor), next-generation targeted sequencing analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant
0543U	Oncology (solid tumor), next-generation sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for single-nucleotide variants, multi-nucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden
G9840	KRAS gene mutation testing performed before initiation of anti-EGFR MoAb
G9841	KRAS gene mutation testing not performed before initiation of anti-EGFR MoAb
S3854	Gene expression profiling panel for use in the management of breast cancer treatment

Not Medically Necessary

Code	Not Medically Necessary
81195	Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (OGM)
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	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
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
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher)
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

Code	Not Medically Necessary
0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)
0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin
0020M	Oncology (central nervous system), analysis of 30000 DNA methylation loci by methylation array, utilizing DNA extracted from tumor tissue, diagnostic algorithm reported as probability of matching a reference tumor subclass
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin-embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score.
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
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
0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Whole Genome Sequencing
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification - Praxis Somatic Transcriptome
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification - Praxis Somatic Optical Genome Mapping
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping
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 **(Do not report 0306U in conjunction with 0307U)**
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 **(Do not report 0307U in conjunction with 0306U)**
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)

Code	Not Medically Necessary
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
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alternations
0362U	Oncology (papillary thyroid cancer), gene expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
0379U	Solid Tumor Expanded Panel, Quest Diagnostics®, Quest Diagnostics®: 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. The test uses a next–generation sequencing (NGS) targeted sequence analysis panel for a tumor specimen to evaluate DNA for 523 genes and RNA for 55 genes. The results may aid with diagnosis, prognosis, or treatment selection for patients with solid tumors.
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
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations
0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative
0497U	Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation
0534U	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score
0578U	Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence
0586U	Oncology, mRNA, gene expression profiling of 216 genes (204 targeted and 12 housekeeping genes), RNA expression analysis, formalin-fixed paraffin-embedded (FFPE) tissue, quantitative, reported as log2 ratio per gene
0592U	Oncology (hematolymphoid neoplasms), DNA, targeted genomic sequence of 417 genes, interrogation for gene fusions, translocations, rearrangements, utilizing formalin-fixed paraffin embedded (FFPE) tumor tissue, results report clinically significant variant(s)
0597U	Oncology (breast), RNA expression profiling of 329 genes by targeted next-generation sequencing and **20 proteins** by multiplex immunofluorescence, formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic analyses to determine tumor-recurrence risk score

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Revised	04/21/2025	11/15/2025	Independent Multispecialty Physician Panel (IMPP) review. General Requirements – clarified genomic testing must have established analytical and clinical validity and be performed in an appropriately certified lab. Solid Tumors – multiple sections: clarified IHC is out of scope for genetic testing and added minor clarifications. General Criteria: Lab developed tests added as medically necessary. Allow genetic biomarker testing per member's health plan drug-specific policy. Tissue-agnostic testing for patients with advanced solid tumors; added FGFR biomarkers. Bladder cancer – removed restrictive criteria for specific biomarker testing. Added NCCN 2A recommendation to positive criteria for Bladder cancer, Breast

Status	Review Date	Effective Date	Action
			cancer, Cholangiocarcinoma, NSCLC, Ovarian cancer, and Prostate cancer. Localized breast cancer – removed Breast Cancer Index (BCI) from early adjuvant setting. Metastatic breast cancer – expanded genetic marker testing from 4 to 50 or fewer. Melanoma – removed restriction requiring previous BRAF V600E testing. Metastatic castration-sensitive and castration-resistant prostate adenocarcinoma specified as necessary types. Expanded Sarcoma criteria. Thyroid Cancer – removed restrictive ITN ultrasound criteria; allow up to ITNs 4 cm in size. Hematologic Malignancies – General Criteria: Somatic Genomic Testing (blood cancer biomarker testing) – NCCN 2A recommendation added to positive criteria; Allow for member's health plan drug-specific policy requirements to positive criteria. Blood Cancer-specific Criteria: Multiple sections – clarified that chromosomal testing is out of scope and added minor clarifications. Added cancer type: pediatric BCP-LBL. AML – added FLT3-ITD as medically necessary. B-cell lymphomas – new criteria. CLL – criteria added for focused NGS panel for risk stratification. CML – focused testing. MDS – added genetic marker to examples. Added references. Added CPT codes 81380 and 81381 (MNWCM); moved 81523, 0046U, 0244U, 0250U, 0414U, 0444U, 0473U, 0499U, 0538U, 0543U, S3854 from NMN to MNWCM.
Revised	04/21/2025	10/05/2025	IMPP review. Localized Breast cancer – added criteria for the Breast Cancer Index in the extended adjuvant setting. Added references.
Updated codes 10/01/2025	n/a	Unchanged	CPT code update: added 0578U, 0586U, 0592U, 0597U (NMN).
Updated codes 04/01/2025	n/a	Unchanged	CPT code update: added 81504, 0019U, 0069U, 0534U, 0538U, 0543U (NMN); removed 0013M, 0332U, 0343U, 0452U, 0467U (NMN).
Revised	01/30/2025	03/23/2025	IMPP review. Expanded medical necessity criteria to include somatic tumor testing for biomarker-linked therapies that are NCCN Category 2A recommended. Clarified that criteria listed under ‘metastatic breast cancer’ also includes locally advanced breast cancer. Clarified that the clinical scenarios for testing in myeloproliferative neoplasms do not apply to primary or secondary myelofibrosis.
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: added 0523U (MNWCM) and 81195 (NMN); removed 0448U. Revised descriptions for 0497U, 0498U, 0499U.
Revised	10/28/2024, 07/16/2024, 04/15/2024	11/17/2024	IMPP review. Revised indications for bladder cancer (expansive for MSI/dMMR), brain cancer (new), metastatic breast cancer (expanded scope of testing AKT1 and PTEN, removed exclusion for tissue testing), metastatic colorectal cancer (expansive for MSI/dMMR and POLE/POLD1 testing), endometrial cancer (expansive for MSI/dMMR and POLE/POLD1 testing, restrictive for panel size), localized NSCLC (expansive for ALK testing), epithelial ovarian cancer (restrictive for HRD testing), pancreatic cancer (expanded targeted somatic testing), metastatic prostate cancer (expansive/restrictive), thyroid cancer (expansive); ALL (restrictive for NGS testing), AML (expansive for focused testing using RT-qPCR), CML (expansive for BCR-ABL1), and MPN (expansive). Clarifications throughout. Added references. Moved CPT codes 81546 and 0049U from NMN to MNWCM. Moved 0177U to Cell-free DNA Testing for Cancer guidelines.
Revised	01/23/2024	10/20/2024	IMPP review. Clarified testing to guide adjuvant therapy for localized breast cancer. Moved CPT codes 81313, 81504, 81551, 0019U, 0069U, 0089U, 0114U to Predictive and Prognostic Polygenic Testing guidelines.

Status	Review Date	Effective Date	Action
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 81407, 0478U, 0481U (MNWCM); 0497U, 0498U, 0499U (NMN). Added/Moved from Polygenic Risk Scores guideline: 81525, 81529, 81540, 81541, 81542, 81552, 0006M, 0013M, 0016M, 0017M, 0020M, 0045U, 0047U, 0120U, 0287U, 0288U, 0315U, 0343U, 0362U (NMN).
Updated codes 07/01/2024	n/a	Unchanged	Added CPT codes 0471U (MNWCM); 0452U, 0465U, 0467U, 0473U (NMN). Removed termed code 0204U (NMN).
Revised	07/18/2023	03/17/2024	IMPP review. Clarification for FDA-approved test moved to umbrella criteria. Expanded BRAF V600E criteria to include RAS variant in localized CRC. Removed Afirma standalone assay for testing ITNs. Restricted testing to 50 genes or fewer for bladder, colorectal, ovarian, ALL, AML, CML, MPN, and MDS. Expanded specimen type in tissue-based testing for ALL, AML, and MDS. For ALL, specimen-type, MRD and BCR-ABL1 monitoring. Added references. MNWCM codes: added 0448U; moved 81455 and 0334U from NMN to MNWCM. NMN codes: added 0444U; moved 81546 from MNWCM to NMN; removed 81525, 81529, 81540, 81541, 81542, 81552, 0005U, 0006M, 0012M, 0013M, 0016M, 0017M, 0045U, 0047U, 0090U, 0113U, 0120U, 0228U, 0287U, 0288U, 0296U, 0313U, 0314U, 0315U, 0317U, 0339U, 0343U, 0362U, 0363U, 0403U. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Added CPT codes 81457, 81458, and 81459. Description changes for 81406, 81445, 81449, 81450, 81451, 81455, 81456.
Revised	04/12/2023	11/05/2023	IMPP review. Tumor-agnostic testing for patients with advanced solid tumors: expanded testing for RET; clarification edits for MMR deficiency. Clarification edits in localized and metastatic breast cancer; expanded testing for ESR1 in metastatic breast. New testing scenario for advanced endometrial carcinoma. Corrected error in metastatic NSCLC. CML: Expanded specimen type to include peripheral blood; separated indication for MPNs and defined peripheral blood indices.
Updated	n/a	10/01/2023	Added CPT codes 81599, 0364U, 0379U, 0391U, 0403U, 0413U, 0414U. Moved 81327, 0007M, 0011M, 0229U, 0285U, 0333U, 0340U to Cell-free DNA Testing for Management of Cancer guidelines. Removed 81173, 81321, 81323, 81353, 0013U, 0014U, 0056U, 0179U, 0208U, 0235U, 0238U, 0239U, 0242U, 0326U, 0356U.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.