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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. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

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

General Information

Guideline Scope

The Carelon Somatic Tumor Testing guidelines apply to molecular testing of single genes, multigene panel tests (MGPT), and DNA and RNA based sequencing tests. Immunohistochemistry, flow cytometry, and fluorescence in situ hybridization (FISH) testing are not within the scope of this guideline. Use of these related technologies may be indicated for somatic tumor in lieu of molecular testing addressed in this guideline. Users are encouraged to refer to professional society guidelines for use of the most appropriate testing technology and clinical indication.

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.

Clinical Indications

General Requirements

Testing should be performed in a laboratory with established experience in this clinical domain that has met quality standards set by the Clinical Laboratory Improvement Amendments (CLIA) program overseen by the Centers for Medicare & Medicaid Services (CMS). Prior to using any test result findings for medical management, it is important to ensure that findings were obtained from not only a CLIA-certified lab but also one accredited by the College of American Pathologists (CAP) to issue a report of findings directly to ordering health care providers. Some states (e.g., New York) may have additional reporting requirements.

The genomic testing must have established analytical and clinical validity.

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

Somatic Testing of Solid Tumors

General Criteria

All components of a somatic tumor comprehensive genomic profiling test must demonstrate clinical utility for the specific indication.

Targeted RNA fusion analysis using NGS is considered **medically necessary** if noted in the cancer-specific 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 U.S. Food and Drug Administration (FDA) or recommended by NCCN as 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
- Contemporaneous or subsequent performance of NGS-based somatic tumor tissue profiling without a change in clinical status, treatment, or intervention **after** performance of genetic liquid biopsy testing is considered **not medically necessary***

  Note: If ctDNA testing is performed initially and results are not detected or uninformative for an actionable variant, reflex tumor tissue testing can be considered **medically necessary with evidence of the ctDNA liquid biopsy test result.*

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.

RNA fusion analysis by next-generation sequencing (NGS) may be considered medically necessary in somatic tumor evaluation due to the importance of detecting gene fusions as actionable drivers that inform diagnosis, prognosis, and targeted therapy selection. RNA-based NGS is particularly valuable because it directly detects expressed fusion transcripts with higher sensitivity and specificity compared to DNA-based methods, especially for complex or novel rearrangements. The National Comprehensive Cancer Network (NCCN) states RNA-based NGS may increase novel fusion detection and splicing variants and can be performed concurrently or sequentially with DNA-based NGS.[1] ESMO endorses RNA-based fusion testing in certain contexts supporting its clinical necessity. A multisite, large, retrospective cohort study by Owen et al. examined patients sequenced between February 2021 and October 2023.[2] This study demonstrated that RNA-based next-generation sequencing (RNA-NGS) provides clinically meaningful incremental value in somatic tumor testing by significantly improving detection of actionable gene fusions and splicing alterations compared with DNA-NGS alone in non-small cell lung cancer. RNA-NGS enables direct detection of expressed fusion transcripts, overcoming known sensitivity gaps of DNA-based assays and capturing established targets, thereby expanding access to guideline-recommended therapies.

The use of reflex tumor tissue testing following performance of liquid biopsy ctDNA without a change in clinical status, treatment, or intervention is not required; however, given the lower sensitivity of liquid biopsy and potential for undetected or uninformative results, reflex tumor tissue testing can be considered acceptable if the result(s) of the ctDNA biomarker are not detected or uninformative.[3] Confirmatory evidence of the ctDNA result to establish necessity of tumor tissue testing in this scenario is required.

Metastatic or Advanced Cancer (Tissue-Agnostic Testing)

Tissue-agnostic Testing for Patients with Advanced Solid Tumors

Multigene panel testing, which may include targeted RNA-based fusion 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 and is aligned with testing as per FDA-labeled tumor agnostic indications:
    - 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
    - NTRK1/2/3 and RET fusion testing
    - BRAF V600E testing
    - HER2 testing
    - Tumor mutational burden (TMB) testing as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb)

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.[4] 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, although descriptive studies continue to report treatment changes based on NGS results.[5, 6] For example, in the Copenhagen Prospective Personalized Oncology (CoPPO) program, actionable alterations were identified in 57% of patients with evaluable genomic profiles, but only 24% of those with an actionable target ultimately received matched targeted therapy.[7] However, in an evaluation of the rigor of peer-reviewed literature cited in the National Coverage Determination Memorandum for FoundationOne®CDx, authors from the National Cancer Institute found significant gaps in the supporting evidence of 113 studies reviewed for broad comprehensive genomic profiling use in patients with solid tumors.[8] They concluded that rigorous studies assessing 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.[9] 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 repotrectinib for NTRK fusions, selpercatinib for RET fusions, and dabrafenib plus trametinib for BRAF V600E, and fam-trastuzumab deruxtecan for HER2-positive solid tumors. Per NCCN, RNA-based MGPT analysis is recognized as the preferred assay for detecting NTRK 1/2/3 gene fusions because of higher sensitivity and accuracy than DNA-based testing for gene fusions.[10] ESMO states that for tissue-based testing, NTRK fusions should preferably be interrogated at the RNA level, using panel-based methods capable of identifying fusion transcripts with known and unknown partners.[11]

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.[9] 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%.[12] IHC, PCR, and NGS-based assays each capture distinct biological features and have complementary strengths and limitations.[13] 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 FoundationOne CDx and MSK-IMPACT use different metrics and bioinformatics methods, complicating equivalence across tests.[14, 15]

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.[16] The tumor-agnostic FDA approval was contentious due to arbitrary TMB cut-offs, lacking clear survival benefits and questioning cost efficiency versus alternatives.[17, 18] 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.[16, 19] 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.[20]

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.[21]

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.[22]

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.[9]

Recent Advances and FDA Approvals

The most recent evidence update did not identify new FDA-labeled tumor agnostic indications requiring changes to the current testing criteria. However, professional guidelines have increasingly focused on processes required to implement precision oncology appropriately and safely, including the implementation of classification systems such as the ESMO Scale of Clinical Actionability of Molecular Targets (ESCAT). The ESMO Precision Oncology Working Group has also published recommendations on molecular tumor board (MTB) structure and quality indicators, emphasizing clinically oriented interpretation, prioritization of complex genomic cases, and standardized reporting to support clinically meaningful treatment recommendations.[23] In terms of regulatory approvals, the FDA granted accelerated approval to zenocutuzumab for adults with advanced, unresectable, or metastatic NSCLC or pancreatic adenocarcinoma harboring an NRG1 gene fusion after progression on prior systemic therapy; because the indication is restricted to specific tumor types, it does not constitute a tissue-agnostic approval and therefore does not expand the tumor-agnostic testing criteria.[24] 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.[25] Molecular tumor boards (MTBs) are increasingly used to support systematic, clinically oriented interpretation of genomic profiling; ESMO has issued recommendations on MTB structure, reporting, and quality indicators to promote consistent, clinically meaningful recommendations.[23] 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.[9] 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.[26] 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 approach.

Cancer-specific Criteria

Biliary Tract Cancer (including Cholangiocarcinoma and Gallbladder Cancer)

Tissue-based somatic tumor testing for P/LP variants, which may include targeted RNA-based fusion testing, is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven cholangiocarcinoma or gallbladder cancer
- The carcinoma is locally advanced, unresectable, or metastatic
- The panel testing to include analysis (at a minimum) of the following predictive biomarkers using methods capable of detecting the relevant alteration:
    - IDH1
    - FGFR fusions/rearrangements
    - HER2/ERBB2
    - NTRK 1/2/3/ fusions
    - RET fusions
    - KRAS G12C
    - BRAF V600 E
    - Mismatch repair deficiency (dMMR; MLH1/MSH2/MSH6/PMS2 by NGS) or microsatellite instability (MSI) by PCR/NGS
- The individual is a potential candidate for biomarker-directed targeted therapy that is FDA approved (and/or recommended by NCCN Category 2A or higher), prescribed on the basis of the panel test results

- The individual has not had prior somatic tumor testing in the advanced/metastatic setting that adequately evaluated the biomarkers listed above including fusions/rearrangements (where applicable)

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 cancers (BTCs) encompass a spectrum of invasive adenocarcinomas, including cholangiocarcinoma (arising in the intrahepatic, perihilar, or distal biliary tree) and gallbladder carcinoma. Distinct patient subgroups with driver pathogenic/likely pathogenic (P/LP) variants suitable for targeted therapy have been identified, and these alterations are frequently mutually exclusive and associated with anatomical subsite.[27] Professional guidelines recommend comprehensive tissue-based molecular profiling when first-line systemic therapy is initiated in patients with locally advanced, unresectable, advanced, or metastatic BTC to enable timely identification of actionable alterations and appropriate use of targeted therapy and/or clinical trial enrollment.[28, 29] Common clinically actionable alterations include IDH1 mutations (~10%-20% in intrahepatic cholangiocarcinoma [iCCA]), FGFR2 fusions/rearrangements (~9%-16% in iCCA), BRAF V600E (~1%-5%), and HER2 (ERBB2) amplification/overexpression (approximately 5%-10% in extrahepatic cholangiocarcinoma and 15%-30% in gallbladder carcinoma).[29] Less common but actionable alterations across BTC subsites include MSI-H/dMMR (~1%-3%), NTRK fusions (<1%), RET fusions (<1%), and KRAS G12C (~1%).[10, 29] Accordingly, comprehensive molecular profiling is standard practice in BTC, particularly for advanced disease and iCCA to identify predictive biomarkers linked to FDA-approved therapies and other guideline supported options.[29-31]

Unfortunately, patients with FGFR2 fusions or IDH1 P/LP variants often experience intrinsic resistance to targeted therapies, and responses may be limited by acquired resistance mechanisms.[32] Rare actionable alterations including NTRK fusions, RET fusions, and MSI-H/dMMR may also occur and can inform use of tumor-agnostic targeted therapy options, supporting inclusion of these biomarkers in up-front tissue testing for BTC.[29] Given the therapeutic relevance of gene fusions (e.g., FGFR2, NTRK, RET), molecular profiling should incorporate fusion detection (often via RNA-based sequencing) or complementary methods to reduce false-negative results.[29] KRAS G12C pathogenic variants are uncommon (~1%) in BTC and matched targeted therapy is considered ESCAT I-C; the adverse prognostic association appears limited primarily to iCCA.[29, 33]

Most patients are diagnosed with advanced disease. In such cases, platinum- and gemcitabine-based chemotherapy (often combined with immune checkpoint inhibition per contemporary professional guidelines) remains foundational in the absence of actionable alterations.[29] Although deleterious alterations in homologous recombination repair (HRR) and other DNA damage response pathways are observed in BTC, available data do not support using HRR status to select platinum therapy, and routine HRR testing solely to predict platinum sensitivity lacks demonstrated clinical utility.[34] In adult patients with unresectable locally advanced or metastatic cholangiocarcinoma harboring IDH1 P/LP variants—identified through an FDA-approved test—ivosidenib is an FDA-approved treatment option following prior systemic therapy.[35]

For patients harboring FGFR2 fusions or rearrangements, registrational single-arm trials of FGFR inhibitors have demonstrated objective response rates of approximately 23%-42% and median progression-free survival of about 7-9 months, supporting the clinical utility of identifying FGFR2 fusions/rearrangements in iCCA.[36, 37] FGFR inhibitors such as pemigatinib and futibatinib are FDA-approved in previously treated disease in this setting. Similarly, clinically meaningful activity has been observed with dabrafenib plus trametinib for BTC with BRAF V600E variants, and with TRK inhibitors (e.g., larotrectinib or entrectinib) for tumors harboring NTRK fusions.[29] For HER2-positive BTC, an expanding evidence base supports HER2 testing (typically by IHC with reflex in situ hybridization or by NGS for ERBB2 amplification/mutations) to guide anti-HER2 therapy selection. Zanidatamab received FDA accelerated approval for previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC based on HERIZON-BTC-01, which demonstrated a clinically meaningful response rate between 23% and 42%, durability in a treatment-refractory population.[38] Trastuzumab combined with pertuzumab remains an evidence-based option for selected HER2-positive BTC, supported by the MyPathway phase 2a study and pooled evidence across anti-HER2 regimens.[39]

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, which may include RNA-based FGFR fusion testing 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 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.[40, 41] 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.[42, 43] Guidelines from the American Urological Association (AUA), European Association of Urology (EAU), the Society of Urological Oncology (SUO), and the NCCN[44] continue to not support genetic testing for risk stratification or management guidance in non-muscle invasive bladder cancer (NMIBC).[45, 46] Driven by the low sensitivity of urine cytology in low-grade tumors, 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.[46]

The EAU NMIBC guideline continues to emphasize clinicopathologic risk stratification; routine somatic tumor testing and multiplex urine-marker panels are not recommended as standard-of-care substitutes for cystoscopic surveillance.[47]

In contrast, for muscle-invasive and advanced urothelial carcinoma, professional guidelines support somatic testing when results have clear therapeutic implications. The 2025 Canadian Urological Association (CUA) muscle-invasive bladder cancer guideline recommends FGFR testing for cystectomy pathology demonstrating high-risk recurrence features (e.g., pT3/4 and/or node-positive disease) and supports reflex FGFR2/3 testing at the time of pathology diagnosis when feasible to facilitate timely access to biomarker-directed therapy if systemic therapy is indicated.[48]

Similarly, EAU guidance for metastatic upper tract urothelial carcinoma recommends FGFR2/3 alteration testing at initial diagnosis in the metastatic setting.[49]

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.[43] FGFR P/LP variants are seen more frequently in upper tract urothelial cancers (≈30%) compared to bladder cancers (≈14%).[50]

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. Contemporary EAU guidance summarizes that defined FGFR2/3 alterations are predictive of response to FGFR inhibitor therapy (e.g., erdafitinib) in unresectable or metastatic urothelial carcinoma, whereas there is insufficient evidence to use tumor mutational burden, broad molecular variant patterns, or immune-expression signatures to guide routine management decisions outside clinical trials.[51]

Guidelines and Emerging Therapies

Updated EAU guidance identifies FGFR2/3 alterations as predictive biomarkers for selection of FGFR inhibitor therapy in locally advanced or metastatic urothelial carcinoma and does not recommend routine use of tumor mutational burden or molecular subtyping to guide management decisions outside clinical trials.[51]

Real-world evidence reinforces that the primary clinical utility of FGFR testing is selection for biomarker-directed FGFR inhibitor therapy, not prediction of immune checkpoint inhibitor benefit. In a clinicogenomic database analysis, FGFR3 alteration status alone was not predictive of outcomes on immune checkpoint inhibitors.[52] Phase II data in cisplatin-ineligible, FGFR-altered metastatic urothelial carcinoma demonstrate meaningful activity of erdafitinib-based regimens, supporting the therapeutic relevance of identifying actionable FGFR alterations in advanced disease.[53] Other candidate genomic predictors (e.g., NECTIN4 amplification) remain investigational and are not recommended to guide therapy selection outside clinical trials.[54]

Conclusion

The status of FGFR3 and other genetic alterations remains a significant focus area for therapeutic research and development in bladder cancer. At present, the somatic testing approach with the clearest demonstrated clinical utility in urothelial carcinoma is targeted assessment for actionable FGFR2/3 alterations in patients with locally advanced, recurrent, or metastatic disease. In contrast, broad molecular subtyping, tumor mutational burden, and immune-expression signatures have not been validated to guide routine management decisions in urothelial cancer outside clinical trials.[48, 51]

Brain Cancer (Malignant Glioma)

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

- The individual has a diagnosis of primary malignant glioma of the brain
- Genetic testing in adults and children includes the following:
    - IDH1 and IDH2
    - BRAF V600E
- Genetic testing in adults and children with suspected or confirmed diffuse midline glioma may include P/LP variants of H3 K27M
- Genetic testing in children should be able to detect BRAF fusions/rearrangements when the individual has confirmed or suspected pediatric low-grade gliomas
- The individual has not had prior testing for these genes

Tissue-based somatic tumor testing for MGMT promoter methylation is considered **medically necessary** for individuals with high grade malignant glioma when **ALL** the following criteria are met:

- Newly diagnosed IDH-wild type malignant glioma (grade 4)
- Clinical decision-making regarding use of alkylating chemotherapy (e.g., temozolomide) is under consideration
- Poor performance status, older age, significant comorbidities, or concerns regarding treatment toxicity such that selection between **EITHER** of the following options will be made based on MGMT promoter methylation status:
    - temozolomide monotherapy
    - radiotherapy alone
- The individual has not had prior MGMT promoter methylation testing on the same tumor specimen

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.[55] 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.[56] These modifications, driven by the IDH pathogenic variant status, restrict the diagnosis of glioblastoma to tumors that are IDH wild type.[57] This updated classification significantly impacts patient prognosis, management, and the design and execution of clinical trials.[55] Incorporation of defining molecular features (e.g., TERT promoter mutation, EGFR amplification, and combined whole-chromosome 7 gain/10 loss in IDH-wildtype diffuse astrocytomas) can support assignment of glioblastoma, IDH-wildtype even when classic histologic features are limited, reinforcing the need for tissue-based molecular profiling as part of routine diagnostic workup.[56, 57]

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. A large real-world pan-tumor analysis of comprehensive genomic profiling demonstrated high sample adequacy and sequencing success for CNS tumor tissue specimens, comparable to other solid tumors, supporting feasibility of tissue-based NGS in routine practice.[58] 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.[55] Given that clinically relevant alterations are often non-overlapping across entities, multigene tissue NGS panels can provide a one-test approach to capture defining mutations (e.g., IDH1/2, TERT promoter, ATRX, EGFR, BRAF, H3 variants) and key copy-number events (e.g., 1p/19q whole-arm codeletion, chromosome 7 gain/10 loss, and CDKN2A/B deletion) that inform integrated diagnosis, prognosis, clinical trial eligibility, and therapy selection.[55, 59] Testing for IDH1 and IDH2 pathogenic variants is crucial as it differentiates tumors' prognostic paths: IDH wild-type tumors typically show poorer outcomes.[57] In addition, IDH mutation status is increasingly predictive for targeted therapy selection.[60] Also, MGMT hypermethylation is a positive predictor of chemotherapy response. 1p/19q codeletion required for WHO-defined oligodendroglioma is often assessed by non-NGS methods (e.g., FISH or PCR/LOH analysis) as part of the diagnostic workflow; NGS-based inference of whole-arm 1p/19q loss may be feasible but is dependent on panel breadth, bioinformatics, and tumor purity.[60]

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.[61, 62] 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.[62] Because primary MMRD gliomas are frequently associated with underlying germline predisposition, identification of tumor MMR gene alterations, hypermutation, or an MMRD phenotype on tissue profiling should prompt consideration of referral for genetic counseling and germline evaluation when clinically appropriate.[61, 62]

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 relapsed/refractory pediatric low-grade glioma, BRAF V600E mutations and BRAF fusions/rearrangements can be predictive biomarkers for targeted therapy selection, including tovorafenib for eligible tumors.[59, 63] In diffuse midline glioma, identification of an H3 K27M mutation has become therapeutically relevant with accelerated approval of dordaviprone for progressive disease following prior therapy.[64] In adults, it serves as a criterion for clinical trial eligibility.

The phase 3 INDIGO trial demonstrated that vorasidenib, an oral brain-penetrant inhibitor of mutant IDH1/2, improved progression-free survival and delayed time to next intervention in patients with grade 2 IDH1- or IDH2-mutant diffuse glioma after surgery.[65] Extended analyses showed reduced volumetric tumor growth and improved seizure control without observed

detriment to health-related quality of life or neurocognition.[66] Consistent with these data, the ASCO-SNO rapid recommendation update includes vorasidenib as an option for selected patients with IDH-mutant CNS WHO grade 2 oligodendroglioma or astrocytoma when radiotherapy and chemotherapy have been (or can be) deferred.[60] Long-term follow-up of CATNON further supports IDH mutation as a predictive biomarker for benefit from adjuvant temozolomide in 1p/19q non-codeleted anaplastic glioma, with no benefit observed in IDH wild-type tumors.[67] However, despite regulatory approvals for NTRK fusion inhibitors and pembrolizumab for specific CNS tumors, the evidence of clinical benefit remains modest.[55, 68] Emerging observational data suggest potential associations between CDK4 amplification and prolonged bevacizumab benefit in glioblastoma, but the evidence remains insufficient to guide routine treatment selection or to define minimum required testing beyond established diagnostic and predictive biomarkers.[69]

MGMT promoter methylation testing is supported by the ASCO–SNO guideline[70] as a clinically actionable biomarker in select populations, as articulated in Recommendation 2.7, which is based on evidence from randomized trials in older or poor-performance-status patients demonstrating a predictive interaction between MGMT status and treatment benefit. Specifically, the NOA-08 and Nordic trials showed that patients with MGMT promoter methylated tumors derive improved overall and progression-free survival with temozolomide, whereas those with unmethylated tumors derive greater benefit from radiotherapy, establishing MGMT as a determinant of optimal monotherapy selection. The guideline's clinical interpretation emphasizes that, in this population where treatment intensity must be individualized, therapy choice (TMZ vs RT vs supportive care) is contingent on MGMT status, making accurate and timely testing essential for appropriate care selection. Although MGMT is not sufficient to guide treatment decisions in younger, fit patients due to limited prospective evidence, the literature review underlying Recommendation 2.7 demonstrates consistent predictive value in elderly/frail cohorts, supporting its use to stratify therapy and avoid ineffective or unnecessarily toxic treatments. Accordingly, MGMT promoter methylation testing is reasonable and medically necessary in this context to guide evidence-based, individualized treatment decisions aligned with ASCO–SNO recommendations.

Breast Cancer

Localized invasive breast cancer; early adjuvant setting, lymph node negative, lymph node omitted, or lymph node micro-metastasis

Premenopausal or age ≤ 50 years:

- Gene expression profiling is considered **medically necessary** to guide adjuvant therapy* treatment-decision making using Oncotype DX®

Postmenopausal or age > 50 years:

- Gene expression profiling is considered **medically necessary** to guide adjuvant therapy* treatment-decision making using Oncotype DX®, MammaPrint®, EndoPredict®, or Prosigna®

AND ALL the following criteria are met for **EITHER** the premenopausal (≤ 50) or postmenopausal population (> 50):

- 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 cN0 if sentinel lymph biopsy was omitted, 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)

Localized invasive breast cancer; early adjuvant setting, axillary lymph node status: 1-3 positive

Gene expression profiling using Oncotype DX®, MammaPrint®, or EndoPredict® is considered **medically necessary** for **females over age 50 or postmenopausal** and **adult males** (referring to the sex assigned at birth) with 1 to 3 positive axillary lymph nodes (clinical or pathological N1a, N1b or N1c) 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)

Ductal carcinoma in-situ (DCIS)

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.

Breast cancer recurrence

Testing recurrent breast cancer is **not medically necessary** if prior breast gene expression profiling has been conducted on the tumor.

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 and within 6 months of starting extended adjuvant therapy
- The individual has not been treated with ovarian suppression, an aromatase inhibitor, a CDK 4/6 inhibitor, or a PARP inhibitor
- Testing is performed on the primary tumor and not on recurrent disease

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** 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 or imlunestrant

- 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.*

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. A prominent test that emerged 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.[71] 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.[72, 73] 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).[74] MammaPrint is recommended for node-negative postmenopausal individuals or those over age 50 with high clinical risk and postmenopausal patients or individuals over age 50 who are node-positive (1–3 positive nodes) with high clinical risk per the 2022 ASCO guideline update.[43] EndoPredict and Prosigna receive moderate recommendations in the postmenopausal, over age 50, node negative category and EndoPredict has a moderate recommendation in the postmenopausal age greater than 50, node positive category.[74] Prosigna is not recommended in the lymph node positive setting.[43] Current data suggest that premenopausal patients with 1-3 positive nodes benefit from chemotherapy regardless of genomic assay result. Therefore, gene expression testing in premenopausal or age less than or equal to 50 individuals who have 1-3 positive lymph nodes is not recommended. For early-stage adjuvant treatment decisions, the Breast Cancer Index is not commonly in use. Recent ASCO guidance on axillary management supports omission of sentinel lymph node biopsy in selected clinically node-negative patients; in such cases, patients may be managed as clinically node-negative for purposes of multigene expression profiling, and eligibility for assays such as Oncotype DX should not be contingent on pathologic nodal staging when axillary surgery is appropriately omitted.[75] Oncotype DX Recurrence Score results obtained from core needle biopsy specimens have shown high concordance with paired surgical excision specimens, supporting use of diagnostic biopsy tissue when timely adjuvant decision-making is needed.[76]

There is currently no established role for emerging biomarkers such as PD-L1, circulating tumor cells, or tumor-infiltrating lymphocytes. In addition, while prospective studies evaluating multigene assays (e.g., the 12-gene DCIS Score) to guide radiotherapy decisions are emerging, evidence remains insufficient to demonstrate clinical utility for routine decision-making in DCIS, and such testing should be considered investigational outside of clinical trials.[77, 78]

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.[79] 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.[80] ASCO guidelines suggest extended therapy offers modest added benefits with challenges of increased toxicity.[74, 81] Decision-making includes risk of recurrence, treatment tolerability, and patient preference, with considerations

including psychological and financial impacts.[82, 83] The role of genomic testing in predicting extended adjuvant therapy benefits requires further prospective studies.[84]

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.[85] and Bartlett et al.[86, 87] 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,[88] 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.[89] Overall, the role of genomic testing as a predictor of benefit for use of extended adjuvant therapy remains to be established in prospective studies,[90] 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 acknowledge the BCI but also recognize the Clinical Treatment Score post-5 years (CTS5), a clinicopathologic calculator that is available online,[91] with similar strength of recommendation for postmenopausal patients. CTS5 has been validated as a prognostic tool for late distant recurrence, although its predictive value for benefit from extended endocrine therapy remains uncertain.[92]

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.[93]

Metastatic Breast Cancer

The ESMO Translational Research and Precision Medicine Working Group developed the ESCAT system classifying molecular aberrations for clinical actionability.[94] 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.[31, 95] Recent guideline updates and regulatory approvals have expanded the actionable HER2 spectrum (including HER2-low and HER2-ultralow by IHC), increasing the importance of accurate and standardized HER2 IHC/ISH interpretation for selection of antibody-drug conjugates in metastatic disease.[96]

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.[97] Alpelisib targets the PIK3CA-mutated, ER-positive/HER2-negative metastatic breast cancer, approved following the Solar-1 trial.[98] 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.[99] Additionally, olaparib is a standard treatment for those with BRCA P/LP variants as per the OlympiaAD trial.[100]

Most recently, the FDA approved capivasertib with fulvestrant for HR-positive, HER2-negative breast cancer with PIK3CA/AKT1/PTEN alterations,[101, 102] and also inavolisib with palbociclib and fulvestrant for similar patients with PIK3CA P/LP variants.[103] The 2023 ASCO guidelines recommend evaluating P/LP variants like ESR1, PIK3CA, or inactivation of PTEN in progression samples.[104] 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. These biomarkers may be assessed on progression specimens using tissue-based molecular methods when adequate tumor tissue is available. 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. Final overall survival analyses from genotype-selected randomized trials have reinforced clinical utility of tissue-based PIK3CA testing to guide targeted endocrine combinations in endocrine-resistant HR-positive/HER2-negative advanced breast cancer.[105]

Most kinase fusion targets are in development, but NTRK inhibitors are approved. Other biomarkers, such as FGFR1/FGFR2, NF1, 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.[106, 107]

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** of the following, with no prior testing
    - MSI testing by PCR
    - BRAF V600E
    - KRAS
    - PIK3CA
    - 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** of the following:
    - MSI testing (if not previously performed)
    - POLE
    - POLD P/LP variants
    - Extended RAS testing (KRAS and NRAS exons 2,3, and 4), including KRAS p.G12C
    - 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.[108] 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).[109, 110]

In early-stage CRC—particularly stage II—MMR status is a key prognostic and predictive biomarker. Deficient MMR (dMMR) is associated with improved prognosis but reduced benefit from fluorouracil-based adjuvant therapy.[111] Professional guidelines recommend that MSI and/or MMR status be assessed in all patients at diagnosis using biopsy material.[112] Recent systematic reviews also highlight high response rates and a favorable safety profile for neoadjuvant immune checkpoint inhibitor therapy in localized dMMR CRC, reinforcing the imperative of dMMR testing in all newly diagnosed CRC cases.[113, 114]

The ALASCCA trial is a randomized, placebo-controlled study that tested adjuvant low –dose aspirin (160 mg dialy for 3 years) in patients with stage I–III colorectal cancer harboring somatic PI3K pathway alterations, including PIK3CA mutations or other PI3K pathway alterations.[115] This trial found that aspirin significantly reduced recurrence in patients with PIK3CA hotspot mutations (exons 9 or 20), establishing PIK3CA status as a predictive biomarker for aspirin benefit in localized colorectal cancer. For those individuals with PIK3CA hotspot mutations, the 3-year recurrence rate was 7.7% with aspirin versus 14.1% with placebo (hazard ratio 0.49, 95% CI 0.24–0.98; P = 0.04) and showed a similar signal among those with other PI3K alterations (3-year recurrence rate was 7.7% with aspirin versus 16.8% with placebo; hazard ratio 0.42, 95% CI 0.21–0.83). This is randomized evidence that tumor PIK3CA testing can guide adjuvant therapy decisions in localized CRC, supporting consideration of PIK3CA testing to identify patients who may benefit from aspirin therapy.

In metastatic CRC, about 5% of tumors are MMR-deficient or MSI-high (MSI-H), making these tumors suitable candidates for immunotherapy.[108] Thus, it is essential to conduct MMR deficiency testing through immunohistochemistry or determine MSI-H status through polymerase chain reaction (or validated NGS-based MSI assays) to screen for Lynch syndrome and refine therapeutic decision-making in both localized and metastatic CRC.

The standard of care in metastatic CRC includes tissue-based molecular profiling for RAS (KRAS and NRAS) to predict lack of benefit from epidermal growth factor receptor (EGFR)-targeting monoclonal antibodies (e.g., cetuximab, panitumumab). Pathogenic/likely pathogenic variants in exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) of KRAS and NRAS are associated with resistance to anti-EGFR therapy, and anti-EGFR antibodies are therefore recommended only for patients with RAS wild-type tumors. More recently, KRAS G12C has become a specific predictive biomarker supporting KRAS G12C-directed therapy in previously treated metastatic CRC.[116, 117] Beyond RAS, HER2 amplification/overexpression is an actionable biomarker in selected patients (typically RAS wild-type), and tucatinib plus trastuzumab has demonstrated activity in chemotherapy-refractory HER2-positive, treatments wild-type unresectable or metastatic CRC.[118] HER2 expression may also have prognostic and predictive value regarding selection of bevacizumab- versus cetuximab-based first-line strategies. Although NTRK gene fusions are rare in CRC, their prevalence is higher in dMMR tumors. In contrast, for localized rectal cancer, the 2025 ESMO Clinical Practice Guideline states that analysis of RAS, BRAF V600E, NTRK, and HER2 status currently has no impact on treatment of localized tumors and cannot be recommended.[112]

BRAF V600E pathogenic variants, present in approximately 5%-10% of metastatic CRC cases, are associated with an aggressive clinical phenotype and poor comes with standard chemotherapy. In the phase 3 BREAKWATER trial, first-line encorafenib plus cetuximab and mFOLFOX6 significantly improved progression-free survival and overall survival versus standard care in BRAF V600E-mutated metastatic CRC, supporting the clinical utility of BRAF V600E testing in advanced disease.[119]

While some studies suggest prognostic value in BRAF and KRAS testing for stage II–III localized CRC, NCCN guidelines indicate that there are insufficient data to support routine use of these biomarkers to estimate recurrence risk or inform adjuvant therapy decisions in localized disease.[120]

The current ESCAT level for KRAS G12D testing in advanced colorectal cancer is Tier III. This classification indicates that its actionability is not yet 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 KRAS G12D-mutant and other RAS-mutant patients overall.[121]

Recent FDA approvals have further expanded biomarker-linked therapeutic options in colorectal cancer, underscoring the importance of accurate tissue-based genotyping. For example, tucatinib combined with trastuzumab is approved for patients with unresectable, HER2-positive, RAS wild-type metastatic CRC after progression on chemotherapy.[118] In KRAS G12C-

mutated CRC, the FDA has approved sotarasib with panitumumab and granted accelerated approved of adagrasib with cetuximab for patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.[122, 123] The FDA also granted accelerated approval to encorafenib with cetuximab and mFOLFOX6 for patients with metastatic CRC with a BRAF V600E pathogenic variant.[124]

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 regardless of stage 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 **ANY** of 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 clinically actionable biomarkers and hereditary cancer risks. In contemporary practice, upfront tumor assessment typically includes MMR/MSI status (to guide immune checkpoint inhibition and universal tumor screening for Lynch syndrome), and molecular classification using POLE sequencing, MMR status, and p53 aberrations to refine prognostic risk stratification and inform adjuvant management.[125] FDA approved companion diagnostics are used to select patients with deficient mismatch repair (dMMR) and microsatellite instability-high (MSI-H) solid tumors 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% and a median progression-free survival of 13.1 months.[126]

These findings demonstrated significant antitumor activity and improved survival outcomes for individuals with MSI-H/dMMR endometrial cancers receiving pembrolizumab. In addition, randomized phase III trials have established clinical benefit for adding immune checkpoint inhibitors to first-line carboplatin/paclitaxel in primary advanced or recurrent endometrial cancer, with particularly large benefits in dMMR/MSI-H tumors, reinforcing the need for routine MMR/MSI testing at diagnosis or first recurrence.[127, 128]

HER2 (ERBB2) amplification/overexpression is enriched in uterine serous carcinoma and other p53-abnormal high-grade endometrial carcinomas and can be therapeutically actionable. A randomized phase II trial demonstrated improved outcomes with the addition of trastuzumab to carboplatin/paclitaxel in HER2-positive advanced or recurrent uterine serous carcinoma.[129] Recent European guidance recommends incorporating HER2 testing (typically by IHC with in situ hybridization confirmation when equivocal) in selected high-grade or p53-abnormal tumors, particularly in the recurrent/metastatic setting, to guide anti-HER2 therapy selection.[125]

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 MLH1 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.[130]

Recent trials have evaluated molecular-integrated risk profiling to guide adjuvant management. PORTEC-4a prospectively compared molecular profile–based adjuvant strategies (incorporating the TCGA-aligned molecular subgroups and additional clinicopathologic risk factors) versus standard clinicopathologic risk assessment; the primary analysis supports feasibility and provides prospective evidence for molecularly informed, risk-adapted adjuvant therapy selection.[131] Somatic tissue testing that includes POLE sequencing, MMR status, and p53 IHC therefore has increasing clinical utility in both systemic therapy selection and risk stratification for endometrial carcinoma.[125]

Melanoma

Diagnostic testing in melanoma

Gene expression profiling of indeterminate cutaneous melanocytic lesions for diagnosis is considered **not medically necessary.**

- The following test example is considered **not medically necessary:**
    - myPath® Melanoma

Prognostic testing in melanoma

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

- The following test examples are considered **not medically necessary:**
    - DecisionDx Melanoma (31-GEP)
    - DecisionDx UM (15-GEP)
        - DecisionDx-PRAME
    - DecisionDx-UMSeq
    - MelaGenix (11-GEP)
    - Merlin (CP-GEP)

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** 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 can provide 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.[132] 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.[132]

MyPath Melanoma is a 23-gene expression profile that evaluates expression of RNA transcripts produced by 14 discriminant genes and 9 control genes for normalization. The test uses a proprietary algorithm combining measurements of gene expression and assigned weight of each gene component to classify lesions as benign (GEP suggestive of benign neoplasm), malignant (GEP suggestive of melanoma), or indeterminate/intermediate risk (GEP cannot exclude malignancy). A study by Reimann et al, in Modern Pathology in 2018 looked at a prospective comparison of MyPath gene expression score with histopathology, FISH, and SNP array. A total of 268 melanocytic lesions (198 morphologically unequivocal and 70 morphologically ambiguous lesions) were evaluated.[133] In the morphologically unequivocal cases (n = 198), agreement with histopathology was 75%, sensitivity 67%, and specificity 81%. These results showed that approximately one-third of melanomas were not detected by the MyPath Melanoma test. In the morphologically ambiguous cases (n = 70), agreement with histopathology was 74%, sensitivity 50%, and specificity of 93%. In the clinically relevant ambiguous lesion population, MyPath Melanoma demonstrated low sensitivity (50**%**), missing half of melanomas; specificity was high (93%). The available evidence demonstrates moderate overall diagnostic agreement, low sensitivity in indeterminate melanocytic lesions, inferior correlation compared with FISH and SNP array, and absence of demonstrated impact on clinical outcomes. The evidence does not establish that MyPath Melanoma improves diagnostic accuracy sufficiently to change patient management or improve health outcomes in histologically indeterminate melanocytic lesions. MyPath Melanoma gene expression testing is considered not medically necessary for the diagnosis of cutaneous melanocytic lesions, including histologically indeterminate lesions, due to lack of demonstrated clinical utility. The NCCN guideline for Cutaneous Melanoma states “Based on the current evidence, the NCCN Melanoma Panel does not recommend incorporation of commercially available GEP tests into melanoma care.”[134]

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.[135] 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].[136] 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.[137] 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.[138]

Use of gene expression profiling (GEP) for categorizing localized (stages 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 versus class 2, rather than providing specific survival predictions.[135] DecisionDx-Melanoma is a prognostic gene expression profiling (GEP) assay that analyzes the activity of 31 genes in primary cutaneous melanoma tumor tissue. The comprehensive result report includes: 31-GEP Class Score, personalized risk estimates for melanoma recurrence within 5 years, and personalized risk estimate for sentinel lymph node biopsy (SLNB) positivity. 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.[139] However, the methodology of this analysis was criticized for lacking a pre-specified protocol and failing to adjust for confounders or assess bias comprehensively.[140] Clinical utility of GEP classifiers is still uncertain, and smaller absolute risk differences were found between the 31-gene tested cohort and unmatched cohorts.[141] These tests should be evaluated alongside traditional phenotypic models and simple outcome algorithms.[142] Of note, the NCCN guidelines for cutaneous melanoma describe a risk classification and suggest systemic imaging based on the scheme.[143] 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 patients with resected stage IIA–C melanoma and uses a prognostic gene expression signature to limit treatment to a subgroup of patients at 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.[144] NCCN guidelines state that “additional prospective investigation will further inform the utility of gene expression profiling tests” and “other analytical models for SLNB risk prediction.”[143] The Society of Surgical Oncology (SSO) Consensus Statement: Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma was published to develop recommendations regarding the use of GEP to guide management of patients with melanoma.[145] The panel performed a systematic review of the literature, including articles published from January 2012 until August 2023. 50 articles met the inclusion criteria. These articles included evidence related to three available GEP tests: 31-GEP, CP-GEP, and 11-GEP. The panel found that current evidence often fails to account for known clinicopathologic risk factors and lacks high-level data. The SSO concluded GEP should currently be considered investigational and not recommended for routine clinical decision-making. The panel emphasized lack of high-level prospective evidence, limited independent validation, frequent industry sponsorship, overlapping datasets across publications, and insufficient proof of improved patient outcomes. The consensus was that the integration of GEP into routine clinical practice for predicting sentinel lymph node status and patient prognosis in melanoma is not currently recommended. Furthermore, the panel determined that GEP should be considered primarily an investigational tool limited for use in the context of clinical trials or specialized research settings at the present time. Current NCCN guidelines do not recommend incorporation of prognostic GEP tests into melanoma care and that the routine use of GEP to predict patient outcome requires further prospective investigation.[143] Furthermore, NCCN states that predictive GEP tests to differentiate melanomas at low versus high risk of nodal metastasis should not replace surgical oncology discussion of pathologic staging with SLNB in eligible patients. The prospective, multicenter, double-blinded prognostic study (MERLIN_001) evaluated the clinicopathologic gene expression profile (CP-GEP; Merlin assay, SkylineDx) in 1,761 patients with T1–T3 clinically node-negative cutaneous melanoma undergoing SLNB.[146] Overall SLN positivity was 17.6%. Thirty-seven percent of patients were classified as low risk, with a 7.1% SLN positivity rate (negative predictive value [NPV] 92.9%), compared with 23.8% positivity in high-risk patients (~3.4-fold higher risk). In clinical stage IB patients (67% of the cohort), nearly half were low risk, with a 6.5% SLN positivity rate versus 18.3% in high-risk patients; however, the primary study objective—demonstrating that low-risk patients would have an upper 95% CI below the 5% SLN positivity threshold—was not met. The study demonstrates prognostic discrimination but does not establish clear clinical utility for safely omitting SLNB under current guideline thresholds. The test may aid shared decision-making in selected patients (e.g., older or comorbid individuals), but it does not justify routine practice change. Therefore, the clinical utility of GEP testing is not supported in this study. Moreover, the manufacturer of the assay funded and participated in study infrastructure and design elements, and multiple authors or institutions received research funding or support from the manufacturer SkylineDx during the conduct of the study. A consensus review on the role of gene expression profile testing in cutaneous melanoma published in JAMA Dermatology by Kashani-Sabet et al. does not recommend GEP testing to guide clinical decision making outside clinical trials until further prospective studies are performed in large datasets of unselected patients.[147] The panel in the Kashani study reached consensus that low-risk GEP results should not override concerning histopathologic features when selecting patients for sentinel lymph node biopsy and did not reach consensus on using high-risk GEP scores to guide imaging or surveillance decisions. Overall, the group concluded that although GEP assays show prognostic associations, their role in routine clinical decision-making remains undefined and requires further prospective validation. Yamamoto et al. report results of the prospective, multicenter DECIDE study evaluating how clinicians used the 31-gene expression profile (31-GEP; DecisionDx-Melanoma) to guide SLNB decisions in patients with T1–T2 cutaneous melanoma.[148] Among 193 patients, clinicians reported that 31-GEP results influenced 85.3% of SLNB decisions, leading to a

significant reduction in SLNB performance compared with a contemporary 78% baseline rate (overall SLNB rate 59.1%, p<0.01), particularly in low-risk Class 1A patients (48.6% SLNB rate; 3.0% SLN positivity), while higher-risk Class 1B/2A and 2B patients underwent SLNB at higher rates with correspondingly higher SLN positivity (13.8% and 22.2%, respectively). The study's primary aim was to evaluate the impact of 31-GEP on SLNB decision-making rather than to independently validate long-term prognostic outcomes. While the authors cite prior studies supporting the 31-GEP's ability to stratify recurrence and metastasis risk, this prospective study does not provide outcome-based evidence demonstrating improved survival or recurrence prediction; long-term outcomes are still pending. Therefore, this study supports the clinical use of 31-GEP for influencing SLNB decisions but does not independently establish or prove prognostic clinical utility (e.g., improved recurrence prediction or survival outcomes) in cutaneous melanoma.

Prognostic Classification of Uveal Melanoma

Uveal melanoma carries a 30%-50% risk of metastasis within five years, mostly to the liver.[149] Metastatic risk has historically been predicted by tumor morphologic and pathologic features such as thickness, diameter, and location, among others.[150] Monosomy 3 and additional copies of 8q have been linked to poor survival.[149]

The 15-gene expression profile test DecisionDX-UM® predicts metastatic risk based on tumor biology and may aid in surveillance program decisions.[151] Another test by Impact Genetics Inc. assesses chromosomal changes and sequences certain genes.[150] However, no survival benefit has been documented for early detection of asymptomatic disease, leaving surveillance recommendations uncertain.[149] 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. The NCCN guidelines for Uveal Melanoma (V1.2026) state that gene expression profiling is recommended to determine whether the tumor is Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk) which in turn should inform the frequency of follow-up.[152] PRAME gene expression is associated with further refinement of risk class with a revised footnote stating that PRAME expression may be associated with an increased risk of metastasis in both Class I and Class 2 uveal melanoma tumors.[120] However, the 15-GEP is not a current standard of care.[153] 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.[154] Surveillance decisions involve consideration of clinical variables such as tumor characteristics (size and location) in conjunction with personal preferences and genetic data.[150] DecisionDx-UMSeq is a targeted next-generation sequencing (NGS) panel performed on uveal melanoma tumor tissue to identify somatic mutations in 7 genes commonly altered in uveal melanoma. Strong outcomes-based clinical utility evidence is not clearly demonstrated for this test.

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.[155] 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.[136, 156]

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.[156] 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.[157]

Metastatic uveal melanoma testing for HLA-A*0201 assists in identifying patients for treatment with tebentafusp, which improved survival in trials.[158] NRAS P/LP variants correlate with poor prognosis, and certain therapies have shown activity in BRAF and NRAS-mutant melanomas.[159, 160] KIT P/LP variants, found in mucosal and acral melanoma subtypes, respond to specific inhibitors, though their exceptionality warrants only optional

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 perioperative/adjuvant targeted therapy used per FDA label or when listed as Category NCCN 2A

Advanced (stage IIIB, IIIC, or IV metastatic) 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, which may include targeted RNA-based fusion testing, 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 variants, rearrangements, fusions, or amplifications) in **ALL** the following genes: EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS, MET, NTRK, and RET
    - If the use of zenocutuzumab-zbco therapy is being considered, then the multigene NGS panel must also contain the gene NRG1 for fusion analysis
- 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 established biomarker-driven 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,[161, 162] and selecting patients based on predictive biomarkers is associated with improved outcomes.[163, 164] ASCO living guidelines emphasize that all patients with advanced NSCLC should have access to biomarker testing with a validated broad multigene panel and validated tissue immunohistochemistry assays for PD-L1—and, where relevant to therapeutic selection, HER2 and MET protein expression; PD-L1 immunohistochemistry alone should not be used to guide treatment decisions.[165, 166]

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.[167] A second wave of specific molecular alterations worthy of routine testing emerged including ERBB2 (HER2), KRAS, RET, MET, and NTRK genes.[167, 168] 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.[169, 170] Multiple additional targeted therapies have been approved for treating metastatic NSCLC, including tepotinib for patients with MET exon 14 skipping alterations,[171] repotrectinib for ROS1-positive

NSCLC,[172] encorafenib with binimetinib for BRAF V600E pathogenic variant-positive NSCLC,[173] pralsetinib for RET fusion-positive NSCLC,[174] and amivantamab-vmjw with carboplatin and pemetrexed for EGFR exon 20 insertion pathogenic variants,[175] ensartinib for ALK-positive NSCLC, and zenocutuzumab-zbco for NSCLC with NRG1 gene fusions.[176] Recent data and approvals have continued to expand the therapeutic implications of tissue-based biomarker testing in metastatic NSCLC, with approved biomarker-directed therapies spanning MET exon 14 skipping, ROS1, BRAF V600E, RET fusions, EGFR exon 20 insertions, and NRG1 fusions, and more recently HER2-mutant disease treated with HER2-directed tyrosine kinase inhibitors and antibody-drug conjugates.[24, 177, 178] In addition, MET protein overexpression (distinct from MET exon 14 skipping) represents a therapeutically relevant biomarker that requires tissue immunohistochemistry assessment.[166] These developments are incorporated into contemporary evidence-based treatment guidelines.[165, 179]

In patients with metastatic NSCLC who progress on biomarker-directed therapy, repeat tissue sampling for resistance profiling may identify new genomic drivers that inform subsequent treatment selection. However, real-world data suggest rebiopsy is feasible in only about half of patients and yields new information in a minority, supporting selective use when results are likely to change management.[180]

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[181] 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.[182] The therapeutic implications of these biomarkers are reflected in updated evidence-based guidelines, including the ESMO living guideline for oncogene-addicted metastatic NSCLC and the ASCO living guideline for stage IV NSCLC with driver alterations.[165, 183]

With increasing use of perioperative systemic therapies and adjuvant targeted therapy, tissue-based biomarker testing is clinically relevant in localized (resectable) NSCLC. ESMO recommends EGFR mutation testing for patients with stage IB (>3 cm or other high-risk features) to IIIC NSCLC to identify candidates for adjuvant or consolidation osimertinib, and ALK alteration testing for resectable stage II (≥4 cm) to IIIA NSCLC to identify candidates for adjuvant alectinib.[184] ESMO also recommends tumor PD-L1 testing before treatment decision making in stage II–III NSCLC being considered for perioperative chemotherapy–immunotherapy and for resected stage II–IIIA NSCLC when preoperative chemotherapy–immunotherapy was not administered; recommended biomarker testing should be carried out as soon as possible as part of the preoperative evaluation, and broad NGS may be considered when feasible.[184] Per NCCN guidelines, RNA-based NGS may increase novel fusion detection and can be performed concurrently or sequentially with DNA-based NGS. If no identifiable driver oncogenes with DNA-based broad molecular profiling are identified, RNA-based testing is recommended.[1] For NRG1 gene fusions, RNA-based NGS is preferable to DNA-based NGS as NRG1 gene fusions are often not detected by DNA-based NGS because the large introns in NRG1 are not commonly included in targeted DNA-based NGS panels or whole exome sequencing. FISH testing for NRG1 fusions requires confirmation by NGS.[1] Similarly for MET exon 14 variants, RNA-based NGS may have improved detection. For RET gene fusions, RNA-based NGS is preferable to DNA-based NGS.

Tissue specimens obtained at diagnostic biopsy and/or surgical resection can be used for biomarker testing before perioperative treatment planning. In patients with resectable stage II–III NSCLC, the addition of neoadjuvant immunotherapy to chemotherapy has minimal to no additional efficacy in tumors with common oncogenic drivers (including EGFR, ALK, ROS1, RET, ERBB2/HER2, and NTRK), supporting upfront biomarker testing when neoadjuvant chemoimmunotherapy is being considered.[185] The investigation of induction (neoadjuvant) targeted therapies is in early stages and should be pursued in the context of clinical trials when available.[185]

Gene expression profiling assays intended to risk-stratify resected early-stage non-squamous NSCLC (e.g., the CLIA-certified 14-gene expression profile marketed as RiskReveal and previously as DetermaRX) have emerging randomized evidence. In the AIM-HIGH phase 3 trial, stage IA–IIA patients classified as molecular high risk had improved disease-free survival with platinum-based adjuvant chemotherapy compared with observation; however, low-risk patients were not randomized, and these results have not yet been incorporated into professional guidelines, so routine clinical use remains investigational.[186]

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.[182]

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 using a validated CLIA-lab certified HRD assay 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, fallopian tube, or primary peritoneal carcinoma

- 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 active treatment or maintenance therapy with a PARP inhibitor per FDA label (or per Category 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.[187] Subsequent trials established clinical utility for identifying both germline and somatic BRCA1/2 pathogenic/likely pathogenic variants and tumor homologous recombination deficiency (HRD) as predictive biomarkers for PARP inhibitor benefit, particularly in advanced-stage disease and maintenance settings.[188] More recent overall survival analyses and FDA regulatory actions have narrowed or withdrawn several PARP inhibitor treatment indications in recurrent ovarian cancer, reinforcing the importance of biomarker-driven patient selection.[189, 190] 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.[191] 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.[192] 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.[31, 193] Given the availability of multiple analytically validated HRD assays[31] and the absence of a guideline requirement for a single named platform, use of any clinically validated, CLIA-certified assay that measures homologous recombination (including genomic instability testing) is appropriate. ASCO guidelines also recommend testing for those with progressive disease on neoadjuvant chemotherapy if they have not already been tested.[188] 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.[194] 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. ASCO further recommends that testing occur at the time of diagnosis or as soon as feasibly possible.[188] International quality standards similarly recommend offering tumor genetic testing for adults newly diagnosed with stage III–IV non-mucinous high-grade epithelial ovarian cancer.[195]

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.[196] The Geneva test, which utilizes the Oncoscan FFPE Assay Kit alongside Large-scale State Transitions (LST) counts, is promising but not yet FDA-approved.[197] Using PAOLA-1 trial specimens, the Geneva HRD test demonstrated predictive value for both progression-free and overall survival benefit with olaparib plus bevacizumab maintenance, with performance comparable to the Myriad MyChoice HRD test.[198] 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 terms of being able to effectively assess HRD-associated genomic instability in the clinical setting.[199]

The FDA's accelerated approval of mirvetuximab soravtansine-gynx in 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.[200] In selected ovarian cancer histologies, somatic alterations beyond HRD

may inform targeted therapy; for example, the FDA granted accelerated approval of avutometinib plus defactinib for KRAS-mutated recurrent low-grade serous ovarian cancer, with KRAS status determined by tumor tissue testing.[201]

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, which may include targeted RNA-based fusion testing, is considered **medically necessary** when **ALL** the following criteria are met:

- The individual has biopsy-proven 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.[202] 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.[203] Tumor molecular profiling is recommended in pancreatic ductal adenocarcinoma to identify actionable alterations (e.g., MSI/dMMR and rare targetable fusions) that may expand therapeutic options and inform clinical trial eligibility, particularly in locally advanced, recurrent, or metastatic disease.[204-206]

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.[207] 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 did not demonstrate improvements in overall survival or quality of life.[208] Given these outcomes and concerns regarding the POLO trial's design165, the clinical utility of maintenance olaparib in this setting remains uncertain.[209]

Although selection of first- and second-line systemic chemotherapy for metastatic pancreatic adenocarcinoma is largely determined by performance status rather than tumor biomarkers,[210] tumor molecular profiling is recommended in pancreatic ductal adenocarcinoma to identify actionable alterations and support clinical trial enrollment.[204-206] In addition, the FDA granted accelerated approval to zenocutuzumab-zbco (Bizengri) for adults with advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring an NRG1 gene fusion with disease progression on or after prior systemic therapy (FDA, 2024). 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.[176] KRAS variants are associated with prognosis and may be predictive of response to fluorouracil-based chemotherapy; however, clinical utility for KRAS subtype-directed selection of standard chemotherapy is not established outside of clinical trials.[204]

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.

The following gene expression test examples are considered **not medically necessary**:

- Decipher®-22 gene classifier
- Oncotype DX® prostate
- Prolaris®
- ProMark®

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 metastatic prostate cancer
- The individual has not had prior MSI or dMMR testing

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

- The individual is a current or likely future candidate for **ONE** of the following therapies:
    - PARP inhibitor (olaparib, rucaparib, niraparib, talazoparib, or another PARP inhibitor FDA approved or per NCCN 2A use in this setting)
- The NGS panel includes BRCA2, BRCA1, and may also include other genes encoding molecules involved in deficient homologous recombination repair (HRD), such as ATM, ATR, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, MRE11A, NBN, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L, MMR genes MLH1, MSH2, MSH6, PMS2, EPCAM and non-HRR genes TP53, PTEN, RB1
- 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.*

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.[211] 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.[212] 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.[213] 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.

Gene Expression Panel Tests in localized prostate cancer

Numerous molecular biomarkers, particularly tissue-based gene expression 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.[214] 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.[215, 216] In a large US claims-based analysis of over 200,000 men with newly diagnosed localized prostate cancer, utilization of biopsy-based genomic classifiers (Decipher, OncotypeDX, Prolaris) rose from <1% to 17% between 2013 and 2022. Younger age, higher income, and high-deductible insurance were associated with increased GC use. Receipt and type of GC were linked to management decisions: GC testing overall was associated with higher odds of active surveillance, while Decipher use correlated more with radiotherapy plus ADT, Prolaris with radical prostatectomy, and OncotypeDX with active surveillance/watchful waiting.[217] Prolaris was ordered more than three times as often in Detroit as in any other city, whereas OncotypeDx was ordered more than twice as often in New York City as in any other city. The study highlights rapid adoption, geographic variation, and real-world influence of genomic classifiers on treatment selection despite ongoing prospective validation trials. Given the absence of prospective clinical trial data, ESMO, 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 ESMO 2025 clinical practice guideline for diagnosis, treatment and follow up in local and locoregional prostate cancer does not recommend routine genomic classifier testing and considers genomic classifiers investigational/adjunctive, not standard of care.[218] Furthermore, this practice guideline does not recommend routine BRCA/ATM testing for treatment decision making in local disease.

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.[215] 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.[219] Overall, it remains uncertain what prognostic endpoints should be prioritized and what magnitude of association with those prognostic endpoints are important. A study looking at cross-comparison of 50,881 men with localized prostate cancer, evaluated concordance between the 22-gene Decipher genomic classifier (GC), Genomic Prostate Score (GPS), and Prolaris cell cycle progression (CCP) signatures and found only minimal-to-moderate correlation between tests. The GPS-derived and CCP-derived models demonstrated poor goodness-of-fit to the 22-gene GC (R^2=0.36 and 0.32, respectively), and multivariable variance analyses showed that approximately 60% of the variation in the 22-gene GC was unexplained by clinical factors or the other genomic signatures. These findings indicate that commercially available genomic classifiers are not interchangeable and should be selected based on their specific validation data and strength of evidence rather than assumed equivalence.[220]

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.[219] The relative accuracy of these biomarker tests compared to other standard tests is unknown.[221] 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.[219]

Gene Expression Panel Tests in intermediate-risk prostate cancer

The randomized phase III NRG/RTOG 0126 trial evaluated the Decipher 22-gene genomic classifier (GC) on pretreatment biopsy tissue from 215 men with intermediate-risk prostate cancer treated with radiation alone (no ADT). The GC was independently prognostic for the composite endpoint of disease progression and for key endpoints including biochemical failure, distant metastasis, metastasis-free survival, and prostate cancer–specific mortality; notably, 10-year distant metastasis was ~4% in GC low versus ~16% in GC high.[222] The authors also report an exploratory interaction suggesting greater absolute benefit from dose-escalated RT among GC intermediate/high patients and conclude that GC improves risk stratification and may aid decision-making in intermediate-risk disease. This study demonstrates strong clinical validity (prognostic performance) and offers hypothesis-generating evidence about predictive interaction with RT dose, but it does not

directly prove clinical utility that GC-guided management changes treatment and improves patient outcomes. The phase III NRG-GU010 (GUIDANCE) randomized trial in unfavorable intermediate-risk prostate cancer using Decipher to guide de-intensification (omit ADT in low Decipher) or intensification (more systemic therapy for higher Decipher) is ongoing.[223] Decipher score in this study is to be used for patient selection and the two variations of treatment to be studied: intensification for higher Decipher score or de-intensification for low Decipher score. The NCCN prostate cancer guidelines list the 22 gene classifier (Decipher) GC as an advanced risk stratification tool with the caveat that advanced prognostic tools are only recommended "when they have the potential ability to change management and should not be ordered reflexively."[224] The footnote within the Advanced Prognostic table states: "In the absence of prospective trials, caution is warranted if using these prognostic tools to influence treatment decisions. The Panel awaits future trials that confirm the initial result."

Gene Expression Panel Tests in high-risk and very-high-risk prostate cancer

Nguyen et al. performed a prespecified individual-patient meta-analysis of biopsy specimens from three NRG/RTOG phase III randomized trials (9202, 9413, and 9902) evaluating high- and very-high-risk localized prostate cancer treated with radiotherapy and androgen deprivation therapy, to validate the Decipher 22-gene genomic classifier (GC). The analysis demonstrated that higher GC scores were independently associated with significantly increased risks of distant metastasis, prostate cancer–specific mortality, and overall survival, even after adjustment for standard clinicopathologic factors, showing that GC provides meaningful additional prognostic stratification within clinically defined high-risk disease.[225] However, because GC testing was conducted retrospectively and treatment in the parent trials was not assigned or modified based on GC results, the study establishes strong clinical validity (prognostic value) but does not prove clinical utility—meaning it does not demonstrate that using the GC to guide treatment decisions improves patient outcomes.

Gene Expression Panel Tests in the setting of biochemical recurrence (BCR) post-radical prostatectomy

An ancillary analysis of the NRG/RTOG 9601 phase III randomized trial evaluated the Decipher 22-gene genomic classifier (GC) using radical prostatectomy specimens from men with biochemically recurrent prostate cancer treated with salvage radiotherapy ± bicalutamide. With a median follow-up of ~13 years, GC scores were independently associated with key clinical outcomes—increased distant metastasis, prostate cancer–specific mortality, and overall survival—after adjusting for standard clinicopathologic factors.[226] The findings suggest that the GC provides prognostic information beyond traditional risk factors in this recurrent setting and indicates that not all men derive equal benefit from the addition of hormone therapy to salvage radiation. It does not definitively establish clinical utility of the Decipher 22-gene genomic classifier—although it provides strong evidence of clinical validity and suggests potential predictive utility. To demonstrate clinical utility, a randomized trial where patients are assigned to GC-guided therapy versus standard clinicopathologic–guided therapy with improved metastasis-free survival or overall survival in the GC-guided arm is needed. NRG-GU009/PREDICT-RT trial is ongoing, but results are not yet available.

Molecular Profiling in Advanced and 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, rucaparib, and niraparib (for those with homologous-recombination gene deficiency).

The prevalence of recurrent genomic alternations varies across various prostate cancer clinical scenarios and also by published cohort. 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.[227] 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.[228] The ESMO Precision Medicine working group recommends multigene NGS panel testing in metastatic prostate cancer to assess for ESCAT level 1 alterations.[227] 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.[229]

The pivotal clinical trials of PARP inhibitors in metastatic castrate resistant prostate cancer include the phase III PROfound trial for olaparib, the phase II Triton2 trial (for rucaparib), and the phase III MAGNITUDE trial (for niraparib). Results from three randomized phase III trials (TALAPRO-2, PROPEL, and MAGNITUDE)[230, 231] have demonstrated that combining an ARPI with a PARPi as first-line treatment for mCRPC significantly improves outcomes in patients with BRCA alterations compared with an ARPI alone.[232] In the final prespecified overall survival analysis of TALAPRO-2, talazoparib plus enzalutamide (ARPI) significantly improved overall survival versus enzalutamide alone in patients with HRR-deficient mCRPC (median 45.1 vs 31.1

months; hazard ratio 0.62, p=0.0005) at a median follow-up of 44.2 months. The survival benefit was most pronounced in patients with BRCA1/2 alterations (hazard ratio 0.50), though benefit extended to non-BRCA HRR alterations. Updated rPFS remained strongly favorable (median 30.7 vs 12.3 months; hazard ratio 0.47).[231] These data establish talazoparib plus enzalutamide as a standard-of-care first-line option for HRR-deficient mCRPC.

More recently, the Phase III AMPLITUDE trial results support the addition of the PARP inhibitor niraparib to abiraterone acetate plus prednisone (AAP) in metastatic castration-**sensitive** prostate cancer (mCSPC) with BRCA2 gene alterations. The phase III AMPLITUDE trial evaluated niraparib plus abiraterone acetate and prednisone (AAP) versus placebo plus AAP in patients with metastatic castration-sensitive prostate cancer (mCSPC) harboring homologous recombination repair (HRR) gene alterations (N=696). The trial met its primary endpoint, demonstrating a significant rPFS improvement in the BRCA subgroup (hazard ratio 0.52; median not reached vs 26 months; P<0.0001) and in the overall HRR-positive intention-to-treat population (hazard ratio 0.63; P=0.0001). Time to symptomatic progression was also significantly improved (hazard ratio 0.44 in BRCA subgroup; hazard ratio 0.50 in intention-to-treat).[233] Adding niraparib to abiraterone in HRR-altered mCSPC significantly prolongs radiologic PFS—most notably in BRCA1/2-mutated disease—establishing PARP inhibition as an effective earlier-line strategy in biomarker-selected metastatic castration-sensitive prostate cancer. BRCA2 was the largest single-gene subgroup and historically had the strongest evidence for PARP sensitivity in prostate cancer and was a trial stratification factor whereas “BRCA1-only” alterations were relatively uncommon, making single-gene conclusions for BRCA1 unsupportable. The FDA label for the mCSPC indication is explicit for BRCA2-mutated disease and presents efficacy results for the BRCA2m subgroup (rPFS hazard ratio 0.46, 95% CI 0.32–0.66). The package insert for niraparib also states patient selection for mCSPC should be based specifically on the presence of a BRCA2 gene alteration whereas in the metastatic castrate resistant prostate cancer group the indication includes both BRCA1 and BRCA2 mutations. Regarding burden of disease, in a large multicenter cohort of 556 patients with metastatic hormone-sensitive prostate cancer (mHSPC), homologous recombination repair (HRR) alterations were present in 28.6%, including 12.4% with BRCA1/2 mutations, and were independently associated with significantly worse radiographic progression-free survival, time to castration resistance, and overall survival despite treatment with ADT plus ARPIs and/or docetaxel. BRCA2 was the most common alteration, and BRCA-mutated tumors had the poorest outcomes across both low- and high-volume disease, underscoring that tumor biology adds prognostic value beyond conventional volume-based risk stratification. Further studies supporting earlier genomic testing in mCSPC are required before considering niraparib therapy in low-volume disease. The NCCN guidelines in prostate cancer V5.2026 recognize the FDA approved combination of niraparib plus abiraterone with ADT for patients with BRCA2-mutated mCSPC for patients with high-volume, synchronous or metachronous, mCSPC.[224] The panel cautions that use in low-volume mCSPC has unclear benefit due to the low numbers of low-volume patients included in the AMPLITUDE trial.

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*, which may include targeted RNA-based fusion testing, 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

Testing for resistance mutations is considered **medically necessary** with a change in clinical status progression on targeted therapy if other targeted therapies may be indicated.

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
Extraskeletal myxoid chondrosarcoma	EWSR1, NR3A3, TAF15, TCF12, TFG

Specific Sarcoma Types	Gene(s)
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.[234] Furthermore, genetic alterations with prognostic or therapeutic implications are increasingly utilized by multidisciplinary teams in specialized sarcoma centers to guide management decisions.[235]

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.[234] Recent expert consensus emphasizes that decisions to perform multigene panels and the interpretation and use of results for diagnostic or therapeutic purposes should occur in sarcoma-expert institutions and be integrated with clinicopathologic context rather than substituting for expert pathologic review.[236]

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.[31] 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,[31] evaluating *KIT* and *PDGFRA* genes is recommended due to their significant diagnostic and therapeutic implications.[237] Additionally, specific gene alterations such as *ALK* in inflammatory myofibroblastic tumors and *INI1/SMARCB1* in epithelioid sarcoma support individualized patient management.[235] Molecular testing is particularly beneficial when the pathologic diagnosis remains uncertain or when the sarcoma exhibits a specific molecular alteration.[94] 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.[238-241] Genetic alterations in relevant genes within various soft tissue tumors have an evidence level of 2A. When multigene sequencing is pursued for treatment selection (including consideration of off-label therapy or clinical trial enrollment), expert consensus recommends sarcoma-specialist oversight (and multidisciplinary review when available) and discourages routine repeat NGS analyses or repeat biopsies solely to obtain therapeutic sequencing results because yield is often low and delays may adversely affect timely delivery of standard therapies.[236]

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.[31] Real-world comparative effectiveness data across TRK fusion cancers (including soft-tissue sarcoma) demonstrate longer overall survival and longer time to next treatment with larotrectinib versus matched real-world controls, supporting clinical utility of identifying NTRK fusions when tumor-agnostic TRK inhibitors are treatment options.[242]

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.[243] 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.[244] In addition, a real-world cohort of adolescents and young adults with sarcoma undergoing tumor NGS found that while a subset had actionable alterations and some accessed NGS-directed therapies (often via trials), objective clinical benefit was uncommon (<5%), reinforcing that broad-panel therapeutic sequencing is most defensible when it addresses diagnostic uncertainty and/or facilitates trial access rather than being ordered routinely for all patients.[245] For uterine leiomyosarcoma, retrospective data suggest meaningful responses to PARP inhibitor-based therapy among tumors harboring pathogenic BRCA alterations (predominantly BRCA2), supporting inclusion of BRCA2 on multigene panels when results could inform clinical trial enrollment or sarcoma-expert targeted therapy consideration.[246]

Epigenetic and methylation-based biomarkers are being explored but remain investigational in sarcoma as current evidence does not establish clinical utility for routine management or surveillance decisions.[247]

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 categories:
    - Bethesda III: Atypia of undetermined significance (AUS)
    - Bethesda IV: Follicular neoplasm (FN)/Oncocytic follicular neoplasm (OFN)
- 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 Genomic Sequence Classifier (GSC)

Somatic testing of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

- Tissue-based somatic genomic testing of NIFTP is considered **not medically necessary**

Somatic genomic testing of recurrent or persistent locoregional medullary thyroid cancer

- Tissue-based testing including RET somatic genomic testing and tumor mutational burden testing as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb) in patients who are germline wild-type or germline unknown is considered **medically necessary**

Somatic genomic testing of metastatic, locally advanced, recurrent, progressive, symptomatic thyroid 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 a diagnosis of metastatic, locally advanced, recurrent, progressive, unresectable, or symptomatic thyroid cancer that is not amenable to radioactive iodine therapy
- The individual has not had prior MSI or dMMR testing

Tissue-based somatic tumor testing, which may include targeted RNA-based fusion testing, is considered **medically necessary** for individuals with advanced thyroid cancer that is not amenable to radioactive iodine therapy when the following criteria* are met:

- The individual has biopsy proven metastatic, locally advanced, recurrent, progressive, unresectable or symptomatic thyroid cancer
- The testing includes assessment for P/LP variants of BRAF V600E, ALK, NTRK, RET, and tumor mutational burden testing as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb)
- The individual is considered a potential candidate for FDA-approved oral targeted therapy based on the results of this testing

Anaplastic thyroid 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 anaplastic cancer of the thyroid
- The individual has not had prior MSI or dMMR testing

Tissue-based somatic tumor testing is considered **medically necessary** for individuals with anaplastic thyroid cancer of any stage

- The testing includes assessment for P/LP variants of BRAF V600E, RET, NTRK, ALK, and tumor mutational burden testing as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb)

**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.[248] 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.[249] Consequently, recent studies have investigated treatment de-escalation, including active surveillance.[250]

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.[251] For suspicious nodules, the 2023 Bethesda System for Reporting Thyroid Cytopathology 3rd edition is recommended by the ATA.[252] This system includes six classifications: I) Nondiagnostic; II) Benign; III) Atypia of Undetermined Significance (AUS); IV) Follicular Neoplasm (FN) or Follicular Oncocytic Neoplasm; V) Suspicious for Malignancy (SUSP); and VI Malignant.[252] Molecular testing, as an adjunct, aims to refine risk stratification, particularly for Bethesda III and IV nodules, which have malignancy rates of 6%-18% and 10%-40%, respectively.[253]

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.[254] Additionally, a multiplatform test combines a mutation panel (ThyGenX) with a microRNA risk classifier (ThyraMIR) for high negative and positive predictive values in ITNs.[255, 256] However, molecular testing is viewed as an adjunct, and no single test has been universally accepted for clinical utility across all indeterminate cases.[257] 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.[258] 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.[259]

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%.[260] 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.[261]

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.[262] Some approaches involve combining a molecular classifier with additional somatic testing to identify molecular variants and fusions.[263] These bundled testing methodologies have not yet established clinical utility, as their net clinical benefit requires comprehensive evaluation.[264] The prevalence of thyroid cancer in these nodules varies significantly across studies and sites.[261, 265] 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 [266-269], sonographic pattern[270], or if surgery is contraindicated for various reasons.[265]

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.[271] 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.[272] Efforts continue to improve the classification accuracy of these nodules[273], yet the reliability of the current molecular tests remains insufficient for informing surgical management.

Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) formerly known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma demonstrates a follicular growth pattern with encapsulation or clear demarcation of the tumor from adjacent tissue no invasion and nuclear features of papillary carcinoma.[274] This neoplasm has low risk for adverse outcomes.[274] Molecular testing for diagnosing NIFTP is currently not validated.

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[31] and for which specific treatment algorithms have emerged.[275] For advanced anaplastic thyroid cancer, regardless of stage, the NCCN recommends molecular testing due to its aggressive progression.[276] Strong genotype–phenotype associations exist with specific RET pathogenic variants, which can help predict the clinical aggressiveness of medullary thyroid cancer.[277] 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.[278] NTRK gene fusions, present in approximately 1.9% of thyroid carcinoma cases, respond favorably to NTRK inhibitors.[279]

Unknown Primary Site 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 or carcinoma not otherwise specified of unknown primary site
- The individual has not had prior testing for MSI or IHC for dMMR

Multigene panel testing, which may include targeted RNA fusion analysis, is considered **medically necessary** when **ALL** the following are true:

- The individual has metastatic or advanced epithelial cancer of unknown primary site
- The individual has adequate performance status for cancer treatment
- Tumor testing includes, at a minimum, **ALL** the following genes that align with testing as per FDA-labeled tumor agnostic indications:
    - Mismatch-repair (MMR) deficiency (MLH1, MSH2, MSH6, PMS2, EPCAM)
    - 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
    - RET fusion
    - BRAF V600E
    - ERBB2/HER2

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.[280]

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%).[281] 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).[282] Rare presentations, such as bone-predominant or lymph node-only CUP, exhibit different survival rates and necessitate unique risk stratification and treatment approaches.[283] 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.[284] 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.[285] 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.[285] 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.[281] A prospective trial involving 158 CUP patients demonstrated that genomic profiling led to treatment recommendation changes in only 2.5% of cases.[286]

In contrast to tissue-of-origin prediction, multi-gene next-generation sequencing (NGS) panels (comprehensive genomic profiling) are used to identify actionable genomic alterations and tumor-agnostic biomarkers that may inform targeted therapy, immunotherapy, or clinical trial eligibility. Although CUP-specific clinical utility data remain limited and the certainty of evidence is generally low to very low, the current NCCN CUP guideline and multiple expert reviews support considering NGS-based tumor profiling in CUP as part of contemporary management.[287-289]

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.[290, 291] 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.[292] 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).[293] 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,[294] 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.[295] 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.[296] 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.

Contemporary guidelines and expert reviews increasingly distinguish[4] tissue-of-origin prediction to select primary-site–directed therapy, and comprehensive genomic profiling to identify actionable alterations and tumor-agnostic biomarkers.[5]

The current NCCN Occult Primary guideline includes consideration of multi-gene NGS panel testing (comprehensive genomic profiling) for CUP; however, the supporting evidence cited is largely extrapolated from the broader precision-oncology literature rather than CUP-specific randomized trials.[287, 297]

ESMO does not recommend routine gene-expression profiling–based site-directed therapy for CUP, reflecting the limited demonstrated clinical utility of tissue-of-origin assays in improving patient-centered outcomes.[298]

Recent expert reviews also emphasize that CUP represents a heterogeneous syndrome and describe evolving paradigms for staging and classification that integrate clinicopathologic context and molecular profiling; these concepts remain evolving and have not yet established clear improvements in survival or quality-of-life outcomes.[288, 299-301] Nevertheless, there is a convergent consensus that multi-gene panel testing, is appropriate in this setting to help select individuals who may benefit from targeted therapy given the poor prognosis with chemotherapy in this increasingly rare clinical scenario. Nomograms based on clinicopathological factors have been developed, providing robust personalized prognostication for decision-making and patient stratification in clinical trials.[302]

Whole Exome, Whole Genome and Whole Transcriptome RNA Analysis

Whole exome and genome sequencing of tumor samples is considered **not medically necessary**.

Whole exome and genome sequencing of paired tumor/germline samples is considered **not medically necessary**.

Whole transcriptome RNA analysis of tumor samples is considered **not medically necessary**.

Rationale

Whole exome, whole genome and whole transcriptome analysis can evaluate many tumor molecular alterations in parallel. regardless of whether each alteration has proven, therapy-directing relevance for a specific cancer type. While the clinical utility of some tumor genetic biomarkers has been established in randomized controlled trials, most molecular alterations identified on whole exome, whole genome or whole transcriptome are either not actionable or have uncertain clinical significance. In addition, response to targeted agents is frequently histology- and context-dependent. Whole exome, whole genome, and whole transcriptome analysis may lead to departures from established, tumor-specific management approaches without clear evidence that such strategies improve clinical outcomes.[4-6, 8, 9, 303]

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 U.S. Food and Drug Administration (FDA) or recommended by NCCN as 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

Tissue, Bone Marrow, or Blood-Agnostic Testing for Patients with Hematological Cancers

Tumor-agnostic testing in bone marrow, blood, or lymphoid tissue for patients with hematological cancers is considered **not medically necessary**.

Targeted RNA fusion analysis using NGS is considered **medically necessary** if noted in the 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), which may include targeted RNA fusion analysis by NGS, 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 aligned with the FDA label or Category NCCN 2A recommendations
- A multigene panel contains genes that are identified with adult or pediatric 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, PDGFRA, iAMP21, 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.[304] The cure rate for pediatric ALL surpasses 80%. Adult cure rates range from 30% to 40%,[305] but modern regimens incorporating targeted therapies and immunotherapies have improved outcomes.[306, 307] Genetic risk factors, such as Down syndrome, are linked to increased susceptibility to ALL, though most patients lack any known inherited risk factors. Enhanced genomic analyses have delineated more than 20 subtypes of B-cell ALL and more than 17 subtypes of T-cell ALL, and many subtypes are defined by cytogenetic and molecular alterations that inform risk-adapted therapy.[307]

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.[304] Adult ALL exhibits more prevalent P/LP variants in genes such as IKZF1, MLL2, and JAK3 compared to pediatric cases but fewer PTPN11 alterations.[308] However, the precise role of these genetic and epigenetic changes in leukemogenesis, drug resistance, and leukemic clone evolution remains an ongoing investigation.[308] Contemporary diagnostic workflows increasingly integrate RNA-based assays for fusion detection and genome-wide copy-number profiling; in a nationwide prospective pediatric cohort, combined whole-transcriptome RNA sequencing and SNP array detected stratifying lesions with high concordance and clinically relevant turnaround times.[309]

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. NCCN guidelines recommend MRD assessment at defined treatment milestones (e.g., end of induction and end of consolidation) and recognize both multiparameter flow cytometry and NGS-based MRD assays as acceptable methodologies.[310] 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.[304] 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.[311]

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.[311] 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.[312] 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.[313] Recent studies further validate MRD testing's role in risk stratification for B-cell precursor ALL,[314] young adult T-cell ALL,[315] and mixed cohort ALL patients on investigational protocols.[316] Guideline-

defined MRD assessment time points generally include completion of induction therapy and end of consolidation, with additional assessments tailored to protocol and clinical context.[310]

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.[314] 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.[315] These biologic subtypes can carry therapeutic implications, including use of tyrosine kinase inhibitors for BCR::ABL1-positive and other kinase-activated ALL and incorporation of immunotherapies (e.g., CD19- or CD22-directed) in both frontline and relapsed settings, reinforcing the need for accurate molecular classification.[306, 307]

Acute Myelogenous Leukemia

Initial Diagnosis

Tissue-based (**OR** alternatively, peripheral blood if morphologically detectable circulating blasts) somatic genetic testing (50 or fewer genes), which may include targeted RNA fusion analysis by NGS, 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 (RUNX1::RUNX1T1 [t(8;21)] or CBFB::MYH11 [inv(16)/t(16;16)])
- 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.[317] The dynamic clonal evolution patterns during relapse likely contribute to therapy resistance.[318] For adults under 60, intensive leukemia treatment results in a cure rate of approximately 40%.[318] 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%.[319]

The 2022 World Health Organization (WHO) Classification of Tumours emphasizes genetic abnormalities over differentiation in defining AML subtypes, including recurrent fusions and rearrangements such as PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, DEK::NUP214, RBM15::MRTFA, and BCR::ABL1, as well as AML-defining pathogenic/likely pathogenic variants in genes such as NPM1 or CEBPA.[320] Comprehensive genomic evaluation (typically integrating cytogenetics/FISH for structural variants and a multigene sequencing panel for sequence variants) increases diagnostic yield relative to conventional cytogenetics alone and can expedite risk stratification and therapeutic planning.[321]

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.[322] The field remains rapidly evolving, with additional genes under investigation.[323]

Somatic alteration profiling increasingly has direct therapeutic implications in AML. In addition to established actionable targets (e.g., FLT3 and IDH1/2), the emergence of menin inhibitors has created new, high-impact indications tied to KMT2A rearrangements and NPM1 mutations. FDA approvals of revumenib for relapsed/refractory acute leukemia with KMT2A translocations and for relapsed/refractory AML with susceptible NPM1 mutations, and approval of ziftomenib for relapsed/refractory NPM1-mutated AML, further underscore the need for timely identification of these lesions using validated assays.[324, 325] An FDA De Novo-authorized KMT2A break apart FISH companion diagnostic is available to determine eligibility for revumenib in KMT2A-rearranged acute leukemia.[326]

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.[327]

Measurable residual disease (MRD) detection using multiparametric flow cytometry and targeted molecular assays has consistent prognostic value across AML subsets.[328, 329] For example, persistence of molecular disease before allogeneic transplantation (including NPM1 and other trackable lesions) is associated with increased relapse risk and inferior survival.[330] Multiparametric flow cytometry remains the most broadly applicable MRD method for routine AML care. For molecularly defined AML subtypes with stable quantitative targets—including acute promyelocytic leukemia (PML::RARA), NPM1-mutated AML, and core-binding factor AML (RUNX1::RUNX1T1 or CBFB::MYH11), RT-qPCR-based MRD is incorporated at defined treatment landmarks in major guideline pathways [331] and in transplant-focused best-practice recommendations.[332] In contrast, multigene-panel NGS approaches to MRD (i.e., broad sequencing panels used longitudinally for disease quantification) remain limited by lack of assay standardization, variable analytic sensitivity/error suppression methods, and uncertain clinical-action thresholds in routine practice. Thus, sequencing-based MRD is best viewed primarily as prognostic and/or investigational outside select, protocolized clinical contexts.[333]

B-cell Lymphomas

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

- The individual has a high-grade B-cell lymphoma (HGBCL) or diffuse large B-cell lymphoma (DLBCL), and testing is for the purpose of stratifying risk or identifying actionable therapeutic targets
- Testing is for the purpose of establishing the diagnosis

Minimal Residual Disease (MRD) testing

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 and cytogenetic testing are important adjuncts in the diagnosis, classification, and management of B-cell lymphomas; however, their utility is greatest when aligned to a specific clinicopathologic question and performed on adequate diagnostic tissue. The diagnostic process routinely integrates morphology, immunophenotyping (IHC/flow cytometry), and targeted cytogenetic/molecular assays selected to refine the differential diagnosis and risk stratification rather than universal broad profiling for every patient.[334] For selected entities, guidelines also emphasize optimal tissue acquisition (e.g., excisional biopsy when feasible in mantle cell lymphoma) and early assessment of key high-risk markers such as TP53.[335]

Fluorescence in situ hybridization (FISH) is a pivotal technique for detecting recurrent chromosomal rearrangements and selected copy-number alterations that define or risk-stratify B-cell lymphoma entities (e.g., MYC, BCL2, and BCL6 rearrangements in high-grade B-cell lymphoma; CCND1/IGH in mantle cell lymphoma; del(17p) in select settings).[336] In contrast, single-nucleotide variants and small indels (e.g., TP53 and MYD88) are detected by sequencing-based assays (targeted PCR or focused NGS panels). TP53 status is increasingly incorporated into risk assessment—particularly in mantle cell lymphoma, where TP53 mutational analysis is recommended at diagnosis and reassessment is recommended when a new treatment is required.[335] Focused NGS panels can identify mutations with established diagnostic/prognostic utility (e.g., MYD88, CD79B, EZH2, TP53) and may support selection of targeted agents in select contexts (e.g., EZH2 inhibitor

tazemetostat for relapsed/refractory follicular lymphoma with an EZH2 mutation).[337] However, for most B-cell lymphomas, selection among FDA-approved therapies is driven primarily by histologic subtype, treatment line, and clinical factors rather than broad tumor mutational profiling.

Challenges in Clinical Application

Comprehensive genomic approaches (e.g., whole-exome sequencing and RNA sequencing) have uncovered multiple genetic subtypes of DLBCL and related entities, including those defined by algorithms such as LymphGen. These classifiers have improved biological understanding and have generated hypotheses for therapy tailoring, but their incremental clinical utility over standard clinicopathologic evaluation remains uncertain. Notably, recent professional guidance for LBCL describes large-panel testing to assign cell-of-origin categories or "dark-zone" signatures as investigational and, therefore, does not recommend routine use outside clinical trials.[338]

Despite the potential benefits, the integration of somatic genetic testing into routine practice is constrained by variable clinical utility across B-cell lymphoma subtypes, limited prospective evidence that genomics-driven treatment intensification improves outcomes, and practical barriers (turnaround time, cost, and access). Consistent with this, recent NCCN B-Cell Lymphomas guidance did not introduce major changes in the core genetic/molecular elements of evaluation, continuing to prioritize morphology, immunophenotype, and targeted cytogenetic/molecular assays directed by histology and clinical scenario.[339] In addition, a substantial fraction of DLBCL cases remain difficult to assign to specific genomic subtypes, highlighting the need for continued validation, harmonized reporting, and standardization of clinically actionable results.[340]

Measurable residual disease

NGS-based MRD assays in lymphoma generally rely on tracking tumor-specific immunoglobulin gene rearrangements or tumor-derived DNA and are analytically distinct from multigene somatic mutation panels used for diagnostic/prognostic profiling. The EHA–EU MCL network guideline references an NGS-based assay for assessing molecular remission after induction in mantle cell lymphoma, but this reflects a specialized MRD approach rather than tumor mutation profiling.[335] Accordingly, multigene panel NGS testing on peripheral blood or bone marrow for the purpose of MRD assessment should not be conflated with these dedicated MRD assays, and routine use remains non-standard across most B-cell lymphoma settings.

Genetic Subtypes and Targeted Therapy

Recent advances in genomic and transcriptomic profiling have expanded understanding of the heterogeneity of B-cell lymphomas, particularly DLBCL. While cell-of-origin classification (germinal center B-cell–like vs activated B-cell–like) and assessment for high-risk cytogenetic features inform prognosis and can influence consideration of clinical trials, current standard-of-care treatment selection remains largely based on histology and clinical risk rather than genomic subtype assignment.[334, 338] Importantly, "double-hit" high-grade B-cell lymphoma is defined by MYC rearrangement with BCL2 and/or BCL6 rearrangements, whereas "double-expressor" lymphoma refers to MYC and BCL2 protein overexpression by immunohistochemistry.[336] Genomic subtypes such as MCD and BN2 highlight distinct oncogenic pathways and prognostic differences; however, prospective evidence supporting routine therapy intensification or selection solely on the basis of these genomic classifiers is limited, and such approaches are best pursued in clinical trials.[340]

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 must include testing of TP53, and may also include optional genes such as SF3B1, NOTCH1, BIRC3, and ATM

Minimal Residual Disease (MRD) testing

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 leukemia of older adults characterized by the accumulation of mature-appearing clonal B lymphocytes in blood, bone marrow, and lymphoid tissues. Diagnostic confirmation typically relies on peripheral blood flow cytometry to establish a clonal B-cell population and exclude mimicking disorders. After diagnosis, somatic and cytogenetic characterization is used primarily when treatment is being contemplated (rather than routinely in early asymptomatic disease) to refine risk stratification and inform therapy selection, particularly through assessment of TP53 disruption and IGHV mutational status.[341]

Genetic Abnormalities and Testing Approaches

Somatic genetic testing in CLL commonly includes interphase fluorescence in situ hybridization (FISH) (or validated array-based approaches) for recurrent chromosomal abnormalities such as del(13q), del(11q), trisomy 12, and del(17p). These abnormalities carry prognostic and (for del[17p]) predictive implications. Because key genetic lesions may evolve throughout the disease course, guidelines recommend assessing del(17p) by FISH and TP53 mutation status as close as feasible to initiation of therapy (e.g., within 6 months) and repeating these assessments before each subsequent line of therapy.[341, 342] Peripheral blood is generally an appropriate and preferred specimen; bone marrow or lymph node tissue are suitable alternatives when the circulating CLL fraction is low (e.g., SLL-predominant presentations).[342]

TP53 disruption (del[17p] and/or TP53 mutation) and immunoglobulin heavy-chain variable region (IGHV) mutational status are among the most clinically relevant biomarkers in CLL, informing prognostication (e.g., CLL-IPI) and treatment selection in the era of targeted therapies.[341, 343] In addition, recurrent somatic mutations in genes such as SF3B1, NOTCH1, BIRC3, and ATM are associated with adverse disease biology and may refine risk stratification and clinical trial eligibility; professional guidelines note these as additional markers that may be studied in clinical trials.[341] Accordingly, when NGS is used for baseline risk stratification and treatment planning, a focused multigene panel that includes TP53 and these recurrent genes can provide clinically relevant information while limiting incidental findings and avoiding very large panels with uncertain incremental utility.

Minimal Residual Disease and its Assessment

Measurable residual disease (MRD) assessment is an evolving tool in CLL that provides prognostic information after therapy. MRD is typically measured using validated multicolor flow cytometry, allele-specific PCR, or dedicated NGS approaches (e.g., immunoglobulin gene rearrangement-based assays) rather than broad somatic multigene panels, which are not designed for highly sensitive MRD quantification. Although undetectable MRD correlates with prolonged progression-free survival across multiple treatment settings, standardized thresholds, optimal timing, and the clinical consequences of MRD positivity remain areas of active investigation.[344, 345]

The standard “undetectable MRD” threshold in CLL is typically defined at $<10^{-4}$, and iwCLL notes that standardized six-color multiparametric flow cytometry using a defined core marker panel is reliably sensitive to this level, supporting its use as an appropriate MRD method in routine settings when MRD is assessed.[343]

Consistent with this evidence base, professional guidelines generally do not recommend routine NGS-based MRD monitoring after therapy outside of clinical studies because management strategies based on NGS MRD status are not yet established.[341] Consensus recommendations similarly emphasize MRD primarily for clinical trial endpoints and as a research tool rather than routine clinical practice.[346]

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 venetoclax-based regimens. Baseline assessment of TP53 disruption and IGHV mutational status is central to choosing among these approaches and to identifying patients in whom chemoimmunotherapy should be avoided or where time-limited targeted combinations are preferred.[341] The BCR::ABL1 fusion is both the defining diagnostic lesion and the therapeutic target of multiple approved tyrosine kinase inhibitors (TKIs), and long-term outcomes with appropriate therapy and monitoring approach those of the general population.[347] More recently, asciminib (a BCR::ABL1 inhibitor specifically targeting the ABL myristoyl pocket) has demonstrated superior molecular response versus investigator-selected TKIs in newly diagnosed chronic-phase CML.[347]

In the UK phase III FLAIR program, multiparametric flow-cytometry based,MRD-adapted combination therapy with ibrutinib plus venetoclax achieved higher rates of undetectable MRD and superior progression-free survival compared with ibrutinib alone or fludarabine-cyclophosphamide-rituximab (FCR), with follow-up suggesting durable disease control in many patients.[348] Despite these encouraging results, MRD-guided treatment discontinuation and MRD-driven escalation strategies remain investigational, and routine MRD-guided management is not broadly recommended outside clinical trials at present.[341, 345]

Future Directions

Future work is focused on improving assay standardization and clarifying how best to integrate MRD and emerging genomic markers into treatment algorithms, including defining when additional genomic profiling at relapse (e.g., to inform clinical trial options) provides actionable benefit. Until such evidence is mature, a pragmatic approach is to use focused baseline genomic testing when it will inform treatment selection and to repeat key predictive biomarkers (del[17p]/TP53) prior to each new line of therapy.

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 (MPNs) (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 MPN is diagnosed
- **ONE or more** of the following clinical scenarios (for MPNs other than primary or secondary myelofibrosis):
    - **At least ONE of the following hematologic abnormalities:**
        - 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

OR

- **At least ONE of the following non-hematologic abnormalities:**
  - Unexplained organomegaly
  - Extramedullary hematopoiesis
  - Unexplained splanchnic, cerebral, or arterial thrombosis
  - Unexplained microcirculatory symptoms (such as vascular migraine and/or erythromelalgia)

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.[341] 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.[342] The BCR::ABL1 fusion is both the defining diagnostic lesion and the therapeutic target of multiple approved tyrosine kinase inhibitors (TKIs), and long-term outcomes with appropriate therapy and monitoring approach those of the general population.[347] More recently, asciminib (a BCR::ABL1 inhibitor specifically targeting the ABL myristoyl pocket) has demonstrated superior molecular response versus investigator-selected TKIs in newly diagnosed chronic-phase CML.[349]

Patients suspected of having CML or MPNs undergo detailed hematological analyses, including peripheral blood smear examination and BCR-ABL1 testing to exclude CML. Absence of the BCR-ABL1 translocation prompts further molecular evaluation for JAK2, CALR, CSF3R, and MPL P/LP variants, alongside bone marrow evaluation, to achieve an accurate diagnosis.[350] While these genetic variants indicate a hematopoietic stem cell disorder, they are not singularly definitive for any specific disease.[341] Distinction between MPN types integrates peripheral blood, molecular, and bone marrow morphologic findings because none alone provide adequate diagnostic specificity.[341] 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.[351] In addition to abnormal blood counts, MPNs may present with splenomegaly/hepatomegaly, microvascular symptoms, or thrombotic events (including unusual-site thrombosis such as splanchnic vein thrombosis), and these clinical features may warrant diagnostic evaluation even when blood counts are not markedly abnormal.[352] Myeloproliferative neoplasms (MPNs) should not be viewed solely as disorders identified by overt erythrocytosis, thrombocytosis, or leukocytosis. Although abnormal blood counts often provide the first clue, classical MPNs may also present through characteristic clinical manifestations that reflect underlying clonal myeloproliferation, abnormal blood cell function, and extramedullary hematopoiesis. These manifestations include splenomegaly or hepatomegaly, microvascular symptoms, and thrombotic events, including thrombosis at unusual venous sites such as the portal, mesenteric, splenic, or hepatic veins (1,2). For that reason, the presence of these features should prompt diagnostic consideration of an MPN even when complete blood count abnormalities are mild, equivocal, or apparently absent.[341, 350]

BCR-ABL1 must be confirmed cytogenetically and through multiplex RT-PCR to diagnose CML. Baseline quantitative RT-PCR is recommended to establish the molecular baseline for subsequent monitoring, although it typically does not alter initial therapeutic decision-making.[342] Targeted therapy using tyrosine kinase inhibitors (TKIs), such as imatinib, has markedly improved the prognosis, with 10-year overall survival rates reaching 80%-90%.[353] The goal of TKI therapy is achieving stable molecular remission, permitting the possibility of treatment-free remission in selected patients with sustained deep molecular response.[347, 354] 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.[355]

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.[354] 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.[354] When treatment failure is suspected, kinase domain P/LP variant analysis can help guide selection of subsequent TKI therapy based on known mutation-drug sensitivity patterns.[347, 354]

Myelodysplastic Syndrome

Somatic testing (i.e., 50 or fewer genes) of bone marrow tissue **OR** peripheral blood (when bone marrow aspirate/biopsy is unavailable or insufficient) 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, NRAS, CBL, ETNK1, BCR-ABL, BCOR, JAK2, JAK3, MPL, CALR, PTPN11, NF1, 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.[356] Professional guidelines emphasize that evaluation of suspected MDS integrates bone marrow morphology with cytogenetic and molecular studies.[357] 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.[358] 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 (TKD or ITD alterations) as well as P/LP variant burden and key co-P/LP variants and cytogenetic abnormalities.[359] 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.[360]

Recent disease classifications increasingly recognize genetically defined MDS entities and highlight the prognostic importance of recurrent somatic alterations. 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. In practice, many targeted panels also include genes relevant to overlap syndromes (e.g., MDS/MPN) to support the differential diagnosis. For example, in MDS with isolated del(5q), TP53 mutations—particularly multi-hit TP53 alterations—are associated with adverse outcomes and may influence risk assessment.[361]

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.[362, 363]

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.[364] Because IPSS-R cytogenetic risk assignment is primarily based on conventional G-banded karyotyping, FISH is generally used as an adjunct when karyotyping is inadequate or fails, rather than as a replacement. More recently, the development and validation of the IPSS-Molecular (IPSS-M) model has integrated somatic mutation data into MDS prognostication.[359, 365, 366] 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.[367] Emerging research using whole-genome sequencing (WGS) to improve post-transplant relapse risk stratification has been reported but remains investigational and is not required for routine somatic testing in MDS.[368]

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**.

Gene expression tests in myeloma that are **not medically necessary** include, but are not limited to, the following examples:

- MyPRS™/GEP70
- SKY92

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

Next-generation sequencing (NGS) or molecular testing in bone marrow is considered **medically necessary** in individuals with newly diagnosed, relapsed multiple myeloma or with disease progression when **ALL** the following criteria are met:

- Testing is performed to determine high-risk disease per IMS-IMWG Consensus Genomic Staging
- Testing is for TP53 mutation AND may include evaluation for del(1p32) (monoallelic or biallelic)

NGS testing is considered **not medically necessary** in the following scenarios:

- Expanded NGS panels that include genes or deletions other than TP53 and del(1p32)
- Routine screening without intent to apply IMS-IMWG risk criteria
- Testing performed solely for surveillance in stable disease without impact on management
- Peripheral blood testing used for initial genomic staging

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** in **EITHER** of the following scenarios:

- MRD testing used prior to initiating new treatment intended to induce myeloma remission
- MRD testing used to assess depth of response at clearly identified landmarks after treatment intended to induce myeloma remission (such landmarks include induction, post ASCT consolidation, or after other response-inducing regimens)

Note: MRD testing for routine surveillance in otherwise stable patients and MRD-guided treatment discontinuation outside a clinical trial/protocolized pathway is considered **not medically necessary**.

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.[369] 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.[370] Baseline bone marrow-based cytogenetics/FISH and myeloma-targeted DNA sequencing are used to identify high-risk genomic abnormalities that inform risk-adapted management.[371, 372] The International Myeloma Society (IMS) and International Myeloma Working Group (IMWG) convened an expert panel to redefine high-risk multiple myeloma (HRMM) in the era of modern triplet/quadruplet therapies using contemporary genomic data rather than older staging systems alone. The Panel established a Consensus Genomic Staging (CGS) system defining HRMM by the presence of at least one of the following: (1) del(17p) with ≥20% clonal fraction and/or TP53 mutation (assessed by NGS on CD138-purified plasma cells); (2) t(4;14), t(14;16), or t(14;20) co-occurring with 1q gain/amplification and/or del(1p32); (3) biallelic del(1p32) or monoallelic del(1p32) with 1q gain; or (4) β2-microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL).[371] The consensus emphasized that NGS-based testing is required for TP53 mutation detection, that FISH alone is insufficient for full risk stratification, and that molecular profiling should be performed on bone marrow CD138-enriched plasma cells, with risk reassessment at relapse. Small deletions in 1p require sequencing and iFISH alone is no longer sufficient to detect these changes.[371] 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.[369] 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.[373, 374] Contemporary definitions of high-risk myeloma

incorporate a limited set of recurrent abnormalities (e.g., del(17p) and/or TP53 mutation; t(4;14), t(14;16), or t(14;20); and 1q gain/amplification with concomitant del(1p32)), supporting focused testing for these alterations.[371]

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.[375] Despite ongoing research into circulating tumor cells, appropriate clinical cut-off levels remain undetermined.[376, 377] 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.[378] [370, 379] Professional guidelines recognize bone marrow MRD assessment using standardized (IMWG) criteria to quantify depth of response at defined treatment landmarks; however, MRD should not be used as the sole measure of efficacy, and MRD-guided treatment adaptation or discontinuation remains investigational outside clinical trials/protocolized pathways.[380, 381]

The ASCO-Ontario Health (Cancer Care Ontario) living guideline recommends using the International Myeloma Working Group criteria to measure response quality and depth after each cycle of response-inducing therapy.[379, 380] [382]The potential to tailor consolidation or maintenance based on MRD dynamics is under active study; however, professional guidelines advise against altering or discontinuing maintenance therapy solely on the basis of MRD status outside a clinical trial/protocolized pathway.[380, 381] 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).[383] 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.[384] In this small field of myeloma, the use of MRD has become widely accepted, particularly as a test to evaluate new therapeutics. In pooled analyses of randomized trials, MRD-negative complete response at 9-12 months (10^-5 threshold) correlates with progression-free and overall survival, supporting MRD as an intermediate endpoint in myeloma drug development.[385] The MIDAS randomized trial illustrates ongoing evaluation of MRD-guided consolidation strategies using NGS-based MRD assessment; however, these data have not established routine MRD-guided selection of autologous transplantation intensity or consolidation outside clinical trials.[386]

Gene expression profiling assays evaluate the expression levels of multiple genes to categorize patients into prognostic risk groups. Examples include the 70-gene MyPRS/GEP70 signature and the 92-gene SKY92 expression signature, which are intended to identify patients with high-risk disease. Although these assays may provide prognostic information regarding disease biology and survival risk, current evidence is insufficient to demonstrate that their use improves patient outcomes beyond established risk stratification methods. Current clinical risk assessment for multiple myeloma relies on validated clinical and cytogenetic markers, including the International Staging System (ISS), Revised International Staging System (R-ISS), and International Myeloma Society/International Myeloma Working Group (IMS-IMWG) genomic risk criteria, which incorporate serum biomarkers and chromosomal abnormalities detected by fluorescence in situ hybridization (FISH) and sequencing-based testing. These established methods are widely available and provide prognostic information that informs treatment decisions. Although gene expression profiling may identify additional molecular subgroups, the available clinical studies primarily demonstrate prognostic associations rather than clinical utility. Evidence has not shown that treatment decisions guided by these assays lead to improved overall survival, progression-free survival, or other clinically meaningful outcomes compared with standard risk stratification approaches. Additionally, major clinical practice guidelines do not recommend routine use of gene expression profiling assays for risk stratification in patients with multiple myeloma outside of clinical trials. As a result, these assays have not been established as standard of care in routine clinical practice.

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

Gene expression profile tests for diagnostic evaluation, risk stratification, or management of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) are considered **not medically necessary**.

Targeted molecular testing by NGS in bone marrow for MYD88 and CXCR4 is considered **medically necessary** in individuals when clinical, morphologic, or immunophenotypic findings suggest WM/LPL when the following criterion is met:

- Testing is for the purpose of establishing or supporting the diagnosis/classification of suspected WM/LPL or another IgM-associated B-cell lymphoproliferative disorder, or for treatment selection when BTK inhibitor sensitivity is clinically relevant

Rationale

MYD88 molecular testing is medically necessary when used to support the diagnosis or classification of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) or related IgM-associated B-cell lymphoproliferative disorders. NCCN recommends testing the bone marrow aspirate for MYD88 (L265P) in the WM/LPL workup as MYD88 mutations are present in the large majority of WM cases.[387] The test is most useful when distinguishing WM/LPL from other IgM-related disorders or small B-cell lymphomas with plasmacytic differentiation. NCCN also notes that a negative MYD88 result does not exclude WM, so the assay should be interpreted in the context of morphology, immunophenotype, and clinical findings. MYD88 testing is not medically necessary for routine evaluation of disorders in which results are not expected to alter diagnosis or management, including typical multiple myeloma workup. International Workshop on Waldenström's Macroglobulinemia (IWWM) guidance supports MYD88 and CXCR4 testing in suspected LPL and before treatment, because these markers can inform differential diagnosis and predict response patterns to covalent BTK inhibitors.[388]

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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)
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)

Code	May Be Medically Necessary When Criteria are Met
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)
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)

Code	May Be Medically Necessary When Criteria are Met
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)
81435	Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
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
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

Code	May Be Medically Necessary When Criteria are Met
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.
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.
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
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

Code	May Be Medically Necessary When Criteria are Met
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
0648U	Oncology (solid tumor), targeted genomic sequencing analysis, to detect deletions, insertions, and substitutions in 42 genes, copy number amplifications in 10 genes, and fusions and splice variants in 18 driver genes from DNA and RNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue
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
81524	Oncology (central nervous system tumor), DNA methylation analysis of at least 10,000 methylation sites, utilizing DNA extracted from formalin-fixed tumor tissue, algorithm(s) reported as probability of matching a reference tumor family and class, and MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation status, if performed
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)

Code	Not Medically Necessary
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
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
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
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
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
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
0630U	Oncology (breast), mRNA, gene expression profiling by microarray of 80 genes (80 content and 465 housekeeping), utilizing formalin-fixed paraffin-embedded tissue (FFPE), algorithm reported as an index that is diagnostic of a molecular subtype (luminal, basal, Her2)
0644U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, blood or bone marrow, personalized assay design and baseline quantification
0645U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, based on digital PCR, blood or bone marrow, reported as not detected or detected with estimated abundance
0686U	Oncology (prostate), mRNA, next-generation sequencing (NGS) gene expression profiling of 22 genes, formalin fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score
0696U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, RNA analysis, 350 or more genes for RNA alterations (eg, gene rearrangements and splice isoforms)

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Revised	04/15/2026	11/15/2026	Independent Multispecialty Physician Panel (IMPP) review. Revised indications in multiple sections contain expansive changes unless otherwise noted. Allow targeted RNA fusion testing as per cancer-specific criteria. Add exception to allow for reflex tissue biopsy after

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			liquid biopsy if an actionable variant result is not detected or uninformative. Solid Tumors – Tissue-agnostic testing (expansive & restrictive); Biliary tract cancer (restrictive); Bladder cancer; Brain cancer; Breast cancer: localized, invasive, early adjuvant (expansive & restrictive), localized, extended adjuvant (restrictive), metastatic/local; Colorectal, localized; NSCLC; Ovarian; Pancreatic; Prostate, metastatic; Sarcoma; Thyroid, noninvasive follicular (restrictive), Thyroid cancer; Unknown primary site (expansive & restrictive). Hematologic Malignancies –Tissue/Bone Marrow/Blood-agnostic testing, ALL/BPLL, AML, B-cell Lymphomas, CLL (restrictive), Myeloproliferative Neoplasms, Myelodysplastic Syndrome, Multiple Myeloma (expansive & restrictive), and new criteria for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Added CPT code 81435 (MNWCM). Moved 0379U from NMN to MNWCM. Added 0090U (NMN) (moved from Predictive and Prognostic Polygenic Testing guidelines). Added references.
Updated codes 10/01/2026	n/a	Unchanged	CPT code update: added new 0686U, 0696U (NMN).
Updated codes 07/01/2026	n/a	Unchanged	CPT code update: added new 0648U (MNWCM), 0644U, 0645U (NMN). Removed 0306U, 0307U (NMN).
Updated codes 04/01/2026	n/a	Unchanged	CPT code update: added 0630U (NMN). Removed 81332 (NMN).
Updated codes 01/01/2026	n/a	Unchanged	CPT code update: added 81524 (NMN).
Revised	04/21/2025	11/15/2025 except for Anthem BCBS OH Medicaid	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 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), and 81332 (NMN); moved 81523, 0046U, 0244U, 0250U, 0414U, 0444U, 0473U, 0499U, 0538U, 0543U, S3854 from NMN to MNWCM.

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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.
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

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			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.