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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Somatic Tumor Testing

Proprietary

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Description and Application of the Guidelines

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

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

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

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

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

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

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, 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.

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 on-going 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 Testing of Solid Tumors

Clinical Indications

General Requirements

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

Umbrella Criteria

Somatic Genomic Testing (Tumor Biomarker Testing)

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

- The genomic testing has established analytical and clinical validity (i.e., FDA-approved test, when available) and is performed in an appropriately certified laboratory
- The genetic test has established clinical utility such that a positive or negative result will meaningfully impact the clinical management (predictive, diagnostic, prognostic, or therapeutic) 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 there are genomic biomarker-linked therapies approved by the U.S. Food and Drug Administration (FDA) for the individual's specific cancer scenario and such therapies are being considered in the near term
    - When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions related therapeutic decisions being considered in the near term
- 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

Rationale

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

Metastatic or Advanced Cancer (Tumor Agnostic Testing)

Tumor-agnostic testing for patients with advanced solid tumors

Multi-gene panel testing is considered **medically necessary** when **ALL** of the following are true:

- The individual has a metastatic or advanced solid tumor and adequate performance status for cancer treatment
- A genomic biomarker-linked therapy has been approved by the FDA for their cancer clinical scenario, or there are established genomic biomarker-based treatment contraindications or exclusions
- There are no existing indications for the planned therapy such that its use does not depend on the results of genetic testing (i.e., immune checkpoint inhibitor indications)
- There are no satisfactory tumor-specific standard therapies available
- Testing falls into **ANY** of the following categories:
    - Mismatch-repair (MMR) deficiency
        - MLH1, MSH2, MSH6, PMS2 or EPCAM genes by PCR or NGS testing
        - Microsatellite testing (MSI) and/or dMMR testing
        - MLH-1 promoter methylation and/or BRAF V600E mutation testing with nuclear expression loss of MLH1 and PMS2 by immunohistochemistry
    - Tumor mutational burden (TMB) testing
    - NTRK and RET fusion testing
    - BRAF V600E mutation testing

Rationale

Oncologists have traditionally chosen therapies and determined prognoses based on site of origin and histology. In select tumor types, oncologists began incorporating biomarkers, such as immunohistochemistry (IHC) for HER2 and estrogen/progesterone receptor status in breast cancer into their decision-making.[1] Today, genomic characterization is increasingly being used to guide treatment decisions, especially in patients with advanced disease. Large-scale sequencing studies such as those of The Cancer Genome Atlas and the International Cancer Genome Consortium have described the genomic landscape of 20-30 solid tumor types, identifying certain alterations as drivers. Subsequent studies have defined a consensus list of cancer driver genes and patterns of co-occurrence and mutual exclusivity of these alterations.[2] Studies of comprehensive next-generation sequencing (NGS) testing in patients with advanced cancer report a wide range of clinically actionable genomic alterations per patient, ranging from 40% to 94%. Furthermore, only 10%-25% of patients actually receive therapy informed by sequencing.[3] The only randomized clinical trial to explore the clinical effects of delivering genomically directed therapy to patients undergoing NGS testing in the setting of advanced cancer found no improvement in progression-free survival for patients receiving molecularly matched therapy.[4] Thus, rather that systematic NGS testing in all advanced cancer patients, the current standard of care involves somatic testing applied in various specific tumor scenarios where such testing is known to be important because of driver alterations that are effectively treated with targeted agents.

In addition to the specific tumor scenarios where NGS testing is indicated, the FDA has also approved the use of treatment regimens for tumor-agnostic indications in several specific scenarios where patients have progressed following previous treatment and have no satisfactory alternative treatments: pembrolizumab for patients with microsatellite instability (since 2017) or high tumor mutational burden (since 2020), larotrectinib (since 2018) or entrectinib (since 2019) for use in patients harboring tumors with NTRK fusions, and dabrafenib plus trametinib (since 2022) when the tumor harbors a BRAF V600E mutation.

Microsatellite instability (MSI) is the result of inactivation of the DNA mismatch repair (MMR) system and is characterized by a high frequency of frameshift mutations in microsatellite DNA. In a portion of tumors, MSI is caused by germline mutations in one of the MMR genes (MLH1, MSH2, MSH6, or PMS2), which results in hereditary Lynch syndrome. However, the majority (80%) of MSI cases are sporadic, often because of hypermethylation of the MLH1 gene promoter.[5] Given this, with MLH1 and PMS2 mismatch repair deficiency (dMMR), BRAF V600E mutation and/or MLH1 promoter methylation testing can be conducted to further identify the need for additional germline testing. [6, 7]The diagnosis of microsatellite instability (MSI) and

dMMR status is made using two reference techniques: molecular biology (polymerase chain reaction) and immunohistochemistry, with 90% to 97% agreement between the two techniques; the sensitivity of next-generation sequencing–based algorithms may not be as robust as immunohistochemistry and polymerase chain reaction.[8] The FDA did not specify which assay should be used to assess for mismatch repair or microsatellite instability, and the College of American Pathologists in collaboration with several other organizations have guidelines pending. In the draft guidelines, for patients being considered for use of checkpoint inhibitors with cancer types other than colorectal, gastroesophageal, small bowel or endometrial cancer, the recommendation is that pathologists should test MMR genes for DNA mismatch repair, although the optimal approach is unknown. Overall, DNA mismatch repair is found in roughly 4% of all adult cancer.[5]

The FDA granted tissue-agnostic accelerated approval in June 2020 for the anti-PD-1 pembrolizumab in TMB ≥10 mutations/Mb solid tumors as determined by an FDA-approved test, for patients that have progressed following prior treatment and who have no satisfactory alternative treatment options. TMB testing is based on the underlying assumption that increasing the numbers of mutant proteins will create antigenic peptides allowing for enhanced immunogenicity.[9] The conceptual definition of TMB is total number of mutations present in a tumor specimen. The actual definition of the type of genetic alterations considered for TMB has varied according to different methodologies.[10] The FoundationOneCDx assay (Foundation Medicine, Inc., CPT 0037U) was the FDA approved a companion diagnostic. The MSK-IMPACT test was cleared through the FDA 510(k) process in 2017 and in the following years other NGS panels have been approved this way too. The Foundation Medicine TMB assay uses a tissue-based specimen and examines a genomic region of approximately 1.1 Mb. For TMB estimation this test includes synonymous and non-synonymous mutations and short indels, while oncogenic drivers are excluded. In addition, germline alterations are excluded based on validated bioinformatics algorithms. There are at least many other TMB tests in the market, including tests from Memorial Sloan Kettering Cancer Center (MSK-IMPACT), Tempus, Qiagen, Neogenomics, Illumina, Guardant Health, Caris, Thermo-Fisher Scientific, and others. Each lab tests a different number of genes, covers a different total region of the genome, and some use only nonsynonymous mutations. Each test uses its own bioinformatics algorithm and the type of specimens used also varies. The equivalence of 10 mut/Mb in FoundationOne CDx cannot be easily determined in other TMB panels. For example, the cutoff of high TMB for the MSK-IMPACT assay was defined at 13.8 mut/Mb based on their cohort.[11] Further alignment in the numerical cutoff of TMB across panels requires calibration tools and reference datasets or materials. The variation between TMB estimates can confuse clinicians and may hinder clinical decision making.[12]

The decision for the FDA to provide accelerated approval drew mixed reactions from the oncology community. On one hand, this was seen as a positive development because of the strong biological rationale for high TMB as a biomarker for immunotherapy sensitivity, and this was felt to address an unmet need for patients with rare cancer types to improve their access to immunotherapy.[13] Critics noted that 10 mut/Mb is an arbitrary cut off that does not separate responders from non-responders and has not been shown to be associated with improved overall survival or quality of life. Additionally, there were concerns that there is insufficient evidence across tumor types for which pembrolizumab was not already approved and insufficient evidence to know if pembrolizumab is more cost effective than alternatives.[14] PD-L1 expression and TMB are not significantly correlated within most cancer subtypes, and TMB may not always correlate with ICI responsiveness.[10] Data examined from over 10,000 patients included in the Cancer Genome Atlas with TMB measured by the FoundationOne CDx assay failed to support the use of TMB-H as a biomarker for immune checkpoint blockade treatment in all tumor types, including at the FDA-approved threshold of 10 mut/Mb.[9] There are still many challenges for the further development of TMB as biomarker with clinical utility. Prospective randomized trials are required to establish the roles of TMB and other ICI biomarkers in a variety of clinical settings. For instance, the predictive value of TMB for combinations of immunotherapies with targeted agents or chemotherapy is not established.

Members of the neurotrophic receptor tyrosine kinase (NTRK) fusion oncogene family, NTRK1/NTRK2/NTRK3, are most prevalent in rare adult cancer types and in several pediatric cancers, although they can occur in a very small proportion of commonly occurring cancer types in adults, including NSCLCs, CRCs, head and neck cancers, thyroid cancers (especially in those with a history of radiation exposure, gliomas, inflammatory myofibroblastic tumors and some other sarcomas, and melanocytic tumors.[5, 15] Evidence of how rare NTRK fusions are comes from an examination of tissue samples from 11,502 patients where 53 gene fusions were analyzed and sequencing of 592 genes was done along with an IHC evaluation of TrkA/B/C. This review found only thirty-one cases (0.27% of the entire cohort) with NTRK fusions.[16] Nevertheless, when NTRK fusions are found, larotrectinib and entrectinib have shown to have significant and durable activity against locally advanced and metastatic solid tumors with NTRK fusions.[16, 17] Notably, this activity was seen regardless of tumor site of origin, histologic classification, or NTRK fusion type. As it relates to the RET fusion gene, the efficacy of selpercatinib was evaluated in the LIBERTTO-1 multicenter, open label, multicohort trial, which evaluated RET fusion-positive tumors (other than NSCLC and thyroid cancers) with disease progression on or following prior systematic treatment. The study demonstrated an objective response rate and duration of response of 43.9% and 24.5 months, respectively, which led to accelerated FDA approval. Tumor types with responses included pancreatic adenocarcinoma, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.[18]

Immunohistochemistry (IHC) is commonly used for NTRK testing and is practical to implement in most laboratories. IHC has variable specificity according to tumor type. While the antibody appears to have 100% specificity in carcinomas of the colon, lung, thyroid, pancreas and biliary tract, decreased specificity is seen in breast and salivary gland carcinomas, as cytoplasmic staining can occasionally be seen. Specificity is lower in sarcomas, particularly those with neural or smooth muscle differentiation.[15] Fluorescence in situ hybridization (FISH) can detect large structural variants at the DNA level. A commercial break-apart probe is available for the ETV6 gene. NGS methods can also be used. NGS testing can be particularly useful for monitoring patients with NTRK fusions for development of resistance mutations. There are some limitations of using NGS testing, however. For example, the sensitivity of DNA-based NGS suffers if fusion breakpoints involve long intronic regions. Also, when novel structural variants are detected, it can be difficult to determine whether such an event results in a functional expressed fusion. Other drawbacks include turnaround time (typically several weeks, and that more material is required for testing. Selection of the appropriate assay for NTRK fusion detection therefore depends on tumor type and genes involved, as well as consideration of other factors such as available material, accessibility of various clinical assays, and whether comprehensive genomic testing is needed concurrently.[19]

The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group launched a collaborative project to propose a classification system for molecular aberrations based on the evidence available supporting their value as clinical targets and established from this work the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[20] The ESCAT acknowledges that for the qualification of (ultra-) rare molecular aberrations it might not be feasible to obtain data from prospective randomized clinical trials (RCTs). Tier I, consisting of targets suitable for routine clinical use, therefore has two subclasses with targets for which alternative evidence is available: tier I-B includes "targets are supported by data from prospective, non-randomized clinical trials that, while unable to provide evidence for survival improvement, have demonstrated clinically meaningful benefit as defined by the ESMO Magnitude of Clinical Benefit Scale"[20] and IC includes targets for which "clinical trials in multiple tumor types, or basket clinical trials, have demonstrated a clinically meaningful benefit for the target-drug pair with similar magnitude of benefit across the different tumor types."[21] Based on ESCAT, NTRK fusions, high TMB status, and microsatellite instability (MSI) are typically ranked IC in this rubric for most solid tumors.

The FDA granted accelerated approval in June 2022 to dabrafenib in combination with trametinib for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. Mutations in BRAF occur in many tumor types and contribute to the dysregulation of processes such as cell proliferation and differentiation. Acquired resistance is common among patients receiving BRAF inhibitor monotherapies. Efforts to overcome this in BRAF V600 mutation-positive melanoma, NSCLC, and ATC have tested combined MEK and BRAF inhibition.[22] The FDA approval was based on safety and efficacy evaluation in 131 adult patients from open-label, multiple cohort trials BRF117019 and NCI-MATCH, 36 pediatric patients from CTMT212X2101, and supported by results in COMBI-d, COMBI-v, and BRF113928. In addition, there have been data published from the phase 2, open-label, single-arm, multicentre, Rare Oncology Agnostic Research (ROAR) basket trial in patients with BRAFV600E-mutated rare cancers with promising findings found in thyroid cancer[23], malignant gliomas[24], and biliary tract cancer.[25]

The most recent FDA action for a tumor agnostic indication occurred in September 2022 when selpercatinib was granted accelerated approval for adult patients with locally advanced or metastatic solid tumors with a rearranged during transfection (RET) gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. This high selective RET-kinase inhibitor had previously shown efficacy in RET-positive lung and thyroid tumors, but it occurs rarely in other tumor types. A pre-specified interim analysis of LIBRETTO-001 was planned to investigate the efficacy and safety of selpercatinib in a tumor-agnostic population of patients with RET fusion-positive advanced solid tumors. The study found objective response in 18 of 41 patients. The most common grade 3 or worse treatment emergent adverse events were hypertension (ten [22%] of 45 patients), increased alanine aminotransferase (seven [16%]), and increased aspartate aminotransferase (six [13%]). Treatment emergent serious adverse events occurred in 18 (40%) of 45 patients. No treatment-related deaths occurred.[18]

Cancer-specific Criteria

Bladder Cancer (Urothelial Carcinoma, including the Upper Tract)

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

- The individual has biopsy-proven urothelial malignancy

- The urothelial malignancy is locally advanced or metastatic
- The individual is a potential candidate for an FDA-approved targeted therapy prescribed on the basis of the FGFR test result
- The individual has not had prior FGFR testing in the metastatic setting

Tissue-based somatic tumor testing for microsatellite instability (MSI testing, to include dMMR IHC) is considered **medically necessary** for individuals with muscle-invasive urothelial tumors of the upper urinary tract.

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 Tumor Agnostic Testing guideline for details.

Rationale

Bladder cancers are biologically diverse and can be separated into "molecular subtypes," based on expression profiling.[26, 27] In these molecular classification systems, over 90% of muscle-invasive bladder cancers classify as either luminal or basal-squamous subtypes. These subtypes associate with clinical behavior, histology, and molecular alterations, though their clinical utility has not been demonstrated at present and use in bladder cancer is not recommended.[28]

Oncogenic alteration of FGFR3 is present in approximately 15% of muscle-invasive bladder cancers. The luminal subtype of bladder cancer is enriched in FGFR3 mutations and FGFR3 overexpression.[28] Also, FGFR mutations are more frequent in the upper tract (≈30%) than the bladder (≈14%).[29] A phase 2 study (BLC2001) in 99 patients with locally advanced and metastatic disease who did not respond to prior therapy found a 40% objective response rate with oral erdafitinib, a pan-FGFR inhibitor.[30] The FDA granted accelerated approval of this drug in patients with advanced or metastatic urothelial carcinoma, with relevant FGFR alterations, whose disease has progressed during or following treatment with platinum-based chemotherapy, including in the adjuvant and neoadjuvant settings. Testing may be performed using the FDA-approved companion diagnostic (a specific RT-PCR kit), or other methods, including next-generation sequencing.[28] The International Society of Urologic Pathology (ISUP) working group does not recommend testing all patients with advanced-stage disease at the time of diagnosis. Instead, the IUSP recommends FGFR testing be performed more selectively, on patients with advanced disease who have progressed following platinum-based therapy, or who have another indication to perform testing, based on the judgment of treating physicians. Additionally, updated European Association of Urology guidelines on metastatic urothelial carcinoma also indicate that platinum-based chemotherapy is the recommended first-line standard therapy for all patients fit to receive either cisplatin or carboplatin. This guideline also notes that patients who are positive for programmed death ligand 1 (PD-L1) and ineligible for cisplatin may receive immunotherapy (atezolizumab or pembrolizumab).[31]

In a series of patients with advanced upper tract urothelial cancer (479 patients) and bladder urothelial cancer (1984 patients), comprehensive genomic profiling revealed 0.7% of the bladder cancers and 3.1% of the upper tract cancers were MSI-H. FGFR3 activating mutations or fusions were found in 18% of the bladder tumors and 25.5% of the upper tract tumors.[32]

Breast Cancer

Localized breast cancer

Gene expression profiling is considered **medically necessary** to guide adjuvant therapy* treatment-decision making for individuals with localized breast cancer using Oncotype DX, MammaPrint, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, or the Breast Cancer Index when **ALL** of 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
- Lymph node status is node-negative (pN0) or axillary lymph node micro-metastasis (pN1mi) less than or equal to 2 mm
- Tumor features include **ANY** of the following:

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

***Note:**

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.

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

Metastatic breast cancer

Testing for somatic pathogenic variants of PIK3CA is considered **medically necessary** for postmenopausal females and adult males when **ALL** of the following criteria are met:

- The individual has ER-positive and HER2-negative metastatic breast cancer
- The individual is a candidate for alpelisib or another FDA-approved PIK3CA-targeted agent
- The individual has not had prior testing for PIK3CA in the metastatic setting

Testing for somatic pathogenic variants of ESR1 is considered **medically necessary** for postmenopausal females and adult males when **ALL** of the following criteria are met:

- The individual has ER-positive and HER-negative metastatic breast cancer
- The individual is a candidate for treatment for elacestrant per the FDA label
- The individual has not had prior testing for ESR1 in the metastatic setting

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

Rationale

Adjuvant therapy for breast cancer

Breast tumors are routinely pathologically evaluated by immunohistochemical staining for the presence of ER, PR, and HER2 overexpression. This information is used to make treatment decisions about hormonal and HER2-targeted therapy. Breast cancer occurs in individuals of any sexual or gender identity. Nearly all the relevant data used to guide treatment decisions are derived from studies that enrolled individuals assigned female sex at birth. Characterizing the tumor's gene expression profile allows for risk stratification for recurrence. Multigene expression assays are currently used in the care of more than one-third of females with breast cancer in the United States.[33] These genetic profiling tests are used to assess the benefit of adjuvant chemotherapy for early-stage breast cancer and ASCO has published a guideline about the use of biomarkers for adjuvant endocrine and chemotherapy use since 2016. The most commonly used test for this purpose is Oncotype DX, a 21-gene assay. The sentinel TAILORx trial, which enrolled 10,273 females, established its clinical utility for use in females with lymph node negative early breast cancer. Results were published in 2018[34] with earlier data about its prospective validation published in 2015,[35] and subsequent data showing how other clinical data added to this test further refined its use.[34] The RXPonder trial, a separate large clinical trial which enrolled 5,083 females, addressed the clinical utility of the Oncotype DX test in females with early stage, lymph node positive breast cancer.[36] Moreover, the clinical utility of another multigene assay, the 70-gene signature MammaPrint, was evaluated in a prospective randomized trial (MINDACT) that was published in 2016. This trial included 6,693 females with node-negative or 1-3 node-positive, early-stage breast cancer.[37] Patients were eligible irrespective of breast cancer subtype, but the majority had ER-positive tumors. Subsequent analyses of MINDACT further refinement of its use based on age.[38] The most recent update of the ASCO guideline in 2022[39] categorized these clinical scenarios based on the lymph node status (node-negative vs 1-3 positive nodes vs ≥4 nodes), age, menopausal status (premenopausal or age ≤ 50 years vs other), and HER2 receptor status. There is insufficient evidence in the realms of HER2 positive disease and for patients with ≥4 nodes. There is high-quality evidence and a strong recommendation for use of Oncotype DX in node-negative females (regardless of age or menopausal status) and in those with 1-3 positive lymph nodes. For MammaPrint, the ASCO guideline indicates intermediate levels of evidence and strong recommendation for node-negative females who are postmenopausal, age ≥50 years, or those with 1-3 positive lymph nodes. For these same categories noted above for MammaPrint, a lower-level recommendation (moderate) was given to several additional tests including EndoPredict, Prosigna, Breast Cancer Index, and use of non-genetic tests like IHC4 (which combines ER, PR, HER2 and Ki67 into one score) or the Ki-67 test. There is no current role for emerging biomarkers in this setting such as PD-L1 testing, evaluation of circulating tumor cells, or measurement of tumor-infiltrating lymphocytes.

The ASCO guideline update on biomarker use in early-stage breast cancer also that extended adjuvant endocrine therapy (beyond 5 years) has demonstrated improved outcomes albeit with modest absolute benefit in disease-free survival and added toxicity and tolerability challenges and no overall survival benefit. In clinical practice, the decision about extended adjuvant therapy is a shared decision negotiated between the patient and physician at the time of the clinical decision (typically within 3 months or so of the time that the 5-year course of adjuvant hormonal therapy is completed). This shared decision-making is highly personal and may take into account the individual patient’s risk of recurrence with or without further adjuvant therapy, fear of recurrence, the physical, psychological and financial tolerability of the adjuvant hormonal therapy, competing risks to health, and sometimes other factors. This is a clinical scenario where prospective data evaluating the clinical utility of incremental information based on genomics is particularly crucial. There are prospective-retrospective studies that demonstrate statistically significant treatment to biomarker interactions, particularly in the subset of ER-positive and lymph node positive patients. [40, 41] Unfortunately, there is no prospective data evaluating whether the use of a multigene classifier like the Breast Cancer Index, based on its ability to refine the risk of recurrence estimates above and beyond what is already known, adds clinical utility to shared decision-making in terms of better health outcomes, less anxiety, distress or decisional regret, or other patient-centered outcomes.

In the ASCO guideline update on biomarker use in breast cancer, the Breast Cancer Index landed with a “may use” statement based on intermediate quality evidence from the Ideal study and two smaller prospective-retrospective studies.[40, 42] These studies each showed evidence of prognostic associations but no prospective data addressing clinical utility such as seen with trials like TailorX, RXPonder, or MindACT in the different clinical setting of initial adjuvant therapy decision-making. Likewise, the Cancer Care Ontario clinical practice guideline provides a soft “may consider” statement about the Breast Cancer Index with a qualification that the evidence is still evolving and the interpretation of the test result should be conditioned on support by other clinical, pathological, or patient-related factors.[43]

Metastatic breast cancer

The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group launched a collaborative project to propose a classification system for molecular aberrations based on the evidence available supporting their value as clinical targets and established from this work the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[20] The ESCAT acknowledges that for the qualification of (ultra-) rare molecular aberrations it might not be feasible to

obtain data from prospective randomized clinical trials (RCTs). Tier I, consisting of targets suitable for routine clinical use, therefore has two subclasses with targets for which alternative evidence is available: tier I-B includes 'targets are supported by data from prospective, non-randomized clinical trials that, while unable to provide evidence for survival improvement, have demonstrated clinically meaningful benefit as defined by the ESMO Magnitude of Clinical Benefit Scale and IC includes targets for which 'clinical trials in multiple tumor types, or basket clinical trials, have demonstrated a clinically meaningful benefit for the target-drug pair with similar magnitude of benefit across the different tumor types.[21] Based on the current evidence, the ESMO Precision Medicine working group does not recommend routine use of large panel NGS testing on tumor samples for patients with metastatic breast cancer.[44] HER2 amplification, germline BRCA1/2 mutations, and PIK3CA mutations were classified in tier of evidence IA based on large randomized trials showing antitumor activity of targeted therapies in patients presenting with these alterations. Neurotrophic receptor tyrosine kinase (NTRK) fusions and microsatellite instability (MSI) were ranked IC.[45]

Genotype-driven targeted therapy using alpelisib has received regulatory approval and become part of routine clinical practice for PIK3CA-mutated ER-positive/HER2-negative metastatic breast cancer based on the Solar-1 trial data.[46] Approximately 40% of patients with ER-positive/HER2-negative disease have activating PIK3CA mutations. In Solar-1, the presence or absence of any PIK3CA mutation by means of polymerase-chain-reaction analysis of mutation hot spots in the C2, helical, and kinase domains of PI3K (corresponding to exons 7, 9, and 20, respectively) with the use of a tumor-tissue sample. In addition, genotype-targeted therapy using elacestrant in metastatic breast cancer individuals with ER-positive and HER2-negative breast tumors has also received regulatory approval. This is based on the phase III Emerald Trial, an open-label trial that enrolled individuals with ER-positive/HER2-negative advanced breast cancer who had progressed/relapsed on or after one or two lines of endocrine therapy, one of which was given in combination with a cyclin-dependent kinase 4/6 inhibitor, and ≤1 line of chemotherapy for advanced disease. Estrogen receptor 1 (ESR1) mutations were defined as any missense mutation in codons 310-547.[47] In addition, for patients harboring germline BRCA1 or BRCA2 mutations, the use of olaparib (a PARP inhibitor) is now a standard treatment option based on data from the OlympiaAD trial.[48] Based on these data, the presence of metastatic breast cancer is an indication for germline BRCA testing, although many patients have already undergone such testing by the time they develop metastatic disease since de novo metastatic breast cancer represents less than 10% of metastatic breast cancer and the indications for BRCA testing are broad.

Most therapies targeting kinase fusions are either still in clinical development or approved in tumor types other than breast cancer except for the NTRK inhibitors which received tumor-agnostic regulatory approval and would be an option for 4 out of 4854 patients (0.08%) of patients with breast cancer (Hilbers). While somatic ESR1 mutations are a well-established mechanism of acquired resistance to aromatase inhibitors, clinical trials have demonstrated that these aromatase inhibitors combined with CDK 4/6 agents remain active in the presence of ESR1 mutations.[49] Other biomarkers such as AKT1, FGFR1/FGFR2, PTEN, NFI, and tumor signatures (APOBEC) are still under investigation in clinical trials. Additional emerging biomarkers include HER2 activating mutations, somatic BRCA 1 or 2 mutations, and germline PALB2 mutations. The data regarding use of targeted agents for these mutations is promising but still limited.[50]

Cholangiocarcinoma (Biliary Tract Cancers)

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

- The individual has biopsy-proven cholangiocarcinoma
- The cholangiocarcinoma is locally advanced, unresectable, or metastatic
- The panel testing is inclusive of the following pathogenic variants: IDH1, FGFR, and BRAF
- The individual is a potential candidate for FDA-approved targeted therapy prescribed on the basis of the panel test results
- The individual has not had prior somatic tumor testing in the metastatic setting

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

Rationale

Biliary tract cancer refers to a spectrum of invasive adenocarcinomas, including cholangiocarcinoma (cancers arising in the intrahepatic, perihilar, or distal biliary tree), and gallbladder carcinoma. Identification of distinct patient subgroups with driver

mutations amenable to targeted therapy have been identified, which are generally mutually exclusive from one another and often associated with the anatomical subsite of the tumor.[51] The most common molecular alterations in biliary tract malignancy are found in IDH1 (mutations found in 13% of intrahepatic cholangiocarcinoma cases), the FGFR pathway, particularly FGFR2 mutations (20% of intrahepatic cholangiocarcinoma), HER2 mutations (found in up to 20% of gallbladder and extra-hepatic cholangiocarcinoma), BRAF V600E mutations (found in 5% of intrahepatic cholangiocarcinoma). To identify these potentially targetable alterations, performing molecular profiling for patients diagnosed with cholangiocarcinoma (especially intrahepatic cholangiocarcinoma) is now considered standard of care.[52] Like other solid tumors, mutations in NTRK or MMR deficiency may also be found rarely.

A majority of patients are diagnosed with advanced disease, when chemotherapy with cisplatin and gemcitabine followed by second-line chemotherapy is the cornerstone of treatment for most patients in the absence of targetable alterations. In adult patients with unresectable locally advanced or metastatic hepatocellular cholangiocarcinoma harboring IDH1 gene mutations—detected by an FDA-approved test—with disease progression after 1 to 2 prior lines of systemic therapy for advanced disease, ivosidenib is an FDA-approved treatment. [53] For patients with FGFR2 fusions or other rearrangements, phase II single-arm registrational trials of FGFR inhibitors in the previously treated, unresectable locally advanced or metastatic cholangiocarcinoma population show an overall response rate in the 23%-42% range and a median progression-free survival of 7 to 9 months and FGFR inhibitors such as pemigatinib and infigratinib can be used in this setting. Likewise, there is activity in treating patients with BRAF V600E mutations with dabrafenib plus trametanib as well as use of entrectinib to treat those with NTRK inhibitors. HER2-directed therapies have some activity, albeit less convincing, in chemo-refractory patients.[52]

Colorectal Cancer

Localized colorectal cancer

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

- The individual has biopsy-proven adenocarcinoma of the colon or rectum
- Includes **ANY** or **ALL** of the following, with no prior testing
    - MSI testing and/or dMMR IHC testing
    - BRAF V600E variant (RAS variants may also be part of some targeted panels)
    - MLH-1 promoter methylation and/or BRAF V600E mutation testing with nuclear expression loss of MLH1 and PMS2 by immunohistochemistry

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 less genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with metastatic colorectal cancer and may be performed on the primary tumor or a metastatic site when **ALL** of the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the colon or rectum
- Assessment includes **ANY** or **ALL** of the following:
    - MSI testing and/or dMMR IHC testing
    - Extended RAS testing (KRAS and NRAS variants)
    - BRAF V600E variant
    - HER2 testing
    - MLH-1 promoter methylation and/or BRAF V600E mutation testing with nuclear expression loss of MLH1 and PMS2 by immunohistochemistry
- There has been no prior 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 Tumor Agnostic Testing guideline for details.

Rationale

Among people diagnosed with colon cancer, 20% have metastatic CRC, and 40% present with recurrence after previously treated localized disease.[54] Among those with localized CRC, approximately 15% are deficient in one or more DNA mismatch repair (MMR) proteins, with one-quarter of these resulting from Lynch syndrome.[55] About 90 to 95 percent of colorectal cancers in patients with Lynch syndrome show evidence of microsatellite instability (MSI).[56] In patients with early-stage (especially stage II) CRC, MMR status provides important prognostic and predictive information, with MMR-deficiency being associated with both a good prognosis and a lack of efficacy from fluorouracil treatment.[57]

Five percent of metastatic CRC tumors are MMR-D or MSI-H (either due to Lynch syndrome or sporadic mutations) and may respond to immunotherapy.[54] All CRC (localized and metastatic) should be tested for either mismatch repair deficiency (MMR-D) via immunohistochemistry or microsatellite instability-high (MSI-H) via polymerase chain reaction to screen for Lynch syndrome and/or to inform therapeutic options. In the metastatic disease setting, in addition to testing for microsatellite instability and MMR-deficiency, extended RAS testing has been the standard of care since the ASCO Provisional Clinical Opinion in 2015 based on evidence indicating that RAS mutations in exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) of both KRAS and NRAS are predictive of resistance to treatment with monoclonal antibodies (such as cetuximab and panitumumab) targeting the epidermal growth factor receptor (EGFR).[58] These anti-EGFR antibody treatments should only be considered for treatment of patients with mCRC who are identified as having tumors with no mutations detected after such extended RAS mutation analysis.

BRAF V600E mutation is also routinely tested in metastatic colorectal cancer. This mutation leads to constitutive BRAF kinase activity and sustained MAPK pathway signaling in colon cancer. Other activating mutations in BRAF in CRC are very rare. The prevalence of this mutation is about 5%–10% in mCRC. BRAF mutation tumors have been associated with female gender, advanced age, proximal colon tumor location, T4 tumors, and poor response to standard chemotherapy.[59, 60] In the BEACON study, BRAF and MEK directed therapy with encorafenib plus cetuximab improved overall survival and overall response rates in the metastatic setting after one or two lines of prior therapy compared with standard palliative chemotherapy.[61] Another biomarker under exploration is HER2 testing. The frequency of HER2 overexpression among patients with CRC is known to be around 5%. Thus far, phase II trials evaluating HER2 targeted therapy have produced mixed results, but such therapy is active when RAS and BRAF are wild-type and several clinical trials are ongoing.[62] Finally, NTRK gene fusions are extremely rare, occurring in approximately 0.35% of colorectal cancer and are more frequently found among patients with MMR-D tumors.[63] Lastly, as it relates to BRAF and KRAS testing in the localized stage II-III CRC setting, some studies have suggested some prognostic value in performing one or both.[39, 64]

Endometrial carcinoma, advanced

Tissue-based somatic tumor testing is considered **medically necessary** for individuals with advanced endometrial carcinoma and may be performed on the primary tumor or a metastatic site when **ALL** of the following criteria are met:

- The individual has biopsy-proven endometrial carcinoma
- Assessment includes the following, as applicable:
    - MSI-H and/or dMMR mismatch repair testing
    - MLH-1 promoter methylation testing with IHC nuclear expression loss of MLH1 and PMS2
- There has been no prior 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 Tumor 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 FDA previously approved both the VENTANA MMR RxDx Panel and FoundationOne CDx as companion diagnostic devices to select patients with dMMR and MSI-H solid tumors, respectively, to identify individuals who are eligible for treatment with pembrolizumab. Approval was based on KEYNOTE-158—a multicenter, non-randomized, open-label, multi-cohort trial, which examined individuals with unresectable or metastatic MSI-H or dMMR endometrial carcinoma within two cohorts. Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. The objective response rate was 48% with a median progression-free survival of 13.1 months. The results demonstrated robust antitumor activity and enhanced survival outcomes in individuals receiving pembrolizumab with MSI-H/dMMR endometrial cancers. [65] As it relates to Lynch syndrome, loss of IHC nuclear expression of MLH1 may be due to Lynch syndrome or methylation of the MLH1 promoter region, as occurs in sporadic MSI carcinoma. Loss of nuclear expression of MHL1 and PMS2 by IHC should be triaged for MLH1 methylation studies. The presence of MLH1 methylation suggests a sporadic tumor rather than a germline mutation, and further germline testing is likely not indicated. Absence of MLH1 methylation suggests Lynch syndrome and germline testing for MLH1 is indicated. Loss of nuclear expression of MSH2 and MSH6, loss of MSH6 only, or loss of PMS2 only all have a high probability of Lynch syndrome and genetic counseling should be considered.[66, 67] Evolving roles of other prognostic-molecular subgroups that have received attention include ultramutated DNA polymerase epsilon (POLE-mut) and p53 (p53abn) variants, which were identified as part of the Cancer Genome Atlas (TCGA) study—they are associated with good and poor prognoses, respectively.[68] Since the identification of these TCGA subgroups, further studies have attempted to evaluate the association between variants and histologic features, as well as their clinical utility. For the latter, the ongoing PORTEC-4a randomized phase III trial study is examining the impact of molecular-risk profiling-directed standard/individualized adjuvant treatment in high-intermediate risk endometrial cancer, although results are yet to be reported.[68-70] Results from an earlier PORTEC-3 trial suggested that p53abn was associated with a beneficial 5-year recurrence-free survival rate with chemotherapy versus radiotherapy alone (59% versus 36%) in high-risk endometrial cancer.[71] Given this evolving field, routine testing for these latter two subgroup variants is not consistently recommended by nationally recognized guidelines.

Melanoma

Diagnostic and prognostic testing in melanoma

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

Somatic tumor testing in advanced melanoma

Tissue-based somatic tumor testing for **BRAF V600E** pathogenic variant by validated IHC, PCR, or NGS methods for individuals with resectable or unresectable stage III or stage IV cutaneous melanoma or high-risk stage IIC 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

Tissue-based somatic tumor testing for individuals with resectable or unresectable stage III or stage IV melanoma or high-risk stage IIC melanoma that is **BRAF V600E wild-type or mucosal melanoma** is considered **medically necessary** when **ALL** of the following criteria are met:

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

Testing of individuals with **metastatic uveal melanoma** for **HLA-A*0201** using is considered **medically necessary** when **ALL** of 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 Tumor 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 great majority of melanocytic lesions. There is, however, a small subset of melanocytic lesions that eludes appropriate classification by conventional light microscopy alone, preventing accurate prediction of clinical behavior and recommendations for appropriate treatment.[72] Ancillary tests such as comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH), have been developed to help guide the diagnosis of ambiguous melanocytic proliferations. Although sometimes used, the correlation between various patterns of chromosomal abnormalities and outcomes are yet unclear.[72] Commercially available gene expression classifiers have also been developed and clinically validated. For example, a 23-gene classifier (MyPath Melanoma) was shown to have up to 92% sensitivity and 93% specificity at distinguishing benign from malignant lesions.[73-75] The clinical utility related to use of this kind of testing has not been demonstrated. Prospective studies controlling the risk of bias and including clinically meaningful outcomes are needed to better understand the role of techniques used to clarify the diagnosis of the target subset of difficult to diagnose melanocytic lesions.

Prognostic classification of localized cutaneous melanoma

There are numerous clinicopathologic features that are accurately associated with melanoma outcome for localized disease (e.g., Breslow thickness, ulceration, and tumor-infiltrating lymphocytes). Currently, prognostication based on pathologic features is quite robust.[76] There is interest, however, in using gene expression profiling (GEP) to categorize localized (stage I and II) cutaneous melanoma according to risk of metastasis and to better guide clinical decisions such as when to consider sentinel lymph node biopsy or adapt the surveillance intensity. Gene expression profiling associates the expression levels of many genes with an outcome, such as melanoma recurrence. Current GEP tests largely assign the patient's tumor to a specific prognostic class (e.g., class 1 vs class 2, or low risk vs high risk) rather than calculating a specific calculated survival.[76] A published meta-analysis of the 31-gene GEP test focused on three selected studies plus data from a novel cohort of 211 patients showed that recurrence-free and distant metastasis-free survival rates were 91.4% and 94.1% for Class 1A patients and 43.6% and 55.5% for Class 2B patients.[77] The methodology of this meta-analysis was criticized by academic dermatologists due to a lack of a pre-specified protocol, lack of adjustment for confounders and missing data, incomplete risk of bias assessment, publication bias, and financial conflicts of interest among the authors who were also meta-analyzing studies they also co-authored.[78] Overall, the clinical utility of GEP classifiers in this setting remains uncertain. These GEP tests also need to be weighed against (or integrated with) the best available phenotypic models and other simple and widely available outcome algorithms.[76] For example, numerous studies have identified risk factors that may be predictive of positive SLN in thin melanoma, such as ulceration, high mitotic rate, and younger patient age. These risk factors are easily determined and inexpensive, and are now referred to as adverse features in guidelines for use in clinical staging and workup.[79]

Prognostic classification of uveal melanoma

Uveal melanoma is a rare intraocular cancer that carries a 30%–50% risk of metastasis within 5 years of diagnosis. Metastases are observed most commonly in the liver and less frequently in the lungs and other organs. Post-treatment surveillance is based on individual judgement and consensus-based guidelines typically involves imaging to evaluate signs and symptoms as indicated, with consideration of blood testing of liver function and liver and chest, abdominal, and pelvic imaging every 6 to 12 months for 10 years. Patients considered high risk may be imaged more frequently, such as every 3 to 6 months over the first 5 years.

The risk of metastases from a uveal melanoma has traditionally been predicted based on the study of the morphologic and pathologic features of the tumor. Tumor thickness, diameter, location, presence of extraocular extension, and histopathology have been consistently shown to independently predict the likelihood of developing metastatic disease.[80] Cytogenetic investigations show that monosomy 3 is the most frequent karyotypic abnormality and is present in approximately 50% to 60% of patients. Monosomy of chromosome 3 and additional copies of 8q have been correlated with reduced survival.[81] A commercially available 15-gene expression profile (DecisionDX-UM®, manufactured by Castle Biosciences, Inc.) is marketed to predict metastatic risk based on primary-tumor biology. This gene expression profile was reported to assist in ultimately managing certain individuals with a less-intensive surveillance program, following a prospective study that looked at 89 patients enrolled from 4 institutions who underwent testing and then based on the results were assigned into either a high- or

low-risk category.[82] It should be noted that conflicts of interest and financial biases existed, such as several authors who were either employees and/or shareholders of Castle Biosciences. Another uveal melanoma genetic test from Impact Genetics Inc. evaluates tumor specimens for complete or partial loss, duplications, or isodisomy of Chromosomes 1p, 3, 6, and 8 with genetic sequencing of the GNAQ and GNA11 genes is offered for select specimens.[80] Importantly, no survival benefit from the early detection of asymptomatic disease in uveal melanoma has been documented. In view of the lack of evidence for the benefit of any specific surveillance strategy, particularly for late relapse, recommendations for these patients and their providers remain uncertain.[81] Factors that are sometimes considered in decisions about surveillance include the patient's enhanced emotional well-being, the potential to identify oligometastatic disease amenable to surgery or other local therapies, the hope for decreased morbidity from advanced disease, and identification of eligibility for clinical trials that assess novel therapies for advanced uveal melanoma.[83] Multiple studies have shown that certain morphologic characteristics of melanoma tumors (size and location) independently predict metastasis, beyond the data provided by either chromosomal analysis or GEP. Clinicians must integrate the entire clinical picture, including tumor size, location, and tumor growth velocity when interpreting the results of genetic analysis of an individual uveal melanoma tumor.[80] Ultimately, the selection of surveillance modality used varies according to local expertise and patient preferences.

Somatic tumor testing for resectable or unresectable stage III or stage IV melanoma

The majority of melanomas have mutations in genes associated with the MAPK pathway such as BRAF, NRAS, or NF1. Activation of the BRAF kinase via mutation is the most common, occurring in 40%–60% of cases, with mutated NRAS, occurring in 15%–30% of cases.[84] More than 90% of the BRAF mutations are V600E, with V600K mutations accounting for most of the remainder.[84] Currently, BRAF mutation status is the only biomarker that predicts a therapeutic response in advanced melanoma and testing for BRAF V600E mutation is the current standard of care in the setting of resectable or unresectable stage III or stage IV melanoma and also highly recommended for resected, high risk stage IIC disease.[85]

The main cutaneous melanoma subtypes are associated with different mutational landscapes: frequently mutated genes aside from BRAF include CDKN2A, NRAS and TP53 in cutaneous melanoma, NRAS, NF1 and KIT in acral melanoma, and SF3B1 in mucosal melanoma.[85] In metastatic uveal melanoma, testing for HLA-A*0201 by a specific assay used to identify patients who may be treated with tebentafusp (a bispecific protein directed to target glycoprotein 100 positive cells), which improved overall survival in a phase 3 trial.[86]

NRAS mutations are present in 15% of melanomas and correlate with poor prognosis.[87] BRAF-mutant and NRAS-mutant melanomas are sensitive to MEK inhibition, and the MEK inhibitor binimetinib has shown clinical activity in a controlled trial in the subset of patients with NRAS -mutant metastatic melanoma.[88] Moreover, c-KIT mutations are also common and found in about 15%–23% of mucosal melanoma, 10%–15% of acral lentiginous melanoma (ALM), and 6%–28% of melanoma arising in chronically sun-damaged skin.[89] A review of 19 single arm studies of use of c-KIT inhibitors in unselected patients with KIT mutations or amplifications showed a response rate of 14% for mucosal melanoma and 22% for acral lentiginous melanoma, with activity in particular for mutations in exons 11 and 13 and minimal activity in KIT amplified tumors.[89] Overall, for patients in whom the melanoma is BRAF wild-type at the V600 locus, testing for less common BRAF mutations and for NRAS and c-KIT mutations is considered an ESMO evidence level IIC recommendation (suggesting that it is optional as there is insufficient evidence for efficacy).[85]

Non-Small Cell Lung Cancer

Localized (stage IB-IIIA) NSCLC

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

- Biopsy-proven, stage IB-IIIA NSCLC with **ANY** of the following characteristics:
    - An adenocarcinoma component on histology
    - Non-squamous, non-small cell histology
    - Any non-small cell histology when **EITHER** of the following clinical features are present:
        - Age 50 years or younger
        - Light or absent tobacco exposure
- Test results will determine candidacy for treatment with osimertinib

Metastatic NSCLC

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

- Biopsy-proven NSCLC with **EITHER** of the following characteristics:
  - An adenocarcinoma component on histology
  - Non-squamous, non-small cell histology
- The panel testing contains, at minimum, testing of appropriate molecular aberrations (mutations, rearrangements, fusions, or amplifications) in **ALL** of the following genes: EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS, MET, NTRK, and RET
- The individual is a candidate for targeted therapy that may be prescribed based on the panel test results
- The individual has not had prior NGS testing in the metastatic setting

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

Rationale

Metastatic non-small cell lung cancer (NSCLC) has historically been classified by histology and treated with cytotoxic chemotherapy. However, in the past decade there has been improved understanding of the disease biology and oncogenic driver mutations. The modern treatment of NSCLC is characterized by molecularly defined subsets 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[90, 91], and selection of patients based on predictive biomarkers is associated with improved patient outcomes.[91] Molecular testing of sensitizing EGFR mutations, BRAF V600E, as well as ALK, ROS1, is now standard-of-care for patients with advanced NSCLC, as is testing for the EGFR T790M mutation upon resistance to first- or second-generation EGFR tyrosine kinase inhibitor therapy.[92] Multiplexed genetic sequencing panels are preferred where available over multiple single gene tests to identify other treatment options beyond EGFR, ALK, BRAF, and ROS1. These larger panels include testing for specific molecular alterations in ERBB2 (HER2), KRAS, RET, MET, and NTRK genes.[92, 93] New targetable alterations are continuing to emerge.

In contrast to metastatic non-squamous NSCLC, the management of early-stage non-squamous NSCLC does not involve routine testing for oncogenic driver mutations. However, for patients with stage Ib to IIIA NSCLC who are being considered for FDA-approved adjuvant therapy with osimertinib (an oral targeted EFGR inhibitor) based on results of the ADAURA study[94], testing for EGFR exon 19 deletions or L858R point mutations is indicated. The ADAURA trial initially showed significant improvement in disease-free survival in patients treated with adjuvant osimertinib.[92] More recent data indicate that use of osimertinib (a targeted agent used to treat EGFR mutated NSCLC) in the adjuvant setting for patients with resected stage Ib-IIIA NSCLC is associated with clinically significant improvements in overall survival.[95] In this scenario, EGFR testing using tissue specimens can be obtained before surgery or at the time of surgery. Meanwhile, preclinical and retrospective clinical data that support hypothesis testing of biomarker-driven treatment strategies in earlier stages of NSCLC with prospective clinical trials currently in progress.[96] While neoadjuvant treatment targeted at EGFR mutations is being explored, it has not been established as effective with major pathological response rates of 15% in recently presented data, which are below the threshold expected.[97]

Ovarian cancer (epithelial)

Targeted (i.e., 50 or less genes) tissue-based somatic testing for pathogenic variants of BRCA1, BRCA2, and to determine HRD status in individuals with recurrent epithelial ovarian cancer is considered **medically necessary** when **ALL** of the following criteria are met:

- The individual has biopsy-proven epithelial ovarian cancer
- The individual is a candidate for treatment with an FDA-approved PARP inhibitor
- The individual has not had prior testing for these genes in the metastatic setting

Germline testing for pathogenic 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 Tumor Agnostic Testing guideline for details.

Rationale

The PARP inhibitor olaparib first received FDA approval in 2014 for females with germline mBRCA-associated (gBRCA) recurrent ovarian cancer. However, subsequent findings from clinical trials of PARP inhibitors have suggested that the importance of mBRCA as a predictive biomarker has diminished.[98] For instance, among females without a germline mBRCA mutation, predictors of PARP activity include a somatic mutation in BRCA and evidence of homologous recombination deficiency. Indeed, FDA approval of the PARP inhibitor rucaparib in 2016 broadened the eligibility for PARP inhibitor treatment beyond gBRCA and included patients with somatic BRCA-associated ovarian cancers. In the subsequent Ariel3 trial, rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy.[99] A novel aspect of this trial was the prospective validation of the tumor-based, NGS HRD test assay. Additionally, an exploratory analysis of progression-free survival in patients with BRCA wild-type and high loss of heterozygosity (LOH) or low LOH tumors revealed that patients with BRCA-mutant tumors did not solely drive rucaparib benefit in the HRD cohort or intention-to-treat population.[100] The FDA approval of rucaparib in April 2018 included approval of a complementary diagnostic test for tumor samples to determine both BRCA and HRD status.

Pancreatic Adenocarcinoma

Germline testing for pathogenic variants is considered **medically necessary** for all individuals with pancreatic adenocarcinoma. *See the Carelon Guidelines for Hereditary Cancer Testing for further details.*

Tissue-based somatic tumor testing for microsatellite instability (MSI testing, to include dMMR IHC) is considered **medically necessary** for individuals with locally advanced or metastatic pancreatic adenocarcinoma.

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 Tumor Agnostic Testing guideline for details.

Rationale

Up to 10% of individuals with pancreatic adenocarcinoma have a pathogenic germline alteration. Individuals with BRCA1 or BRCA2 mutations or microsatellite instability (MSI) resulting from a pathogenic germline mutation or somatic mutation in DNA mismatch repair (MMR) genes.[101] Affected individuals may benefit specifically from platinum-based therapies or PARP inhibitors.[102] For this reason, individuals with newly diagnosed pancreatic cancer at any stage should have multidisciplinary evaluation and management, germline testing, and integrated supportive care.[103]

The enthusiasm for use of PARP-inhibition as targeted therapy for patients with BRCA-mutated pancreatic cancer came from the POLO trial published in 2019, a trial that randomized 154 patients with metastatic pancreatic adenocarcinoma and germline BRCA mutation to maintenance olaparib versus placebo after 16 weeks of first line platinum-based chemotherapy.[104] The POLO trial showed a statistically significant advantage in progression-free survival for olaparib (median 7.4 vs 3.8 months, hazard ratio 0.53). However, mature data have since been published showing no statistical or clinically meaning improvement on overall survival.[105] Based on the absence of survival or quality of life improvement with olaparib and other concerns about the POLO trial design[106], enthusiasm for the use of olaparib as maintenance therapy has declined. A phase II trial is underway exploring the role of another PARP inhibitor, rucaparib, for maintenance therapy in patients with advanced pancreatic carcinoma and germline or somatic mutation of BRCA1, BRCA2, or PALB2.[107] These phase II data show that, like olaparib, rucaparib is active and tolerable. Ongoing randomized studies will further elucidate whether there are clinically meaningful benefits to using PARP inhibitors in the maintenance or adjuvant settings.

Prostate Cancer

Localized prostate cancer

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

Metastatic prostate cancer

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

- The individual has biopsy-proven adenocarcinoma of the prostate
- The individual is a candidate for **ONE** of the following therapies:
    - FDA-approved PARP inhibitor (olaparib, rucaparib, or another PARP inhibitor approved for use in this setting)
    - FDA-approved PD-1 inhibitor (pembrolizumab or another checkpoint inhibitor approved for use in this setting)
- The NGS panel includes BRCA2, BRCA1, and ATM, and may also include other genes encoding molecules involved in homologous recombination DNA damage repair (DDR) such as PALB2, FANCA, RAD51D, CHEK1/2, BARD1, and CDK12, among others
- The individual has not had prior NGS testing in the metastatic setting

Tissue-based somatic tumor testing for microsatellite instability (MSI testing, to include dMMR IHC) is considered **medically necessary** for individuals with locally advanced or metastatic prostate cancer.

Germline testing for pathogenic variants is considered **medically necessary** for all individuals with metastatic prostate adenocarcinoma. *See the Carelon Guidelines for Hereditary Cancer Testing 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 Tumor 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.[108] 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.[109] 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 used 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.[110] Prognostic approaches are sometimes explored using other, surrogate endpoints such as time to radiographic progression assessed by blinded independent central review, development of distant metastases, risk of adverse pathology during active surveillance, and others. Ultimately, management decisions for localized prostate cancer are typically made after appropriate options have been discussed with a multidisciplinary team (including urologists, radiation oncologists, medical oncologists, pathologists, and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered in shared decision-making with the patient.

Numerous molecular biomarkers, particularly tissue-based genomic biomarker tests, have been developed to improve risk stratification and patient management. One of the unique challenges for use of these biomarkers is the complex spatial heterogeneity of prostate cancer.[111] While few of these genomic panels have undergone extensive validation, there are

several are 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.[112, 113] Given the absence of prospective clinical trial data, NCCN and ASCO guidelines do not recommend routine ordering of any molecular tests to guide decision-making in localized prostate cancer regarding the role of active surveillance or the use of post-prostatectomy adjuvant versus salvage radiation therapy. The ASCO guideline on molecular biomarkers in localized prostate cancer emphasizes that there is a paucity of prospective studies assessing the short and long-term outcomes of patients when these biomarkers are integrated into clinical decision-making.[112] 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.[114] Overall, it remains uncertain what prognostic endpoints should be prioritized and what magnitude of association with those prognostic endpoints are important. Nevertheless, in recent years, there has been more than 10-fold increase in tissue-based genomic biomarker testing related to prostate cancer with striking regional variability.[115] Practice patterns also vary widely within regions.[116] 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.[114] The relative accuracy of these biomarker tests compared to other standard tests is unknown.[116] 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.[114]

Similar to the prognostic/risk-stratifying GEPs discussed above, several proprietary-diagnostic marker assays (e.g., 4Kscore, ConfirmMDx, SelectMDx, ExoDx, and Progensa, among others) also exist, and vary in testing methodology, to include DNA hypermethylation, mRNA expression, exosomal RNA expression, and serum kallikreins, among others—some of which are FDA approved. The use of such assays include assistance in evaluating general/early diagnosis, identifying clinically significant disease, and deciding whether to repeat biopsy. Although there is interest in further exploration of these assays, impactful prospective studies, standardized cut-off scores (when applicable), and routine-testing recommendations from national guidelines are lacking.[117]

Metastatic prostate cancer

Patients with metastatic prostate cancer have multiple treatment options with varied mechanisms of action beyond androgen deprivation therapy alone. Such options include androgen-receptor-targeted agents, taxane-based chemotherapies, bone-targeted radiopharmaceutical radium-223, and biomarker-driven therapy with the immune-checkpoint inhibitor pembrolizumab (for those with mismatch-repair deficiency (dMMR) or microsatellite instability (MSI)) and the PARP inhibitors olaparib and rucaparib (for those with homologous-recombination gene deficiency). Practice patterns vary in terms of the sequencing of therapies for both castrate-sensitive and castrate-resistant patients, and also variation in responses between patients with any given therapy.

The prevalence of recurrent genomic alternations varies across various prostate cancer clinical scenarios and also by published cohort. Common aberrations are typically not actionable and involve the androgen receptor (observed in >50% of cases); TP53 (in >40% of cases); genes encoding components of the PI3K pathway, such as PTEN (in 45% of cases); loss of RB1, which encodes the tumor suppressor Rb (in ~20% of cases); and others.[118] 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.[44] 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.[118] The ESMO Precision Medicine working group recommends multi-gene NGS panel testing in metastatic prostate cancer to assess for ESCAT level 1 alterations.[44] Commercially available prostate-cancer specific NGS panels include 11-14 genes.[119] 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 mutations coexisting with microsatellite instability are likely bystander events that may not result in sensitivity to poly (ADP-ribose) polymerase inhibitors.[120]

The pivotal clinical trials of PARP inhibitors in metastatic castrate resistant prostate cancer are the phase III Profound trial (for olaparib) and the phase II Triton2 trial (for rucaparib). In the Profound trial[121, 122], there was a randomization to olaparib versus enzalutamide or abiraterone for patients who had either BRCA1, BRCA2, or ATM mutations (cohort A) or alterations in any of

12 other HRD genes (cohort B). The statistically significant benefit in progression free survival (7.4 months vs 3.6 months, HR 0.34) and overall survival (19.1 vs 14.7 months, HR 0.69) was limited to the cohort A patients. The phase II TRITON2 study of rucaparib included patients with mCRPC and deleterious BRCA or non-BRCA DNA damage-repair gene alterations treated after 1-2 lines of next-generation androgen-receptor directed therapy and 1 prior taxane-based regimen. In the BRCA mutated patients, the overall response rate was 43.5%[123], and for those with non-BRCA DNA damage-repair alterations the responses were much lower for PALB2, FANCA, BRIP1 and RAD51B and non-existent for ATM, CDK12, and CHEK2.[124]

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** of the following criteria are met:

- There has been no prior testing of the same thyroid nodule
- Initial cytopathology is reported as **ANY** of the following (Bethesda III or IV) categories:
    - Atypia of undetermined significance (AUS)
    - Follicular lesion of undetermined significance (FLUS)
    - Suspicious for follicular neoplasm (SFN)
    - Follicular neoplasm (FN)
- The ITN is <4 cm in size **AND** does NOT have findings highly suspicious for malignancy on ultrasound (American Thyroid Association high suspicion pattern or American College of Radiology TIRADS 5)
- **ONE** of the following gene expression classifiers will be used:
    - ThyGeNEXT/ThyraMIR multiplatform test
    - ThyroSeq Genomic Classifier

Somatic genetic testing of thyroid malignancy

BRAF V600E testing is considered **medically necessary** for individuals with thyroid malignancy when the following criteria* are met:

- The individual has biopsy proven anaplastic thyroid cancer
- The individual is considered a potential candidate for FDA-approved oral targeted therapy based on the results of this testing

ALK, NTRK, and RET gene fusion testing is considered **medically necessary** for individuals with locally advanced, recurrent or metastatic thyroid carcinoma that is not amenable to radioactive iodine therapy when the following criteria are met:

- The individual has biopsy proven locally advanced, recurrent, or metastatic thyroid carcinoma
- The individual is considered a potential candidate for FDA-approved oral targeted therapy based on the results of this testing

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

Rationale

Molecular testing of indeterminate thyroid nodules

Roughly 4%-7% of the population have palpable thyroid nodules and as much as 30% or more have ultrasound detectable nodules. Indeterminate thyroid nodules (ITNs) are a challenging problem because these nodules are frequently discovered but usually benign and not requiring treatment.[125] The goal of care is to reduce overtreatment of such nodules and yet to detect and appropriately treat the proper subset of nodules that may cause morbidity or mortality due to thyroid malignancy. Fortunately, the majority of patients diagnosed with thyroid cancer are low risk for recurrence (<5%) and their risk of cancer-

related death is even lower.[126] Indeed, recent studies have explored the role of de-escalation of treatment[126] including active surveillance.[127]

When a thyroid nodule is found, the standard of care is to perform fine needle aspiration of the nodule for cytopathology. The American Thyroid Association (ATA) updated its guidelines for management of ITNs in 2015, recommending using the Bethesda System for Reporting Thyroid Cytopathology. This system includes six classifications: (I) nondiagnostic/ unsatisfactory; (II) benign; (III) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (IV) follicular neoplasm/suspicious for follicular neoplasm (FN); (V) suspicious for malignancy (SUSP); and (VI) malignant. Notably, the Bethesda System replaces the traditional single “indeterminate” category with three classifications, AUS/FLUS, FN, and SUSP.

Molecular testing is an increasingly utilized adjunct when evaluating indeterminate thyroid nodules in an effort to avoid unnecessary surgical or diagnostic risk to a patient.[125] The potential use of such tests is to improve risk stratification in the intermediate risk subgroups such as Bethesda III and IV groups. The second edition Bethesda System for Reporting Thyroid Cytology estimated 6%-18% malignancy rate of category III and 10%-40% for category IV nodules.[128] A single institution retrospective cohort study noted in a 5-year review that malignancy rates at their institution of Bethesda III and IV surgical cases were 20%-25% with a fairly large range between years.[129] In recent years, several commercial multi-gene classifiers have emerged that are intended to help classify these indeterminate nodules.[130] One example is ThyroSeq v3, a third-generation DNA, and RNA sequencing test which identifies mutations, gene fusion, gene expression alterations, and copy number variations. In contrast, the Afirma GSC, another third-generation classifier, is a machine learning derived classification system detecting RNA transcriptome expression, mitochondrial RNA, and genomic copy number alterations including loss of heterozygosity. Finally, a multiplatform test (MPT) approach that combines a mutation panel test (ThyGenX) and a microRNA risk classifier test (ThyraMIR) has also been shown to provide both high negative predictive value (NPV) and high positive predictive value (PPV) for malignancy when tested in indeterminate nodules.[131, 132] Meta-analyses of the second generation molecular tests to assess ITNs indicated that the high sensitivity and high NPV of these tests are similar.[133, 134] Of note, an altogether different classifier Afirma Xpression Atlas detects gene variants and fusions in thyroid nodule FNA samples from a curated panel of 511 genes using whole-transcriptome RNA-sequencing. Its intended use is distinct from those above focusing on cytologically indeterminate nodules that are Afirma GSC suspicious, Bethesda V/VI nodules, or known thyroid metastases.[135] More recently, the Afirma GSC and Afirma Xpression Atlas tests are only offered as composite tests and, therefore, no longer limit testing to Bethesda III and IV groups.

The ATA 2015 guidelines regarding evaluation and management of ITNs addressed the role of using molecular classifiers and biomarkers.[136] The guidelines indicated that an ideal ‘‘rule-in’’ test would have a positive predictive value (PPV) for histopathologically proven malignancy similar to a malignant cytologic diagnosis (98.6%), and an ideal ‘‘rule-out’’ test would have a negative-predictive value similar to a benign cytologic diagnosis (96.3%). These guidelines commented on the limitations in the current literature, including lack of blinding of pathologists and clinicians, lack of controlled studies and direct comparisons of different evaluation methods, concerns about the reproducibility of findings across populations[137], lack of clarity about how test results change surgical management, and lack of long-term outcome data. Overall, these ATA guidelines were praised by community oncologists and European specialists for more strongly emphasizing nodule and tumor morphology and topography and for showing less enthusiasm for molecular biomarkers for risk stratification (compared to their prior guideline), emphasizing the relative importance of clear, comprehensive ultrasonographic and pathology reports.[138] Molecular testing is thus viewed as an adjunct that may facilitate decision-making in selected patients. The ATA guideline rationales are that no single molecular test or combination of tests yet has proved useful in terms of clinical utility across all indeterminate cases and that molecular testing continues to evolve.[139] Subsequent studies, including a large, blinded, multicenter study of Thyroseq v3 showed that the testing did not meet the ATA threshold for a “rule-in” test due to the low PPV and its potential value as a rule-out test varied by cancer prevalence but was sufficiently high (NPV 97%) when that prevalence was 28%.[140] A systematic review and meta-analysis of published gene expression classifier studies in this realm observed that the published validation cohorts were not representative of the populations in whom these tests have been used, particularly because of differences in the underlying prevalence rates of cancer which affect the negative predictive value of the test.[141]

Overall, several molecular classifiers have demonstrated analytical and clinical validity in the evaluation of ITNs, although the supporting studies should be interpreted in light of high levels of diagnostic review bias, verification bias, and study design limitations.[133] However, for any biomarker test to have clinical utility, it must also be shown to improve outcomes compared with if the biomarker test results are not known.[142] The prevalence of thyroid cancer in these nodules varies considerably between studies and between sites in the multicenter studies.[141, 143] Thus, to apply these molecular test results in patient management, clinicians must know the prevalence of cancer in their own patient population where the test would be applied. Furthermore, clinicians must be careful in deciding when to use the test, because for patients with an indication for surgery based on cytology alone or based on the size of the nodule[144, 145] or the risk of malignancy based on the sonographic pattern [146], or contraindication for surgery based on various reasons, there is little value in pursuing this type of testing.[143]

There is special interest in ITNs with Hürthle cells. Hürthle cells are thyroid follicular-derived epithelial cells with oncocytic cytology, and accurately classifying nodules with these cells is difficult with fine-needle aspiration. There has been interest in the use of third generation molecular classifiers for this subset of ITNs. Although patients with advanced oncocyte carcinoma of the thyroid (previously known as Hürthle cell carcinoma) have a poor prognosis, patients presenting with minimally invasive, early disease have an excellent prognosis.[147] The majority of these lesions have low-risk or no molecular alterations and are benign on follow-up. Unfortunately, no single molecular alteration defines cytologically indeterminate Hürthle cell lesions; and molecular testing is not definitive in determining which cases may be managed conservatively.[148] There are ongoing efforts to improve classification of these nodules [149], but thus far the accuracy of these molecular classifier tests falls short of providing clinical utility to guide surgical management.

Unknown Primary Site Cancer

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

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 Tumor Agnostic Testing guideline for details.

Rationale

Cancer of unknown primary site (CUP) refers to a diverse set of malignancies where the tissue of origin remains unclear the standard set of detailed investigations (clinic, laboratory, pathology, and imaging) have been completed. These may also be called occult primary cancers. With the advent of modern imaging and immunohistochemistry diagnostic techniques, the incidence of CUP has decreased from around 3%–5% in the 1990s to 1%–2% in the current era.[150] CUP is categorized into four histological types that include adenocarcinoma of good-to-moderate differentiation (50%), followed by poorly undifferentiated adenocarcinomas (30%), squamous cell carcinoma (15%) and undifferentiated neoplasms (5%).[151] In most patients, the disease is disseminated and incurable. The majority of patients present with visceral disease, mainly to liver and lungs. CUP was once treated as a distinct cancer and investigated with phase 2 treatment trials response rates of 25% to 35% and survival ranging from 6 to 16 months. Survival has been longer for patients with nodal, pleural, or serous peritoneal disease (14 to 16 months) than for patients with visceral metastatic disease (6 to 9 months).[152] Less common, presentations such as bone predominant CUP (with median survival around 15 months) or lymph node-only CUP (median survival over 30 months) drive unique approaches in terms of their risk stratification and treatment.[153] In a broad phase II trial using pembrolizumab to treat rare cancers, 22 patients with CUP were enrolled with no complete responses, 3 partial responses, and 4 patients with stable disease.[154]

Various tissue of origin (TOO) classifiers have been developed TOO classifiers have been developed on data from a wide range of molecular methods including targeted DNA sequencing, whole exome and whole genome DNA sequencing, RNA profiling, and methylation profiling.[155] Several whole genome sequencing (WGS) based have been developed and are able to discriminate between 18 and 35 cancer types but with different performance across sub-cohorts of common cancer types (such as breast and colorectal cancer) compared to various other types of uncommon cancers.[155-157] There is also some variation based on TOO classifiers that are testing untreated versus treated metastatic cancers.[155] Unfortunately, advances in diagnostics have not yielded clinical utility as yet through translation into a survival benefit, as no differences in outcome were reported between empirical and molecularly guided treatments.[151] The European Society for Medical Oncology (ESMO) makes no recommendation for the use of gene expression profiling-based site-directed therapy (i.e., tissue of origin prediction).[158, 159] Meanwhile, user-friendly nomograms using readily available clinicopathological factors (not based on molecular testing) can provide robust personalized prognostication and aid in decision-making and selection or stratification of patients for clinical trial enrollment.[160]

Somatic Testing of Hematologic Malignancies

Clinical Indications

General Requirements

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

Umbrella Criteria

Somatic Genomic Testing (Tumor Biomarker Testing)

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

- The genomic testing has established analytical and clinical validity (i.e., FDA-approved test, when available) and is performed in an appropriately certified laboratory
- The genetic test has established clinical utility such that a positive or negative result will meaningfully impact the clinical management (predictive, diagnostic, prognostic, or therapeutic) 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 there are genomic biomarker-linked therapies approved by the U.S. Food and Drug Administration (FDA) for the individual's specific cancer scenario and such therapies are being considered in the near term
    - When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions related therapeutic decisions being considered in the near term
- 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

Rationale

Nearly every malignancy will have somatic mutations that have been described, although most known mutations 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.

Cancer-specific Criteria

Acute Lymphocytic Leukemia

Tissue- (**OR** bone marrow-) based (**OR** alternatively, peripheral blood if morphologically detectable circulating blasts) somatic genetic testing (i.e., 50 or less genes) is considered **medically necessary** for children and adults with acute lymphoblastic leukemia (ALL) to establish the diagnosis or to identify actionable therapeutic targets when the following criterion is met:

- A multi-gene panel contains, at a minimum, the following genes: ABL1, ABL2, CRLF2, CSF1R, FLT3, IL7R, JAK1, JAK2, JAK3, PDGFRB, SH2B3, TP53, and IKZF1

Chromosomal analyses of bone marrow specimens (or alternatively, peripheral blood if morphologically detectable circulating blasts), which may also include FISH testing, to detect and characterize clonal chromosomal abnormalities that have important diagnostic, prognostic, and therapeutic implications are considered **medically necessary** for children and adults with ALL.

The use of NGS testing on bone marrow specimen is considered **medically necessary** to detect or quantify measurable/minimal residual disease (MRD) in children or adults with ALL.

BCR-ABL kinase domain point mutation 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) has a bimodal age distribution, the first peak occurring at approximately 5 years of age and the second at approximately 50 years. ALL may be of B-cell precursor or T-cell lineage. In the United States, ALL is the most common cancer among children and the most frequent cause of death from cancer before 20 years of age.[161] The cure rate of pediatric ALL is at least 80%, in adults closer to 30% to 40%.[162] Several genetic factors (such as Down's syndrome) are associated with an increased risk of ALL, but most patients have no recognized inherited factors.

On average, childhood ALL genomes contain 10 to 20 non-silent coding mutations at the time of diagnosis and about twice as many at the time of relapse. Many mutations the transcriptional regulation of lymphoid development and differentiation; cell-cycle regulation; the TP53–retinoblastoma protein tumor-suppressor pathway; growth factor receptor, Ras, phosphatidylinositol 3-kinase, and JAK-STAT signaling; nucleoside metabolism; and epigenetic modification.[161] Adult patients have been found to have more gene mutations, especially IKZF1, MLL2, and JAK3, but fewer alterations of PTPN11 compared with pediatric patients.[163] The precise contribution of these genetic or epigenetic abnormalities to leukemogenesis, the development of drug resistance and leukemic clone evolution remains to be defined.[163]

Quantification of measurable/minimal residual disease (MRD) detected by quantitative polymerase chain reaction (PCR), flow cytometry, or next generation sequencing (NGS). The risk of ALL treatment failure and death is 3 to 5 times as high among children with levels of minimal residual disease that are 0.01% or higher at the end of induction therapy and at later time points than among those with levels that are lower than 0.01%.[161] Overall, MRD testing has prognostic implications in various subsets of both pediatric and adult ALL across therapies, methods of and times of MRD assessment, cutoff levels, and disease subtypes based on a meta-analysis of 39 publications comprising over 13,000 patients.[164] There are caveats with this testing. Although MRD is a direct measure of disease burden and treatment response in ALL, there may be sanctuary sites in the body that contribute to relapse but are not measurable by conventional methods. Also, technical difficulties can give misleading results, and standardized methods for MRD determination are not widely available outside of specialized centers.[164] A randomized clinical trial of intensification of therapy for patients with higher levels of minimal residual disease has been conducted showing non-significant improvement in survival but demonstrating the promise of this method of patient selection for clinical trials.[165] MRD monitoring has become integral to clinical trials developed by the St. Jude Consortium, the Children's Oncology Group, and the Dana-Farber Cancer Institute ALL Consortium, and has also been recognized as an essential component of patient evaluation over the course of sequential therapy in consensus-based guidelines.[166]

Acute Myelogenous Leukemia

Tissue-based (**OR** alternatively, peripheral blood if morphologically detectable circulating blasts) somatic genetic testing (i.e., 50 or less genes) is considered **medically necessary** for individuals with acute myelogenous leukemia (AML) to establish the diagnosis and to identify actionable therapeutic targets when the following criterion is met:

- A multi-gene panel contains, at a minimum, the following genes: FLT3, IDH1, IDH2, NPM1 CEBPA, DDX41, TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2

Chromosomal analyses of preferred bone marrow specimens, which may also include FISH testing, to detect and characterize clonal chromosomal abnormalities that have important diagnostic, prognostic, and therapeutic implications are considered **medically necessary** for individuals with AML.

Rationale

Acute myelogenous leukemia (AML) is a disease characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated hematopoietic cells. Most cases of AML are characterized by clonal heterogeneity at the time of diagnosis. Leukemic relapse invariably arises from a pre-existing—or at least a closely genetically-related—clone.[167] Various patterns of dynamic clonal evolution that occur at relapse probably contribute to resistance to therapy.[168] Adults under age 60 years are cured with intensive leukemia treatment around 40% of the time.[168] However, this is generally a disease of older adults with a median age at diagnosis of 68 years and escalating incidence with increasing age, with older adults having a much worse prognosis and cure rate closer to 10%.[169]

The World Health Organization (WHO) Classification of Tumours 5th edition was updated in 2022 wherein the classification of AML emphasizes recent breakthroughs in how this disease is understood and managed. Foremost is the separation of AML with defining genetic abnormalities from AML defined by differentiation.[170] The defining genetic abnormalities include the following: fusions of PML::RARA, RUNX1::RUNX1T1CBFB::MYH11, DEK::NUP214, RBM15::MRTFA, and BCR:ABL1, rearrangements of KMT2A, MECOM, NUP98, NPM1, or CEBPA, and mutations of NPM1 or CEBPA. Genomic evaluation of patients with AML has been demonstrated to have a higher diagnostic yield compared to conventional cytogenetic analysis.[171]

The most widely used consensus risk stratification guidelines in AML are those from the European LeukemiaNet (ELN), an international working group of several dozen AML experts. The 2022 ELN recommendations are for screening for the following specific gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets: FLT3, IDH1, IDH2, NPM1 CEBPA,DDX41, TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2.[172] The ELN acknowledges that additional genes are investigational in this rapidly evolving field and are not currently required for establishing the diagnosis or for the identification of actionable therapeutic targets. Leukemia experts have advocated for the principle that risk groups are dynamic as newer therapies emerge for specific disease subsets and updated approaches may be recognized and widely adopted by nationally and internationally.[173]

Measurable/minimal residual disease (MRD) can be detected by polymerase chain reaction (PCR), flow cytometry, or next generation sequencing (NGS). MRD testing has prognostic implications in various subsets of AML and at various times throughout treatment.[174, 175] This testing may define molecular persistence after intensive chemotherapy, molecular progression or relapse after intensive chemotherapy, or molecular relapse, progression, or persistence post stem cell transplantation.[176] Testing is often pursued to assess eligibility in MRD-directed clinical trials. The proven therapeutic implications of MRD remain mostly unresolved.[167, 172]

Chronic Myeloid Leukemia

Bone marrow tissue-based **OR** peripheral blood somatic genetic testing (i.e., 50 or less genes) 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 mutation 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

Chromosomal analyses of bone marrow specimens to detect and characterize clonal chromosomal abnormalities that have important diagnostic, prognostic, and therapeutic implications are considered **medically necessary** for individuals with CML.

PCR testing for BCR-ABL1 quantification is considered **medically necessary** for response assessment every 3 months during active treatment and every 6 weeks in the first year after treatment discontinuation.

Myeloproliferative Neoplasms

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

- PCR, FISH, or NGS testing is targeting applicable JAK2, CALR, CSF3R, and MPL genes
- **ONE** of the following clinical scenarios:
  - Hemoglobin ≥16.5 g/dL in male and hemoglobin ≥16.0 g/dL in female
  - Hematocrit greater than 49% in male and hematocrit greater than 48% in female
  - Platelet count ≥450 X 10^9/L
  - Leukocytosis (white blood cell) ≥11 X 10^9/L

Rationale

Elevated peripheral blood cell counts, such as leukocytosis, thrombocytosis, and polycythemia, are often the presenting symptom in patients with myeloproliferative neoplasms (MPN), and their thresholds are further defined by the World Health Organization. These diseases include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytosis (ET), primary myelofibrosis (PM), chronic neutrophilic leukemia (CNL), and several other less common subtypes.[170] PMNs are characterized by the abnormal proliferation of mature bone marrow cell lineages and a clinical course that is usually prolonged, but ultimately leads to marrow fibrosis and acute leukemia. These are hematopoietic stem-cell disorders that share mutations that constitutively activate the physiologic signal-transduction pathways responsible for hematopoiesis.[177] Likewise, CML is a disease of hematopoietic stem cells arising from a translocation t(9;22)(q34;q11) with the shortened chromosome 22. The translocation leads to a juxtaposition of the ABL1 gene from chromosome 9 and the BCR gene from chromosome 22, resulting in a BCR-ABL1 fusion gene that codes for BCR-ABL1 transcripts and fusion proteins with high tyrosine kinase activity.[178] Like MPN, patients with CML typically present with elevated peripheral blood counts, particularly excessive granulocytes and a left shift of granulopoiesis, and common signs and symptoms include fatigue, weight loss and splenomegaly.

Patients with signs and symptoms consistent with CML or MPN are typically evaluated with review of the peripheral blood smear review and BCR-ABL1 analysis undertaken for consideration of CML. In the absence of BCR-ABL1 translocation and lack of dysplasia, molecular characterization of JAK2, CALR, CSF3R, and MPL are pursued as well as bone marrow morphologic review for an accurate diagnosis.[179] A positive finding for a mutation established the presence of a hematopoietic stem cell disorder and rules out myelodysplasia, but none of these mutations are disease-defining.[177] Distinction between the MPN types is based on integrating peripheral blood findings with molecular data and bone marrow morphologic evaluation findings, as none of these parameters alone provide sufficient diagnostic specificity.[170] Several other somatic mutations have been reported in persons with JAK2, MPL or CALR mutations including epigenetic modifiers (ASXL1, TET2, EZH2, IDH1, IDH2, DNMT3A), RNA splicing factors (SRSF2, U2AF1, SF3B1) and transcriptional regulators (TP53, IKZF1, NF-E2, CUX1). These mutations do not cause myeloproliferation.[180] The cytogenetic landscape of MPNs is limited and does not differ substantially according to the type of neoplasm. Moreover, driver mutation status is not associated with the time to leukemic transformation or survival after transformation.[177] While identification of additional somatic mutations has been incorporated into some prognostic scoring tools[181, 182], more research is needed to establish the clinical utility of expanded prognostic testing along with other clinical considerations to guide patient management.[183]

For CML specifically, the diagnosis must be confirmed by cytogenetics showing t(9;22)(q34;q11) and by multiplex RT-PCR showing BCR-ABL1 transcripts. At baseline, neither quantitative RT-PCR measuring BCR-ABL1 transcripts level nor BCR-ABL1 mutation analysis are advised at baseline since these data are not necessary for decision-making.[178] Tyrosine kinase inhibitor therapy (such as imatinib and other agents) and careful disease monitoring has reduced the incidence of progression to advanced phase and the 10-year overall survival rate for CML is now 80%-90%.[184] A principal goal of CML therapy with TKIs is the achievement of a stable molecular remission which accords successful discontinuation of therapy, a concept now known as 'treatment-free remission.[180] Monitoring of treatment is now almost exclusively done molecularly by quantitative PCR measurement of BCR-ABL1 transcripts according to the International Scale with optimal response, warning category, and treatment failure defined.[185] BCR-ABL1 ≤1% has been determined to be equivalent to complete cytogenetic remission; greater than 10% BCR-ABL1 at 3 months indicates treatment failure when confirmed. Response milestones are the same for first and second-line therapy and include measurements at baseline and every 3 months thereafter with more intense monitoring (every 4-6 weeks) for the first year after treatment discontinuation.[178] Achieving specific time-dependent molecular milestones, as defined by global therapeutic guidelines, has been established as critical in maximizing optimal outcomes while identifying patients at risk of therapy failure.[186]

More than 100 different kinase domain mutations of BCR-ABL1 that impair TKI binding have been reported in patients who develop TKI resistance.[184] Resistance to imatinib occurs in 10%–15%, and to second generation TKIs in <10% of patients in first-line treatment. Mutations account for resistance in about one-third of resistant patients in chronic phase, and in about two-thirds of resistant patients in accelerated or blast phase.[187] A prospective multicenter study has demonstrated that NGS provides a more accurate picture of BCR-ABL1 mutation status compared to standard Sanger sequencing and demonstrated the clinical relevance of low level mutations[188], thus NGS is the recommended technology for detecting BCR-ABL1 resistance mutations in patients not adequately responding to TKI therapy.[187]

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**.

Chromosomal analyses of bone marrow specimens

Chromosomal analyses of bone marrow specimens to detect and characterize clonal chromosomal abnormalities that have important diagnostic, prognostic, and therapeutic implications are considered **medically necessary** for individuals with multiple myeloma.

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

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

Rationale

Multiple myeloma is the second most common hematological malignancy, accounting for about 2% of cancer deaths in the United States. Almost all patients with multiple myeloma evolve from an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS), and the rate of progression is influenced by the underlying cytogenetic findings.[189] The diagnosis requires the presence of clonal plasma cells in the bone marrow or in a biopsy-proven bone or extramedullary plasmacytoma. The majority of patients with myeloma present with symptoms related to organ involvement (hypercalcemia, renal insufficiency, anemia, and bone lesions). Less commonly, patients may be diagnosed based on abnormal blood or urine tests.[190]

Multiple myeloma is increasingly recognized as more than one disease, characterized by marked cytogenetic, molecular, and proliferative heterogeneity. Risk stratification is important for prognostication, patient selection for clinical trials, and comparison of treatment approaches. Risk stratification is complex and involves cytogenetic classification combined with disease stage, host factors, and other prognostic factors.[189] The revised ISS(R-ISS) was introduced in 2015 and has been widely validated.[191] More recently, additional cytogenetic abnormalities have been found and newer, validated models are

available such as the Mayo Additive Staging System[192] and evolving tools such as the Mayo Clinic mSMART risk stratification method (www.msmart.org).[189]

Given the high rates of complete response seen in patients with multiple myeloma with new treatment approaches, new response categories have emerged that focus on detection of residual tumor cells in the bone marrow using modern flow cytometry or next-generation sequencing (NGS) techniques. The clinical utility of peripheral blood-based evaluation of minimal residual disease remains unknown.[193] For circulating cell-free DNA testing, the data show that this approach lacks sensitivity compared to bone marrow assessment for measurable/minimal residual disease (MRD) evaluation.[194] Testing for circulating tumor cells in the peripheral blood is also being explored, but the establishment of appropriate cut-off levels associated with clinical utility is not yet clear.[195, 196] Bone marrow testing is the evidence-based standard for MRD testing, with MRD negativity defined as the absence of tumor plasma cells within 1,000,000 bone marrow cells, a threshold that indicates the best results for the prediction of both progression-free and overall survival.[197] Detailed aspects of this approach to detecting MRD were outlined in 2016 by the International Myeloma Working Group (IMWG)[193], and guidelines from the American Society and Cancer Care Ontario[190] and from the European Society of Medical Oncology and the European Hematology Association[197] have since endorsed routine use of MRD testing for response assessment. The ASCO guideline makes a strong recommendation that the quality and depth of response should be assessed by IMWG criteria, with the recommendation based on high-quality evidence. MRD is recommended to test the depth of response after each cycle of therapy intended to induce remission. The use of MRD to assess disease status during maintenance therapy is being explored but is not yet established.[198] For example, it is unclear whether maintenance therapy in MRD-negative patients can be stopped or whether treatment needs to be changed in MRD-positive patients.[197] ASCO considers the evidence strength low and recommendation weak for MRD testing during maintenance therapy, and makes a moderate strength recommendation not to modify maintenance therapy based on depth of response information.[190]

Myelodysplastic Syndrome

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

- Testing is for the purpose of establishing the diagnosis or to identify actionable therapeutic targets
- A targeted multi-gene panel contains, at a minimum, the following genes: ASXL1, DNMT3A, EZH2, NRAS, RUNX1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, ZRSR2

Chromosomal analyses of preferred bone marrow specimens to detect and characterize clonal chromosomal abnormalities that have important diagnostic, prognostic, and therapeutic implications are considered **medically necessary** for individuals with myelodysplastic syndrome.

Rationale

Myelodyplastic syndromes (MDS) are clonal hematopoietic neoplasms defined by cytopenias and morphologic dysplasia. MDS occurs mainly, but not exclusively, in older adults, with the median age being 70 years. MDS evolves to AML through a process of clonal selection, with the pattern of transformation occurring in different patterns depending on the subtype and mutation drivers.[199] In subtypes of MDS at lower risk of transformation, treatment is focused mainly on improving anemia and other cytopenias. In higher risk disease, the focus is more on delaying disease progression and prolonging survival. Allogeneic stem cell transplantation is the only potentially curative therapy, but it is rarely applicable since most patients are older adults.[200] The World Health Organization (WHO) Classification of Tumours 5th edition was updated in 2022 wherein the classification of MDS now features genetically defined disease types rather than risk-based grouping based on features such as blast percentage, ring sideroblasts, and number of lineages with dysplasia.[170] Somatic mutations with an overall incidence of 5% or greater in MDS include ASXL1, DNMT3A, EZH2, NRAS, RUNX1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, and ZRSR2.[201]

To meet the challenge of the heterogeneity in clinical course and outcomes for MDS, the International Prognostic Scoring System–Revised (IPSS-R), was developed by the International Working Group for Prognosis in MDS and set the course for risk stratification, clinical trial design, and treatment recommendations.[202] More recently, a clinical-molecular prognostic model (IPSS-Molecular [IPSS-M]) has been validated.[117] In multivariable analysis, the top genetic mutations found to be predictors of adverse outcomes were identified in TP53, FLT3, and KMT2A (MLL), while SF3B1 mutations were associated with favorable outcomes. Moreover, mutations in ASXL1, BCOR, EZH2, NRAS, RUNX1, STAG2, and U2AF1 were significantly associated with adverse risk for several key outcomes as well.

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Codes

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

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

CPT/HCPCS

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

Code	May Be Medically Necessary When Criteria are Met
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
81307	*PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
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)

Code	May Be Medically Necessary When Criteria are Met
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)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81479	Unlisted molecular pathology procedure
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score (Endopredict)
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
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)
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
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3- kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
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
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.
0448U	Oncology (lung and colon cancer), DNA, qualitative, next-generation sequencing detection of single-nucleotide variants and deletions in EGFR and KRAS genes, formalin-fixed paraffin-embedded (FFPE) solid tumor samples, reported as presence or absence of targeted mutation(s), with recommended therapeutic options
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
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

Not Medically Necessary

Code	Not Medically Necessary
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

Code	Not Medically Necessary
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
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)
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
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
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
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
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0114U	Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus
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
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
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
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
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Whole Genome Sequencing
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification - Praxis Somatic Transcriptome
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification - Praxis Somatic Optical Genome Mapping
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD u(Do not report 0306U in conjunction with 0307U)t
0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD(Do not report 0307U in conjunction with 0306U)

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
0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint–inhibitor therapy
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
0379U	Solid Tumor Expanded Panel, Quest Diagnostics®, Quest Diagnostics®: Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite 'instability, and tumor mutational burden. The test uses a next–generation sequencing (NGS) targeted sequence analysis panel for a tumor specimen to evaluate DNA for 523 genes and RNA for 55 genes. The results may aid with diagnosis, prognosis, or treatment selection for patients with solid tumors.
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations
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)
0452U	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer
0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative
0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of **60** genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
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
S3854	Gene expression profiling panel for use in the management of breast cancer treatment

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Revised	01/23/2024	10/20/2024	Independent Multispecialty Physician Panel (IMPP) review. Clarified testing to guide adjuvant therapy for localized breast cancer.
Updated codes 07/01/2024	n/a	Unchanged	Added CPT codes 0471U (MNWCM) and 0452U, 0465U, 0467U, 0473U (NMN). Removed termed CPT code 0204U.
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 less 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

Status	Review Date	Effective Date	Action
			0448U; moved 81455 from NMN to MNWCM. NMN codes: added 0444U; moved 81546 from MNWCM to NMN; removed 81525, 81529, 81540, 81541, 81542, 81552, 0005U, 0006M, 0012M, 0013M, 0016M, 0017M, 0045U, 0047U, 0090U, 0113U, 0120U, 0228U, 0287U, 0288U, 0296U, 0313U, 0314U, 0315U, 0317U, 0339U, 0343U, 0362U, 0363U, 0403U. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Added CPT codes 81457, 81458, and 81459. Description changes for 81406, 81445, 81449, 81450, 81451, 81455, 81456.
Revised	04/12/2023	11/05/2023	IMPP review. Tumor-agnostic testing for patients with advanced solid tumors: expanded testing for RET; clarification edits for MMR deficiency. Clarification edits in Localized and Metastatic breast cancer; expanded testing for ESR1 in Metastatic breast. New testing scenario for advanced endometrial carcinoma. Corrected error in Metastatic NSCLC. CML: Expanded specimen type to include peripheral blood; separated indication for MPNs and defined peripheral blood indices.
Updated	n/a	10/01/2023	Added CPT codes 81599, 0364U, 0379U, 0391U, 0403U, 0413U, 0414U. Moved 81327, 0007M, 0011M, 0229U, 0285U, 0333U, and 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, and 0356U.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.