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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Somatic Tumor Testing

Proprietary

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Description and Application of the Guidelines

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

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

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

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

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

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

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

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

General Clinical Guideline

Clinical Appropriateness Framework

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

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

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

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

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

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

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

Additionally, either of the following may apply:

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

Repeat Diagnostic Intervention

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

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

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

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

Repeat Therapeutic Intervention

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

Somatic 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 US Food and Drug Administration (FDA) or recommended by NCCN as a Category 2A for the individual's specific cancer scenario and such therapies are being considered in the near term
    - 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 (Tissue Agnostic Testing)

Tissue-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 or is recommended by NCCN as a Category 2A for the individual's specific 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 as determined by an FDA-approved test with reporting using the threshold of ≥10 mutations/megabase (mut/Mb)
    - 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] Additionally, INFORM, a pediatric registry explored whether biomarkers other than ALK, NTRK, or BRAF might be associated with progression-free survival (PFS) or overall survival (OS) benefit when treated with matched targeted therapy (MTT), and did not find evidence of survival benefit with other molecular findings.[5] Thus, rather than 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 tissue-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.[6] 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. [7, 8]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.[9] 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.[6]

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.[10] 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.[11] The FoundationOneCDx assay (Foundation Medicine, Inc., CPT 0037U) was FDA-approved as 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,[12] while the TAPUR trial defined high tumor mutational burden (HTMB) as ≥9 mut/Mb.[13] 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.[14]

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.[15] Critics noted that 10 mut/Mb is an arbitrary cut off that does not separate responders from non-responders and it 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.[16] PD-L1 expression and TMB are not significantly correlated within most cancer subtypes, and TMB may not always correlate with ICI responsiveness.[11] 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.[10] 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.[6, 17] 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.[18] 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.[18, 19] 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 LIBRETTO-001 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.[20]

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.[17] 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.[21] When NTRK testing is applied across a broad range of tumor types, the yield is low and a very low proportion of tested patients benefit. For example, in a study conducted in the United States Veteran Affairs system, only 0.12% of all patients with solid tumors sequenced through the National Precision Oncology Program had evidence of an NTRK fusion or rearrangement. A retrospective analysis identified only 12 patients treated with TRK inhibitor therapy of whom none responded.[22]

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).[23] 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 IB 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"[23] 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."[24] 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.[25] 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, data have been published from the phase 2, open-label, single-arm, multicenter, Rare Oncology Agnostic Research (ROAR) basket trial in patients with BRAF V600E-mutated rare cancers with promising findings found in thyroid cancer[26], malignant gliomas[27], and biliary tract cancer.[28]

A further 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.[20]

Cancer-specific Criteria

Bladder Cancer (Urothelial Carcinoma, including the Upper Tract)

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

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

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

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

Targeted (i.e., 50 or 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 (stage IIIB), recurrent, or metastatic (stage IV)
- 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 locally advanced, recurrent, or metastatic setting

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

Rationale

Bladder cancers are biologically diverse and can be separated into “molecular subtypes,” based on expression profiling.[29, 30] 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.[31] Additionally, a guideline from the American Urological Association (AUA) and the Society of Urological Oncology (SUO) does not suggest a role for genetic testing in risk stratification or guiding management of non-muscle invasive bladder cancer.[32]

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.[31] Also, FGFR mutations are more frequent in the upper tract (≈30%) than the bladder (≈14%).[33] 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.[34] A global phase 3 trial of erdafitinib compared this drug with chemotherapy in patients with metastatic urothelial carcinoma with susceptible FGFR 3/2 alterations who had progression after one or two prior treatments including an anti-PD-1 or anti-PD-L1. Both progression-free survival and overall survival were longer with erdafitinib than with chemotherapy, and treatment-related adverse events leading to death were lower in the group treated with erdafitinib.[35] An open-label, single-arm, phase II trial of another FGFR1-3 inhibitor, pemigatinib, reported that this drug demonstrated clinical activity in previously treated, unresectable or metastatic urothelial carcinoma with FGFR3 mutations or fusions/rearrangements.[36] On January 19, 2024, the FDA-approved this drug for use in patients with advanced or metastatic urothelial carcinoma, with relevant FGFR alterations, whose disease has progressed during or following treatment with at least one line of prior systemic therapy, including in the adjuvant and neoadjuvant settings. Testing may be performed using the FDA-approved companion diagnostic (a specific RT-PCR kit),[31] For high risk, non-muscle invasive bladder cancer (NMIBC), the use of erdafitinib is also being explored for individuals with FGFR alterations.[37] However, there has only been phase II data published in this setting and FGFR testing as a predictive biomarker for erdafinitib use is not guideline concordant and erdafinitib is not FDA-approved in that setting. 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).[38] Carelon Guidelines for FGFR testing are consistent with NCCN[39] and European Association of Urology (EAU) guidelines.[40]

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.[41] American Urological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction jointly recommend against the use of urinary biomarkers in patients with a history of low-risk cancer and a normal cystoscopy AND the use of urinary biomarkers in place of cystoscopy evaluation for surveillance of non-muscle invasive bladder cancer (NMIBC).[42] NCCN states that tumor marker evaluation during surveillance of high-risk NMIBC may be considered (category 2B recommendation) and states “it remains unclear whether these tests offer additional useful information for detection and management of non-muscle invasive bladder cancer.”[39]

Brain Cancer (Malignant Glioma)

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

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

Tissue-based somatic tumor testing for microsatellite instability (MSI by PCR) or mismatch repair deficiency (dMMR by IHC) is considered **medically necessary** when **ALL** of the following criteria are met:

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

Rationale

Most primary brain tumors in adults are of glial origin. The average annual age-adjusted incidence rate for all glial tumors is 5·95 per 100,000 people in the US, the majority being glioblastoma (3·23 per 100 000 people).[43] The World Health Organization published the fifth edition of the Classification of Tumors of the Central Nervous System in 2021, updating the 2016 version. This classification incorporates advances in understanding the molecular pathogenesis of brain tumors with histopathology. The previous broad category of adult-type diffuse gliomas has been consolidated into 3 types: astrocytoma, isocitrate dehydrogenase (IDH) mutant; oligodendroglioma, IDH mutant and 1p/19q co-deleted; and glioblastoma, IDH wild type. These major changes are driven by IDH mutation status and include the restriction of the diagnosis of glioblastoma to tumors that are IDH wild type.[44] This revised classification has a substantial impact on the prognosis and management of patients, as well as on the design and conduct of clinical trials.[43]

The appropriate molecular testing strategy for individuals with malignant gliomas depends on the specific tumor entity, the patient’s stage and clinical status, and available treatment options including clinical trials. While immunohistochemistry screening is used in certain restricted circumstances, NGS panels are a more efficient way to identify pathogenic variants that have diagnostic, prognostic, and/or predictive utility. In malignant gliomas, IDH1 and IDH2 mutation testing has both diagnostic and prognostic utility. IDH wild-type tumors have a worse prognosis compared to IDH-mutant tumors. MGMT hypermethylation is associated with better response to chemotherapy treatment. Mismatch repair deficiency is rare, occurring in fewer than 1% of patients overall, but it is relatively more common in individuals under age 50 who are IDH wild type.[45] BRAF V600E has

value as a predictive biomarker in low grade glioma in children [46] with some preliminary data in high grade pediatric gliomas as well.[47] It is used in adults to identify patients for clinical trials and sometimes compassionate use. In adults, an oral penetrant inhibitor of IDH was studied in the INDIGO trial showing a strong signal of progression-free survival improvement.[48]

Despite tumor agnostic regulatory approval for NTRK fusion inhibiting agents in patients with NTRK fusions and of pembrolizumab in 'tumor mutational burden high tumors, the evidence of benefit of these targeted treatments in CNS tumors is limited.[49]

Breast Cancer

Localized breast cancer; early adjuvant setting

Gene expression profiling is considered **medically necessary** to guide adjuvant therapy* treatment-decision making for individuals with localized breast cancer using Oncotype DX, MammaPrint, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, 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)

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)

Localized breast cancer; extended adjuvant setting

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

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

Metastatic and/or locally advanced breast cancer

Testing of tumor tissue for somatic pathogenic variants of PIK3CA, AKT1, PTEN, and 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 HER2-negative metastatic breast cancer
- The individual is a candidate for treatment per FDA-label with alpelisib or capivasertib plus fulvestrant, **AND/OR** the individual is a candidate for treatment per FDA label with elacestrant
- The individual has not had prior tissue-based testing for the targeted gene(s) of interest in the metastatic setting

Notes:

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

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

Rationale

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.[50] 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[51] with earlier data about its prospective validation published in 2015,[52] and subsequent data showing how other clinical data added to this test further refined its use.[51] 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.[53] 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.[54] 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.[55] The most recent update of the ASCO guideline in 2022[56] 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.

Extended adjuvant therapy for breast cancer

The risk of recurrence for hormone receptor-positive breast cancer never goes away; it can recur post-5 years of adjuvant endocrine therapy.[68] Extended hormonal therapy consideration is backed by trials like MA17, ABCSG, aTToM, ATLAS, IDEAL, and NSABP-B42, along with newer AERAS trial data demonstrating improved disease-free survival with extended anastrozole.[62] ASCO guidelines suggest extended therapy offers modest added benefits with challenges of increased toxicity.[56, 69] Decision-making includes risk of recurrence, treatment tolerability, and patient preference, with considerations including psychological and financial impacts.[70, 71] The role of genomic testing in predicting extended adjuvant therapy benefits requires further prospective studies.[72]

The Breast Cancer Index (BCI) test has been proposed as a tool to guide decision-making about extended adjuvant hormonal therapy in patients with hormone receptor-positive (HR+) early-stage breast cancer. However, recent evaluations and guideline updates reflect significant concerns about its clinical utility, prompting a reassessment of whether BCI should be deemed medically necessary for this purpose. The BCI test relies heavily on data from retrospective analyses. Studies by Noordhoek et al.[60] and Bartlett et al.[59, 73] evaluated data from the previously conducted IDEAL and aTToM trials, respectively, and described treatment to biomarker interactions to explore the value of the BCI for predicting endocrine therapy benefits. The Noordhoek study was positive, although only 53% of the eligible patients had BCI testing. The Bartlett study was negative in the overall population, but the node-positive subset was explored and emphasized as positive. The B-42 trial, presented at ASCO 2021 and finally published in 2024 by Mamounas [74], failed to confirm the predictive performance of BCI, casting doubt on the reliability of previous findings. Likewise, a similar study focused on the utility of the 70-gene MammaPrint assay for this same use as a predictor of benefit from extended adjuvant therapy was conducted from a sample of 1886 patients who were treated in the context of the B-42 trial and this study was also negative.[75] Overall, the role of genomic testing as a predictor of benefit for use of extended adjuvant therapy remains to be established in prospective studies [76], results of prospective-retrospective studies have been inconsistent, and it has not yet been integrated into multiple trials for extended adjuvant therapies. In 2024, the NCCN acknowledged limitations of the BCI data in a footnote but still considers this testing to be NCCN 2A. ASCO guidelines[56] acknowledge the BCI but similarly acknowledge with the same strength of evidence and strength of recommendation a free online calculator called the CTS5 [63] to help guide clinicians in shared decision-making for postmenopausal patients in the extended adjuvant setting.

The Breast Cancer Index has also been recently explored in a cohort of premenopausal women. The study was designed as a prospective-retrospective translational investigation utilizing tumor tissue samples from 1687 premenopausal women involved in the Suppression of Ovarian Function Trial (SOFT). Contrary to the study's hypothesis, patients with BCI-low tumors derived significant benefit from ovarian suppression therapy, while those with BCI-high tumors did not. This finding diverges from prior research where BCI-high tumors seem to suggest greater benefit from extended endocrine therapy in postmenopausal populations. The biological mechanisms underlying this discrepancy remain unclear, and the findings require validation in larger, independent cohorts to confirm the predictive and prognostic utility of BCI in this specific population.[77]

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).[23] 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.[24] 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.[78] 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.[79]

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.[80] 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.[81] 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.[82] 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.

On November 16, 2023, the FDA approved capivasertib with fulvestrant for adult patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.[83] Post-marketing approval was also given for the FoundationOne®CDx assay as a companion diagnostic test to identify patients with breast cancer for treatment with capivasertib with fulvestrant.[84] The approval of capivasertib with fulvestrant was based on data from the CAPItello-291 trial, which reported significantly longer progression-free survival for capivasertib-fulvestrant compared to fulvestrant alone in patients with HR-positive advanced breast cancer whose disease had progressed during or after prior aromatase inhibitor therapy with or without a CDK4/6 inhibitor. This trial assessed patients with AKT-pathway-altered tumors, including PIK3CA, AKT1, and PTEN.[85] An ASCO rapid guideline update was published in 2023 recommending multiple lines of endocrine therapy, frequently paired with targeted agents for metastatic hormone receptor positive and HER2-negative breast cancer patients, specifying that these choices should be informed by routine testing (using tissue or blood obtained at the time of progression) for activating mutations in ESR1, PIK3CA, or AKT1, or inactivation of PTEN.[86]

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.[87] Other biomarkers such as FGFR1/FGFR2, 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.[66]

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 to include analysis of pathogenic variants in these genes: 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 for IDH1, FGFR, and BRAF in the metastatic setting

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

Rationale

Biliary tract cancer 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.[88] 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.[89] Unfortunately, targeted therapies for patients with FGFR2 fusions or IDH1 mutations are often met with intrinsic resistance or a short durability of response owing to acquired resistance.[90] Like other solid tumors, mutations in NTRK or MMR deficiency may also be found rarely and may also lead to use of targeted agents.[91]

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.[92] 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 tremetanib 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.[89] NCCN lists trastuzumab + pertuzumab as a subsequent-line therapy option for biliary tract cancers with disease progression, indicating that it is “useful in certain circumstances.” This is based on a multicenter, open-label, phase 2a, multiple basket study in which nine of 39 patients achieved a partial response (objective response rate 23%) and ten patients had serious treatment-emergent adverse events.[93]

Colorectal Cancer

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

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

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

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

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

Localized colorectal cancer

Targeted (i.e., 50 or 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 by PCR and/or dMMR IHC testing
    - BRAF V600E
    - KRAS
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)

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

Metastatic colorectal cancer

Targeted (i.e., 50 or less genes) tissue-based somatic tumor testing is considered **medically necessary** for individuals with recurrent or metastatic colorectal cancer and may be performed on the primary tumor or a metastatic site when **ALL** 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:
    - POLE/POLD1 mutations
    - Extended RAS testing (KRAS and NRAS exons 2,3, and 4)
    - BRAF V600E
    - HER2 amplification testing
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)
- There has been no prior testing for these molecular aberrations

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

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

Rationale

Among people diagnosed with colon cancer, 20% have metastatic CRC, and 40% present with recurrence after previously treated localized disease.[94] 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.[95] About 90 to 95 percent of colorectal cancers in patients with Lynch syndrome show evidence of microsatellite instability (MSI).[96] 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.[97] Additionally, neoadjuvant immunotherapy is associated with a high response rate and excellent safety profile in patients with early-stage dMMR CRC, highlighting the importance of dMMR testing in all newly diagnosed patients with CRC.[98, 99]

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.[94] 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).[100] 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. The randomized phase II PanaMa trial evaluated consensus molecular subtypes (CMSs) in patients with RAS wild-type mCRC receiving fluorouracil and folinic acid with or without panitumumab (Pmab) after Pmab + mFOLFOX6 induction. This study illustrated the importance of extended RAS testing as a predictive and prognostic biomarker.[101]

On January 19, 2023, the FDA granted accelerated approval to tucatinib in combination with trastuzumab for RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This approval was based on data from the MOUNTAINEER trial, which reported clinically significant anti-tumor activity in patients receiving 3rd line treatment or beyond for HER2-positive, RAS wild-type unresectable or metastatic CRC.[102]

Guidelines from the National Comprehensive Cancer Network (NCCN) include POLE/POLD1 testing for patients with recurrent or metastatic CRC.[103, 104] 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.[105, 106] 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.[107] Seven clinical trials from the ACCENT/IDEA database were analyzed and highlighted the utility of KRAS and BRAF V600E testing in prognostication and, in some cases, pursuit of clinical trials in high-risk patients.[108] Another biomarker under exploration is HER2 testing. The frequency of HER2 overexpression among patients with CRC is known to be around 5%, and HER2 overexpression/amplification has been associated with worse progression-free survival and overall survival in patients with RAS wild-type metastatic CRC who received anti-EGFR therapy.[109] 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.[110] 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.[111] 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.[56, 112] Guidelines from the European Society for Medical Oncology (ESMO) highlight the role of molecular testing in the treatment algorithms for colorectal cancer, including a focus on dMMR/MSI, RAS, and BRAF status as well as HER2 status in RAS-wt patients.[113] Another emerging testing method marketed for colorectal cancer is gene expression analysis. Guidelines from NCCN question the added value of prognostic genetic tests for colon cancer and cite insufficient data to recommend its use to estimate recurrence risk or determine adjuvant therapy.[103]

Endometrial Carcinoma

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

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

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

- The individual has biopsy-proven endometrial carcinoma
- Assessment includes the following, as applicable:
    - MLH-1 promoter methylation (applicable when there is nuclear expression loss of MLH1 and PMS2 by IHC)
    - POLE mutation testing (NGS)
    - P53 mutation testing (NGS or IHC)
- There has been no prior testing for these molecular aberrations

Note: Tumor agnostic genetic testing indications may also apply, depending on the clinical scenario (e.g., there are no satisfactory tumor-specific standard therapies available, there are no indications for planned therapy that would apply independent of the results of genetic testing [such as immune checkpoint inhibitor indications], and progression of disease). See the Tissue Agnostic Testing guideline for details. 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.[114] 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.[115, 116] 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.[117] 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. Data from the PORTEC-1 and PORTEC-2 trials showed that at 5 years, there were no locoregional recurrences in POLE-mutant endometrial cancer regardless of adjuvant radiotherapy; there was similar locoregional recurrence-free survival in mismatch repair-deficient endometrial cancer after EBRT, vaginal brachytherapy (VBT), and no adjuvant therapy; there was significantly better locoregional recurrence-free survival in p53-abnormal endometrial cancer with EBRT compared with VBT and no adjuvant therapy; and there was significantly better locoregional recurrence-free survival in endometrial cancer with no specific molecular profile, with both EBRT and VBT compared with no adjuvant therapy. This highlights the importance of molecular-risk profiling in directing treatment.[118] 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.[117, 119, 120] Results from an earlier PORTEC-3 trial suggested that pathogenic mutations of p53 was associated with a beneficial 5-year recurrence-free survival rate with chemotherapy versus radiotherapy alone (59% versus 36%) in high-risk endometrial cancer.[121] Given this evolving field, routine testing for these latter two subgroup variants is now reflected in nationally recognized guidelines.[122]

Melanoma

Prognostic testing in melanoma

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

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

Somatic tumor testing in advanced melanoma

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

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

Tissue-based somatic tumor testing for individuals with resectable or unresectable high-risk stage IIC, stage III or stage IV 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** 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 Tissue Agnostic Testing guideline for details.*

Rationale

Diagnosis of indeterminate melanocytic lesions

Light microscopic evaluation by a trained pathologist can provide an accurate diagnosis for the 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.[123] 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.[123]

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.[124] 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.[124] 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.[125] 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.[126] Overall, the clinical utility of GEP classifiers in this setting remains uncertain. A population-based analysis using SEER data between 2016-2018 revealed only small absolute risk differences between the 31-gene tested cohort and an unmatched cohort[127], and evidence remains lacking for the clinical utility for identifying such small difference for clinical decision-making. 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.[124] 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.[128]

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.[129] 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.[130] 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.[131] 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.[129] 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.[130] 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.[132] 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.[129] 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.[133] More than 90% of the BRAF mutations are V600E, with V600K mutations accounting for most of the remainder.[133] 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.[134]

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.[134] 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.[135]

NRAS mutations are present in 15% of melanomas and correlate with poor prognosis.[136] 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.[137] 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.[138] 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.[138] 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).[134]

Non-Small Cell Lung Cancer

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

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

Localized (stage IB-IIIA) NSCLC

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

- Biopsy-proven, stage IB-IIIA NSCLC with **ANY** of the following characteristics:
  - An adenocarcinoma component on histology
  - Non-squamous, non-small cell histology
  - Squamous cell carcinoma histology when **ANY** of the following clinical features are present:
    - Age 50 years or younger
    - Those who never smoked cigarettes (<100 cigarettes in a lifetime)
    - Those who quit smoking >15 years ago
- Test results will determine candidacy for treatment with osimertinib or alectinib

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 **ANY** of the following characteristics:
    - Any adenocarcinoma component on histology
    - Non-squamous, non-small cell histology
    - Squamous cell carcinoma histology when **ANY** of the following clinical features are present:
        - Age 50 years or younger
        - Those who never smoked cigarettes (<100 cigarettes in a lifetime)
        - Those who quit smoking >15 years ago
- The multi-gene NGS 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 exon 14 skipping, 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, unless **BOTH** of the following are met:
    - There is evidence of disease progression while on EFGR-targeted therapy
    - Tissue biopsy of a progressing lesion is being used for additional testing

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

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

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

Rationale

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[139, 140], and selection of patients based on predictive biomarkers is associated with improved patient outcomes.[140] 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.[141] 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.[141, 142] New targetable alterations are continuing to emerge. Several targeted therapies have been approved for the treatment of metastatic non-small cell lung cancer, Included among these are tepotinib for adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations[143], repotrectinib for patients with locally advanced or metastatic ROS1-positive NSCLC[144], encorafenib with binimetinib for adult patients with metastatic NSCLC with a BRAF V600E mutation[145], pralsetinib for patients with metastatic RET fusion-positive NSCLC[146], and amivantamab-vmjw with carboplatin and pemetrexed for first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations.[147] Of note, the approval of amivantamab plus chemotherapy in non-small cell lung cancer with EGFR exon 20 insertions was based on data from the Papillon study.[148] Insertions in exon 20 are the third most common type of EGFR mutation, representing up to 12% of all EGFR-mutated NSCLCs. While this protocol involved collection of blood samples at baseline and follow-up testing and ultimately supported the FDA PMA application for Guardant 360 liquid testing, the Papillon protocol involved use of standard tissue biopsy and testing performed at a CLIA-certified lab. Thus, these data were not driven by liquid testing results—those samples were

collected as part of the investigational protocol. Thus, tissue testing remains a standard approach for exon 20 insertions and an acceptable approach for selecting patients for amivantamab plus chemotherapy. Overall, the newly approved targeted agents are reflected in the updated evidence-based guidelines for oncogene-addicted metastatic non-small cell lung cancer from ESMO.[149] This ESMO guideline identifies the subset of patients with pure squamous cell carcinoma histology who may also benefit from molecular testing. Likewise, these new agents are highlighted in the ASCO living guideline for stage IV non-small cell lung cancer with driver alternations which includes a table summarizing the evidence type, quality, and strength around 1st and 2nd line treatment choices when there are driver alternations found.[150]

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[151], 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.[141] 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.[152] 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.[153] 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.[154]

There is a specific subset of patients with pure squamous cell histology who may benefit from molecular testing. The European Society for Medical Oncology (ESMO) recommends against molecular testing in patients with a confident diagnosis of squamous cell lung carcinoma except in unusual cases such as a patient under 50 years of age, those who have never smoked (less than 100 cigarettes in a lifetime), or those who quit using all forms of tobacco more than 15 years ago.[149]

In the setting of progressive disease while on EGFR-targeted therapy, there is a role for repeat NGS testing, which may inform mechanisms of resistance and subsequent treatment choices.[155]

Ovarian Cancer (Epithelial)

Targeted (i.e., 50 or less genes) tissue-based somatic tumor testing to determine HRD status by testing for pathogenic variants of BRCA1, BRCA2 with concomitant evaluation for genomic instability through an FDA-approved test is considered **medically necessary** in individuals with locally advanced (stage III), metastatic (stage IV), or recurrent epithelial ovarian cancer when **ALL** of the following criteria are met:

- The individual has biopsy-proven epithelial ovarian cancer
- The individual does not have previously established pathogenic variants of BRCA 1 or BRCA2 through germline testing
- The individual has not had prior testing that establishes HRD status in the locally advanced (stage III), metastatic (stage IV), or recurrent setting
- The individual is a candidate for treatment with an FDA-approved PARP inhibitor

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 Tissue 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.[156] 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.[157] 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.[158] 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. ESGO-ESMO-ESP consensus recommendations in ovarian cancer also emphasize the importance of testing HRD status using clinically validated genomically validated genomic instability tests (Lederman JA, 2024; 38307807). This guideline emphasizes that non-BRCA homologous gene mutations (i.e., ATM, BARD1, BRIP1, CDK12, CHEK ½, FANCL, PALB2, RAD51 B/C/D, RAD54L, etc.) are not required. However, these genes are typically part of a large gene panel for commercially available tests that measure HRD.

Other test methodologies are in development, including targeted gene capture assays to calculate a genome-wide loss of heterozygosity (LOH) score. This test methodology shows promise in high-grade non-clear cell ovarian carcinoma. However, it shows poor correlation with treatment outcomes and therefore is not an effective predictive biomarker.[159] The Geneva test, which uses the Oncoscan FFPE Assay Kit plus the number of Large-scale State Transitions (LST), has also shown promising findings but is not an FDA-approved test at this time.[160]

On November 14, 2022, the FDA granted accelerated approval to mirvetuximab soravtansine-gynx for adult patients with folate receptor alpha (FRα) positive, platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. This approval was based on data from the MIRASOL trial, which reported a significant benefit for this therapy compared to chemotherapy with respect to progression-free survival, overall survival, and objective response.[161] However, FRα is an immunohistochemical test rather than a genetic test, and is therefore outside the scope of these guidelines.

Pancreatic Adenocarcinoma

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

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

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

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

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

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

Rationale

Up to 10% of individuals 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.[162] Affected individuals may benefit specifically from platinum-based therapies or PARP inhibitors.[163] For this reason, individuals with newly diagnosed pancreatic cancer at any stage should have multidisciplinary evaluation and management, germline testing, and integrated supportive care.[164]

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.[165]

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.[166] Based on the absence of survival or quality of life improvement with olaparib and other concerns about the POLO trial design[167], 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.[168] 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.

Practice guidelines, including from the European Society for Medical Oncology (ESMO)[169] and the National Comprehensive Cancer Network (NCCN).[170] recommend somatic tumor testing, including BRCA and KRAS pathogenic variants as well as NTRK fusions, in the setting of advanced pancreatic cancer, noting the utility of such testing in treatment decision-making.

Prostate Cancer

Localized prostate cancer

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

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

Metastatic prostate cancer

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

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

Tissue-based NGS panel testing is considered **medically necessary** to identify 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 may also include other genes encoding molecules involved in homologous recombination DNA damage repair (DDR), such as ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PABLB2, RAD51B, RAD51C, RAD51D, and RAD54L
- The individual has not had prior NGS testing in the metastatic setting

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

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

Rationale

Localized prostate cancer

Prostate cancer is usually suspected on the basis of a digital rectal exam (DRE) and/or an elevated prostate-specific antigen (PSA) test. Definitive diagnosis depends on histopathologic verification. Abnormal DRE is an indication for biopsy, but as an

independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound.[171] 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.[172] The decision to proceed with a further staging workup is guided by which treatment options are available, taking into account the patient's preference and comorbidity. There are currently 10 or more pretreatment risk stratification tools for use in prostate cancer care, all of which use clinical and/or imaging factors without incorporating somatic genetic test information. The most commonly used are the D'Amico-derived systems (NCCN, NICE, GUROC, EAU, AUA) which involve categorization into 5 ordinal categories of risk: very low, low, intermediate, high, or very high. The Memorial Sloan Kettering nomogram, Cancer of the Prostate Risk score, and the Cambridge Prognostic Group are other systems and these perform slightly better in predicting prostate cancer death.[173] 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.[174] While few of these genomic panels have undergone extensive validation, there are several commercially available tests (Oncotype DX prostate, Prolaris, Decipher, and ProMark) that have been shown in retrospective analyses to provide additional information beyond standard clinical models in prognostication or patient selection for therapy.[175, 176] 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.[175] 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.[177] 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.[178] Practice patterns also vary widely within regions.[179] 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.[177] The relative accuracy of these biomarker tests compared to other standard tests is unknown.[179] 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.[177]

Metastatic prostate cancer

Patients with metastatic prostate cancer have multiple treatment options with varied mechanisms of action beyond androgen deprivation therapy alone. Such options include androgen-receptor-targeted agents, taxane-based chemotherapies, bone-targeted radiopharmaceutical radium-223, and biomarker-driven therapy with the immune-checkpoint inhibitor pembrolizumab (for those with mismatch-repair deficiency (dMMR) or microsatellite instability (MSI)) and the PARP inhibitors olaparib and rucaparib (for those with homologous-recombination gene deficiency). Olaparib was approved by the FDA on May 31, 2023, for adult patients with deleterious or suspected deleterious BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC), as determined by an FDA-approved companion diagnostic test. Such tests include BRCAnalysis CDX, Foundation One CDX, and Foundation One Liquid CDX. This was based on data from the PROpel trial, which showed that significant clinical benefit for Olaparib + abiraterone was restricted to the subset of patients with BRCA mutations.[180] 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.[181] 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.[78] 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.[181] The ESMO Precision Medicine working group recommends multi-gene NGS panel testing in metastatic prostate cancer to assess for ESCAT level 1 alterations.[78] Commercially available prostate-cancer specific NGS panels include 11-14 genes.[182] 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.[183]

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[184, 185], 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%[186], 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.[187] Subsequent studies include TRITON3, which showed that testing for BRCA mutations and treating castrate-resistant patients who had progressed on a second-generation androgen receptor pathway inhibitor (ARPI) have median imaging-based PFS improvements of slightly less than 5 months, supporting the value of BRCA testing in castrate-resistant prostate cancer.[188] The ongoing phase III MAGNITUDE trial has thus far shown improved radiographic progression-free survival in patients with BRCA 1/2-altered mCRPC when treated with niraparib plus abiraterone acetate with prednisone.[189]

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 may be used when performed as a stand-alone classifier test:
    - ThyGeNEXT/ThyraMIR multiplatform test
    - ThyroSeq Genomic Classifier
    - Afirma GSC

Somatic genetic testing of thyroid malignancy

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

- The individual has biopsy proven unresectable, locally advanced, recurrent, or metastatic thyroid carcinoma or anaplastic thyroid carcinoma (any stage)
- The testing includes assessment for pathogenic variants of BRAF V600E, ALK, NTRK, and RET

- The individual is considered a potential candidate for FDA-approved oral targeted therapy based on the results of this testing

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

Rationale

Molecular testing of indeterminate thyroid nodules

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.[190] 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.[191] Indeed, recent studies have explored the role of de-escalation of treatment[191] including active surveillance.[192]

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.[193]

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.[190] 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.[194] 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.[195] In recent years, several commercial multi-gene classifiers have emerged that are intended to help classify these indeterminate nodules.[196] 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.[197, 198] Meta-analyses of the second generation molecular tests to assess ITNs indicated that the high sensitivity and high NPV of these tests are similar.[199, 200] Of note, an altogether different classifier Afirma Xpression Atlas (XA) 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.[201] The clinical utility of the Afirma XA has not been demonstrated. Afirma XA is promoted for the management of cytologically indeterminate thyroid nodules, particularly those classified as suspicious by the Afirma Genomic Sequencing Classifier (GSC). The XA test is used to detect gene variants and fusions to help with risk stratification and inform clinical decision-making. Babazadeh et al. reported that the Afirma XA test was predictive of follicular cell-derived thyroid cancer, with a positive predictive value (PPV) of 83.7% for nodules that were XA-positive, which is comparable to the PPV of GSC-suspicious results alone.[202] This suggests that while XA adds molecular detail, its overall predictive value for malignancy is similar to that of the GSC. Munoz-Zuluaga et al. found that the Afirma XA test improved risk stratification for GSC-suspicious nodules, with a 100% risk of malignancy in XA-positive cases that underwent surgery. However, a negative XA result should not be used as a rule-out test, as the risk of malignancy in XA-negative nodules was still significant at 42%.[203]

Angell et al. provided analytical and clinical validation of the XA test, demonstrating high reproducibility and accuracy in detecting gene variants and fusions. The study highlighted that the XA test supplements the GSC by providing additional genomic insights, but it is not clear what outcomes are generate by such insights and further study is needed to get beyond the clinical validity of this testing.[201]

In summary, the Afirma Xpression Atlas test enhances the molecular characterization of indeterminate thyroid nodules, although its PPV is similar to that of the GSC alone and the clinical utility of its use has yet to be determined.

The ATA 2015 guidelines regarding evaluation and management of ITNs addressed the role of using molecular classifiers and biomarkers.[193] 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[204], 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.[205] 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.[206] A 2023 clinical practice guideline from the European Thyroid Association offers a comprehensive overview of the standard of care in management of thyroid nodules, and affirms the role of molecular testing in Bethesda III and IV nodules.[207] Similarly, the risk-based approach for managing indeterminate nodules and the clinical utility specifically associated with molecular testing of Bethesda III/IV nodules is highlighted in a clinical review in Lancet by Chen and colleagues.[208] Various contemporary 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%.[209] 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.[210]

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.[199] Some molecular testing approaches involve bundling a molecular classifier with other somatic testing to identify expressed molecular variants and fusions.[211] Such bundled testing approaches have not been established to have clinical utility as the entire platform and its use requires evaluation of the net clinical benefit. 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.[212] The prevalence of thyroid cancer in these nodules varies considerably between studies and between sites in the multicenter studies.[210, 213] 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 [214, 215] or the risk of malignancy based on the sonographic pattern [216], or contraindication for surgery based on various reasons, there is little value in pursuing this type of testing.[213]

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.[217] 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.[218] There are ongoing efforts to improve classification of these nodules[219], but thus far the accuracy of these molecular classifier tests falls short of providing clinical utility to guide surgical management.

Unresectable, advanced, and anaplastic thyroid cancer

NTRK gene fusions are reported in about 1.9% of patients with thyroid carcinoma. However, treatment of patients with this molecular aberration using TRK inhibitors (larotrectinib or entrectinib) shows promising results, with response rates of 60-70%. In addition to the importance of NTRK testing for locally advanced disease, an expert panel suggests that testing in patients with unresectable disease also has a role in guiding management.[220]

The National Comprehensive Cancer Network (NCCN) guidelines for thyroid carcinoma support molecular testing for anaplastic thyroid cancer regardless of stage, because of the very high risk of rapidly progressive disease for this histology.[221]

Unknown Primary Site Cancer

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

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

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

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

Rationale

Cancer of unknown primary 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.[222] 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%).[223] 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).[224] 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.[225] 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.[226]

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.[227] 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.[227-229] There is also some variation based on TOO classifiers that are testing untreated versus treated metastatic cancers.[227] 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.[223] The National Comprehensive Cancer Network (NCCN) recommendations for cancers of unknown primary site focus on immunohistochemical (IHC) testing and not on genomic profiling.[230] 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).[231, 232] 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.[233] A prospective trial of 158 patients conducted at a single academic institution evaluated the feasibility and value of genomic profiling in cancer of unknown primary site and found that 4/158 (2.5%) of patients had the genomic profiling trigger a change in treatment recommendation and implementation.[234] Among these 4 patients, it is unclear whether such changes in treatment would be associated with net clinical benefit. Likewise, a retrospective study of 578 tumor patient samples from individuals found that the most common molecular aberrations were KRAS (35%), CDKN2A (15%), TP53 (15%), and ERBB2 (12%).[235] Overall, the feasibility of molecular profiling in this setting is not in doubt, the challenge is establishing the clinical utility of routine, initial molecular testing compared to standard of care approaches in CUP that include genomic profiling for selected patients after initial evaluation based on current, standard criteria for tumor agnostic testing.

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 (50 or fewer genes) is considered **medically necessary** for children or adults with acute lymphoblastic leukemia (ALL) when **BOTH** of the following criteria are met:

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

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** in children or adults with ALL to measure minimal residual disease (MRD) at the end of initial treatment induction and end of initial consolidation and at similar defined points over the course of sequential therapies.

BCR-ABL kinase domain point 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.[236] The cure rate of pediatric ALL is at least 80%, in adults closer to 30% to 40%.[237] 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.[236] Adult patients have been found to have more gene mutations, especially IKZF1, MLL2, and JAK3, but fewer alterations of PTPN11 compared with pediatric patients.[238] The precise contribution of these genetic or epigenetic abnormalities to leukemogenesis, the development of drug resistance and leukemic clone evolution remains to be defined.[238]

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%.[236] 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.[239] 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.[239] 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.[240] 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.[241] Several more recent studies also confirm the role of MRD testing in B-cell precursor ALL[242], in young adult T-cell ALL[243], and in mixed cohorts of ALL patients treated on investigational protocols.[244] Regarding the timing of MRD monitoring, Carelon guidelines are in concordance with the National Comprehensive Cancer Network (NCCN) guideline recommendations.[245]

Acute Myelogenous Leukemia

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

- Testing is for the purpose of establishing the diagnosis, to stratify risk, or to identify actionable therapeutic targets
- A multi-gene panel contains genes that are identified with AML, such as FLT3, IDH1, IDH2, NPM1, CBFB, MYH1, CEBPA, MLLT3, KMT2A, DEK, NUP214, KAT6A, CREBBP, GATA2, EVI1, DDX41, TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and ZRSR2

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.

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

The use of focused testing of peripheral blood or bone marrow using RT-qPCR is considered **medically necessary** to measure minimal residual disease (MRD) in acute promyelocytic leukemia, or NPM1 or core binding factor AML when used at appropriate defined points over the course of therapy such as at the end of initial treatment induction, at the end of initial consolidation, or at the completion of other sequential therapies.

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.[246] Various patterns of dynamic clonal evolution that occur at relapse probably contribute to resistance to therapy.[247] Adults under age 60 years are cured with intensive leukemia treatment around 40% of the time.[247] 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%.[248]

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.[249] 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.[250]

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.[251] 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.[252]

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.[253, 254] 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.[255] Testing is often pursued to assess eligibility in MRD-directed clinical trials. The proven therapeutic implications of MRD remain mostly unresolved.[246, 251] Recent expert reviews emphasize that multiparametric flow cytometry is the gold standard for serial monitoring of patients with AML, but there are certain subsets of AML (acute promyelocytic

leukemia, or NPM1 or core-binding-factor associated AML are exceptions that can be monitored with focused NGS testing, and the poor prognosis and limited treatment options for relapsed, refractory AML have stimulated the emerging literature that relates to MRD testing to drive specific therapeutic approaches.[256, 257]

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 with tyrosine kinase inhibitor therapy.

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

Myeloproliferative Neoplasms

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

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

Rationale

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.[249] 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.[258] 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.[259] 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.[260] 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.[258] 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.[249] 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.[261] 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.[258] While identification of additional somatic mutations has been incorporated into some prognostic scoring tools [262, 263], more research is needed to establish the clinical utility of expanded prognostic testing along with other clinical considerations to guide patient management.[264]

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.[259] 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%.[265] 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.[261] 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.[266] 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.[259] 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.[267]

More than 100 different kinase domain mutations of BCR-ABL1 that impair TKI binding have been reported in patients who develop TKI resistance.[265] 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.[268] 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[269], thus NGS is the recommended technology for detecting BCR-ABL1 resistance mutations in patients not adequately responding to TKI therapy.[268]

Myelodysplastic Syndrome

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

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

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.[270] 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.[271] 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.[249] 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.[272]

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is caused by somatic mutations in UBA1. VEXAS-associated myelodysplastic syndrome is a distinct entity from classical MDS, both in presentation and clinical course, highlighting the role of UBA1 testing.[273]

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.[274] More recently, a clinical-molecular prognostic model (IPSS-Molecular [IPSS-M]) has been validated.[275, 276] 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. The IPSS-M model has also been explored to improve MDS prognostication for selection of candidates for hematopoietic stem cell transplantation.[277]

Multiple Myeloma

Gene expression profile tests

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

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

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.[278] 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.[279]

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.[278] The revised ISS(R-ISS) was introduced in 2015 and has been widely validated.[280] More recently, additional cytogenetic abnormalities have been found and newer, validated models are available such as the Mayo Additive Staging System[281] and evolving tools such as the Mayo Clinic mSMART risk stratification method (www.msmart.org).[278]

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.[282] 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.[283] 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.[284, 285] 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.[286] Detailed aspects of this approach to detecting MRD were outlined in 2016 by the International Myeloma Working Group (IMWG)[282], and guidelines from the American Society and Cancer Care Ontario[279] and from the European Society of Medical Oncology and the European Hematology Association[286] 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.[287] 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.[286] 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.[279]

References

1. Kurnit KC, Dumbrava EEI, Litzenburger B, et al. Precision Oncology Decision Support: Current Approaches and Strategies for the Future. Clin Cancer Res. 2018;24(12):2719-31.
2. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. 2022;40(11):1231-58.
3. Cobain EF, Wu YM, Vats P, et al. Assessment of Clinical Benefit of Integrative Genomic Profiling in Advanced Solid Tumors. JAMA Oncol. 2021;7(4):525-33.
4. Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol. 2015;16(13):1324-34.
5. Heipertz AE, Pajtler KW, Pfaff E, et al. Outcome of Children and Adolescents With Relapsed/Refractory/Progressive Malignancies Treated With Molecularly Informed Targeted Drugs in the Pediatric Precision Oncology Registry INFORM. JCO Precis Oncol. 2023;7:e2300015.
6. El-Deiry WS, Goldberg RM, Lenz HJ, et al. The current state of molecular testing in the treatment of patients with solid tumors, 2019. CA Cancer J Clin. 2019;69(4):305-43.
7. Bessa X, Ballesté B, Andreu M, et al. A prospective, multicenter, population-based study of BRAF mutational analysis for Lynch syndrome screening. Clin Gastroenterol Hepatol. 2008;6(2):206-14.
8. Domingo E, Niessen RC, Oliveira C, et al. BRAF-V600E is not involved in the colorectal tumorigenesis of HNPCC in patients with functional MLH1 and MSH2 genes. Oncogene. 2005;24(24):3995-8.
9. André T, Cohen R, Salem ME. Immune Checkpoint Blockade Therapy in Patients With Colorectal Cancer Harboring Microsatellite Instability/Mismatch Repair Deficiency in 2022. Am Soc Clin Oncol Educ Book. 2022;42:1-9.
10. McGrail DJ, Pilié PG, Rashid NU, et al. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann Oncol. 2021;32(5):661-72.

11. Jardim DL, Goodman A, de Melo Gagliato D, et al. The Challenges of Tumor Mutational Burden as an Immunotherapy Biomarker. Cancer Cell. 2021;39(2):154-73.
12. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017;23(6):703-13.
13. Duvivier HL, Rothe M, Mangat PK, et al. Pembrolizumab in Patients With Tumors With High Tumor Mutational Burden:Results From the Targeted Agent and Profiling Utilization Registry Study. J Clin Oncol. 2023;41(33):5140-50.
14. Sung MT, Wang YH, Li CF. Open the Technical Black Box of Tumor Mutational Burden (TMB): Factors Affecting Harmonization and Standardization of Panel-Based TMB. Int J Mol Sci. 2022;23(9).
15. Subbiah V, Solit DB, Chan TA, et al. The FDA approval of pembrolizumab for adult and pediatric patients with tumor mutationalburden (TMB) ≥10: a decision centered on empowering patients and their physicians. Ann Oncol. 2020;31(9):1115-8.
16. Prasad V, Addeo A. The FDA approval of pembrolizumab for patients with TMB >10 mut/Mb: was it a wise decision? No. Ann Oncol. 2020;31(9):1112-4.
17. Solomon JP, Benayed R, Hechtman JF, et al. Identifying patients with NTRK fusion cancer. Ann Oncol. 2019;30(Suppl_8):viii16-viii22.
18. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21(2):271-82.
19. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018;378(8):731-9.
20. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022;23(10):1261-73.
21. Solomon JP, Linkov I, Rosado A, et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol. 2020;33(1):38-46.
22. Zhou KI, Vashistha V, Guo A, et al. Real-world Experience With Neurotrophic Tyrosine Receptor Kinase Fusion-positive Tumors and Tropomyosin Receptor Kinase Inhibitors in Veterans. JCO Precis Oncol. 2023;7:e2200692.
23. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018;29(9):1895-902.
24. Hilbers FS, Aftimos P. Expanding the landscape of actionable genomic alterations in metastatic breast cancer: comprehensive genomic profiling for all? Ann Oncol. 2020;31(8):967-9.
25. Subbiah V, Baik C, Kirkwood JM. Clinical Development of BRAF plus MEK Inhibitor Combinations. Trends Cancer. 2020;6(9):797-810.
26. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study. Ann Oncol. 2022;33(4):406-15.
27. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23(1):53-64.
28. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21(9):1234-43.
29. Matulay JT, Kamat AM. Advances in risk stratification of bladder cancer to guide personalized medicine. F1000Res. 2018;7.
30. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell. 2017;171(3):540-56.e25.
31. Warrick JI, Knowles MA, Yves A, et al. Report From the International Society of Urological Pathology (ISUP) Consultation Conference On Molecular Pathology Of Urogenital Cancers. II. Molecular Pathology of Bladder Cancer: Progress and Challenges. Am J Surg Pathol. 2020;44(7):e30-e46.
32. Holzbeierlein JM, Bixler BR, Buckley DI, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment. J Urol. 2024:101097ju0000000000003846.
33. Lenis AT, Lec PM, Chamie K, et al. Bladder Cancer: A Review. JAMA. 2020;324(19):1980-91.
34. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2019;381(4):338-48.
35. Loriot Y, Matsubara N, Park SH, et al. Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2023;389(21):1961-71.
36. Necchi A, Pouessel D, Leibowitz R, et al. Pemigatinib for metastatic or surgically unresectable urothelial carcinoma with FGF/FGFR genomic alterations: final results from FIGHT-201. Ann Oncol. 2024;35(2):200-10.
37. Catto JWF, Tran B, Rouprêt M, et al. Erdafitinib in BCG-treated high-risk non-muscle-invasive bladder cancer. Ann Oncol. 2024;35(1):98-106.
38. Cathomas R, Lorch A, Bruins HM, et al. The 2021 Updated European Association of Urology Guidelines on MetastaticUrothelial Carcinoma. Eur Urol. 2022;81(1):95-103.

39. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Bladder Cancer, Version 7.2024. 2024.
40. Rouprêt M, Seisen T, Birtle AJ, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2023 Update. Eur Urol. 2023;84(1):49-64.
41. Necchi A, Madison R, Pal SK, et al. Comprehensive Genomic Profiling of Upper-tract and Bladder Urothelial Carcinoma. Eur Urol Focus. 2021;7(6):1339-46.
42. Holzbeierlein JM, Bixler BR, Buckley DI, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment. J Urol. 2024;211(4):533-8.
43. van den Bent MJ, Geurts M, French PJ, et al. Primary brain tumours in adults. Lancet. 2023;402(10412):1564-79.
44. Berger TR, Wen PY, Lang-Orsini M, et al. World Health Organization 2021 Classification of Central Nervous System Tumors and Implications for Therapy for Adult-Type Gliomas: A Review. JAMA Oncol. 2022;8(10):1493-501.
45. Benusiglio PR, Elder F, Touat M, et al. Mismatch Repair Deficiency and Lynch Syndrome Among Adult Patients With Glioma. JCO Precis Oncol. 2023;7:e2200525.
46. Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus Trametinib in Pediatric Glioma with BRAF V600 Mutations. N Engl J Med. 2023;389(12):1108-20.
47. Hargrave DR, Terashima K, Hara J, et al. Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/Refractory BRAF V600-Mutant Pediatric High-Grade Glioma. J Clin Oncol. 2023;41(33):5174-83.
48. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023;389(7):589-601.
49. Capper D, Reifenberger G, French PJ, et al. EANO guideline on rational molecular testing of gliomas, glioneuronal, and neuronal tumors in adults for targeted therapy selection. Neuro Oncol. 2023;25(5):813-26.
50. Bhutiani N, Egger ME, Ajkay N, et al. Multigene Signature Panels and Breast Cancer Therapy: Patterns of Use and Impact on Clinical Decision Making. J Am Coll Surg. 2018;226(4):406-12.e1.
51. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in BreastCancer. N Engl J Med. 2018;379(2):111-21.
52. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015;373(21):2005-14.
53. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47.
54. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016;375(8):717-29.
55. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22(4):476-88.
56. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2022;40(16):1816-37.
57. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast Cancer Index Is a Predictive Biomarker of Treatment Benefit and Outcome from Extended Tamoxifen Therapy: Final Analysis of the Trans-aTTom Study. Clin Cancer Res. 2022;28(9):1871-80.
58. Noordhoek I, Treuner K, Putter H, et al. Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HR(+) Early-stage Breast Cancer for 10 Years of Endocrine Therapy. Clin Cancer Res. 2021;27(1):311-9.
59. Mamounas EP, Bandos H, Rastogi P, et al. Breast Cancer Index and Prediction of Extended Aromatase Inhibitor Therapy Benefit in Hormone Receptor-positive Breast Cancer from the NRG Oncology/NSABP B-42 Trial. Clin Cancer Res. 2024.
60. Richman J, Dowsett M. Beyond 5 years: enduring risk of recurrence in oestrogen receptor-positive breast cancer. Nat Rev Clin Oncol. 2019;16(5):296-311.
61. Dowsett M, Sestak I, Regan MM, et al. Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor-Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5. J Clin Oncol. 2018;36(19):1941-8.
62. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up(†). Ann Oncol. 2023.
63. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017;377(19):1836-46.
64. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. 2019;37(5):423-38.
65. Bekes I, Huober J. Extended Adjuvant Endocrine Therapy in Early Breast Cancer Patients-Review and Perspectives. Cancers (Basel). 2023;15(16).
66. Walsh EM, Nunes R, Wilkinson MJ, et al. Extended Endocrine Therapy for Early-Stage Breast Cancer: How Do We Decide? Curr Oncol Rep. 2020;22(12):123.

67. Bottosso M, Miglietta F, Vernaci GM, et al. Gene Expression Assays to Tailor Adjuvant Endocrine Therapy for HR+/HER2- Breast Cancer. Clin Cancer Res. 2024;30(14):2884-94.
68. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019;30(11):1776-83.
69. Mamounas EP, Bandos H, Rastogi P, et al. Breast Cancer Index and Prediction of Extended Aromatase Inhibitor Therapy Benefit in Hormone Receptor-Positive Breast Cancer from the NRG Oncology/NSABP B-42 Trial. Clin Cancer Res. 2024;30(9):1984-91.
70. Rastogi P, Bandos H, Lucas PC, et al. Utility of the 70-Gene MammaPrint Assay for Prediction of Benefit From Extended Letrozole Therapy in the NRG Oncology/NSABP B-42 Trial. J Clin Oncol. 2024;42(30):3561-9.
71. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(2):159-82.
72. O'Regan RM, Zhang Y, Fleming GF, et al. Breast Cancer Index in Premenopausal Women With Early-Stage Hormone Receptor-Positive Breast Cancer. JAMA Oncol. 2024;10(10):1379-89.
73. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020;31(11):1491-505.
74. Condorelli R, Mosele F, Verret B, et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2019;30(3):365-73.
75. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380(20):1929-40.
76. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol. 2022;40(28):3246-56.
77. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-33.
78. US Food & Drug Administration. FDA Approves Capivasertib with Fulvestrant for Breast Cancer [February 1, 2024]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer#:~:text=On%20November%2016%2C%202023%2C%20the,one%20or%20more%20PIK3CA%2FAKT1%2F.
79. US Food & Drug Administration. FoundationOne CDx - P170019/S014 [February 1 2024]. Available from: https://www.fda.gov/medical-devices/recently-approved-devices/foundationone-cdx-p170019s014.
80. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023;388(22):2058-70.
81. Burstein HJ, DeMichele A, Somerfield MR, et al. Testing for ESR1 Mutations to Guide Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol. 2023;41(18):3423-5.
82. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 2016;34(25):2961-8.
83. Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet. 2021;397(10272):428-44.
84. Lamarca A, Edeline J, Goyal L. How I treat biliary tract cancer. ESMO Open. 2022;7(1):100378.
85. Ilyas SI, Affo S, Goyal L, et al. Cholangiocarcinoma - novel biological insights and therapeutic strategies. Nat Rev Clin Oncol. 2023;20(7):470-86.
86. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Biliary Tract Cancers, Version 2.2024. 2024.
87. Casak SJ, Pradhan S, Fashoyin-Aje LA, et al. FDA Approval Summary: Ivosidenib for the Treatment of Patients with Advanced Unresectable or Metastatic, Chemotherapy Refractory Cholangiocarcinoma with an IDH1 Mutation. Clin Cancer Res. 2022;28(13):2733-7.
88. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021;22(9):1290-300.
89. Biller LH, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. JAMA. 2021;325(7):669-85.
90. Stadler ZK, Battaglin F, Middha S, et al. Reliable Detection of Mismatch Repair Deficiency in Colorectal Cancers Using Mutational Load in Next-Generation Sequencing Panels. J Clin Oncol. 2016;34(18):2141-7.
91. Lynch HT, Lynch PM. Molecular screening for the Lynch syndrome--better than family history? N Engl J Med. 2005;352(18):1920-2.
92. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003;349(3):247-57.
93. Chakrabarti S, Grewal US, Vora KB, et al. Outcome of Patients With Early-Stage Mismatch Repair Deficient Colorectal Cancer Receiving Neoadjuvant Immunotherapy: A Systematic Review. JCO Precis Oncol. 2023;7:e2300182.
94. Emiloju OE, Sinicrope FA. Neoadjuvant Immune Checkpoint Inhibitor Therapy for Localized Deficient Mismatch Repair Colorectal Cancer: A Review. JAMA Oncol. 2023;9(12):1708-15.

95. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol. 2016;34(2):179-85.
96. Stahler A, Hoppe B, Na IK, et al. Consensus Molecular Subtypes as Biomarkers of Fluorouracil and Folinic Acid Maintenance Therapy With or Without Panitumumab in RAS Wild-Type Metastatic Colorectal Cancer (PanaMa, AIO KRK 0212). J Clin Oncol. 2023;41(16):2975-87.
97. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. Lancet Oncol. 2023;24(5):496-508.
98. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Colon Cancer, Version 4.2024. 2024.
99. NCCN. Clinical Practice Guidelines in Oncology (NCCN Guidelines) Rectal Cancer, Version 1.2024. 2024.
100. Korphaisarn K, Kopetz S. BRAF-Directed Therapy in Metastatic Colorectal Cancer. Cancer J. 2016;22(3):175-8.
101. Corcoran RB, Atreya CE, Falchook GS, et al. Combined BRAF and MEK Inhibition With Dabrafenib and Trametinib in BRAF V600-Mutant Colorectal Cancer. J Clin Oncol. 2015;33(34):4023-31.
102. Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study. J Clin Oncol. 2021;39(4):273-84.
103. Taieb J, Sinicrope FA, Pederson L, et al. Different prognostic values of KRAS exon 2 submutations and BRAF V600E mutation in microsatellite stable (MSS) and unstable (MSI) stage III colon cancer: an ACCENT/IDEA pooled analysis of seven trials. Ann Oncol. 2023;34(11):1025-34.
104. Bekaii-Saab TS, Lach K, Hsu LI, et al. Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer: A Systematic Literature Review and Meta-Analysis of Clinical Outcomes. Oncologist. 2023;28(10):885-93.
105. Xu Y, Xing L, Su J, et al. Model-based clustering for identifying disease-associated SNPs in case-control genome-wide association studies. Sci Rep. 2019;9(1):13686.
106. Solomon JP, Hechtman JF. Detection of NTRK Fusions: Merits and Limitations of Current Diagnostic Platforms. Cancer Res. 2019;79(13):3163-8.
107. Formica V, Sera F, Cremolini C, et al. KRAS and BRAF Mutations in Stage II and III Colon Cancer: A Systematic Review and Meta-Analysis. J Natl Cancer Inst. 2022;114(4):517-27.
108. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(1):10-32.
109. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. J Clin Oncol. 2022;40(7):752-61.
110. Casey L, Singh N. POLE, MMR, and MSI Testing in Endometrial Cancer: Proceedings of the ISGyP Companion Society Session at the USCAP 2020 Annual Meeting. Int J Gynecol Pathol. 2021;40(1):5-16.
111. McConechy MK, Talhouk A, Li-Chang HH, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol. 2015;137(2):306-10.
112. Vermij L, Smit V, Nout R, et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020;76(1):52-63.
113. Horeweg N, Nout RA, Jürgenliemk-Schulz IM, et al. Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer. J Clin Oncol. 2023;41(27):4369-80.
114. van den Heerik A, Horeweg N, Nout RA, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer. 2020;30(12):2002-7.
115. Wortman BG, Bosse T, Nout RA, et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 2018;151(1):69-75.
116. León-Castillo A, de Boer SM, Powell ME, et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020;38(29):3388-97.
117. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Uterine Neoplasms, Version 2.2024. 2024.
118. Miedema J, Andea AA. Through the looking glass and what you find there: making sense of comparative genomic hybridization and fluorescence in situ hybridization for melanoma diagnosis. Mod Pathol. 2020;33(7):1318-30.
119. Chan WH, Tsao H. Consensus, Controversy, and Conversations About Gene Expression Profiling in Melanoma. JAMA Dermatol. 2020;156(9):949-51.
120. Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. J Am Acad Dermatol. 2020;83(3):745-53.
121. Marchetti MA, Dusza SW, Bartlett EK. Problematic methodology in a systematic review and meta-analysis of DecisionDx-Melanoma. J Am Acad Dermatol. 2020;83(5):e357-e8.

122. Bailey CN, Martin BJ, Petkov VI, et al. 31-Gene Expression Profile Testing in Cutaneous Melanoma and Survival Outcomes in a Population-Based Analysis: A SEER Collaboration. JCO Precis Oncol. 2023;7:e2300044.
123. Kovarik CL, Chu EY, Adamson AS. Gene Expression Profile Testing for Thin Melanoma: Evidence to Support Clinical Use Remains Thin. JAMA Dermatol. 2020;156(8):837-8.
124. Seider MI, Mruthyunjaya P. MOLECULAR PROGNOSTICS FOR UVEAL MELANOMA. Retina. 2018;38(2):211-9.
125. Chattopadhyay C, Kim DW, Gombos DS, et al. Uveal melanoma: From diagnosis to treatment and the science in between. Cancer. 2016;122(15):2299-312.
126. Aaberg TM, Covington KR, Tsai T, et al. Gene Expression Profiling in Uveal Melanoma: Five-Year Prospective Outcomes and Meta-Analysis. Ocul Oncol Pathol. 2020;6(5):360-7.
127. Francis JH, Patel SP, Gombos DS, et al. Surveillance options for patients with uveal melanoma following definitive management. Am Soc Clin Oncol Educ Book. 2013:382-7.
128. Cheng L, Lopez-Beltran A, Massari F, et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod Pathol. 2018;31(1):24-38.
129. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30(12):1884-901.
130. Nathan P, Hassel JC, Rutkowski P, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021;385(13):1196-206.
131. Devitt B, Liu W, Salemi R, et al. Clinical outcome and pathological features associated with NRAS mutation in cutaneous melanoma. Pigment Cell Melanoma Res. 2011;24(4):666-72.
132. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(4):435-45.
133. Steeb T, Wessely A, Petzold A, et al. c-Kit inhibitors for unresectable or metastatic mucosal, acral or chronically sun-damaged melanoma: a systematic review and one-arm meta-analysis. Eur J Cancer. 2021;157:348-57.
134. Griesinger F, Eberhardt W, Nusch A, et al. Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). Lung Cancer. 2021;152:174-84.
135. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. J Clin Oncol. 2022;40(6):611-25.
136. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(9):911-9.
137. Ionescu DN, Stockley TL, Banerji S, et al. Consensus Recommendations to Optimize Testing for New Targetable Alterations in Non-Small Cell Lung Cancer. Curr Oncol. 2022;29(7):4981-97.
138. FDA. FDA approves tepotinib for metastatic non-small cell lung cancer. 2024.
139. FDA. FDA approves repotrectinib for ROS1-positive non-small cell lung cancer. 2023.
140. FDA. FDA approves neoadjuvant/ adjuvant pembrolizumab for resectable non-small cell lung cancer. 2023.
141. FDA. FDA approves pralsetinib for non-small cell lung cancer with RET gene fusions. 2023.
142. FDA. FDA approves amivantamab-vmjw for EGFR exon 20 insertion-mutated non-small cell lung cancer indications. 2024.
143. Zhou C, Tang KJ, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med. 2023;389(22):2039-51.
144. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(4):339-57.
145. Jaiyesimi IA, Leighl NB, Ismaila N, et al. Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.3. J Clin Oncol. 2024;42(11):e1-e22.
146. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020;383(18):1711-23.
147. Tsuboi M, Herbst RS, John T, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med. 2023;389(2):137-47.
148. Singhi EK, Gay CM. Narrative review of the emerging role of molecular biomarkers in guiding the definitive management of unresectable non-small cell lung cancer. Transl Lung Cancer Res. 2020;9(5):2051-8.
149. Aredo JV, Urisman A, Gubens MA, et al. Phase II trial of neoadjuvant osimertinib for surgically resectable EGFR-mutated non-small cell lung cancer. J Clin Oncol. 2023;41(16_suppl):8508-.
150. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC Cancer (Version 1.2024). Available at http://www.nccn.org. National Comprehensive Cancer Network, 2024. 2024.

151. Dizon DS. PARP inhibitors for targeted treatment in ovarian cancer. Lancet. 2017;390(10106):1929-30.
152. Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(5):710-22.
153. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949-61.
154. Krumm N, Khasnavis NS, Radke M, et al. Diagnosis of Ovarian Carcinoma Homologous Recombination DNA Repair Deficiency From Targeted Gene Capture Oncology Assays. JCO Precis Oncol. 2023;7:e2200720.
155. Christinat Y, Ho L, Clément S, et al. Normalized LST Is an Efficient Biomarker for Homologous Recombination Deficiency and Olaparib Response in Ovarian Carcinoma. JCO Precis Oncol. 2023;7:e2200555.
156. Moore KN, Angelergues A, Konecny GE, et al. Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer. N Engl J Med. 2023;389(23):2162-74.
157. Rainone M, Singh I, Salo-Mullen EE, et al. An Emerging Paradigm for Germline Testing in Pancreatic Ductal Adenocarcinoma and Immediate Implications for Clinical Practice: A Review. JAMA Oncol. 2020;6(5):764-71.
158. Golan T, Hammel P. Management of BRCA Mutation Carriers With Pancreatic Adenocarcinoma. J Natl Compr Canc Netw. 2021;19(4):469-73.
159. Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. JAMA. 2021;326(9):851-62.
160. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019;381(4):317-27.
161. Kindler HL, Hammel P, Reni M, et al. Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer. J Clin Oncol. 2022:Jco2101604.
162. Nishikawa G, Booth C, Prasad V. Olaparib for BRCA mutant pancreas cancer: Should the POLO trial change clinical practice? Cancer. 2020;126(18):4087-8.
163. Reiss KA, Mick R, O'Hara MH, et al. Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in BRCA1, BRCA2, or PALB2. J Clin Oncol. 2021;39(22):2497-505.
164. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(11):987-1002.
165. National Comprehensive Cancer Network (NCCN). Pancreatic Cancer Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. 2023.
166. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-29.
167. Eggener SE, Berlin A, Vickers AJ, et al. Low-Grade Prostate Cancer: Time to Stop Calling It Cancer. J Clin Oncol. 2022:Jco2200123.
168. Zelic R, Garmo H, Zugna D, et al. Predicting Prostate Cancer Death with Different Pretreatment Risk Stratification Tools: A Head-to-head Comparison in a Nationwide Cohort Study. Eur Urol. 2020;77(2):180-8.
169. Haffner MC, Zwart W, Roudier MP, et al. Genomic and phenotypic heterogeneity in prostate cancer. Nat Rev Urol. 2021;18(2):79-92.
170. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020;38(13):1474-94.
171. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer (Version 4.2023). Available at http://www.nccn.org. National Comprehensive Cancer Network, 2023. 2023.
172. Lin DW, Nelson PS. Prognostic Genomic Biomarkers in Patients With Localized Prostate Cancer: Is Rising Utilization Justified by Evidence? JAMA Oncol. 2021;7(1):59-60.
173. Leapman MS, Wang R, Ma S, et al. Regional Adoption of Commercial Gene Expression Testing for Prostate Cancer. JAMA Oncol. 2021;7(1):52-8.
174. Hu JC, Tosoian JJ, Qi J, et al. Clinical Utility of Gene Expression Classifiers in Men With Newly Diagnosed Prostate Cancer. JCO Precis Oncol. 2018;2.
175. Fallah J, Xu J, Weinstock C, et al. FDA Approval Summary: Olaparib in Combination With Abiraterone for Treatment of Patients With BRCA-Mutated Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2024;42(5):605-13.
176. Mateo J, McKay R, Abida W, et al. Accelerating precision medicine in metastatic prostate cancer. Nat Cancer. 2020;1(11):1041-53.
177. Giri VN, Morgan TM, Morris DS, et al. Genetic testing in prostate cancer management: Considerations informing primary care. CA Cancer J Clin. 2022;72(4):360-71.
178. Sokol ES, Jin DX, Fine A, et al. PARP Inhibitor Insensitivity to BRCA1/2 Monoallelic Mutations in Microsatellite Instability-High Cancers. JCO Precis Oncol. 2022;6:e2100531.

179. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091-102.
180. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;383(24):2345-57.
181. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. 2020;38(32):3763-72.
182. Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study. Clin Cancer Res. 2020;26(11):2487-96.
183. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or Physician's Choice in Metastatic Prostate Cancer. N Engl J Med. 2023;388(8):719-32.
184. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol. 2023;34(9):772-82.
185. Hanba C, Khariwala SS. What is the Utility of Genetic Testing in Indeterminate Thyroid Nodules? Laryngoscope. 2021;131(11):2399-400.
186. Leboulleux S, Bournaud C, Chougnet CN, et al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. N Engl J Med. 2022;386(10):923-32.
187. Zanocco KA, Hershman JM, Leung AM. Active Surveillance of Low-Risk Thyroid Cancer. JAMA. 2019;321(20):2020-1.
188. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
189. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017;27(11):1341-6.
190. Deaver KE, Haugen BR, Pozdeyev N, et al. Outcomes of Bethesda categories III and IV thyroid nodules over 5 years and performance of the Afirma gene expression classifier: A single-institution study. Clin Endocrinol (Oxf). 2018;89(2):226-32.
191. Mayson SE, Haugen BR. Molecular Diagnostic Evaluation of Thyroid Nodules. Endocrinol Metab Clin North Am. 2019;48(1):85-97.
192. Sistrunk JW, Shifrin A, Frager M, et al. Clinical impact of testing for mutations and microRNAs in thyroid nodules. Diagn Cytopathol. 2019;47(8):758-64.
193. Lupo MA, Walts AE, Sistrunk JW, et al. Multiplatform molecular test performance in indeterminate thyroid nodules. Diagn Cytopathol. 2020;48(12):1254-64.
194. DiGennaro C, Vahdatzad V, Jalali MS, et al. Assessing Bias and Limitations of Clinical Validation Studies of Molecular Diagnostic Tests for Indeterminate Thyroid Nodules: Systematic Review and Meta-Analysis. Thyroid. 2022;32(10):1144-57.
195. Lee E, Terhaar S, McDaniel L, et al. Diagnostic performance of the second-generation molecular tests in the assessment of indeterminate thyroid nodules: A systematic review and meta-analysis. Am J Otolaryngol. 2022;43(3):103394.
196. Angell TE, Wirth LJ, Cabanillas ME, et al. Analytical and Clinical Validation of Expressed Variants and Fusions From the Whole Transcriptome of Thyroid FNA Samples. Front Endocrinol (Lausanne). 2019;10:612.
197. Babazadeh NT, Sinclair TJ, Krishnamurthy V, et al. Thyroid nodule molecular profiling: The clinical utility of Afirma Xpression Atlas for nodules with Afirma Genomic Sequencing Classifier-suspicious results. Surgery. 2022;171(1):155-9.
198. Munoz-Zuluaga CA, Heymann JJ, Solomon JP, et al. Use of the Afirma Xpression Atlas for cytologically indeterminate, Afirma Genomic Sequencing Classifier suspicious thyroid nodules: Clinicopathologic analysis with postoperative molecular testing. Am J Clin Pathol. 2024;161(5):463-8.
199. Marti JL, Avadhani V, Donatelli LA, et al. Wide Inter-institutional Variation in Performance of a Molecular Classifier for Indeterminate Thyroid Nodules. Ann Surg Oncol. 2015;22(12):3996-4001.
200. Luster M, Aktolun C, Amendoeira I, et al. European Perspective on 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Proceedings of an Interactive International Symposium. Thyroid. 2019;29(1):7-26.
201. Twining CL, Lupo MA, Tuttle RM. Implementing Key Changes in the American Thyroid Association 2015 Thyroid Nodules/Differentiated Thyroid Cancer Guidelines Across Practice Types. Endocr Pract. 2018;24(9):833-40.
202. Durante C, Hegedüs L, Czarniecka A, et al. 2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management. Eur Thyroid J. 2023;12(5).
203. Chen DW, Lang BHH, McLeod DSA, et al. Thyroid cancer. Lancet. 2023;401(10387):1531-44.
204. Steward DL, Carty SE, Sippel RS, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019;5(2):204-12.
205. Valderrabano P, Hallanger-Johnson JE, Thapa R, et al. Comparison of Postmarketing Findings vs the Initial Clinical Validation Findings of a Thyroid Nodule Gene Expression Classifier: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2019;145(9):783-92.

206. Ladenson PW, Klopper JP, Hao Y, et al. Combined Afirma Genomic Sequencing Classifier and TERT promoter mutation detection in molecular assessment of Bethesda III-VI thyroid nodules. Cancer Cytopathol. 2023;131(10):609-13.
207. Hayes DF. Defining Clinical Utility of Tumor Biomarker Tests: A Clinician's Viewpoint. J Clin Oncol. 2021;39(3):238-48.
208. Marti JL, Shaha AR. Molecular Testing for Indeterminate Thyroid Nodules-When the Rubber Meets the Road. JAMA Otolaryngol Head Neck Surg. 2019;145(9):792-3.
209. Barnes AB, Justice-Clark T, Li W, et al. Molecular Testing for Indeterminate Thyroid Nodules: Association of Negative Predictive Value With Nodule Size. Am Surg. 2022;88(11):2745-51.
210. Dublin JC, Papazian M, Zan E, et al. Predictive Value of a Genomic Classifier in Indeterminate Thyroid Nodules Based on Nodule Size. JAMA Otolaryngol Head Neck Surg. 2022;148(1):53-60.
211. Hu TX, Nguyen DT, Patel M, et al. The Effect Modification of Ultrasound Risk Classification on Molecular Testing in Predicting the Risk of Malignancy in Cytologically Indeterminate Thyroid Nodules. Thyroid. 2022;32(8):905-16.
212. Doerfler WR, Nikitski AV, Morariu EM, et al. Molecular alterations in Hürthle cell nodules and preoperative cancer risk. Endocr Relat Cancer. 2021;28(5):301-9.
213. Schatz-Siemers N, Brandler TC, Oweity T, et al. Hürthle cell lesions on thyroid fine needle aspiration cytology: Molecular and histologic correlation. Diagn Cytopathol. 2019;47(10):977-85.
214. Hao Y, Duh QY, Kloos RT, et al. Identification of Hürthle cell cancers: solving a clinical challenge with genomic sequencing and a trio of machine learning algorithms. BMC Syst Biol. 2019;13(Suppl 2):27.
215. Haddad R, Elisei R, Hoff AO, et al. Diagnosis and Management of Tropomyosin Receptor Kinase Fusion-Positive Thyroid Carcinomas: A Review. JAMA Oncol. 2023;9(8):1132-41.
216. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Thyroid Carcinoma, Version 1.2024 2024.
217. Rassy E, Pavlidis N. The currently declining incidence of cancer of unknown primary. Cancer Epidemiol. 2019;61:139-41.
218. Rassy E, Assi T, Pavlidis N. Exploring the biological hallmarks of cancer of unknown primary: where do we stand today? Br J Cancer. 2020;122(8):1124-32.
219. Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med. 2014;371(8):757-65.
220. Huey RW, Smaglo BG, Estrella JS, et al. Cancer of Unknown Primary Presenting as Bone-Predominant or Lymph Node-Only Disease: A Clinicopathologic Portrait. Oncologist. 2021;26(4):e650-e7.
221. Naing A, Meric-Bernstam F, Stephen B, et al. Phase 2 study of pembrolizumab in patients with advanced rare cancers. J Immunother Cancer. 2020;8(1).
222. Nguyen L, Van Hoeck A, Cuppen E. Machine learning-based tissue of origin classification for cancer of unknown primary diagnostics using genome-wide mutation features. Nat Commun. 2022;13(1):4013.
223. Jiao W, Atwal G, Polak P, et al. A deep learning system accurately classifies primary and metastatic cancers using passenger mutation patterns. Nat Commun. 2020;11(1):728.
224. Salvadores M, Mas-Ponte D, Supek F. Passenger mutations accurately classify human tumors. PLoS Comput Biol. 2019;15(4):e1006953.
225. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Occult Primary (Cancer of Unknown Primary [CUP]) Version 1.2024. 2023.
226. Ding Y, Jiang J, Xu J, et al. Site-specific therapy in cancers of unknown primary site: a systematic review and meta-analysis. ESMO Open. 2022;7(2):100407.
227. Krämer A, Bochtler T, Pauli C, et al. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(3):228-46.
228. Raghav K, Hwang H, Jácome AA, et al. Development and Validation of a Novel Nomogram for Individualized Prediction of Survival in Cancer of Unknown Primary. Clin Cancer Res. 2021;27(12):3414-21.
229. Huey RW, Shah AT, Reddi HV, et al. Feasibility and value of genomic profiling in cancer of unknown primary: real-world evidence from prospective profiling study. J Natl Cancer Inst. 2023;115(8):994-7.
230. Wang X, Beharry A, Sheffield BS, et al. Feasibility of Point-of-Care Genomic Profiling in the Diagnosis and Treatment of Cancer of Unknown Primary. Oncologist. 2023;28(6):474-8.
231. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2015;373(16):1541-52.
232. Jabbour E, Pui CH, Kantarjian H. Progress and Innovations in the Management of Adult Acute Lymphoblastic Leukemia. JAMA Oncol. 2018;4(10):1413-20.
233. Liu YF, Wang BY, Zhang WN, et al. Genomic Profiling of Adult and Pediatric B-cell Acute Lymphoblastic Leukemia. EBioMedicine. 2016;8:173-83.
234. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017;3(7):e170580.

235. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2014;15(8):809-18.
236. Brown P, Inaba H, Annesley C, et al. Pediatric Acute Lymphoblastic Leukemia, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(1):81-112.
237. Kim R, Bergugnat H, Pastoret C, et al. Genetic alterations and MRD refine risk assessment for KMT2A-rearranged B-cell precursor ALL in adults: a GRAALL study. Blood. 2023;142(21):1806-17.
238. O'Connor D, Demeulemeester J, Conde L, et al. The Clinicogenomic Landscape of Induction Failure in Childhood and Young Adult T-Cell Acute Lymphoblastic Leukemia. J Clin Oncol. 2023;41(19):3545-56.
239. Pieters R, de Groot-Kruseman H, Fiocco M, et al. Improved Outcome for ALL by Prolonging Therapy for IKZF1 Deletion and Decreasing Therapy for Other Risk Groups. J Clin Oncol. 2023;41(25):4130-42.
240. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Pediatric Acute Lymphoblastic Leukemia, Version 3.2024. 2023.
241. Aitken MJL, Ravandi F, Patel KP, et al. Prognostic and therapeutic implications of measurable residual disease in acute myeloid leukemia. J Hematol Oncol. 2021;14(1):137.
242. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015;373(12):1136-52.
243. Nabhan C, Kamat S, Karl Kish J. Acute myeloid leukemia in the elderly: what constitutes treatment value? Leuk Lymphoma. 2019;60(5):1164-70.
244. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-19.
245. Duncavage EJ, Schroeder MC, O'Laughlin M, et al. Genome Sequencing as an Alternative to Cytogenetic Analysis in Myeloid Cancers. N Engl J Med. 2021;384(10):924-35.
246. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. Blood. 2022.
247. Short NJ, Tallman MS, Pollyea DA, et al. Optimizing Risk Stratification in Acute Myeloid Leukemia: Dynamic Models for a Dynamic Therapeutic Landscape. J Clin Oncol. 2021;39(23):2535-8.
248. Ivey A, Hills RK, Simpson MA, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med. 2016;374(5):422-33.
249. Short NJ, Zhou S, Fu C, et al. Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA Oncol. 2020;6(12):1890-9.
250. Dillon R, Potter N, Freeman S, et al. How we use molecular minimal residual disease (MRD) testing in acute myeloid leukaemia (AML). Br J Haematol. 2021;193(2):231-44.
251. El Chaer F, Hourigan CS, Zeidan AM. How I treat AML incorporating the updated classifications and guidelines. Blood. 2023;141(23):2813-23.
252. Thol F, Döhner H, Ganser A. How I treat refractory and relapsed acute myeloid leukemia. Blood. 2024;143(1):11-20.
253. Spivak JL. Myeloproliferative Neoplasms. N Engl J Med. 2017;377(9):895-6.
254. Hochhaus A, Saussele S, Rosti G, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv261.
255. Wong WJ, Pozdnyakova O. Myeloproliferative neoplasms: Diagnostic workup of the cythemic patient. Int J Lab Hematol. 2019;41 Suppl 1:142-50.
256. Mughal TI, Gotlib J, Mesa R, et al. Recent advances in the genomics and therapy of BCR/ABL1-positive and -negative chronic myeloproliferative neoplasms. Leuk Res. 2018;67:67-74.
257. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol. 2018;36(4):310-8.
258. Vannucchi AM, Guglielmelli P. Molecular prognostication in Ph-negative MPNs in 2022. Hematology Am Soc Hematol Educ Program. 2022;2022(1):225-34.
259. Luque Paz D, Kralovics R, Skoda RC. Genetic basis and molecular profiling in myeloproliferative neoplasms. Blood. 2023;141(16):1909-21.
260. Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017;376(10):917-27.
261. Cross NC, White HE, Colomer D, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. Leukemia. 2015;29(5):999-1003.
262. Shanmuganathan N, Hughes TP. Molecular monitoring in CML: how deep? How often? How should it influence therapy? Hematology Am Soc Hematol Educ Program. 2018;2018(1):168-76.
263. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-84.

264. Soverini S, Bavaro L, De Benedittis C, et al. Prospective assessment of NGS-detectable mutations in CML patients with nonoptimal response: the NEXT-in-CML study. Blood. 2020;135(8):534-41.
265. Cazzola M. Myelodysplastic Syndromes. N Engl J Med. 2020;383(14):1358-74.
266. Fenaux P, Platzbecker U, Ades L. How we manage adults with myelodysplastic syndrome. Br J Haematol. 2020;189(6):1016-27.
267. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Myelodysplastic Syndromes, Version 1.2024. 2024.
268. Gutierrez-Rodrigues F, Kusne Y, Fernandez J, et al. Spectrum of clonal hematopoiesis in VEXAS syndrome. Blood. 2023;142(3):244-59.
269. Garcia-Manero G, Chien KS, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(11):1399-420.
270. Aguirre LE, Al Ali N, Sallman DA, et al. Assessment and validation of the molecular international prognostic scoring system for myelodysplastic syndromes. Leukemia. 2023;37(7):1530-9.
271. Lee WH, Tsai MT, Tsai CH, et al. Validation of the molecular international prognostic scoring system in patients with myelodysplastic syndromes defined by international consensus classification. Blood Cancer J. 2023;13(1):120.
272. Sauta E, Robin M, Bersanelli M, et al. Real-World Validation of Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. J Clin Oncol. 2023;41(15):2827-42.
273. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548-67.
274. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol. 2019;37(14):1228-63.
275. Tandon N, Rajkumar SV, LaPlant B, et al. Clinical utility of the Revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer J. 2017;7(2):e528.
276. Abdallah NH, Binder M, Rajkumar SV, et al. A simple additive staging system for newly diagnosed multiple myeloma. Blood Cancer J. 2022;12(1):21.
277. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e46.
278. Ye X, Li W, Zhang L, et al. Clinical Significance of Circulating Cell-Free DNA Detection in Multiple Myeloma: A Meta-Analysis. Front Oncol. 2022;12:852573.
279. Bertamini L, Oliva S, Rota-Scalabrini D, et al. High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma. J Clin Oncol. 2022;40(27):3120-31.
280. Garcés JJ, Cedena MT, Puig N, et al. Circulating Tumor Cells for the Staging of Patients With Newly Diagnosed Transplant-Eligible Multiple Myeloma. J Clin Oncol. 2022;40(27):3151-61.
281. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). Ann Oncol. 2021;32(3):309-22.
282. Paiva B, Manrique I, Dimopoulos MA, et al. MRD dynamics during maintenance for improved prognostication of 1280 patients with myeloma in the TOURMALINE-MM3 and -MM4 trials. Blood. 2023;141(6):579-91.

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)

Code	May Be Medically Necessary When Criteria are Met
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
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

Code	May Be Medically Necessary When Criteria are Met
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
81307	*PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
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)

Code	May Be Medically Necessary When Criteria are Met
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81479	Unlisted molecular pathology procedure
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score (Endopredict)
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)
81599	Unlisted multianalyte assay with algorithmic analysis
0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
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

Code	May Be Medically Necessary When Criteria are Met
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
0154U	Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3- kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
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
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0364U	clonoSEQ® Assay, Adaptive Biotechnologies: Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden. The test analyzes a blood or bone marrow specimen from a hematolymphoid (blood/lymph) cancer patient using next generation sequencing (NGS) to track the levels of specific (clonal) DNA sequences related to the cancer. Repeating the test allows clinicians to determine whether the patient has remaining cancer cells, called minimal residual disease (MRD), during and after treatment.
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
0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
0481U	IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (eg, central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions)
0523U	Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change
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
81195	Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (OGM)
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
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

Code	Not Medically Necessary
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher)
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)
0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin
0020M	Oncology (central nervous system), analysis of 30000 DNA methylation loci by methylation array, utilizing DNA extracted from tumor tissue, diagnostic algorithm reported as probability of matching a reference tumor subclass
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin-embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score.
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
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
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)

Code	Not Medically Necessary
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Whole Genome Sequencing
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification - Praxis Somatic Transcriptome
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification - Praxis Somatic Optical Genome Mapping
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification - Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD **(Do not report 0306U in conjunction with 0307U)**
0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD **(Do not report 0307U in conjunction with 0306U)**
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)
0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alternations
0362U	Oncology (papillary thyroid cancer), gene expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
0379U	Solid Tumor Expanded Panel, Quest Diagnostics®, Quest Diagnostics®: Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite 'instability, and tumor mutational burden. The test uses a next–generation sequencing (NGS) targeted sequence analysis panel for a tumor specimen to evaluate DNA for 523 genes and RNA for 55 genes. The results may aid with diagnosis, prognosis, or treatment selection for patients with solid tumors.
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations
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)
0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative
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
0497U	Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation
0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffin-embedded (FFPE) tissue, next-generation sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection

Code	Not Medically Necessary
0534U	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score
0538U	Oncology (solid tumor), next-generation targeted sequencing analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant
0543U	Oncology (solid tumor), next-generation sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for single-nucleotide variants, multi-nucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden
0578U	Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence
0586U	Oncology, mRNA, gene expression profiling of 216 genes (204 targeted and 12 housekeeping genes), RNA expression analysis, formalin-fixed paraffin-embedded (FFPE) tissue, quantitative, reported as log2 ratio per gene
0592U	Oncology (hematolymphoid neoplasms), DNA, targeted genomic sequence of 417 genes, interrogation for gene fusions, translocations, rearrangements, utilizing formalin-fixed paraffin embedded (FFPE) tumor tissue, results report clinically significant variant(s)
0597U	Oncology (breast), RNA expression profiling of 329 genes by targeted next-generation sequencing and **20 proteins** by multiplex immunofluorescence, formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic analyses to determine tumor-recurrence risk score
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	04/21/2025	10/05/2025	Independent Multispecialty Physician Panel (IMPP) review. For localized breast cancer, added criteria for the Breast Cancer Index in the extended adjuvant setting. Added references.
Updated codes 10/01/2025	n/a	Unchanged	CPT code update: added 0578U, 0586U, 0592U, 0597U (NMN).
Updated codes 04/01/2025	n/a	Unchanged	CPT code update: added 81504, 0019U, 0069U, 0534U, 0538U, 0543U (NMN); removed 0013M, 0332U, 0343U, 0452U, 0467U (NMN).
Revised	01/30/2025	03/23/2025	IMPP review. Expanded medical necessity criteria to include somatic tumor testing for biomarker-linked therapies that are NCCN Category 2A recommended. Clarified that criteria listed under ‘metastatic breast cancer’ also includes locally advanced breast cancer. Clarified that the clinical scenarios for testing in myeloproliferative neoplasms do not apply to primary or secondary myelofibrosis.
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: added 0523U (MNWCM) and 81195 (NMN); removed 0448U. Revised descriptions for 0497U, 0498U, 0499U.
Revised	10/28/2024, 07/16/2024, 04/15/2024	11/17/2024	IMPP review. Revised indications for bladder cancer (expansive for MSI/dMMR), brain cancer (new), metastatic breast cancer (expanded scope of testing AKT1 and PTEN, removed exclusion for tissue testing), metastatic colorectal cancer (expansive for MSI/dMMR and POLE/POLD1 testing), endometrial cancer (expansive for MSI/dMMR and POLE/POLD1 testing, restrictive for panel size), localized NSCLC (expansive for ALK testing), epithelial ovarian cancer (restrictive for HRD testing), pancreatic cancer (expanded targeted somatic testing), metastatic prostate cancer (expansive/restrictive), thyroid cancer (expansive); ALL (restrictive for NGS testing), AML (expansive for focused testing using RT-qPCR), CML (expansive for

Status	Review Date	Effective Date	Action
			BCR-ABL1), and MPN (expansive). Clarifications throughout. Added references. Moved CPT codes 81546 and 0049U from NMN to MNWCM. Moved 0177U to Cell-free DNA Testing for Cancer guidelines.
Revised	01/23/2024	10/20/2024	IMPP review. Clarified testing to guide adjuvant therapy for localized breast cancer. Moved CPT codes 81313, 81504, 81551, 0019U, 0069U, 0089U, 0114U to Predictive and Prognostic Polygenic Testing guidelines.
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 81407, 0478U, 0481U (MNWCM); 0497U, 0498U, 0499U (NMN). Added/Moved from Polygenic Risk Scores guideline: 81525, 81529, 81540, 81541, 81542, 81552, 0006M, 0013M, 0016M, 0017M, 0020M, 0045U, 0047U, 0120U, 0287U, 0288U, 0315U, 0343U, 0362U (NMN).
Updated codes 07/01/2024	n/a	Unchanged	Added CPT codes 0471U (MNWCM); 0452U, 0465U, 0467U, 0473U (NMN). Removed termed code 0204U (NMN).
Revised	07/18/2023	03/17/2024	IMPP review. Clarification for FDA-approved test moved to umbrella criteria. Expanded BRAF V600E criteria to include RAS variant in localized CRC. Removed Afirma standalone assay for testing ITNs. Restricted testing to 50 genes or fewer for bladder, colorectal, ovarian, ALL, AML, CML, MPN, and MDS. Expanded specimen type in tissue-based testing for ALL, AML, and MDS. For ALL, specimen-type, MRD and BCR-ABL1 monitoring. Added references. MNWCM codes: added 0448U; moved 81455 and 0334U from NMN to MNWCM. NMN codes: added 0444U; moved 81546 from MNWCM to NMN; removed 81525, 81529, 81540, 81541, 81542, 81552, 0005U, 0006M, 0012M, 0013M, 0016M, 0017M, 0045U, 0047U, 0090U, 0113U, 0120U, 0228U, 0287U, 0288U, 0296U, 0313U, 0314U, 0315U, 0317U, 0339U, 0343U, 0362U, 0363U, 0403U. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Added CPT codes 81457, 81458, and 81459. Description changes for 81406, 81445, 81449, 81450, 81451, 81455, 81456.
Revised	04/12/2023	11/05/2023	IMPP review. Tumor-agnostic testing for patients with advanced solid tumors: expanded testing for RET; clarification edits for MMR deficiency. Clarification edits in localized and metastatic breast cancer; expanded testing for ESR1 in metastatic breast. New testing scenario for advanced endometrial carcinoma. Corrected error in metastatic NSCLC. CML: Expanded specimen type to include peripheral blood; separated indication for MPNs and defined peripheral blood indices.
Updated	n/a	10/01/2023	Added CPT codes 81599, 0364U, 0379U, 0391U, 0403U, 0413U, 0414U. Moved 81327, 0007M, 0011M, 0229U, 0285U, 0333U, 0340U to Cell-free DNA Testing for Management of Cancer guidelines. Removed 81173, 81321, 81323, 81353, 0013U, 0014U, 0056U, 0179U, 0208U, 0235U, 0238U, 0239U, 0242U, 0326U, 0356U.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.