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Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

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abstract

PURPOSE An ASCO provisional clinical opinion offers timely clinical direction to ASCO's membership following publication or presentation of potentially practice-changing data from major studies. This provisional clinical opinion addresses the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.

CLINICAL CONTEXT An increasing number of therapies are approved to treat cancers harboring specific genomic biomarkers. However, there is a lack of clarity as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection.

PROVISIONAL CLINICAL OPINION Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease. Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.

Additional information is available at www.asco.org/assays-and-predictive-markers-guidelines.

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INTRODUCTION

Multigene panels for next-generation sequencing (NGS) are now US Food and Drug Administration (FDA)-approved in several tumor types.[1] In 2020 alone, 28 targeted therapies were approved by the FDA in patient populations defined by specific molecular biomarkers,[2] and many clinical trials now often use genomic sequencing to define patient eligibility. The population of patients who may benefit from genomic sequencing expanded with the approval of the anti–programmed death-1 (anti-PD1) antibody, pembrolizumab, in all mismatch repair deficient (dMMR) solid tumors[3] and with cancer site–agnostic approvals of pembrolizumab and larotrectinib in tumor mutation burden-high (TMB-H)[4] and neurotrophic tyrosine receptor kinase (*NTRK*) fusion–positive solid tumors,[4] respectively.

The interpretation of genomic sequencing data is complex. Not all tumors have alterations within therapeutically targetable or actionable genes, and not all alterations detected within a therapeutically actionable gene may confer sensitivity to genomic biomarker–linked therapies. Many alterations in actionable genes do not alter gene function, and many agents are only active against specific alterations. Basket trials enrolling multiple tumor types with the same or similar genomic alterations have shown that responses to the same genomic alteration may vary among tumor types.[5-7] Information from paired tumor and germline analyses and knowledge of co-occurring alterations, mutational heterogeneity, and subclonal mutations add to the complexity of interpreting genomic sequencing.[8]

ASCO has convened an expert panel to provide guidance on using genomic sequencing to inform treatment selection for patients with metastatic or advanced solid tumors. The neoadjuvant and adjuvant treatment settings were specifically excluded from the scope of the project as were patients with nonsolid tumors (eg, lymphoma). The panel recognizes that

ASSOCIATED CONTENT
Appendix
Data Supplement
Author affiliations and support information (if applicable) appear at the end of this article.
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THE BOTTOM LINE

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

Research Question

What are appropriate recommendations for genomic testing in metastatic or advanced cancer?

Target Population

Patients with metastatic or advanced solid tumors. Note that the neoadjuvant and adjuvant treatment settings are specifically excluded from this Provisional Clinical Opinion (PCO), as were nonsolid tumor cancers (eg, lymphoma).

Target Audience

Oncologists, pathologists, and other clinicians involved in deciding appropriate care for patients with metastatic or advanced cancer, as well as patients and caregivers.

Methods

Informal consensus is based on the review of existing approved testing and therapy combinations, available marker prevalence data, and expert opinion. As no formal systematic review of the clinical trial evidence was conducted for this PCO, and all the recommendations are based on the informal consensus of the Expert Panel, no recommendation-by-recommendation statement of evidence quality is provided. The strength of the recommendation is defined in the Appendices (Table A2, online only).

Provisional Clinical Opinion

Section 1: Framework for decision making on multigene panel–based genomic sequencing with disease-specific approved markers.

For what clinical scenarios are there biomarker-linked regulatory approvals for the treatment of specific genomic alterations?

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong).

When should multigene panel–based genomic testing be performed when there is only a single genomic biomarker or small numbers of genomic biomarkers linked to regulatory approvals of anticancer drugs?

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

What are other important considerations when ordering and interpreting genomic testing?

PCO 1.3. If the genomic sequencing results are used to inform clinical care, such testing must be performed in an appropriately certified laboratory (strength of recommendation: strong).

PCO 1.4. Clinical decision making should incorporate (1) the known or predicted impact of a specific genomic alteration on protein expression or function and (2) clinical data on the efficacy of targeting that genomic alteration with a particular agent (strength of recommendation: strong)

PCO 1.5. Germline testing for genetic alterations linked to approved therapies should be performed in patients with metastatic or advanced solid tumors considered for such treatment. It should not be limited by family history–based or clinical criteria used for familial risk assessment. Patients with pathogenic or likely pathogenic (P/LP) variants should be referred for genetic counseling for education about secondary cancer risks, possible inheritance of germline mutations among blood relatives, and the differences between germline and somatic mutations, if they did not receive pretest counseling (strength of recommendation: strong).

Qualifying statement

Germline testing and genetic counseling may still be needed in patients with personal or family histories suggestive of an inherited predisposition, even when no germline alterations are identified during tumor genomic sequencing using various sequencing panels.

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THE BOTTOM LINE (CONTINUED)

Section 2: Assessment of dMMR and/or microsatellite instability-high status and tumor mutational burden.
What is the role of multigene panel–based tumor genomic sequencing in dMMR and/or microsatellite instability-high testing?

PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel–based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

What is the role of multigene panel–based tumor genomic sequencing in TMB testing?

PCO 2.2. When TMB may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

Section 3: Testing for gene fusions and exon skipping variants.
When should patients be tested for fusions?

PCO 3.1. In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease (strength of recommendation: strong).

When should patients be tested for fusions outside of disease-specific approvals?

PCO 3.2.1. *NTRK* fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types (strength of recommendation: strong).

PCO 3.2.2. Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing (strength of recommendation: moderate).

When should patients be tested for exon skipping?

PCO 3.3. Testing for *MET* exon 14 skipping should be performed for patients with all types of non–small-cell lung cancer (NSCLC; strength of recommendation: strong).

Section 4: Framework for decision making on panel tests with no approved disease-specific markers.
When should multigene panel–based testing be used in diseases where there are no approved disease-specific biomarkers?

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

What evidence of actionability should be present for a clinician to recommend a therapy on the basis of panel testing in the absence of approved indications?

PCO 4.2. For tumors with actionable genomic alterations without approved genomic biomarker–linked targeted therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options (strength of recommendation: strong).

PCO 4.3. Off-label and off-study use of genomic biomarker–linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy (strength of recommendation: strong).

Section 5: Elements to consider while reviewing genomic testing results.
Provides detailed discussion of tumor-only testing versus matched tumor-normal testing, sequencing approaches, reporting of the tested genes, and how genomic alterations should be described.

Section 6: Additional topics.
Provides detailed discussion of testing circulating free DNA (cfDNA); testing for minimal residual disease; pharmacogenomic biomarkers; testing cancers of unknown primary (CUP); mutational signatures; homologous recombination deficiency (HRD) assays; the diagnostic and prognostic value of NGS; intertumoral and intratumoral heterogeneity (ITH); assessing genomic coalterations; and rationale for repeat genetic testing.

See the PCO for more details, including a discussion of health disparities and cost considerations.

Additional Resources

More information, including slide sets and clinical tools and resources, is available at www.asco.org/assays-and-predictive-markers-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this PCO. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

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genomic sequencing may also inform diagnosis or prognosis, but this provisional clinical opinion (PCO) is limited to its use in the metastatic or advanced setting to identify therapeutically actionable alterations and guide subsequent treatment decisions. For a comprehensive list of definitions of terms used in this PCO, see Table 1.

Genomic alterations that provide a selective advantage to cancer cells and promote cancer development, growth, and survival are called drivers, whereas alterations that are not currently considered essential for tumorigenesis are described as passengers. A genomic alteration is considered therapeutically actionable if its presence in a specific tumor type is predictive of possible response or resistance to a therapy (either approved by regulatory bodies or investigational).

Large-scale sequencing studies such as those of The Cancer Genome Atlas[9] and the International Cancer Genome Consortium[10] 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[11] and patterns of co-occurrence and mutual exclusivity of these alterations across different cancer types.[12] Numerous groups maintain knowledge bases[13] of actionable alterations and their associated therapeutic implications.[14-19] These knowledge bases incorporate overlapping frameworks to describe genetic alterations by their current level of clinical actionability. The list of genomic alterations considered clinically actionable is dynamic and must be continually updated as the clinical data that support their actionability evolves as new drugs become available.

ASCO has established a rigorous, evidence-based approach—the PCO—to offer a response to emerging data in clinical oncology. This PCO seeks to guide clinicians on the appropriate use of tumor genomic testing for patients with metastatic or advanced cancer, defining clinical scenarios where there is established evidence for antitumor efficacy of genomic biomarker–linked therapies as indicated by regulatory approval of agents on the basis of specific genomic alterations. The PCO will also guide clinicians when an alteration suggests the possibility of response to a particular targeted therapy, but there is no approved agent for the specific clinical setting. ASCO's PCOs reflect expert consensus on the basis of clinical evidence and literature available when they are written and are intended to assist clinicians in clinical decision making and identify questions and settings for further research. Precision oncology, the use of molecular biomarkers to aid in the diagnosis, prognosis, or treatment of cancer, is a rapidly evolving field. There are many ongoing trials that may affect the utility of specific markers in selected situations, while novel therapeutics may expand the utility of genomic sequencing by increasing alterations considered actionable.

METHODS

This PCO was developed by a multidisciplinary Expert Panel, including a patient representative and an ASCO guidelines staff member with health research methodology expertise. The members of the Expert Panel on somatic genomic testing in patients with metastatic or advanced cancer are listed in Appendix Table A1 (online only). The Expert Panel met via webinar and corresponded through e-mail. The authors contributed to the development of the PCO, provided critical review, and finalized the PCO statements. The statements were sent for an open-comment period of two weeks allowing the public to review and comment on the statements after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the statements. Members of the Expert Panel were responsible for reviewing the penultimate version of PCO, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guideline products are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. All funding for the administration of the project was provided by ASCO.

For all sections of this ASCO PCO, the recommendations were developed on the basis of the opinion and consensus of the convened Expert Panel and were informed using the following methodology:

Consideration of Existing Frameworks of Actionability

The expert panel leadership (F.M.-B., M.R., D.C., and A.J.) considered the literature for key frameworks and recommendations provided by key professional societies including ASCO, Association of Molecular Pathology, College of American Pathologists,[20] American Association for Cancer Research, and the European Society of Medical Oncology.[21] Next, publications of key knowledge bases currently operating in the space of clinical oncology were also identified and evaluated by surveying all members of the cross-institutional Expert Panel as to which knowledge bases their institutes use for clinical decision making. Knowledge bases were also identified by their participation in the Variant Interpretation Cancer Consortium project of the Global Alliance for Genomic Health.[19]

Approved Biomarker and Therapy Combinations for Section 1

The Memorial Sloan Kettering Cancer Center (MSK) OncoKB[15] and MD Anderson Precision Oncology Decision Support (PODS)[22] databases of biomarker and therapy information were selected as the key sources to identify agents that the FDA approves for use in patients with metastatic or advanced solid tumor cancers harboring specific biomarkers, including germline or somatic mutations with a search cutoff date of June 2, 2021 (Table 2). Both the OncoKB and PODS databases regularly assess the

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TABLE 1. Definitions of Commonly Used Terms in Precision Oncology

Term	Definition
Basket trial	A trial investigating the efficacy of a therapy within various tumor types (baskets) that all harbor the same type of genomic alteration(s).
Biomarker	A biologic marker that can be detected and measured by a validated test to diagnose or treat disease. Cancer biomarkers include, but are not limited to, genes, genomic alterations, RNA transcripts, proteins, post-translationally modified forms of proteins, and signatures of combinations of the aforementioned biomarkers.
ctDNA	Tumor DNA shed into the plasma. **ctDNA-based genomic testing:** NGS sequencing performed on isolated ctDNA for the detection of somatic variants.
CLIA-certified	The laboratory performing the test has met specific standards of proper laboratory management and testing procedures, as defined by CLIA.
Clonal	Tumor cells derived from the division of a common ancestral tumor cell. **Clonal mutations:** identical mutations found within clonal cells derived from a common ancestral tumor cell. **Subclonal mutations:** mutations arising in distinct subpopulations of tumor cells that generally give further fitness advantages, such as those acquired after treatment. **Clonal sweep:** as a new driver mutation occurs that induces clonal expansion, these clones replace the existing population of cells
CDx (nucleic acid–based test)	A specific test approved by the FDA to detect the presence of biomarkers that are prescriptive for a therapy.
Genomic alteration	Alteration of a gene from its original wild-type (normal) status through mutation, CNV, or rearrangement.
CNV	Deviation from the expected two copies of a gene within a cell. **Amplification:** An increase in the number of gene copies within a cell beyond the expected two copies. Amplifications may be focal and limited to a specific gene or part of a broader, typically lower level, chromosomal gain. **Deletion:** A decrease in the number of copies of a gene because of the loss of a single copy (heterozygous deletion) or both copies (homozygous deletion).
Fusion	A novel gene product that is created from two previously separate and independent genes. Gene fusions may arise from genomic rearrangements such as: **Chromosomal translocations:** the joining of DNA that previously resided within different chromosomal locations. **Interstitial deletions:** deletions that occur because of two breakpoints and the rejoining of the terminal end to the main chromosome. **Inversions:** a region of chromosomal DNA that is reversed. **Tandem duplications:** replication of the portion of the genomic sequence immediately adjacent to the duplication.
Mutation	A change in the nucleotide sequence encoding for a gene. Subtypes of mutations include but are not limited to: **Extension:** The normal stop codon is lost, and translation continues past this point. **Frameshift:** The insertion or deletion of nucleotides that shifts the reading frame so that novel amino acids are encoded and generally leads to premature truncation. **Indel:** The replacement of more than one nucleotide by other nucleotides These alterations are also referred to as deletion-insertions. **In-frame deletion:** The loss of nucleotides that occurs as a multiple of three so that the reading frame is maintained. **In-frame insertion:** The insertion of nucleotides that occurs as a multiple of three so that the reading frame is maintained. **Missense:** The substitution of the normal, wild-type amino acid for an alternate amino acid. **Silent/synonymous:** A change in the nucleotide sequence that does not alter the encoded amino acid. **SNV:** The substitution of one DNA nucleotide for another nucleotide. These may be somatic or germline and may result in synonymous or nonsynonymous mutations. **Splice site:** A mutation typically (but not always) involving one of the conserved nucleotides at the exon-intron boundary that disrupts or has the potential to disrupt RNA splicing. Splice-site mutations may result in exon skipping, intron retention, a frameshift in the coding frame, and/or premature protein truncation. **Truncating/nonsense:** A mutation that introduces a premature stop codon. The origin of the mutation may be either germline or somatic. **Germline:** Mutations (variants) that are present within the egg and sperm that united to form the zygote from which an individual develops and are thus heritable. Inherited germline mutations are present within both tumor and normal samples sequenced. **Somatic:** Mutations that only occur within somatic cells and not within reproductive cells. In cancer, somatic mutations are found within the tumor and not within normal, nontumor samples. DNA from both tumor and nontumor sites must be sequenced to definitively ascertain if a mutation is somatic. Mutations detected in cancer may be characterized by their functionality as: **Driver mutations:** Genomic alterations that provide a selective advantage to cancer cells, promoting cancer growth, development, and/or survival. **P/LP variants:** Variants known or suspected to be causative of disease **Passenger mutations:** Mutations that do not affect development, growth, or survival for the development, growth, or survival of cancer cells.

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TABLE 1. Definitions of Commonly Used Terms in Precision Oncology (continued)

Term	Definition
Mutational signature	Combination of mutations that are characteristic of a specific mutagenesis process leading to or contributing to the disease
SV	Large genomic alterations, generally defined as > 50 bp in size, that typically contain CNVs, translocations, inversions, deletions, and/or insertions. SVs may be balanced where no genomic material is lost or gained or unbalanced.
FISH	A laboratory assay using a DNA probe that typically is used to bind to target nucleotide sequences in the DNA of chromosomes, which may be within intact cells, commonly used to detect CNVs or gene fusions under a fluorescence microscope. **DNA probe:** a small DNA sequence with a fluorescent molecule attached to it that binds to the target DNA of interest and is used by FISH
Genomic instability	A high frequency of mutations within the tumor's genome, which may be caused by loss of expression or function of proteins that direct DNA repair and/or are involved in mitotic checkpoints.
GIS	A measurement of genomic instability that reflects HRD. The CDx for niraparib uses a GIS, which measures the presence of TAI, LOH, and LST, ie, large structural variants.
HRD	Cells that cannot efficiently repair damaged DNA via homologous recombination. The CDx for niraparib defines HRD-positive as detection of deleterious or suspected deleterious mutations within the *BRCA1* or *BRCA2* genes or a positive GIS.
LOH	The loss of the wild-type allele of a gene that was previously in a heterozygous state because of a germline or somatic mutation. LOH can occur at a single gene or as a genome-wide event because of defective DNA repair and be indicative of HRD.
MSI	The presence of nucleotide insertions or deletions at microsatellite loci, which indicates a dMMR that normally corrects these errors. **Microsatellites:** highly polymorphic, short, tandem repeats of DNA nucleotides distributed throughout the human genome, prone to replication errors. **MSI-H:** the presence of a high level of mutations at the sequenced microsatellite loci.
dMMR	The loss of function or expression of one or more of the components of the mismatch repair machinery (typically PMS2, MLH1, MSH2, and MSH6) that recognize mismatches within DNA as a result of injury and initiate the repair process.
Genomic biomarker–linked therapy	Therapy selected to target specific genomic alterations detected within the tumor. This includes targeted therapy designed to inhibit gain-of-function mutations in oncogenes, loss-of-function mutations in tumor suppressors, or other pathways sensitive to specific therapies because of the presence of a genomic alteration.
Genomic biomarker–selected trials	Clinical trials that specify the presence of specific genomic alterations as part of the eligibility criteria.
Hotspot	A recurrently altered amino acid within a gene detected in a disease. **Hotspot panels:** sequencing of select hotspot codons, and not the entire coding region, of the genes included on the panel.
IHC	A test that uses an antibody to detect the expression, or loss of expression, of a specific protein or mutated protein form.
Immunotherapy	A type of therapy that activates the body's immune system to target cancer cells.
Intertumoral heterogeneity	The evolution of tumor cells over time so that the genomic profile differs between the primary and the metastatic sites and/or among multiple metastatic lesions.
ITH	Within the same tumor, different populations of cells within distinct spatial regions have unique genomic alterations.
Knowledge base	A repository of expertly curated information. **Precision oncology knowledge base:** a repository containing expertly curated information regarding some or all of the following types of information: cancer genes, oncogenic mutations, genomic biomarker–linked therapies, genomically matched clinical trials, and levels of evidence for using a therapy within the context of a specific genomic alteration and tumor type.
MRD	The presence of tumor cells that have spread from the primary tumor but are not detectable by imaging.
Multigene panel	An NGS test that sequences a defined list of genes with at least 50 genes in total.
Neoantigens	Tumor-specific antigens that result from nonsynonymous somatic mutations and may trigger an immune response to cancer.
NGS	A technology that performs massively parallel DNA sequencing to detect genomic alterations.
Pathognomonic	Characteristic of a particular disease type.
Precision oncology	The use of molecular biomarkers to aid in the diagnosis, prognosis, or treatment of cancer.
Targeted therapy	A therapy that is designed to selectively inhibit cells that harbor a specific genomic alteration or protein.
Therapeutically actionable alteration	A genomic alteration predicted to confer sensitivity or resistance to an available therapy (FDA-approved or investigational). These alterations are typically functionally significant, in that they confer a change in the property of the encoded protein that promotes tumorigenesis, but may also affect drug binding and inhibition without affecting the activity of the protein.

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TABLE 1. Definitions of Commonly Used Terms in Precision Oncology (continued)

Term	Definition
Therapeutically actionable gene	Alterations of the gene that confer sensitivity or resistance to an available therapy (FDA-approved or investigational)
TMB	A measurement of the number of somatic mutations per megabase of DNA sequenced.
VAF	The fraction of alleles sequenced within a single tumor sample that contain the genomic alteration of interest.
Whole-exome sequencing	Sequencing of all of the protein-encoding regions (exons) of genes in the genome.
Whole-genome sequencing	Sequencing of the entire genome, including protein-coding and non–protein-coding regions.

Abbreviations: CDx, companion diagnostic; CLIA, Clinical Laboratory Improvement Amendments; CNV, copy-number variation; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization; GIS, genomic instability score; HRD, homologous recombination deficiency; IHC, immunohistochemistry; ITH, intratumoral heterogeneity; LOH, loss of heterozygosity; LST, large-scale state transitions; MRD, minimal residual disease; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; P/LP, pathogenic or likely pathogenic; SNV, single-nucleotide variation; SV, structural variant; TAI, telomeric allelic imbalance; TMB, tumor mutation burden; VAF, variant allele fraction.

Drugs@FDA website maintained by the FDA to ensure content is kept current. All procedures used to curate and maintain targeted-therapy data are publicly available.[23,24]

Additional Methods for Section 4

To estimate the tumor type–specific prevalence of standard care alterations in representative patient populations, the AACR Project GENIE[25] v9 patient cohort (n = 112,935) was analyzed using the open-source cBioPortal for Cancer Genomics (Fig 1).[26,27] The publicly available GENIE Cohort v9.0-public was used for the analysis in Figure 1 using the provided R-script to count the number of samples per major cancer type carrying the specified alteration. For each major driver alteration, sample IDs of the specified cancer type that carried an oncogenic or likely oncogenic alteration (as defined by the MSK knowledge base OncoKB[23]) were selected. Samples were then counted by cancer type (Fig 1). The percentage of the alteration was calculated as a fraction of the total number of cancer-specific samples.

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PCO and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methdology). All members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Panel did not disclose any relationships constituting a conflict under the Policy.

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TABLE 2. Selected Genetic Alterations Linked to FDA Approvals as of June 2021[a]

Genetic Alterations	Tumor Type	Targeted Therapeutics
FDA-approved treatments for specific genetic alterations in specific tumor types		
ALK fusions	NSCLC	Crizotinib, ceritinib, alectinib Brigatinib, lorlatinib
BRAF V600E	Melanoma	Dabrafenib, vemurafenib
		Dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib, trametinib
	Anaplastic thyroid cancer	Dabrafenib + trametinib
	NSCLC	Dabrafenib + trametinib
	CRC	Encorafenib + cetuximab
BRAF V600K	Melanoma	Dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib, trametinib
Deleterious or suspected[a] deleterious germline or somatic mutations in *BRCA1* and/or *BRCA2*	Ovarian cancer, fallopian tube cancer, peritoneal cancer	Olaparib,[a] rucaparib, niraparib[a]
	Prostate cancer	Olaparib,[a] rucaparib[a]
Deleterious or suspected deleterious germline mutations in *BRCA1* and/or *BRCA2*	Ovarian cancer, pancreatic adenocarcinoma	Olaparib
	HER2-negative breast cancer	Olaparib, talazoparib
Deleterious or suspected deleterious germline or somatic mutations in *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*	Prostate cancer	Olaparib
EGFR exon 19 deletions, L858R	NSCLC	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib
EGFR exon 20 insertions		Amivantamab
EGFR nonresistant mutations other than exon 19 deletions and L858R		Afatinib
EGFR T790M		Osimertinib
ERBB2 amplification	Breast cancer	Ado-trastuzumab emtansine, capecitabine + trastuzumab + tucatinib, neratinib, pertuzumab + trastuzumab, trastuzumab, trastuzumab deruxtecan
	Esophagogastric cancer	Trastuzumab
	Gastric cancer, gastroesophageal junction cancer	Trastuzumab deruxtecan
FGFR2 fusions	Bladder cancer	Erdafitinib
	Cholangiocarcinoma	Pemigatinib, infigratinib
FGFR3 fusions	Bladder cancer	Erdafitinib
Oncogenic mutations in *FGFR3*		
GIS-positive or HRD-positive	Ovarian cancer	Niraparib
KRAS G12C	NSCLC	Sotorasib
MET exon 14 skipping	NSCLC	Capmatinib, tepotinib
dMMR and/or MSI-H	CRC	Ipilimumab + nivolumab, nivolumab
	Endometrial cancer	Dostarlimab
PDGFRA exon 18 mutations	Gastrointestinal stromal tumor	Avapritinib
Oncogenic mutations in *PIK3CA*	HR+ HER2– breast cancer	Fulvestrant + alpelisib

(continued on following page)

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TABLE 2. Selected Genetic Alterations Linked to FDA Approvals as of June 2021[a] (continued)

Genetic Alterations	Tumor Type	Targeted Therapeutics
RET fusions	NSCLC, thyroid cancer	Pralsetinib, selpercatinib
Oncogenic mutations in *RET*	Medullary thyroid cancer	Pralsetinib, selpercatinib
ROS1 fusions	NSCLC	Crizotinib, entrectinib
FDA-approved treatments for specific biomarkers in tumor type–agnostic indications		
NTRK1 or *NTRK2* or *NTRK3* fusions	Solid tumors	Entrectinib, larotrectinib
MSI-H, TMB-H	Solid tumors	Pembrolizumab
FDA-approved treatments that are not biomarker-linked in solid tumors characterized by specified genetic alterations		
Oncogenic mutations in *NF1*	Neurofibroma	Selumetinib
COL1A1-PDGFB fusions	Dermatofibrosarcoma protuberans	Imatinib
SMARCB1 deletions	Epithelioid sarcoma	Tazemetostat
Oncogenic mutations in *TSC1* and *TSC2*	SEGA	Everolimus
KIT exon 11, 9, 13, 14, and 17 mutations	Gastrointestinal stromal tumor	Imatinib, sunitinib (postprogression on imatinib), regorafenib (postprogression on imatinib and sunitinib), ripretinib (postprogression on ≥ 3 kinase inhibitors including imatinib)
FDA-listed genetic alterations contraindicated for specific treatments		
KRAS and/or *NRAS* exon 2, 3, and 4 mutations	CRC	Panitumumab, cetuximab
NTRK1 and *NTRK3* known acquired resistance mutations (eg, *NTRK1* G595R and G667C; *NTRK3* F617L, G623R, and G696A)	Solid tumors	Entrectinib, larotrectinib
FDA-approved combination treatments with nontargeted therapies for specific genetic alterations		
BRAF V600	Melanoma	Atezolizumab + cobimetinib + vemurafenib
Deleterious germline or somatic mutations in *BRCA1* and/or *BRCA2*	Fallopian tube, ovarian, primary peritoneal carcinoma	Bevacizumab + olaparib
EGFR exon 19 deletions, L858R	NSCLC	Erlotinib + ramucirumab
ERBB2 amplification	Breast cancer	Hyaluronidase-zzxf/pertuzumab/trastuzumab + chemotherapy (docetaxel)
		Trastuzumab + pertuzumab + (docetaxel) chemotherapy
		Trastuzumab + (docetaxel + carboplatin) or (doxorubicin + cyclophosphamide + paclitaxel or docetaxel) or paclitaxel
		Lapatinib + capecitabine or letrozole
		Neratinib + capecitabine
		Margetuximab + chemotherapy
	Esophagogastric cancer	Trastuzumab + cisplatin + capecitabine or fluorouracil

Abbreviations: CRC, colorectal cancer; dMMR, mismatch repair deficiency; FDA, US Food and Drug Administration; GIS, genomic instability score; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; NSCLC, non–small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; SEGA, subependymal giant-cell astrocytomas; TMB-H, tumor mutation burden-high.

[a]The table summarizes FDA approvals at data cutoff of June 2, 2021. Precision oncology is a rapidly evolving field, and this table is a static snapshot of the approved targeted therapies at a specific point in time and therefore is expected to be outdated beyond the date it was published. The table is being included to provide examples of approved agents linked to genomic biomarkers or in disease with common genomic drivers.

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	No.	ALK Fusions (%)	BRAF V600 (%)	BRCA1 Drivers (%)	BRCA2 Drivers (%)	EGFR Drivers (%)	ERBB2 Amplification (%)	EZH2 Drivers (%)	FGFR2 Fusions (%)	FGFR3 Drivers (%)	FGFR3 Fusions (%)	IDH1 Drivers (%)	IDH2 Drivers (%)	KIT Drivers (%)	KRAS G12C (%)	NTRK1/2/3 Fusions (%)	PDGFRA Drivers (%)	PIK3CA Drivers (%)	RET Fusions (%)	RET Drivers (%)	ROS1 Fusions (%)
Bladder Cancer	2,718	0.1	0.1	1.3	2.2	2.5	4.3	0.6	0.1	21.9	2.0	0.2	0.1	0.1	0.4	0.1		19.4	0.1	0.1	
Breast Cancer	12,724		0.1	1.3	1.9	1.3	10.4	0.3	0.2	0.1	0.1	0.1		0.3	0.1	0.2	0.2	38.1	0.1	0.1	0.1
Cervical Cancer	659			1.1	0.9	0.2	2.1	0.3		0.9	0.6				0.5			27.6			0.2
Cholangiocarcinoma	1,361		1.5	0.7	2.0	1.1	2.2	0.4	7.3		0.4	14.5	3.5	0.1	1.0	0.2	0.3	4.5	0.1	0.1	0.2
Colorectal Cancer	11,019	0.1	7.6	0.9	2.2	1.4	1.4	0.2	0.1	0.1		0.5	0.1	0.2	2.9	0.2	0.1	17.8	0.1	0.2	
Cutaneous Melanoma	1,666	0.1	31.7	0.9	1.4	0.9		1.1		0.1		2.6	0.3	3.9		0.2	0.8	2.2		0.1	0.1
Endometrial Cancer	3,400		0.1	1.4	4.1	1.2	3.5	1.1	0.1	0.1	0.3	0.3		0.1	1.2	0.1	0.3	48.5		0.3	
Esophagogastric Cancer	3,075		0.1	0.8	1.7	4.8	10.8	0.5	0.6	0.1	0.1		0.1	0.1	0.3	0.2	0.1	7.8	0.3	0.2	
Gallbladder Cancer	223			1.8	3.6	3.1	5.4				0.4				0.9	1.8		10.8	0.9		
Gastrointestinal Stromal Tumor	1,118	0.1	0.4		0.1	0.2		0.1				0.4	0.1	78.9		0.1	10.3	1.3		0.1	
Head and Neck Cancer	1,680	0.1	0.1	1.1	1.0	4.5	0.7	0.2	0.1	1.7	0.1	0.1	0.5	0.5	0.2	0.1	0.4	18.4	0.1	0.1	
Non-Small Cell Lung Cancer	16,669	2.0	1.3	0.6	0.9	26.9	0.8	0.3	0.1	0.1	0.1	0.3	0.1	0.4	11.3	0.1	0.3	5.2	1.0	0.1	0.8
Ovarian Cancer	4,208	0.1	0.9	5.7	2.9	0.4	1.7	0.3	0.1		0.1		0.1	0.1	0.4		0.1	9.9		0.1	0.1
Pancreatic Cancer	4,411	0.2	0.6	0.6	2.4	0.2	0.7	0.2	0.2			0.2			1.1	0.2		2.1		0.1	0.2
Prostate Cancer	4,010			0.5	5.0	0.4	0.1	0.3			0.1	0.4		0.1		0.2	0.1	3.8		0.1	0.1
Renal Cell Carcinoma	1,837	0.2		0.4	0.6	0.3		0.3		0.1				0.2	0.1		0.2	2.9	0.1		
Salivary Gland Cancer	791	0.8	0.4	0.6	0.5	0.5	4.6		0.1			0.5	0.1	1.4	0.1	3.4	1.3	8.7	0.1		0.3
Thyroid Cancer	1,614	0.4	38.0	0.3	0.9	0.2		0.1	0.1	0.1		0.1		0.2	0.2	1.9	0.1	3.7	5.1	8.1	

FIG 1. Frequency of known and standard care drivers in major cancer types in the American Association for Cancer Research GENIE data set. CRC, colorectal cancer; NSCLC, non–small-cell lung cancer.

ASCO PCO

NOTE: All the recommendations are based on the informal consensus of the Expert Panel.

Section 1: Framework for Decision Making on Multigene Panel–Based Genomic Sequencing With Disease-Specific Approved Markers.

Clinical question

- For what clinical scenarios are there biomarker-linked regulatory approvals for the treatment of specific genomic alterations?

PCO 1.1.

Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong).

Clinical interpretation and discussion

Genomic testing should be performed in patients with metastatic or advanced solid tumors if there are genomic biomarker–linked therapies for that disease approved by the relevant regulatory agency (Table 2). For example, genomic testing should be performed in patients with metastatic melanoma to screen for *BRAF* V600E mutations because RAF and MEK inhibitors are FDA-approved in this disease.[28] The presence of a genomic alteration predictive of response to an approved agent is not sufficient to determine clinical treatment strategy. The optimal treatment choice for a patient is a clinical decision that takes account of the availability, effectiveness, and side-effect profiles of other treatment options as well as patient-specific factors (eg, comorbidities) and patient preference. For instance, immunotherapy is usually given as first-line therapy in patients with melanoma rather than targeted therapy with RAF and MEK combinations, even when there is a BRAF V600E mutation.[29]

Genomic testing should also be performed in patients with metastatic or advanced solid tumors if there are clearly defined resistance markers for a treatment being considered. For example, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab or panitumumab) are ineffective in *KRAS*-mutant colorectal cancer (CRC).[30-34] Patient performance status, comorbidities, and cancer stage should also be considered when determining the appropriateness of genomic sequencing for the potential use of genomic biomarker–linked therapies. Inherent to genomic sequencing is the time taken for patient consent, laboratory processing, and communication of sequencing results necessitating patients to have adequate performance status or anticipated life expectancy. This PCO has been

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written to address the role of genomic testing in metastatic or advanced (inoperable locally advanced or locally recurrent) solid tumors. Although virtually all genomic biomarker–linked therapies with regulatory approval have been approved in the late-stage setting, a select number have additional approvals as adjuvant therapy. Examples include the 2018 FDA approval of dabrafenib plus trametinib for adjuvant treatment of *BRAF* V600E or K mutant melanoma[35] and the 2021 FDA approval of osimertinib for adjuvant therapy after tumor resection in NSCLC bearing *EGFR* exon 19 deletions or exon 21 L858R mutations.[36] The panel anticipates that there will be expanding roles for genomic biomarker–linked therapies in the neoadjuvant and adjuvant settings, with an increasing utilization of genomic testing in patients with earlier-stage cancers.

Clinical question

- When should multigene panel–based genomic testing be performed when there is only a single gene biomarker or small numbers of genomic biomarkers linked to regulatory approvals of anticancer drugs?

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

Clinical interpretation and discussion

If more than one biomarker is linked to approved genomic biomarker–linked therapies within the patient's tumor type, multigene panel–based testing should be considered part of the standard evaluation. Although some targeted therapies are associated with a non–NGS-based companion diagnostic (CDx; eg, brigatinib is associated with a fluorescent in situ hybridization [FISH] CDx for the detection of *ALK* rearrangements), multigene panel–based testing provides the most efficient use of limited tumor biopsy tissue, enabling simultaneous testing for multiple approved therapeutic targets.

Since the approval of three tumor agnostic biomarkers (mismatch repair deficient [dMMR] and/or microsatellite instability-high [MSI-H], TMB-H, and *NTRK* fusions), multigene sequencing is preferred for patients with metastatic solid tumors even if only a single approved genomic biomarker–linked treatment is available. Limited testing (eg, single-gene or hotspot testing) cannot accurately determine dMMR and/or MSI-H or TMB status.[37] dMMR refers to a deficiency in the DNA mismatch repair (MMR) process and is not a biomarker per se. Rather, phenotypic evidence of tumor dMMR is measurable by MSI status composed of polymerase chain reaction (PCR)-based assessment of changes in the DNA of microsatellite loci or by performing immunohistochemistry (IHC) to detect loss of any of four commonly inactivated MMR proteins (MSH2, MSH6, PMS2, and MLH1). Inclusion of the term dMMR in the FDA label for pembrolizumab refers to the determination of dMMR by MMR protein loss using IHC. Although both dMMR and MSI testing may be performed for a patient sample, differences in the nature of the assay (IHC *v* PCR) requires separate testing, which is inefficient and may not be possible if tissue is limited. Although approximately 50% of patients may carry a potentially actionable alteration if dMMR and/or MSI-H and TMB-H status is included in actionable alterations,[8,37] the decision to perform multigene panel–based testing must consider the likelihood of detecting a potentially actionable biomarker within the patient's tumor type (Fig 1). Therefore, the choice between multigene panel–based sequencing versus limited testing should be individualized, considering the relative costs and availability of tissue, or suitability of clinical trials for a particular patient.

Multigene testing should be performed for efficiency and tissue preservation if there is more than one biomarker-linked therapy for a patient's disease. Multigene panel–based testing may identify genomic alterations that suggest possible benefits from an agent not yet approved for the patient's specific clinical circumstance. Whenever possible, off-label genomic biomarker–linked treatments should be delivered in the context of a clinical trial because alterations that may be predictive of response in one tumor type may not be predictive in another.

Clinical question

- What are other important considerations when ordering and interpreting genomic testing?

PCO 1.3. If genomic sequencing results are to be used to inform clinical care, such testing must be performed in an appropriately certified laboratory (strength of recommendation: strong).

Clinical interpretation and discussion

In the United States, genomic sequencing must be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.[38] Cross-institutional studies have shown high concordance in mutations reported among different CLIA-certified laboratories in both the solid tumor[39] and hematologic malignancy[40] settings. Other studies have shown equivalent performance between laboratory-developed tests and FDA-approved commercial kits or assays.[41,42] Concordance among CLIA laboratories using different assays is approximately 95%, signifying that various qualified laboratory sites assessing similar genomic regions are likely to identify the same variants. However, discrepancies between laboratories may persist, particularly for copy-number variations, structural variants, and mutational signatures. Thus, confirmation of findings using

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orthogonal methods (eg, FISH or microarray hybridization analysis) may be appropriate in certain situations such as detection of *MET* amplification in NSCLC, which indicates the use of crizotinib.

Although concordance is high in analyzed regions, laboratories may differ in the genes they analyze and the gene regions evaluated. For example, for oncogenes that are typically activated in cancer and characterized by the presence of a select number of recurrently altered amino acids (so-called hotspots),[43,44] laboratories may choose to either sequence only those hotspots or the entire oncogene. By contrast, tumor suppressor genes may be inactivated by missense and truncating mutations across most of the gene. Laboratories may choose to sequence the entire tumor suppressor gene or a limited number of regions. Thus, limited testing may not reveal all potentially actionable alterations. In addition to DNA-based NGS, other assay types are available to assess single-nucleotide variants, copy-number variation, fusions, insertion-deletions, larger structural variants, and MSI,[45] such as IHC, FISH, microarray hybridization analysis, RNA-based sequencing, or PCR. However, there are limitations and caveats to consider for each test type that varies by biomarker and tumor type.[46-50] Clinicians need to consider the assay's characteristics and scope when interpreting genomic sequencing reports. For example, assays designed only to detect single-nucleotide variants, whether by NGS or alternative methods, will not identify potentially actionable fusions, such as *ALK* fusions that occur in NSCLC.

Different laboratories often use different approaches to interpret sequencing data.[51] For instance, some laboratories sequence only the tumor sample, relying on bioinformatic pipelines to determine cancer-specific changes by comparing the tumor sequence to a database that contains an averaged normal human genome. Other laboratories may require a patient-matched normal sample with bioinformatic pipelines directly comparing the patient tumor and normal DNA sequences. Changes in both the normal and tumor samples may be filtered out as incidental germline variants (substraction of normal), or if clinically significant, reported separately (with appropriate consent). Importantly, in two independent retrospective patient cohort studies from the University of Michigan[52] and MSK,[53] where patients had matched tumor with normal sample sequencing performed, P/LP germline variants were found in 15.8% (n = 1,015) and 17% (n = 11,947) of the cohorts, respectively, with 5% and 8% of patients carrying P/LP therapeutically actionable germline variants.

Since many, but not all, FDA-approved agents were developed with a CDx test, the information about drug efficacy from clinical trials may be limited to select genomic alterations identified with the CDx. In some cases, the language in the FDA indication may be broader. For example, the FDA indication of alpelisib indicates treatment for *PIK3CA*-mutated breast cancers, and erdafitinib is indicated for susceptible *FGFR3* or *FGFR2* genetic alterations. Yet, only select alterations within these genes (11 hotspots in *PIK3CA*, four missense mutations, and one fusion partner with *FGFR3*) are included in the associated CDx tests. Caution is needed before extrapolating the significance of the clinical trial's results to other alterations.

PCO 1.4. Clinical decision making should incorporate (1) the known or predicted impact of a specific genomic alteration on protein expression or function and (2) clinical data on the efficacy of targeting that genomic alteration with a particular agent (strength of recommendation: strong).

Clinical interpretation and discussion

Consider the functional significance of an identified genomic alteration when making clinical decisions. Clinicians should not only review the list of genomic alterations in tumor reports, but also should read what is sometimes referred to as the functional annotations, descriptions of what is known about the effect of a specific alteration on gene function and therapeutic sensitivity.

Most alterations detected by genomic sequencing are passengers with no impact on cancer development.[54] A smaller fraction of alterations are drivers.[55] A subset of driver mutations potentially predict response to targeted therapies and are considered therapeutically actionable biomarkers.[8] Most therapeutically actionable biomarkers (Table 2) constitutively activate a kinase directly (mutation in the kinase domain of an oncogene or its fusion with a portion of another gene) or indirectly (inactivation of a tumor suppressor gene that regulates the function of a kinase) mechanisms, and the targeted agent is a gene-specific kinase inhibitor. However, some actionable genes are tumor suppressors. Inactivating mutations or deletions may lead to changes in the cancer cell that create vulnerabilities that can be targeted. For example, the activity of poly(ADP-ribose) polymerase (PARP) inhibitors in *BRCA*-mutant cancers arises through a synthetic lethal mechanism whereby the combined inhibition of PARP activity with loss of BRCA function results in cancer cell death.[56,57]

A major challenge in precision oncology is determining whether a specific genomic alteration in a potentially targetable gene is a passenger, actionable driver, or non-actionable driver. Not all alterations (variants, copy-number changes, or fusions) in actionable genes confer sensitivity to available drugs. However, some drug approvals refer to specific alterations of genes on the basis of clinical studies performed only in tumors with that alteration (eg, BRAF inhibitors such as vemurafenib and dabrafenib in multiple indications specify *BRAF* V600E and not other alterations within the *BRAF* gene, Table 2). Although known differences in drug sensitivities among different gene variants may have been established through robust preclinical studies, the clinical efficacy for other alterations in the same gene may remain unknown. For example, although *BRAF* V600E in melanoma has been established to be sensitizing

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to BRAF inhibitors vemurafenib or dabrafenib,[58,59] the mutation *BRAF* K601E is resistant to the same RAF inhibitors.[60] Preclinical studies have culminated in classifying activating *BRAF* variants into three classes of mutations on the basis of their biochemical properties.[61]

Other regulatory approvals are broader in scope. For example, olaparib is approved for patients with breast cancer and deleterious or suspected deleterious germline mutations in *BRCA1* or *BRCA2*[62]; erdafatinib is approved for urothelial cancers with susceptible *FGFR2* and *FGFR3* genetic alterations.[63] In these examples, the clinician must be confident that an identified genomic alteration is deleterious or suspected deleterious or susceptible before recommending the treatment. In this context, using knowledge bases that have collated information about the functional significance of different mutations in a specific gene emerge as important clinical decision support tools.

PCO 1.5.

Germline testing for genetic alterations linked to approved therapies should be performed in patients with metastatic or advanced solid tumors considered for such treatment. It should not be limited by family history–based or clinical criteria used for familial risk assessment. Patients with P/LP variants should be referred for genetic counseling for education about secondary cancer risks, possible inheritance of germline mutations among blood relatives, and the differences between germline and somatic mutations, if they did not receive pretest counseling (strength of recommendation: strong).

Qualifying statement. Germline testing and genetic counseling may still be needed in patients with personal or family histories suggestive of an inherited predisposition, even when no germline alterations are identified during tumor genomic sequencing using various sequencing panels.

Clinical interpretation and discussion

Certain agents (eg, PARP inhibitors) are approved for patients with inherited P/LP variants in specific genes (Table 2). Clinical criteria for identifying patients carrying such variants were developed before there were treatment implications. These criteria are imperfectly sensitive for detecting P/LP variants, as demonstrated by identifying P/LP alterations in patients not previously identified by routine clinical practice in several studies.[52,64,65] Therefore, these clinical criteria should not restrict germline testing in patients who may benefit from these agents. Multigene germline testing (as opposed to more limited testing) may identify unexpected P/LP variants that have implications for the patient and/or family cancer screening and treatment (eg, P/LP variants in MMR genes).[53] Patients who are found to have P/LP germline alterations during genomic testing should be offered genetic counseling. Tumor genomic sequencing is not a substitute for dedicated germline testing as germline variants may be missed on tumor sequencing.[66] This may occur for several reasons (eg, inadequate coverage at the site of the P/LP, loss of the mutant allele, or structural variant that is not identified on limited testing). Therefore, patients with personal or family histories suggestive of an inherited predisposition should be referred for genetic counseling even if no suggestive variant is identified on tumor sequencing. ASCO has initiated a new guideline on germline genetic testing, including genetic counseling, which is planned for completion by Spring 2023.

Section 2: Assessment of dMMR and/or MSI-H Status and TMB

Clinical question

- What is the role of multigene panel–based tumor genomic sequencing in dMMR and/or MSI-H testing?

PCO 2.1. dMMR should be evaluated in patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel–based testing to assess MSI. Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

Clinical interpretation and discussion

In 2017, the FDA approved the anti-PD1 antibody pembrolizumab for patients with unresectable or metastatic dMMR and/or MSI-H solid cancers—the first tissue and/or site-agnostic drug approval. This approval was based on the results across five multicohort, multicenter, single-arm clinical trials (KEYNOTE-061, -164, -012, -028, and -158)[67-71] in 149 patients prospectively tested for dMMR and/or MSI-H using either PCR- or IHC-based testing. Although most patients across these five trials had CRC and experienced an objective response rate (ORR) of 36% (95% CI, 26 to 46), an ORR of 46% (95% CI, 33 to 59) was also observed across 14 other cancer types (eg, endometrial, gastric, and pancreatic cancers).[72]

MMR is the process of detecting and repairing mistakes of nucleotide incorporation as DNA is synthesized during DNA replication or recombination. In cancer, the cause of deficiencies in MMR proteins is most often inactivation of one of four genes (MLH1, MSH2, MSH6, and PMS2) encoding the principal proteins that recognize mismatches and initiate the repair process,[73-77] the loss of which results in widespread cancer cell genomic instability presenting as MSI or elevated spontaneous mutation rates associated with high TMB.

MSI refers to errors in DNA replication of short repetitive sequences of nucleotides, termed microsatellites, that are highly polymorphic in repeat number within the human population.[78-80] Changes in the lengths of microsatellites are convenient biomarkers to assess dMMR since these sequences are particularly prone to additions or deletions of repeat units in the absence of effective MMR. Conventionally, PCR amplification across a series of five designated

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microsatellites (two mononucleotide and three dinucleotide repeats) in DNA from a patient's tumor and a matched benign sample, followed by electrophoresis of the PCR products, is used to identify tumors with dMMR.[81-83] According to the National Cancer Institute–issued guidelines of 1997, alterations in the size of two or more of these microsatellites is termed microsatellite high, or MSI-H.[84] MSI-H, in turn, correlates with increased mutations in the cancer (ie, TMB), increased translation of mutated peptides, and increased presentation of immunogenic neoantigens, with better response to immune checkpoint therapy.

IHC has also been used to directly evaluate tissues for the loss of one or more of the four most clinically relevant MMR proteins.[85] In general, the results of IHC and PCR-based MSI testing agree,[86] although some mutated proteins retain immunoreactivity, and dMMR (and MSI) may occasionally arise from mutations in genes other than the four mentioned previously.

Larger NGS panels may include numerous microsatellites used to identify MSI, and algorithms have recently been developed to detect MMR deficiency without comparing microsatellite lengths in the patient's normal tissue. Validation against MSI PCR and MMR IHC assays showed 99.4% concordance.[87] Furthermore, NGS panels that include MMR genes may permit the detection of mutations of these genes to confirm the likelihood of dMMR. Moreover, if germline DNA is also analyzed, NGS panels can identify Lynch syndrome caused by inherited heterozygous mutations in one of the MMR genes. The presence of a mutation in an MMR gene does not by itself prove that a cancer is MSI-H or dMMR since both copies of the MMR gene must be inactivated to generate the dMMR phenotype.

Clinical question

- What is the role of multigene panel–based tumor genomic sequencing in TMB testing?

PCO 2.2. When TMB may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

Clinical interpretation and discussion

In 2020, pembrolizumab was approved in its second tumor agnostic indication for the treatment of adult and pediatric patients with unresectable or metastatic, high TMB (defined as $\geq$ 10 mutations per Mb) solid tumors on the basis of the single-arm KEYNOTE-158 study of 129 patients across 10 different cancer types that demonstrated a 29% ORR in the high TMB cohort not fully accounted for by MSI status.[88] Notably, not all MSI-H tumors have high TMB.[89]

TMB refers to the number of somatic mutations per megabase of DNA sequenced and often varies from tumor type to tumor type.[90] Melanoma and NSCLC cancers, exposed to external mutagens such as ultraviolet light and tobacco smoking, respectively, are typically associated with high TMB.[91] They were the first two cancer types in which the anti-PD1 therapy pembrolizumab was approved because of 33%-34% and 45% response rates in melanoma[92] and NSCLC,[93] respectively. Since then, high TMB has predicted response to immune checkpoint blockade inhibitors in several studies.[94-98]

The benchmark method to measure TMB is whole-exome sequencing that interrogates approximately 22,000 genes or approximately 30 Mb of coding regions of the genome (ie, approximately 1% of the genome), but clinical whole-exome sequencing is not commonly used. Instead, multigene panel–based sequencing with fewer genes (324-595 genes in currently available panels) and coding regions (0.8-2.4 Mb) is more often used to estimate TMB.[90,99-107] Panel sequencing–derived measurements of TMB can vary significantly from panel to panel because of variations in the size of genomic territory interrogated by the assay (known as the assay coverage). There are ongoing large-scale efforts, such as the Friends of Cancer Research TMB harmonization project, to generate consistent guidelines for TMB reporting in larger genomic panels.[108]

Section 3: Testing for Gene Fusions and Exon Skipping Variants

Clinical question

- When should patients be tested for fusions?

PCO 3.1. In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease (strength of recommendation: strong).

Clinical interpretation and discussion

The terms rearrangements and fusions are often used synonymously in the clinical and scientific communities. These terms refer to a DNA-level rearrangement resulting from a chromosomal translocation, interstitial deletion, tandem duplication, or inversion event linking two individual genes normally separated in the genome and that gives rise to a protein-level chimeric fusion product. Using cytogenetic methods, fusions were initially described as recurrent, characteristic molecular features in hematologic malignancies (*BCR-ABL1* in chronic myelogenous leukemia[109,110] and *PML-RARA* in acute promyelocytic leukemia[111]) and sarcomas (*EWSR1-FLI1* in Ewing's Sarcoma[112] and *SS18-SSX1* in synovial sarcomas[113]). Later, fusions were also found in carcinomas (*PAX8-PPARG1* fusion in follicular thyroid cancer[114] and *TMPRSS2* fusions in prostate cancer[115]).

Fusions involving kinases first emerged as significant, clinically relevant treatment targets with the discovery that the *BCR-ABL1* encoded fusion, which is pathognomonic to chronic myeloid leukemia,[109,116] and targetable using the kinase inhibitor imatinib.[117] Overall, approximately 3% of The Cancer Genome Atlas patient solid tumor samples

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contain fusion events involving an intact kinase domain,[118] and kinase fusions most commonly arise in thyroid cancer.[118,119]

Despite their relative rarity, the treatment of cancers harboring kinase fusion events can be highly effective. In the setting of lung cancer, *ALK* and *ROS1* fusions are observed in approximately 2% and 0.8% of NSCLC, respectively (Fig 1). Clinical trials that led to the FDA approval of crizotinib in *ALK* and *ROS1* fusion–positive patients reported a 65% and 72% ORR, respectively.[120,121] In addition to *ALK* and *ROS1* fusions in NSCLC, RET targeted agents such as selpercatinib are FDA-approved[122] for *RET* fusion–positive lung and thyroid cancers. Also, multiple pan-FGFR inhibitors are approved for bladder cancer and cholangiocarcinoma. Specifically, erdafitinib[63] is FDA-approved for *FGFR* fusion–positive bladder cancer (*FGFR3* approximately 2%), whereas pemigatinib[123] and infigratinib[124] are FDA-approved for *FGFR* fusion–positive cholangiocarcinoma (*FGFR2* approximately 7%).

Clinical question

- When should patients be tested for fusions outside of disease-specific approvals?

PCO 3.2.1. *NTRK* fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types (strength of recommendation: strong).

PCO 3.2.2. Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing (strength of recommendation: moderate).

Clinical interpretation and discussion

NTRK gene fusions involving *NTRK1*, *2*, or *3* (encoding neurotrophin receptors TRKA, TRKB, and TRKC, respectively) are oncogenic drivers. Like the oncogenic fusions observed with the *ALK* and *ROS1* genes, *NTRK* gene fusions arise when the 3′ portion of the *NTRK* gene containing the catalytic tyrosine kinase domain forms an in-frame fusion to the 5′ portion of a partner gene that constitutively activates the kinase domain. Treatment of patients with *NTRK* fusion–positive solid tumors, using the first-generation TRK inhibitors larotrectinib or entrectinib, was associated with high response rates regardless of histology.[125,126] Specifically, for larotrectinib, an ORR of 75% (95% CI, 61 to 85) across 17 tumor types and for entrectinib, an ORR of 57.4% (95% CI, 43.2 to 70.8) across 10 tumor types led to tumor-agnostic FDA approvals. The prevalence of *NTRK* fusions in cancer is relatively low, and in a single-institution study, 74 (0.28%) of 26,312 patients' tumors were found to have *NTRK* fusions.[127] Although *NTRK* fusions are actionable in all solid tumors, the prevalence of *NTRK* fusions varies widely by disease. Thus, the pretest probability of fusion detection may be considered while pursuing *NTRK* fusion testing independent of multigene panel genomic sequencing.[128] *NTRK* fusions are relatively common in select rare solid tumors, including secretory breast cancer,[129] mammary analogue secretory carcinoma of the salivary gland, congenital infantile fibrosarcoma, and congenital mesoblastic nephroma.[128] For these diseases, *NTRK* fusion testing should be routinely performed. *NTRK* fusions are found less commonly, but at clinically relevant frequencies (> 1%), in several other tumor types, including inflammatory myofibroblastic tumor (17.7%)[130] and thyroid cancer (2.3%).[130] Although fusions are rare in CRC (0.3%), many *NTRK* fusion CRCs are also dMMR and/or MSI-H. Thus, patients with *RAS* or *RAF* WT, dMMR, and/or MSI-H may be enriched for *NTRK* fusions.[131,132]

RNA-based fusion testing (see 'Additional considerations in fusion testing' section for discussion of RNA-based testing) is recommended for patients with no other oncogenic driver detected by DNA, multigene panel–based genomic sequencing (particularly those with lung cancer, sarcoma, or rare tumor types specified earlier), and patients without other standard care options. Emerging data suggest that NSCLC fusions involving actionable genes, such as *BRAF* and *FGFR3*, as well as novel fusion partners (eg, *NRG1*), may represent candidate biomarkers predicting response to specific targeted agents or combination therapies.[133-135]

Clinical question

- When should patients be tested for exon skipping?

PCO 3.3. Testing for *MET* exon 14 skipping should be performed for patients with all types of NSCLC (strength of recommendation: strong).

Clinical interpretation and discussion

The *MET* gene encodes a receptor tyrosine kinase that induces downstream signaling through RAS or RAF and phosphoinositide 3-kinase pathways. *MET* abnormalities because of splice-site alterations can lead to loss of exon 14 from the *MET* transcript. These splice-site alterations can result from point mutations, insertions, or deletions that disrupt the donor or acceptor splice site for *MET* precursor RNA splicing or from whole-exon deletions. As a result of exon 14 skipping, the MET juxtamembrane domain containing a binding site (Y1003) for E3 ubiquitin ligase Casitas B-Lineage Lymphoma (CBL) is deleted, impairing MET ubiquitination and increasing MET protein stability and MET signaling. *MET* exon 14 skipping is an actionable alteration in NSCLC, with FDA approvals for the MET inhibitors capmatinib and tepotinib. *MET* exon skipping alterations occur in 2.7% of patients with lung cancer and often occur in elderly patients.[136] They are enriched in adenosquamous histologic subtype and sarcomatoid histology.[136]

Additional considerations in fusion testing. Until recently, fusions were detected through approaches other than NGS. FISH, a highly sensitive detection method for many gene

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fusions, and quantitative real-time PCR have been used, but typically only test for a single-fusion gene and cannot identify novel fusions, small deletion-associated fusions, tandem duplications, or complex rearrangements. Many multigene, DNA-based NGS panels now also detect selected fusions. In these targeted hybridization capture–based NGS assays, introns of specific genes involved in actionable fusions can be sequenced with probes tiled across breakpoint regions to capture and detect these alterations.[137] However, DNA-based NGS assays have limitations, including restrictions in detecting certain fusion genes, selected fusion partners, and an inability to determine whether a functional fusion is expressed when there is a novel fusion partner. RNA-based approaches avoid the challenges of sequencing through introns required by DNA methods and are superior, in general, for detecting expressed fusions. However, RNA-based fusion assays do not describe the exact breakpoints for fusions, which may be important for some investigational applications, and cannot detect fusions that encode loss of expression. RNA-based methods for detecting gene fusions include multiplex PCR with panels of real-time PCR primer sets as well as capture-based approaches for targeted or whole-transcriptome sequencing.

Although incorporating testing for *NTRK* and other actionable fusions into NGS panels may be the most streamlined approach, this may not be feasible in all settings. Notably, pan-Trk IHC has been used as an alternate screening platform for *NTRK* fusions[138] and may be considered for screening in solid tumors with a low prevalence of *NTRK* fusions. However, some studies have reported limited sensitivity with this method, particularly for *NTRK3* fusions[130,137,139] or low expression of fusion genes identified.[140] Sensitivity and specificity vary with the tumor type and antibody used. Algorithms have been proposed considering these variables and the prevalence of *NTRK* fusion and NTRK protein expression within specific tumor types.[141]

Section 4: Framework for Decision Making on Panel Tests With No Approved Disease-Specific Markers

Clinical question

- When should multigene panel–based testing be used in diseases where there are no approved disease-specific biomarkers?

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

Clinical interpretation and discussion

With the tumor-agnostic FDA approvals of pembrolizumab in dMMR and TMB-H solid tumors (≥ 10 mutations per Mb DNA) and of larotrectinib and entrektinib in *NTRK* fusion–positive solid tumors, multigene panel–based genomic sequencing in solid tumors is appropriate in progressive metastatic or advanced solid tumors without tumor type–specific regulatory-approved genomic biomarker–linked therapies. This approach does not apply to countries where there are no tumor type–agnostic approvals. Broad panel or whole-exome testing may also identify other gene alterations for which therapies are approved in specific tumor types other than the patient's tumor type (Fig 1). It should be noted that the frequency of potentially actionable alterations varies substantially by tumor type, with high frequency in diseases such as gastrointestinal stromal tumor but lower frequency in tumors such as renal cell carcinoma (Fig 1).[25]

Clinical question

- What evidence of actionability should be present for a clinician to recommend a therapy on the basis of panel testing in the absence of approved indications?

PCO 4.2. For tumors with actionable genomic alterations without approved genomic biomarker–linked therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options (strength of recommendation: strong).

Clinical interpretation and discussion

Several hundred genes and their mutant protein products have been linked to increased cell signaling, proliferation, and survival in cell lines or mouse models and thus proposed to be cancer drivers. However, at this time, few genomic alterations have been clinically proven as therapeutic targets (Table 2). Therefore, in addition to the functional effects of mutations on protein chemistry and signaling, evidence of clinical relevance should be considered. Clinical trials are critical to developing this evidence and should therefore be the preferred option for those tumors with actionable alterations for which there is no approved therapy.

To determine whether a genomic biomarker–linked therapy would be appropriate, the specific clinical context must be considered. This consideration would include whether the mutated gene of interest is a predictor of response, as demonstrated by data from genomic biomarker–selected trials and the strength of these data. There are instances where the clinical data are anecdotal at best or absent, such as when the gene alteration comprises the eligibility criteria for phase I and phase II clinical trials of novel targeted agents. In this situation, a robust biologic rationale and the strength of preclinical data that alterations of specific functional impact within the gene are predictive of response to the investigational targeted agent should be considered. Examples of high-level preclinical data would include whether there are isogenic models that demonstrate the functional impact of a gene variant and whether the agent of interest is associated with growth inhibition or, preferably, tumor regression in relevant in vivo models. Principles of assessing the strength of data have been incorporated into levels of evidence scales developed by several

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investigative teams: PODS,[142] OncoKB,[15] Association for Molecular Pathology,[20] NCI-MATCH,[143] Van Allen et al,[144] Andre et al, and ESCAT (European Society of Medical Oncology Scale for Clinical Actionability for Molecular Targets),[21] and CIViC (Clinical Interpretation of Variants in Cancer).[145]

In addition to the level of evidence of a target and therapy pair, other factors to consider for genomic biomarker–linked therapy include the patient-specific coalteration pattern, especially the presence of known resistance mechanisms or potential alternative drivers. Variant allele fraction (VAF; ie, the fraction of alleles sequenced containing the mutation, see Table 1) and copy number reflecting the level of gene amplification are also factors to consider. Higher mutation VAF and amplification copy number yield greater confidence that an alteration is a driver event; however, mutations at lower VAF or copy-number threshold may still have important implications, particularly for the potential to confer resistance to targeted therapies.[146-150] Additionally, clinical decisions should consider prior treatment history and the anticipated adverse event profile, and the efficacy expected with other, nongenomically selected options.

PCO 4.3.

Off-label and off-study use of genomic biomarker–linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy (strength of recommendation: strong).

Clinical interpretation and discussion

Genomic alterations may be appropriate to consider as therapeutic targets in the off-label setting if there is a strong scientific rationale, depending on the clinical scenario. In some cases, the activity of agents may have been reviewed by expert panels in professional organizations with the incorporation of treatments into management guidelines (eg, National Cancer Center Network[151] guidelines recommend pertuzumab and trastuzumab, trastuzumab and lapatinib, or trastuzumab and tucatinib in *ERBB2*-amplified *KRAS* wild-type colon cancer). In select instances, compelling data demonstrating activity with regulatory approval for a drug or drug combination in one disease may suggest sensitivity to that drug or drug combination in another disease with the same genomic alteration lacking FDA approval, such as dabrafenib and trametinib in *BRAF* V600E mutant cholangiocarcinoma.[152] However, response in one tumor type does not assure a response in another cancer. Although targeting some genomic alterations such as *NTRK* fusions have shown frequent and durable responses across tumor types, note that many therapies linked to putative driver alterations lack compelling antitumor efficacy in trials such as NCI-MATCH or TAPUR.[153-156] This highlights the importance of treating patients on clinical trials instead of off-label use whenever possible so that efficacy and lack of efficacy can be captured and efficacious biomarker-therapy pairs receive regulatory approvals, enabling greater access to effective treatments.

Section 5: Elements to Consider While Reviewing Genomic Testing Results

When interpreting a genomic test result, consider the test performed, including the laboratory reliability. To optimally assist in clinical decision making, genomic test reports should cover certain essential elements as previously described in the Association of Molecular Pathology, ASCO, and College of American Pathologists joint-consensus recommendation[20] and briefly covered here:

- **Tumor only testing versus matched tumor-normal testing:** The tests should clearly state whether only the tumor was sequenced, or whether both the tumor and a patient-matched normal sample (typically blood, buccal swab, or saliva DNA for solid tumors, and nails or cultured fibroblast samples for hematologic malignancies) were sequenced. For testing with tumor-matched normal samples, the sequencing reports should specify whether P/LP germline alterations are separately reported, or if all germline alterations detected are filtered out irrespective of pathogenicity and therefore not reported. Laboratories should have a clear and documented process for handling secondary or incidental P/LP germline findings. When performing tumor-only testing, clinicians should pursue genetic counseling and further germline testing when P/LP alterations are found in genes associated with germline alterations.[79]
- **Targeted sequencing approach:** Multigene panel–based sequencing reports should specify which of the primarily two targeted NGS capture-based methods are used[157]: (1) Amplicon sequencing is faster and requires less DNA input, typically preferable for smaller panels with limitations in detecting copy-number changes and fusions; or (2) Multiplex PCR amplification of the DNA of select genes or genomic mutational hotspots using sequence-specific primers or whole-exome sequencing. The second hybridization-based capture method uses biotinylated oligonucleotide probes or baits that tile broad genomic regions to hybridize to sheared sample DNA, which is then enriched and sequenced. Hybridization capture methods have the advantage of detecting more regions of interest, with a more faithful representation of copy number and improved fusion detection. Still, it requires more input DNA and time to complete.
- **Genes tested:** Multigene panel–based sequencing reports should clearly state which genes are contained in the panel and whether the gene's entire open reading frame is sequenced versus hotspot testing or testing of selected exons or introns. In each report, which genes or regions of the genome sequenced failed analysis, for

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example, because of inadequate coverage should be noted.

- **Descriptions of genomic alterations:** Gene alterations should include the nucleotide change, position of the change within DNA, variant type, variant consequence on the gene products, and, when applicable, amino acid change. Nomenclature guidelines by the Human Genome Variation Society should be followed.[158] Specific information regarding the breakpoints involved in fusion events (ie, the intronic sites of breakpoints and/or the exons joined in the fusion transcript) should be included, and nonspecific terminology should be avoided such as rearrangement or truncation without identifying the specific structure of the fusion and/or specific genomic breakpoints. The human genome reference sequence used to identify differences between the patient sequence reads and the reference should be specified, as alternative reporting exists of variant names on the basis of different transcripts for the same gene. Therefore, it is critical to note which transcript was used to correctly identify the alteration(s) found in the gene and the location within the DNA stated.[41,73]
  a. *Functional annotation of variants:* Not all variants affect gene function. Genomic reports should include functional data of the variant observed, protein function and possible role as a cancer driver. Likewise, reports should state if the variant lacks a known function and role in oncogenesis, these are often referred to as variants of unknown significance.
  b. *Whether fusions are tested, and if so, which ones:* Some DNA-based genomic testing panels test for fusions, while others do not. Furthermore, some NGS tests routinely couple RNA-based assays with DNA-based sequencing runs, whereas others are separate assays and require individual ordering. Genomic reports should specify whether fusion testing was performed, DNA- or RNA-based assays were used, and testing was limited to specific fusion partners (or optimally, the entire set of possible fusions listed) to enhance clarity. Clinicians should be familiar with different genomic testing platforms available in their practices to ensure fusion testing is performed when indicated.
  c. *Therapeutic implications:* Not all variants that affect gene function are therapeutically actionable. The advent of tumor NGS testing and the growing number of genomic events representing predictive biomarkers to approved or investigational targeted therapies has increasingly placed the communication burden of variant-specific therapeutic implications onto molecular pathology sequencing laboratories. Since not all variants that affect gene function are therapeutically actionable, genomic sequencing reports should include specific information addressing variant-specific and disease-specific therapeutic implications, methods for functional annotations and therapeutic implication classifications, and information sources used to assert the therapeutic actionability of a variant. Variants of unknown significance should also be clearly indicated, particularly in genes considered therapeutically actionable. Resources that guide clinicians to approved local, national, or international trials are strongly encouraged. As precision oncology rapidly evolves, clinicians must also recognize that genomic sequencing reports are static documents, and the information provided may quickly become outdated. Therefore, oncologists must be aware of the approved variant and drug combinations or those under investigation and not rely exclusively on the NGS report. New data on the impact of specific alterations and the results from clinical trials are constantly emerging, potentially making previously nonactionable alterations actionable and vice versa. Additionally, novel investigational drugs are increasingly available via clinical trial enrollment. Clinicians, therefore, need to stay informed of these changes. In such a setting, precision oncology knowledge databases are essential tools to assist clinicians in staying up to date.
  d. *Mutational clonality:* Mutations arise randomly throughout a patient's disease. Those which arise early in the tumor evolution are clonal and present in virtually all tumor cells. Those mutations that occur late in tumor progression are present only in a proportion of cells (subclonal), and may be neutral or contribute to the malignant phenotype in a fraction of the tumor cells. Tumor cells harboring such subclonal mutations may expand in response to selective pressures imposed through systemic therapies or during metastasis and have consequences on the efficacy of systemic targeted therapies. Genomic sequencing data can infer mutation clonality using VAF estimates in combination with copy number to derive cancer cell fractions. However, at this time, many genomic platforms and laboratories do not report copy number or VAF, as multiple factors affect these numbers. For example, these values and their interpretation are heavily influenced by tumor cell concentration within the tissue analyzed, and reliable estimation of tumor cell concentration by either microscopy or computational genomic approaches can be problematic. Nevertheless, this information may help with treatment selection when several actionable alterations arise in a patient's tumor sample.

Section 6: Additional Topics

This section addresses other topics that the panel believes will be of relevance and importance to the readers of the PCO.

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Testing cfDNA. There is a growing body of evidence on the clinical utility of genomic testing on cfDNA in the plasma, so-called liquid biopsies.[159] Studies have shown substantial concordance between cfDNA-based testing and tumor testing,[160] with the caveat that copy-number changes may be more difficult to assess in cfDNA, and fusion testing may be more limited in common cfDNA tests used currently. However, cfDNA has the advantage of being noninvasive and expediting testing because of the lack of need to retrieve archival blocks or arrange for a new biopsy. There are already FDA approvals on the basis of cfDNA-based genomic testing (eg, osimertinib for EGFR T790M mutation in lung cancer).[161] Therefore, in patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA. Genomic testing on cfDNA is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible. cfDNA is more commonly reported with mutant allelic fractions of individual mutations, compared with solid tumor panels, thus facilitating assessment of clonality. cfDNA testing has the additional advantage of capturing tumor heterogeneity because of pooling in the blood of DNA from throughout the tumor or from multiple tumors and is a promising tool for assessing genomic mechanisms of acquired resistance.[162] Furthermore, cfDNA levels themselves may be prognostic,[163] and early cfDNA dynamics may serve as an early predictor of therapy response or resistance.[164,165] Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies. However, longitudinal monitoring of mutant allele fractions may inform therapeutic efficacy and identify potential resistance conferring mutations.[159] ASCO and the College of American Pathology have previously published a systematic review on cfDNA testing and interpretation,[159] and this will be updated over the next few years.

Testing for minimal residual disease. There is significant interest in detecting minimal residual disease of tumor cells that have spread from the primary tumor but is not yet detectable by imaging. Studies in several tumor types have shown the potential for ctDNA testing to identify patients at higher risk of distant recurrence.[166,167]

Pharmacogenomic biomarkers. Germline polymorphisms in specific genes may affect the patient's ability to metabolize anticancer therapies, leading to drug efficacy or toxicity consequences.[168] For example, a deficiency in dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for catabolizing the majority of administered fluorouracil, leads to severe toxicities when patients are treated with these therapies. DPD deficiency can be detected through germline sequencing of four main polymorphisms within the *DPYD* gene or by measuring DPD enzyme activity.[169] The European Medicines Agency now recommends DPD testing before any fluoropyrimidine-based treatment. Additionally, germline polymorphisms or deletions in the *CYP2D6* gene in approximately 7% of the US population is primarily responsible for the bioconversion of the antiestrogen tamoxifen into its active metabolite endoxifen.[170] Some studies reported an association between *CYP2D6* polymorphisms and clinical outcomes in patients with hormone receptor–positive breast cancer treated with tamoxifen.[170] Bioconversion of tamoxifen to endoxifen varies as a function of *CYP2D6* variant zygosity, and altered tamoxifen dosage strategies have been suggested for patients heterozygous for *CYP2D6* SNPs.[171,172] Conversely, nucleotide substitutions in the *UGT1A1* gene that encodes the hepatic enzyme uridine diphosphate glucuronosyltransferase isoform 1A1 have been associated with a predisposition to gastrointestinal toxicities in patients treated with irinotecan because of its altered metabolism.[173]

Testing in CUP. Growing evidence suggests genomic testing in patients with CUP. Both retrospective[174,175] and prospective[52,176] studies have demonstrated that CUP (primarily adenocarcinoma CUP) may harbor therapeutically actionable alterations (eg, *BRAF* V600E, *ERBB2* amplification, *EGFR* mutations). Importantly, selected patients with CUP treated with genomic biomarker–linked therapies have experienced clinical benefit, signifying that genomic profiling may assist in identifying therapeutic opportunities in CUP.[176] Furthermore, in cases with uncertainty regarding a tumor's status as a new primary or a recurrence or metastasis, dual testing of tumors and comparing tumor profiles may provide further clinical insight.

Mutational signatures. Characteristic patterns of somatic mutations (eg, single and double base substitutions, indels, genomic rearrangements, and chromosomal copy-number changes) discerned by computational analysis of large numbers of alterations at many sites may indicate endogenous or exogenous mutational processes occurring in cancer cells. Like other integrative features (eg, TMB and genome-wide loss of heterozygosity), these so-called mutational signatures are measured best in whole-exome or whole-genome sequencing but can also be imputed in large-panel sequencing assays. Mutational signatures may identify processes, such as dMMR or HRD, that may be missed by other assays and can guide therapeutic strategies targeting these pathway alterations. The presence of specific mutation signatures, such as a smoking signature or ultraviolet signature, and select patterns of driver mutations, can help identify tumor origin and tumor classification in CUP or rare cancers and complement standard histologic and IHC analyses.

HRD assays. The *BRCA1* and *BRCA2* tumor suppressors are critical to the homologous recombination–based DNA damage repair pathway. HRD tumors because of *BRCA* loss are uniquely sensitized to PARP inhibition because of a synthetic lethal interaction between BRCA and PARP.[56,57] HRD tumors manifest a characteristic and identifiable pattern of genomic alterations that can be scored.[177] Similar patterns may also be observed in the absence of identifiable

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pathogenic germline or somatic variants in *BRCA1* or *BRCA2*, because of genomic mutations or expression abnormalities of other genes affecting homologous recombination. These alteration patterns represent genomic scars indicating HRD at some point in tumor evolution. Notably, the presence of genomic scars does not mean that the cancer is necessarily HRD when it is being assessed, as the homologous recombination pathway may be reestablished without resolution of the existing scars. For example, patients with HRD-positive ovarian cancer, as assessed by a commercial assay, may have a greater likelihood of responding to PARP inhibitors.[178-181] Studies have not established the utility of these assays to predict the benefit of PARP inhibitors or other DNA-damaging agents in diseases beyond ovarian cancer, and the degree of equivalency between available assays has not been assessed.

The diagnostic and prognostic value of NGS. Genomic testing can also assist in diagnosis, for example, in selected pathognomonic fusions for specific tumor types (eg, *EWSR1* fusions in Ewing sarcoma). Mutations in some genes may also be associated with prognosis (eg, *TP53* mutations have poor prognosis in many tumor types[182]). Germline sequencing can also identify alterations in genes that predispose to other diseases, or that can affect drug metabolism and/or risk of adverse events.

Intertumoral and intratumoral heterogeneity. During tumor evolution, mutation accumulation followed by clonal sweeps (clonal expansion due to new driver mutations, lineage plasticity, or epigenetic changes) can result in intratumoral (ITH) and/or intertumoral heterogeneity.[183,184] ITH is the concept that individual tumors comprise cell populations with distinct and varying molecular features, and that different spatial regions within the same tumor may have unique molecular alterations.[185] Additionally, intertumoral heterogeneity describes varying molecular features that occur between the primary tumor and metastatic sites or among multiple metastatic lesions,[184] which challenges the efficacy of systemic targeted therapies. ITH may affect the value of using a single tumor biopsy for treatment selection and often underlies mechanisms of therapeutic resistance. Studies have supported the concept of branched evolution, with variable ITH in different tumor types.[185,186] The presence of additional cancer drivers or specific coalterations may limit targeted therapy efficacy. Early research has also suggested that a larger subclonal mutation fraction may be associated with a risk of relapse.[185] Further studies are needed to determine how to incorporate baseline ITH assessment into clinical care. Ongoing studies include using alternate approaches, such as sequencing multiple, spatially distinct regions of the tumor or even single-cell sequencing for assessment of ITH.

Assessing genomic coalterations. When assessing a genomic sequencing report, it is important to note the mutational context of the actionable genomic alteration. Other coincident cancer drivers may represent additional actionable alterations that require a choice to be made for subsequent treatment strategy or may limit the activity of the selected targeted therapy. Although most precision oncology clinical trials include a single genomic alteration in the trial eligibility criteria when testing a specific targeted therapy, coalterations may affect the efficacy of the therapy or patient prognosis thereby modifying the predictive value of the genomic alteration being tested. For instance, the role of activating *KRAS* mutations as intrinsic resistance markers for systemic therapy with monoclonal anti–EGFR-targeted antibodies cetuximab or panitumumab in patients with CRC is well established in the field and incorporated as an exclusionary criterion in the regulatory approval for these drugs (Table 2). As more multiplex testing is performed, we anticipate more information about coalterations and their impact on therapeutic efficacy to emerge.

Rationale for repeat genomic testing. Repeat genomic testing may be justified for patients initially sequenced with limited NGS panels. One prospective clinical series found that 71% of the 521 patients tested with a 46- or 50-gene NGS panel lacked any alterations in the limited panel's actionable genes. Repeat testing using a 409-multigene panel detected at least one new actionable tumor alteration, not previously identified in the smaller panel, in 214 (41%) of the same 521 patients. Of these 214 patients, 40 (19%) were matched to a genomic biomarker–linked therapy on the basis of the larger multigene NGS panel's results.[187] However, few studies have systematically studied the utility of repeat testing for patients who have had larger-panel testing on an alternate panel or with whole-exome or whole-genome sequencing, in the absence of intervening treatments that may change tumor genomics.[188] For several targeted therapies, prolonged selection pressure because of treatment has been shown to lead to genomic mechanisms of acquired resistance. Commonly acquired alterations can be on-target mutations, gene mutations encoding the targeted protein (eg, *ALK*, *EGFR*, *ERBB2*, *ESR1*, *FGFR*, *mTOR*, *NTRK*, *RET*, and *ROS*).[189-194] Several of these alterations confer resistance to the initially prescribed therapy, and different acquired resistance mutations may have differential sensitivity to next-line therapies. Genomic alterations may affect drug sensitivity, as seen in *BRCA* reversion mutations that occur with PARP inhibitor treatment in patients with germline *BRCA* mutation[195]; these mutations confer proficiency of homologous repair. Acquired genomic alterations can also include the loss of target (eg, loss of *ERBB2* amplification with human epidermal growth factor receptor 2–targeted therapy)[196] or alternate resistance mechanisms such as *MET* amplification with EGFR inhibitor treatment.[197-204] Repeat genomic testing may be performed for patients with acquired resistance on targeted therapies, especially when known acquired resistance mechanisms may affect the choice of next-line therapy. Repeat testing

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TABLE 3. Demographics of Published Large-Scale Genomic Data Sets

Ethnicity	2020 US Demographics (%)[a]	Rate Per 100,000 (year of diagnosis = 2018)	AACR-GENIE v10.0 (%)[25]	Pan-Cancer TCGA (%)[12]	MSK-IMPACT 2017 (%)[107]	UMich Metastatic Solid Cancer (%)[215]
White	61.6	480.3	69.8	67.5	80.3	92
Black	12.4	445.2	5.6	7.9	5.7	4.8
Native American and/or Pacific Islander	1.3	315.1	< 0.5	< 0.5	< 0.5	NA
Asian	6.0	307.9	4.9	5.9	5.9	2.6
Hispanic	18.7	355.3	5.4	3.2	3.3	0.6

Abbreviations: AACR, American Association for Cancer Research; MSK, Memorial Sloan Kettering Cancer Center; NA, not applicable; TCGA, The Cancer Genome Atlas.

[a]US Census Bureau, 2010 Census Public Law Redistricting Data File (P.L. 94-171) Summary File; 2020 Census Public Law Redistricting Data File (P.L. 94-171) Summary File.

may also assist in identifying new targets in tumors after progression or after prolonged stable disease on targeted therapies. As always, the expected clinical utility should determine when to perform repeat genomic testing, keeping cost considerations in mind.

EXTERNAL REVIEW AND OPEN COMMENT

The draft statements were released to the public for open comment from August 24, 2021, through September 10, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for every proposed statement, with 13 written comments received. A total of 100% of the eight respondents either agreed or agreed with slight modifications to the recommendations across all recommendations. The cochairs reviewed comments from all sources and determined whether to maintain original draft statements, revise with minor language changes, or consider major recommendation revisions, with approval by the Expert Panel. All changes were incorporated before EBMC review and approval.

The draft was submitted to two external reviewers with content expertise on genetic testing and oncology of which one completed review. The review was favorable, limited to editorial corrections and referencing improvements rather than fundamental recommendation or content changes. All comments were reviewed by the cochairs, with approval of the Expert Panel, and changes integrated into the final manuscript before final approval by the EBMC. In addition, an implementablilty review was conducted by the Practice Guidelines Implementation Network representative on the Expert Panel (J.H.). These results were considered in the final draft, and are available in the Data Supplement (online only).

HEALTH DISPARITIES

Although ASCO clinical practice guideline products represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is essential to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation, gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[205] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor quality care than other Americans.[206,207] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this PCO, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[205]

Although it is clear that no two cancers are alike, it has been through research efforts examining molecular biomarker recurrence in large powered data sets that new treatment paradigms have emerged.[43,44] Currently, there are hundreds of targeted therapies either approved by a regulatory agency or being tested in clinical trials. However, minority populations are under-represented in research efforts directed toward genomic biomarker discovery, drug development, and approval. This under-representation occurs despite the observation that certain cancers in the Black patient population are often of a different and more aggressive etiology than those in Whites.[208-212] Yet, our ability to study these differences is often hampered by the lack of statistical power in sample collection to perform the necessary subgroup analyses.[213] Multigene-panel genomic studies rarely report race or ancestry in the metadata relative to age or sex.[214] If reported, such as in the selection of studies in Table 3, Black, Hispanic, Asian, and Native

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American or Pacific Islander samples are consistently under-represented compared with White samples.

Academic partnerships with minority-serving institutions (hospitals) would help to provide minority patients access to clinical sequencing as part of their routine cancer management and, with appropriate consent, to ascertain their samples for research purposes and thus expand the diversity of these collections. Efforts to build trust to enable such collections are urgently needed to overcome the longstanding disparities in tumor genomic sequencing as well as access to approved genomic biomarker–linked therapies and biomarker-driven clinical trials.

COST CONSIDERATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[216] Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.[217,218]

Discussion of cost is an integral part of shared decision making.[219] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease, and there are two or more comparable treatment options in terms of benefits and harms.[219]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[219]

On the basis of clinical considerations, when genomic testing is pursued, opting for a multigene panel that sequences all potentially actionable alterations including those genomic biomarker(s) that are linked to a regulatory-approved tumor type–agnostic therapies (ie, dMMR and/or MSI-H testing, TMB, specific fusions such as NTRK1 or 2 or 3), rather than serial testing, is preferable as it is more resource- and time-effective and less likely to lead to tissue exhaustion. The multiplex genomic testing approach is optimal for cancers with approved genomic biomarker–linked targeted therapies where genomic testing would be recommended early in the management of metastatic cancer, as well as in diseases without approved genomic biomarker–linked therapies, when genomic testing is considered an appropriate step to drive therapy choice. However, no formal systematic review of cost-effectiveness was performed for this PCO. Furthermore, multiplex genomic testing is not reimbursed in many countries around the world. This PCO does not take into consideration the accessibility and reimbursement of genomic testing.

ADDITIONAL RESOURCES

More information, including slide sets and clinical tools and resources, is available at www.asco.org/assays-and-predictive-markers-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINE

- Patient-Clinician Communication[220] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

Additional information, including a supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/assays-and-predictive-markers-guidelines.

EQUAL CONTRIBUTION

M.R. and F.M.-B. were expert panel cochairs. D.C. and A.J. contributed equally to this work.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

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Employment: MD Anderson Cancer Center
Honoraria: Rutgers Cancer Institute of New Jersey
Consulting or Advisory Role: Samsung Bioepis, Xencor, Debiopharm Group, Silverback Therapeutics, IBM Watson Health, Roche, PACT Pharma, eFFECTOR Therapeutics, Kolon Life Sciences, Tyra Biosciences, Zymeworks, Puma Biotechnology, Zentalis, Alkermes, Infinity Pharmaceuticals, AbbVie, Black Diamond Therapeutics, Eisai, OnCusp Therapeutics, Lengo Therapeutics, Tallac Therapeutics, Karyopharm Therapeutics, Biovica
Speakers' Bureau: Chugai Pharma
Research Funding: Novartis (Inst), AstraZeneca (Inst), Taiho Pharmaceutical (Inst), Genentech (Inst), Calithera Biosciences (Inst), Debiopharm Group (Inst), Bayer (Inst), Aileron Therapeutics (Inst), PUMA Biotechnology (Inst), CytomX Therapeutics (Inst), Jounce Therapeutics (Inst), Zymeworks (Inst), Curis (Inst), Pfizer (Inst), eFFECTOR Therapeutics (Inst), AbbVie (Inst), Boehringer Ingelheim (I), Guardant Health (Inst), Daiichi Sankyo (Inst), GlaxoSmithKline (Inst), Seattle Genetics (Inst), Taiho Pharmaceutical (Inst), Klus Pharma (Inst), Takeda (Inst)
Travel, Accommodations, Expenses: Beth Israel Deaconess Medical Center

No other potential conflicts of interest were reported.

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APPENDIX

TABLE A1. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer Expert Panel

Name	Affiliation and/or Institution	Role and Area of Expertise
Mark Robson, MD (cochair)	Memorial Sloan Kettering Cancer Center, New York City, NY	Medical oncology
Funda Meric-Bernstam, MD (cochair)	University of Texas MD Anderson Cancer Center, Houston, TX	Precision oncology
Fabrice André, MD, PhD	PRISM, Precision Medicine Center, Institut Gustave Roussy, Villejuif, France	Medical oncology
Nilofer Azad, MD	Johns Hopkins, Baltimore, MD	Drug development, novel targets, epigenetics
Mitesh Borad, MD	Mayo Clinic, Phoenix, AZ	Medical oncology
Debyani Chakravarty, PhD	Memorial Sloan Kettering Cancer Center, New York City, NY	Molecular genetics and clinical cancer genomics
Shridar Ganesan, MD, PhD	Rutgers Cancer Institute of New Jersey, New Brunswick, NJ	Medical oncology and cancer genomics
Stacy Gray, MD, AM	City of Hope, Duarte, CA	Medical oncology and genetics, health services research
Jimmy Hwang, MD	Levine Cancer Institute, Charlotte, NC	Medical oncology, PGIN representative
Amber Johnson, PhD	UT MD Anderson Cancer Center, Houston, TX	Precision oncology
Christopher Lieu, MD	University of Colorado, Denver, CO	Medical oncology
Neal I. Lindeman, MD	Brigham and Womens' Hospital, Harvard Medical School, Boston, MA	Pathology, CAP representative
Christine M. Lovly, MD, PhD	Vanderbilt University Medical Center, Nashville, TN	Medical oncology
Kathleen Moore, MD	The Stephenson Cancer Center, Oklahoma City, OK	Gynecologic oncology
Jane Perlmutter, PhD	—	Patient representative
Jeffrey Sklar, MD, PhD	Yale School of Medicine, New Haven, CT	Molecular pathology
Laura Tafe, MD	Dartmouth-Hitchcock Medical Center and The Geisel School of Medicine at Dartmouth, Darmouth, NH	Molecular pathology (CAP representative)
Hans J. Messersmith, MPH	ASCO, Alexandria, VA	ASCO practice guideline staff (health research methods)

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TABLE A2. Strength of Recommendation Definitions

Strength of Recommendation	Definitions
Strong	There is high confidence that the recommendation reflects best practice. This is based on:
	Strong evidence for a true net effect (eg, benefits exceed harms)
	Consistent results, with no or minor exceptions
	Minor or no concerns about study quality; and/or
	The extent of panelists' agreement
	Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on:
	Good evidence for a true net effect (eg, benefits exceed harms)
	Consistent results with minor and/or few exceptions
	Minor and/or few concerns about study quality; and/or
	The extent of panelists' agreement
	Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on:
	Limited evidence for a true net effect (eg, benefits exceed harms)
	Consistent results, but with important exceptions
	Concerns about study quality; and/or
	The extent of panelists' agreement
	Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

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