ASCO special articles

# Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline

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abstract

**PURPOSE** The College of American Pathologists (CAP) has developed a guideline on testing for mismatch repair (MMR) and microsatellite instability (MSI) for patients considered for immune checkpoint inhibitor therapy. ASCO has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

**METHODS** The CAP guideline was reviewed for developmental rigor by methodologists. An ASCO Endorsement Panel subsequently reviewed the content and the recommendations.

**RESULTS** The ASCO Endorsement Panel determined that the recommendations from the CAP guideline, published on August 3, 2022, are clear, thorough, and based on the most relevant scientific evidence. ASCO endorses *Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: Guideline From the College of American Pathologists in Collaboration With the Association for Molecular Pathology and Fight Colorectal Cancer*.

**RECOMMENDATIONS** Within the guideline, MMR immunohistochemistry (IHC), MSI polymerase chain reaction, and MSI next-generation sequencing are all recommended testing options for colorectal cancer, MMR-IHC and MSI-polymerase chain reaction for gastroesophageal and small bowel cancer, and only MMR-IHC for endometrial cancer. No recommendation in favor of any testing method over another could be made for any other cancer. Tumor mutational burden was not recommended as a surrogate for DNA MMR deficiency. If MMR deficiency consistent with Lynch syndrome is detected, it should be communicated to the treating physician.

Additional information is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

The College of American Pathologists (CAP) published a guideline in collaboration with the Association for Molecular Pathology and Fight Colorectal Cancer (CRC) on mismatch repair (MMR) and microsatellite instability (MSI) testing for immune checkpoint inhibitor therapy in 2022.[1] This guideline addresses multiple issues around such testing across multiple cancer types and provides recommendations as to the appropriate modality of testing (immunohistochemistry [IHC], polymerase chain reaction [PCR], or next-generation sequencing [NGS]). ASCO has recently published two guidelines that recommend testing for MMR in breast cancer[2] and epithelial ovarian cancer.[3] In addition, the panel for ASCO's recent provisional clinical opinion on somatic genomic testing[4] was unable to provide specific guidance on the type of testing for MMR and MSI. The CAP guideline was thus a prime candidate for endorsement by ASCO as it meets an unmet need in clinical practice and complements existing ASCO guidance.

## OVERVIEW OF THE ASCO GUIDELINE ENDORSEMENT PROCESS

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership (Appendix Table A1, online only). The ASCO endorsement process includes an assessment by ASCO staff of candidate guidelines for methodological quality using the "Rigor of Development" subscale of the Appraisal of Guidelines for Research and

## THE BOTTOM LINE

### Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline

ASCO endorses the College of American Pathologists (CAP) Guideline.

#### Guideline Question

What test best identifies defects in DNA mismatch repair (MMR)?

#### Target Population

Patients with cancer undergoing DNA MMR testing to help select immune checkpoint inhibitor therapy.

#### Target Audience

Clinicians conducting and making use of DNA MMR testing.

#### Methods

An ASCO Expert Panel was convened to consider endorsing the recommendations that were based on a systematic review of the medical literature. The ASCO Expert Panel considered the methodology used in the CAP guideline by considering the results from the Appraisal of Guidelines for Research and Evaluation II review instrument. The ASCO Expert Panel carefully reviewed the CAP guideline content to determine appropriateness for ASCO endorsement.

#### Recommendations

These recommendations and good practice statements are reprinted from the CAP guideline. The strengths of recommendation definitions are those used in the guideline and are described in Appendix Table A2 (online only). Please see the discussion section for additional commentary from the ASCO endorsement panel.

***Recommendation 1.*** For patients with CRC, being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-immunohistochemistry (IHC) and/or microsatellite instability (MSI) by polymerase chain reaction (PCR) for the detection of DNA MMR defects. Although MMR-IHC or MSI by PCR is preferred, pathologists may use a validated MSI by next-generation sequencing (NGS) assay for the detection of DNA MMR defects. *Note: MSI by NGS assay must be validated against MMR-IHC or MSI by PCR and must show equivalency*. (Strong recommendation)

***Recommendation 2.*** For patients with gastroesophageal and small bowel cancer, being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR over MSI by NGS for the detection of DNA MMR defects. *Note: This recommendation does not include esophageal squamous cell carcinoma*. (Strong recommendation)

***Recommendation 3.*** For patients with endometrial cancer, being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA MMR defects. (Strong recommendation)

***Recommendation 4.*** For patients with cancer types other than CRC, gastroesophageal adenocarcinoma, small bowel, and endometrial being considered for immune checkpoint inhibitor therapy, pathologists should test for DNA MMR although the optimal approach for the detection of MMR defects has not been established. *Note: Assays must be adequately validated for the specific cancer type being tested with careful consideration of performance characteristics of MMR-IHC and MSI by NGS or PCR for the detection of DNA MMR defects*. (Conditional recommendation)

***Recommendation 5.*** For all cancer patients being considered for immune checkpoint inhibitor therapy based on defective MMR, pathologists should not use tumor mutation burden (TMB) as a surrogate for the detection of DNA MMR defects. If a tumor is identified as TMB-high, pathologists may perform IHC and/or MSI by PCR to determine if high TMB is secondary to MMR deficiency. (Strong recommendation)

***Recommendation 6.*** For cancer patients being considered for immune checkpoint inhibitor therapy, if a MMR deficiency consistent with Lynch syndrome is identified in the tumor, pathologists should communicate this finding to the treating physician. (Strong recommendation)

#### Good Practice Statements

1. Discordant results: In the event of discordant results, pathologists should interpret any evidence of MMR deficiency by IHC or MSI by NGS or PCR as a positive result for patients to be eligible for immune checkpoint inhibitor therapy. Discordant results should be reviewed to ensure that the discordance is not due to an interpretive error.
2. Indeterminate results: In the event of an indeterminate result in any method, pathologists should perform an alternative technique or repeat on a different tumor block. Laboratories should have a robust peer review process for indeterminate cases.

(continued on following page)

 

**THE BOTTOM LINE (CONTINUED)**

3. Subclonal loss: In the event of a clonal loss by MMR-IHC, pathologists should perform MSI by PCR specifically in a dissected area of tumor that has IHC loss of MMR protein if the patient is being considered for checkpoint inhibitor clinical trials.

**Additional Resources**

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

A link to the CAP guideline can be found at https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/mismatch-repair-and-microsatellite-instability-testing-for-immune-checkpoint-inhibitor-therapy. Recommendations and table of recommendation strength definitions are reprinted with permission of CAP.

**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.**

Evaluation II (AGREE II) instrument (Data Supplement, online only for more details).

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### Guideline and Conflicts 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-methodology). All members of the Expert 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 Expert Panel did not disclose any relationships constituting a conflict under the Policy.

## CLINICAL QUESTIONS AND TARGET POPULATION

The CAP guideline addressed the following key questions

- Key question (KQ)1a. In patients being considered for immune checkpoint inhibitor therapy, does MMR protein loss by IHC, PCR-based MSI analysis, or NGS-based MSI analysis accurately detect defects in DNA MMR?
- KQ1b. Does TMB by NGS have adequate performance characteristics to act as a surrogate for PCR- and NGS-based MSI assays?

- KQ1c. In patients being considered for immune checkpoint inhibitor therapy, which DNA MMR assay best predicts improved patient outcomes?
- KQ2. When comparing MMR-IHC and PCR- or NGS-based MSI, does any assay have better performance characteristics in specific cancer types?
- KQ3. What are the diagnostic test characteristics of MMR-IHC, PCR-based MSI analysis, and NGS-based MSI analysis when predicting germline Lynch mutations?

The target population for the CAP guideline is patients with cancer who are being tested for DNA MMR to determine appropriate therapy with immune checkpoint inhibitors.

## SUMMARY OF THE CAP GUIDELINE DEVELOPMENT METHODOLOGY

The CAP guideline was developed by an author Expert Panel and a scientific advisory panel that included experts in pathology and oncology, and research and development. The literature search of Ovid MEDLINE and Elsevier Embase.com spanned January 1, 2008, to March 30, 2021. Details of the search strategies and the study inclusion criteria and outcomes of interest are available in the CAP guideline publication.[1] The searches identified 103 articles for inclusion in the guideline's qualitative synthesis of the literature. The identified studies were all cohort studies, the majority retrospective, but some were prospective. Three testing types were evaluated: MMR by IHC, MSI by PCR, and MSI by NGS. The primary outcomes of interest were diagnostic test characteristics and test status concordance (eg, between MMR by IHC and MSI by PCR).

## RESULTS OF THE ASCO METHODOLOGY REVIEW

The methodology review of the CAP guideline was completed independently by two ASCO guideline staff members using the Rigor of Development subscale from the AGREE II instrument.[5] Detailed results of the scoring for this guideline are available in the Data Supplement. Overall, the CAP guideline scored 96%. The preliminary ASCO content reviewer of the CAP guideline, as well as the ASCO Expert Panel, found that the recommendations well supported in the original guideline. Each section, including an introduction, was clear and well referenced from the systematic review. This is the most recent information as of the publication date. As the literature search was relatively recent and the Expert Panel did not indicate any concerns about missing evidence, no updated literature review was conducted by ASCO.

## RESULTS OF THE ASCO CONTENT REVIEW

The ASCO Expert Panel reviewed the CAP guideline and concurs that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. Overall, the ASCO Expert Panel agrees with the recommendations as stated in the guideline, with additional context and considerations provided in the Discussion.

## DISCUSSION

The CAP guideline is appropriately and reasonably focused on recommendations to guide testing for MMR and MSI by IHC, PCR, and NGS to determine appropriate immune checkpoint inhibitor therapy. However, because of this focus, there are many important areas that are not addressed in the systematic review or in the recommendations that a reader may hope to find guidance on, such as use of liquid biopsy, programmed cell death protein 1 and programmed death-ligand 1 testing, and MMR and MSI testing for other purposes, for example, Lynch syndrome. Some of these areas are addressed at least partially in the discussion and conclusions text of the CAP guideline. Others will hopefully be addressed by future guidelines. ASCO is currently developing a guideline on the use of circulating free DNA testing in solid tumors, and CAP is developing a guideline on the use of programmed cell death protein 1 testing in lung cancer. The ASCO endorsement panel believed that two areas warranted further comment.

The ASCO Endorsement Panel endorses Recommendations 1, 2, and 3 as written as the questions asked by the guideline. However, other potentially important information can be gained via NGS testing beyond MSI detection, for example, detection of human epidermal growth factor receptor 2 amplification (particularly in GI tract carcinomas), high tumor mutational burden because of non-MSI mechanisms, fusion detection, and, in some laboratories, paired germline-somatic analysis. These potential uses should be considered in decision making. This can be important when the amount of available tissue limits the ability to perform multiple sequential tests. IHC and NGS are likely to prove most effective when used as complementary tools, particularly when one or the other generates equivocal results, and one should not necessarily be used to the exclusion of another. Importantly, this testing should not be perceived as duplicative or unnecessary (eg, by payors) when a reasonable need for both types of testing exists.

The CAP guideline makes clear that it focuses solely on the analytical and interpretive phases of testing and that preanalytical issues are outside of its scope. This was a reasonable choice on the part of the CAP guideline panel. It is important to recognize, however, that preanalytical compromise of specimens can and does occur, especially in resection specimens, where preanalytical factors (like cold ischemia time) are more varied than with biopsy specimens. The fact that the CAP guideline does not make recommendations on preanalytical topics should not be construed as minimizing the importance of good laboratory practices regarding cold ischemia time, fixative type, adequacy of tissue processing, and fixation time. The ASCO Endorsement Panel wants to reinforce the concept that

 

standardizing preanalytical procedures according to recommendations from authoritative sources such as the CAP, Clinical and Laboratory Standards Institute, or International Organization for Standardization is good practice.

## ENDORSEMENT RECOMMENDATION

ASCO endorses *Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: Guideline From the College of American Pathologists in Collaboration With the Association for Molecular Pathology and Fight Colorectal Cancer.*[1]

**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.**

## ADDITIONAL RESOURCES

More information, including slide sets and clinical tools and resources, is available at www.asco.org/molecular-testing-and-biomarkers-guidelines. Patient information is available at www.cancer.net.

## RELATED ASCO GUIDELINES

- Patient-Clinician Communication[6] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer[4] (https://ascopubs.org/doi/10.1200/JCO.21.02767)
- Biomarkers for Systemic Therapy in Metastatic Breast Cancer[2] (https://ascopubs.org/doi/10.1200/JCO.22.01063)
- Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer[3] (https://ascopubs.org/doi/10.1200/jco.19.02960)
- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy[7] (https://ascopubs.org/doi/10.1200/JCO.21.01440)


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## EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

## EQUAL CONTRIBUTION

P.V. and T.J. were Expert Panel cochairs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline**

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No other potential conflicts of interest were reported.

## APPENDIX

**TABLE A1.** Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement Expert Panel Membership

| Name | Affiliation | Role and Area of Expertise |
|---|---|---|
| Praveen Vikas, MD | University of Iowa, Iowa City, IA | Medical Oncology (Breast), Cochair |
| Tyler Johnson, MD | Stanford University Hospital, Palo Alto, CA | Medical Oncology (GI), Cochair |
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| Anjee Davis | Fight Colorectal Cancer, Springfield, MO | Patient representative |
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| Aliza Leiser, MD | Rutgers Cancer Institute of New Jersey, New Brunswick, NJ | Medical Oncology, Practice Guidelines Implementation Network representative |
| Anne M. Mills, MD | University of Virginia, Charlottesville, VA | Pathology, Member of the CAP guideline panel |
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| Lynette Sholl, MD | Brigham and Women's Hospital, Boston, MA | Pathology |
| Davendra Sohal, MD | University of Cincinnati, Cincinnati, OH | Medical Oncology (GI) |
| Richard C. Turkington, MD, PhD | Queen's University Belfast, Northern Ireland, United Kingdom | Medical Oncology (GI) |
| Hans Messersmith, MPH | American Society of Clinical Oncology, Alexandria, VA | ASCO Practice Guideline Staff (Health Research Methods) |

**TABLE A2.** College of American Pathologists Strength of Recommendations Definitions

| Designation | Recommendation | Evidence to Decision Judgment |
|---|---|---|
| Strong recommendation | Recommend for or against a particular practice (can include "must" or "should") | Supported by assessment with the GRADE EtD framework showing EP consensus of judgments directed to the far right or far left poles of the framework |
| Conditional recommendation | Recommend for or against a particular practice (can include "should" or "may") | Supported by assessment with the GRADE EtD framework showing EP consensus of judgments directed toward the center of the framework or with a dispersed pattern |

Abbreviations: EP, Expert Panel; EtD, evidence to decision framework; GRADE, Grading of Recommendations Assessment, Development and Evaluation.