COLLEGE of AMERICAN PATHOLOGISTS

MMR and MSI Testing in Patients being Considered for Checkpoint Inhibitor Therapy – in Collaboration with AMP, ASCO, and Fight Colorectal Cancer

Draft Recommendations with Strength of Recommendations

Colorectal cancer (CRC) patients
1. Strong Recommendation: In CRC patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC and/or MSI by PCR for the detection of DNA mismatch repair defects. Although MMR IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA mismatch repair defects. *Note:* MSI by NGS assay must be validated against MMR IHC or MSI by PCR and must show equivalency.
Gastroesophageal and Small Bowel Cancer Patients
2. Strong Recommendation: In gastroesophageal and small bowel cancer patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC and/or MSI by PCR over MSI by NGS for the detection of DNA mismatch repair defects. 1. *Note: This recommendation does not include esophageal squamous cell carcinoma.*
Endometrial Cancer Patients
3. Strong Recommendation: In endometrial cancer patients being considered for checkpoint blockade therapy, pathologists should use MMR IHC over MSI by PCR or NGS for the detection of DNA mismatch repair defects.
All Other Cancer Types
4. Conditional Recommendation: In patients with cancer types other than CRC, GEA, small bowel, and endometrial being considered for checkpoint blockade therapy, pathologists should test for DNA mismatch repair, although the optimal approach for the detection of MMR defects has not been established. 2. *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 for the detection of DNA mismatch repair defects.
The Role of TMB in MMR Testing
5. Strong Recommendations: For all cancer patients being considered for checkpoint blockade therapy based upon defective mismatch repair, pathologists should NOT use TMB as a surrogate for the detection of DNA mismatch repair 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 mismatch repair deficiency. 3. *Note:* In patients being considered for checkpoint blockade therapy, pathologists should not use TMB as a surrogate based on DNA mismatch repair defects.
Evaluation for Lynch Syndrome
6. Strong Recommendation: For cancer patients being considered for checkpoint blockade therapy, if an MMR deficiency is identified, pathologists should recommend follow-up evaluation for Lynch Syndrome.

Good Practice Statements
1. Discordant results In the event of discordant results, pathologists should interpret any evidence of MMR deficiency by IHC, MSI by NGS or PCR as a positive result for patients to be eligible for checkpoint blockade 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 indeterminate result in any method, pathologists should perform an orthogonal technique or repeat on a different tumor block. Laboratories should have a robust peer review process for indeterminate cases. **3. Clonal 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 deficiency.