**Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Endometrium**

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CAP Endometrium Biomarker Template Revision History

**Version Code**

The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

**Version:** EndometriumBiomarkers 1.1.0.0

**Summary of Changes**

Deleted MLH1 permitted value.

Minor typographical and terminology changes.

Biomarker Reporting Template

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Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

**ENDOMETRIUM**

**Select a single response unless otherwise indicated.**

***Note:*** *Use of this template is optional.*

**+ RESULTS**

**+ Estrogen Receptor (ER) Status (Note A)**

+\_\_\_ Positive

+Percentage of cells with nuclear positivity: \_\_\_ %

+\_\_\_ Negative

+\_\_\_ Internal control cells present and stain as expected

+\_\_\_ Internal control cells absent#

+\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+\_\_\_ Equivocal##

+\_\_\_ Internal control cells present; no immunoreactivity of either tumor cells orinternal controls

+\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*# When a tumor is negative but no internal control cells are present, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative. This should include consideration of histologic type and grade, cold ischemia and fixation times, and the status of external controls, as well as if testing is performed on archived (weeks) unstained tissue sections. If the pathologist decides that hormone receptor status cannot be determined, the test should be reported as such and repeated on another block or specimen.*

*## Technical issues prevent the test from being reported as positive or negative. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed.*

+ **Progesterone Receptor (PgR) Status (Note A)**

+\_\_\_ Positive

+ Percentage of cells with nuclear positivity: \_\_\_\_\_ %

+\_\_\_ Negative

+\_\_\_ Internal control cells present and stain as expected

+\_\_\_ Internal control cells absent#

+\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+\_\_\_ Equivocal##

+\_\_\_ Internal control cells present; no immunoreactivity of either tumor cells orinternal controls

+\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*# When a tumor is negative but no internal control cells are present, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative. This should include consideration of histologic type and grade, cold ischemia and fixation times, and the status of external controls, as well as if testing is performed on archived (weeks) unstained tissue sections. If the pathologist decides that hormone receptor status cannot be determined, the test should be reported as such and repeated on another block or specimen.*

*## Technical issues prevent the test from being reported as positive or negative. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed.*

**+ Immunohistochemistry (IHC) Testing for Mismatch Repair (MMR) Proteins (select all that apply) (Note B)**

+ \_\_\_ MLH1

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ MSH2

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ MSH6

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ PMS2

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Background nonneoplastic tissue/internal control with intact nuclear expression

**+ IHC Interpretation**

+ \_\_\_ No loss of nuclear expression of MMR proteins: low probability of microsatellite instability-high (MSI-H)#

+ \_\_\_ Loss of nuclear expression of MLH1 and PMS2: testing for methylation of the *MLH1* promoter is indicated (the presence of *MLH1* methylation suggests that the tumor is sporadic and germline evaluation is probably not indicated; absence of *MLH1* methylation suggests the possibility of Lynch syndrome, and sequencing and/or large deletion/duplication testing of germline *MLH1* is indicated)#

+ \_\_\_ Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *MSH2* is indicated, and, if negative, sequencing and/or large deletion/duplication testing of germline *MSH6* is indicated. If both are negative, sequencing and/or large deletion/duplication testing of germline *EPCAM* is indicated.)#

+ \_\_\_ Loss of nuclear expression of MSH6 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *MSH6* is indicated)#

+ \_\_\_ Loss of nuclear expression of PMS2 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline *PMS2* is indicated)#

*# There are exceptions to the above IHC interpretations. These results should not be considered in isolation, and clinical correlation with genetic counseling is recommended to assess the need for germline testing.*

**+ Microsatellite Instability (MSI) (Note C)**

+ \_\_\_ MSI – Stable (MSS)

+ \_\_\_ MSI – Low (MSI-L)

+ \_\_\_ 1% - 29% of the National Cancer Institute (NCI) or mononucleotide markers exhibit instability

+ \_\_\_ 1 of the NCI or mononucleotide markers exhibit instability

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ MSI – High (MSI-H)

+ \_\_\_ ≥30% of the NCI or mononucleotide markers exhibit instability

+ \_\_\_ 2 or more of the NCI or mononucleotide markers exhibit instability

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ MSI – Equivocal

+ Cellularity

+ Percentage of tumor cells present in specimen: \_\_\_\_\_\_%

**+ *MLH1* Promoter Methylation Analysis (Note D)**

+ \_\_\_ *MLH1* promoter methylation present

+ *\_\_\_ MLH1* promoter methylation *a*bsent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ p53 Expression (Note E)**

+ \_\_\_ Normal expression

+ \_\_\_ Abnormal strong diffuse overexpression (>90%)

+ \_\_\_ Abnormal null expression (complete loss of expression)

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ METHODS**

**+ Dissection Method(s) (select all that apply) (Note F)**

+ \_\_\_ Laser capture microdissection

+ Specify test name#: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Manual under microscopic observation

+ Specify test name#: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Manual without microscopic observation

+ Specify test name#: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Cored from block

+ Specify test name#: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Whole tissue section (no tumor enrichment procedure employed)

+ Specify test name#: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

# *If more than 1 dissection method used, please specify which test was associated with each selected dissection method.*

**+ Estrogen Receptor**

+ Primary Antibody

+ \_\_\_ SP1

+ \_\_\_ 6F11

+ \_\_\_ 1D5

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Progesterone Receptor**

+ Primary Antibody

+ \_\_\_ 1E2

+ \_\_\_ 636

+ \_\_\_ 16

+ \_\_\_ SP2

+ \_\_\_ 1A6

+ \_\_\_ 1294

+ \_\_\_ 312

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Microsatellite Instability (MSI)**

+ Number of MSI markers tested (specify): \_\_\_\_\_\_\_\_

**+ MLH1 Promoter Methylation**

+ Testing Method

+ \_\_\_ Methylation-specific real-time polymerase chain reaction (PCR)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ p53 Immunohistochemistry**

+ Primary Antibody

+ \_\_\_ DO-1

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (www.genenames.org; accessed May 25, 2016).*

*All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org; accessed May 25, 2016).*

Explanatory Notes

**A. ER and PgR Immunohistochemistry**

Hormone receptor expression is occasionally assessed on primary invasive endometrial carcinomas at the request of the treating clinician in order to predict response to endocrine therapy. Guidelines for reporting results of hormone receptor testing in breast carcinomas published by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) require recording specific preanalytic and analytic variables that can affect test results.1 Such information has not been required for endometrial carcinomas. However, details regarding assay validation or verification should be available in the laboratory. Any deviation(s) from the laboratory’s validated methods should be recorded. Appropriate positive and negative controls should be used and evaluated.

Hormone receptor status is typically performed in formalin-fixed, paraffin-embedded tissue sections by immunohistochemistry (IHC). Only nuclear staining is considered positive. There are many tissue and technical variables that can affect test results, and the assays must be validated to ensure their accuracy. External proficiency testing surveys for estrogen receptor (ER) and progesterone receptor (PgR) for breast cancer are available from the CAP and other organizations and may be useful tools to help ensure that assays perform as expected. To avoid false-negative results, appropriate internal and external controls should be positive. In the endometrium, benign endometrial glands, endometrial stroma, or myometrium can serve as internal control tissue. If internal controls are not present, consider repeating the test on another specimen (if available). Reasons for false-negative results include the following:

* Exposure of tumor cells to heat (eg, carcinomas transected by using cautery during surgery)
* Prolonged cold ischemic time, which may result in antigenic degradation. One hour or less is preferable
* Under- or overfixation; fixation for at least 6 hours in buffered formalin is recommended, and prolonged fixation can also diminish immunoreactivity
* Type of fixative: ER is degraded in acidic fixatives such as Bouin’s and B-5; formalin should be buffered to ensure pH range between 7.0 and 7.4
* Decalcification, which may result in loss of immunoreactivity
* Non-optimized antigen retrieval or use of old (weeks) tissue sections
* Type of antibody
* Dark hematoxylin counterstain obscuring faintly positive diaminobenzidine (DAB) staining

False-positive results occur less frequently. Rare reasons would be the use of an impure antibody that cross-reacts with another antigen or misinterpretation of entrapped normal or hyperplastic cells as invasive carcinoma. False-positive tests can also be generated by image analysis devices that mistakenly count overstained nuclei.

**Reporting Guidelines**

There are currently no outcome-driven consensus opinions that have been developed for the reporting of the results of immunohistochemical assays for ER and PgR for endometrial cancer. In absence of robust data, the CAP recommends using a similar reporting format that is used for reporting the results of immunohistochemical assays for ER and PgR for breast cancer (Table 1).2

As there is a wide range of receptor levels in individual cancers, a uniform reporting scheme using the proportion of positive cells as well as the intensity of immunoreactivity is recommended:

• Number of positive cells: The number of positive cells can be reported as a percentage or within discrete categories.

• Intensity: Refers to degree of nuclear positivity (ie, pale to dark). The intensity can be affected by the amount of protein present, as well as the antibody used and the antigen retrieval system. In most cancers, there is heterogeneous immunoreactivity with pale to darkly positive cells present.

**Table 1.**

**Reporting Results of Estrogen Receptor (ER) and Progesterone Receptor (PgR) Testing**

|  |  |  |
| --- | --- | --- |
| **Result** | **Criteria** | **Comments** |
| Positive | Immunoreactive tumor cells present (≥1%) | The percentage of immunoreactive cells may be determined by visual estimation or quantitation. Quantitation should be provided by reporting the percentage of positive cells in the entire section. If there is significant regional variation, that too should be reported. |
| Negative | <1% immunoreactive tumor cells present |  |

**B. Mismatch Repair Immunohistochemistry Testing**

Immunohistochemical (IHC) testing for DNA MMR protein expression (ie, MLH1, MSH2, MSH6, and PMS2 expression) is performed on formalin-fixed, paraffin-embedded tissue. Loss of DNA MMR protein expression is likely to be due to mutation (either genetic or somatic) in one of the mismatch repair genes.3-5 This information will help identify the gene that is most likely to have a mutation (eg, a patient whose tumor shows loss of MSH2 and MSH6 expression, but retention of MLH1 and PMS2 expression, may have an *MSH2* germline mutation).

If the results of DNA MMR IHC and MSI testing are discordant (eg, MSI-H phenotype with normal IHC or abnormal IHC with MSS phenotype), then the laboratory should make sure that the same sample was used for MSI and IHC testing and that there was no sample mix-up.6 Other possible sources of discordance include low tumor volume in the MSI sample. Note that loss of MSH6 protein expression may occur in absence of MSI-H phenotype.

Any positive reaction in the nuclei of tumor cells is considered as intact expression (normal), and it is common for intact staining to be somewhat patchy. An interpretation of expression loss in tumor cells should be made only if a positive reaction is seen in internal control cells, such as the nuclei of stromal, inflammatory, or nonneoplastic epithelial cells. Loss of expression of MLH1 may be due to Lynch syndrome or methylation of the *MLH1* promoter region (as occurs in sporadic MSI colorectal carcinoma).

**C. Microsatellite Instability Testing**

Detection of hereditary defective mismatch repair has clinical implications for treatment of the affected patient and family members. Patients with a microsatellite instability-high (MSI-H) phenotype in their cancer tissues may have a germline mutation in one of several DNA mismatch repair (MMR) genes (eg, *MLH1, MSH2, MSH6,* or *PMS2*) or an altered *EPCAM (TACSTD1)* gene.3-5 After appropriate genetic counseling, patients may want to consider testing to identify the causative heritable abnormality. An MSI-H phenotype is more frequently observed in sporadic endometrial cancers (about 15% of cases) due to somatic abnormalities, usually hypermethylation of the *MLH1* gene promoter.

MSI testing protocols are similar to those developed for colon cancer. These are briefly summarized here, but more complete details are available in the separately issued “Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Colon and Rectum.”7 Testing is generally performed with at least 5 microsatellite markers, generally mononucleotide or dinucleotide repeat markers. In 1998, a National Institutes of Health consensus panel proposed that laboratories use a 5-marker panel consisting of 3 dinucleotide and 2 mononucleotide repeats for MSI testing. Recent data suggest that dinucleotide repeats may have lower sensitivity and specificity for identifying tumors with an MSI-H phenotype. As a consequence, there has been a move towards including more mononucleotides and fewer dinucleotides in MSI testing panels. Many laboratories now use a commercially available kit for MSI testing that utilizes 5 mononucleotide markers.

If DNA MMR IHC has not been performed, this testing should be recommended for any case that shows an MSI-H phenotype, because this information will help identify the gene that is most likely to have a germline (or somatic) mutation.

**D. *MLH1* Promoter Methylation Analysis**

Defective mismatch repair in sporadic endometrial cancer is most often due to inactivation of the *MLH1* gene promoter by methylation (epigenetic silencing). Most laboratories utilize a methylation-specific real-time polymerase chain reaction (PCR) assay to determine the presence of methylation.

**E. p53 Expression**

The distinction between endometrioid and serous type endometrial carcinomas is typically based on morphologic evaluation. Analysis for *p53* gene mutations can occasionally be useful for diagnostically challenging tumors which are not morphologically distinguishable between endometrioid and serous phenotypes. The vast majority of serous type endometrial carcinomas exhibit mutations in *p53*. While most low-grade endometrioid endometrial tumors are not associated with *p53* mutations, a significant subset of high-grade endometrioid tumors are; thus, any ancillary testing for the presence of a *p53* mutation should be performed with an awareness of the limitations of the result with respect to providing a conclusive answer as to exact tumor type.8-9 On occasion, *p53* testing may be requested for treatment purposes.

Extent of p53 specific nuclear immunostaining can be used to assess *p53* gene integrity in endometrial carcinoma. Normal endometrial glands with an intact *p53* gene express the protein at low levels, reaching a threshold of immunohistochemical detection (positive staining) in only a small percentage of cells. Generally this is 1% to 5% of nuclei, but may increase under conditions of cellular damage or repair. Two different staining patterns are each considered diagnostic of abnormalities of the *p53* gene itself. Most common are mutations resulting in a qualitatively abnormal p53 protein that stabilizes the p53 complex, resulting in intense nuclear staining in >90% of affected cells. In most cases that harbor mutations in *p53* that are associated with overexpression, intense nuclear staining is present in over 90% of affected cells. Second is genomic damage causing loss of expression, with complete absence of protein in all affected cells. The latter null phenotype must be distinguished from a failed stain. Low levels of expression within internal control tissues (stroma, or nonmalignant epithelium) can be used for this purpose. It should be noted that p53 expression is significantly affected by non-optimized antigen retrieval or use of archival (weeks) tissue sections.

**F. Dissection Method**

Please denote the manner in which the tissue was dissected and specify the biomarker test only if different dissection methods are used for different tests.

* Laser capture microdissection (LCM): Use of a laser-equipped microscope to isolate and retrieve specific cells of interest from a histopathologic region of interest.
* Manual under microscopic observation: Hematoxylin-and-eosin (H&E) slide is examined under a light microscope and marked by a pathologist for subsequent tumor dissection and retrieval.
* Manual without microscopic observation: H&E slide is examined without a microscope and marked by a pathologist for subsequent tumor dissection and retrieval.
* Cored from block: Area of interest is cored from a paraffin-embedded tissue block.
* Whole tissue section: No tumor enrichment procedure employed for tissue retrieval.

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