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Review Articles

Immunohistochemical and Molecular Biomarkers Bridging Pathogenesis and Precision Medicine in Endometrial Carcinoma: A Systematic Review

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Endometrial carcinoma is a heterogeneous malignancy driven by diverse molecular alterations. Immunohistochemical and molecular biomarkers have increasingly been incorporated into diagnostic algorithms, linking histopathology with genomic profiling and facilitating precision oncology. This systematic searching approach followed PRISMA 2020 guidelines and was registered in PROSPERO (CRD420251184261). A comprehensive search of PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar (January 2000–March 2025) identified studies evaluating immunohistochemical and/or molecular biomarkers in atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia or endometrial carcinoma. Fifty-nine studies met the inclusion criteria. Investigated biomarkers included PTEN, PAX2, β-catenin, p53, mismatch repair proteins, HER2, ER, PR, Ki67, and PD-L1. These markers delineate the molecular continuum from precursor lesions to invasive carcinoma and correspond closely to The Cancer Genome Atlas molecular subtypes. MMR deficiency and PD-L1 expression predict response to immune checkpoint inhibitors, whereas HER2 amplification characterizes aggressive serous carcinoma. PTEN and PAX2 loss characterized AEH/EIN, while p53 abnormalities identify copy-number-high tumors associated with adverse prognosis.

Key words: Endometrial carcinoma; atypical endometrial hyperplasia; immunohistochemistry; molecular biomarkers; TCGA classification.

Introduction

Endometrial carcinoma (EC) is the most common malignancy of the uterine corpus and remains a major global health burden, with incidence continuing to rise due to increasing life expectancy, obesity, metabolic syndrome, and hormonal factors [36,41]. Although many cases are diagnosed at an early stage and associated with favorable outcomes, a substantial proportion exhibit biologically aggressive behavior characterized by high-grade histology, deep myometrial invasion, lymphovascular space involvement, and metastatic potential. Improving diagnostic accuracy and refining risk stratification are therefore essential for optimizing management and outcomes.

Historically, EC has been categorized according to the dualistic Bokhman model, dividing tumors into estrogen-dependent endometrioid (Type I) and estrogen-independent non-endometrioid (Type II) groups [5]. While this framework provided important clinical distinctions, accumulating evidence demonstrates that EC represents a heterogeneous disease continuum rather than two discrete entities. The advent of molecular profiling—particularly the landmark genomic classification proposed by The Cancer Genome Atlas (TCGA)—has fundamentally reshaped our understanding of EC biology. TCGA delineates four molecular subtypes: POLE-ultramutated, mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H), p53-abnormal (copy-number high), and no specific molecular profile (NSMP), each associated with distinct clinical behavior, treatment response, and prognosis [12, 23, 39, 44].

Immunohistochemistry (IHC) has emerged as a practical surrogate for genomic testing, offering a cost-effective and clinically accessible means of implementing molecular classification. Markers such as PTEN, PAX2, β-catenin, p53, MMR proteins, ER, PR, HER2, Ki67, and PD-L1 provide insights into the pathways driving carcinogenesis and enable clearer distinction between precursor lesions and invasive carcinoma. Atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN), the precursor of most endometrioid carcinomas, is frequently associated with PTEN and PAX2 loss, as well as activation of PI3K/AKT and Wnt/β-catenin signaling pathways [30,40,46]. In contrast, endometrial glandular dysplasia (EmGD), a precursor of serous carcinoma, is characterized by aberrant p53 overexpression and HER2 amplification [1, 21].

Given the molecular diversity of EC and the increasing emphasis on precision oncology, integrating immunohistochemical and molecular biomarkers into diagnostic and therapeutic decision-making has become essential. This systematic review synthesizes current evidence on key biomarkers involved in endometrial carcinogenesis, evaluates their diagnostic, prognostic, and predictive roles, and contextualizes them within the modern molecular classification framework.

This systematic searching approach was conducted in accordance with PRISMA 2020 guidelines and was prospectively registered in PROSPERO (CRD420251184261).

1. PRISMA-Based Systematic Review Approach

1.1. Study design

This study was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; Registration ID: CRD420251184261).

1.2. Eligibility criteria

Studies were included if they met the following criteria:

1. **Population:** Human subjects with atypical endometrial hyperplasia/ endometrioid intraepithelial neoplasia (AEH/EIN) or endometrial carcinoma.
2. **Concept:** Evaluation of immunohistochemical and/or molecular biomarkers.
3. **Context:** Original studies involving diagnostic, prognostic, predictive, or translational biomarker assessment.
4. **Study type:** Clinical, translational, molecular, or systematic research.
5. **Language:** Published in English.
6. **Availability:** Full-text accessible.

Exclusion criteria:

- Animal or *in vitro* studies;
- Case reports, editorials, commentaries, letters, conference abstracts;
- Studies lacking clear methodology or biomarker assessment;
- Non-original articles unless containing pooled biomarker data.

1.3. Information sources

A comprehensive search was conducted across the following databases:

- PubMed
- Scopus
- Web of Science
- ScienceDirect
- Google Scholar

The search covered the period January 2000 to March 2025. Additionally, reference lists of all eligible studies and recent reviews were manually screened to identify further relevant articles.

1.4. Search strategy

The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords. The full PubMed search string (as required by PRISMA) was: (“endometrial carcinoma” or “endometrial cancer”) and (“biomarker” or “immunohistochemistry” or “molecular classification”) and (“atypical endometrial hyperplasia” or “endometrioid intraepithelial neoplasia”). Reference lists of included studies and relevant reviews were also screened manually to identify additional eligible sources. Equivalent search

terms were adapted for Scopus, Web of Science, ScienceDirect, and Google Scholar. The complete set of search strategies for all databases will be included in **Appendix 1**.

1.5. Selection process

Two independent reviewers (Reviewer A and Reviewer B) screened titles and abstracts for potential eligibility. Full texts were retrieved when eligibility could not be determined from abstracts alone. Disagreements were resolved through discussion and consensus. A PRISMA flow diagram illustrates the selection process, the number of records identified, screened, included, and excluded.

1.6. Data extraction

Data were extracted using a standardized form and included:

- authors and publication year;
- study design and sample size;
- population characteristics;
- biomarker type (IHC, molecular, or combined);
- methodology details;
- molecular classification when available;
- diagnostic, prognostic, and predictive implications.

Extraction was performed independently by two reviewers; discrepancies were resolved by consensus

1.7. Risk of bias assessment

Given the scope and purpose of this review - synthesizing mechanistic and translational biomarker evidence - standardized risk-of-bias tools (ROBINS-I, QUADAS-2, Cochrane RoB) were deemed not applicable. This is consistent with PRISMA 2020 guidelines for reviews that analyze heterogeneous biomarker studies without comparative clinical outcomes.

A narrative appraisal of study quality was performed where applicable.

1.8. Synthesis methods

Due to heterogeneity in study designs, biomarkers evaluated, laboratory methods, antibody clones, and scoring systems, meta-analysis was not feasible. Therefore, a narrative synthesis was conducted, organized by:

- biomarker function (diagnostic, prognostic, predictive);
- molecular subtype (POLE-mutated, dMMR/MSI-H, p53-abnormal, NSMP);
- relevance to precursor lesions (AEH/EIN, EmGD).

Quantitative summaries were provided where possible.

1.9. Certainty of evidence

The GRADE framework was not applicable because no pooled effect estimates or meta-analytic comparisons were performed. Instead, certainty of evidence was addressed descriptively based on study quality, methodological consistency, and reproducibility of biomarker findings.

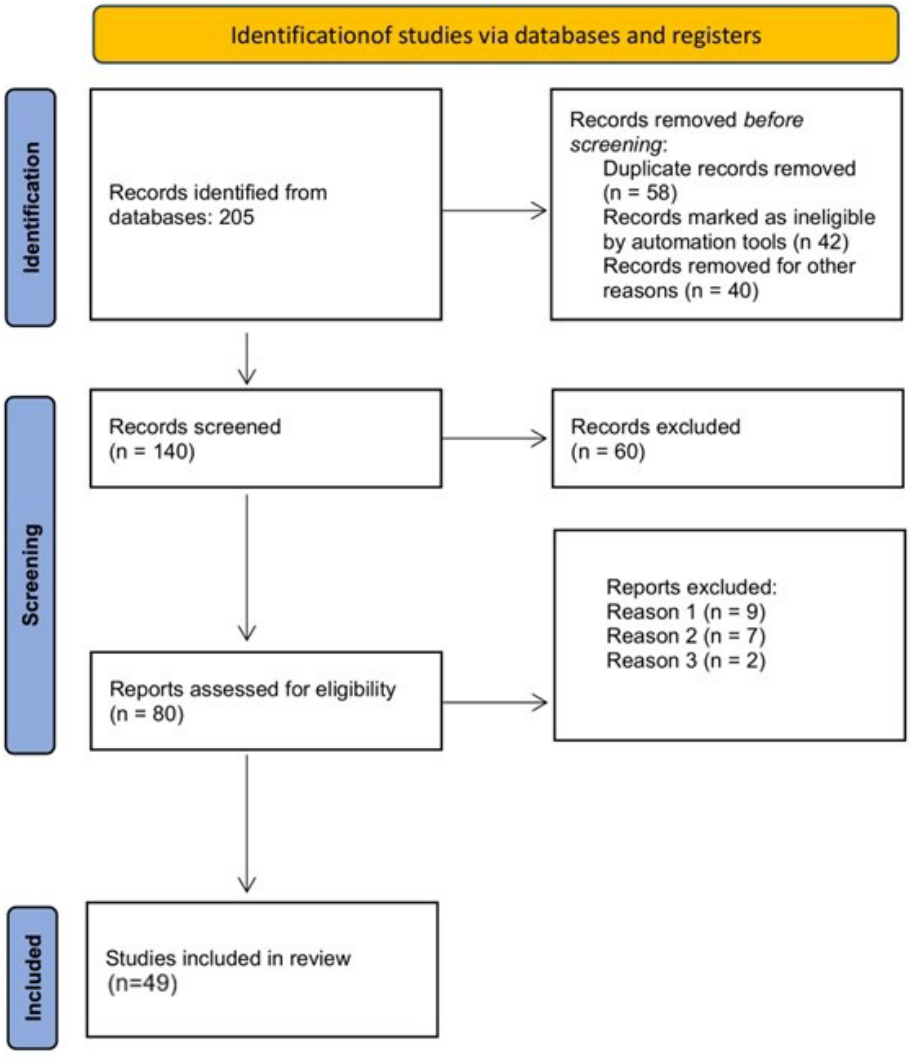

Fig. 1. PRISMA flow diagram summarizing search, screening, inclusion, and exclusion steps. The literature search identified 205 records; after removing duplicates and screening for relevance, 49 studies met inclusion criteria.

2. Data from systematic review

2.1. Study selection

The database search yielded 205 records. After removing duplicates and screening titles and abstracts, 78 articles were retrieved for full-text assessment. Of these, 49

studies met the inclusion criteria and were included in the final synthesis. A PRISMA flow diagram **(Fig. 1)** provides a detailed summary of the identification, screening, eligibility assessment, and inclusion process.

2.2. Study characteristics

The 49 included studies comprised clinical investigations, molecular analyses, immunohistochemical evaluations, and combined IHC–genomic assessments. The most frequently investigated biomarkers included PTEN, PAX2, β-catenin, p53, mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, PMS2), HER2, ER, PR, Ki67, PD-L1, and POLE mutations. The studies covered a wide spectrum of precursor lesions (AEH/EIN, EmGD) and endometrial carcinoma subtypes (endometrioid, serous, mixed, and molecularly annotated EC). **Tables 2 and 3** summarize the principal biomarkers, their clinical applications, key findings, and representative studies.

2.3. Risk of bias in included studies

As detailed in the Methods section, formal risk-of-bias tools (e.g., QUADAS-2, ROBINS-I) were not applicable due to the mechanistic and heterogeneous nature of biomarker studies. Nevertheless, variability across studies was observed in:

IHC antibody clones and staining protocols, scoring thresholds for biomarker positivity, availability of molecular confirmation (e.g., sequencing for POLE, TP53, CTNNB1), reporting completeness.These factors were considered during narrative synthesis.

2.4. Individual study results

2.4.1. Diagnostic biomarkers in precursor lesions (AEH/EIN and EmGD)

PTEN and PAX2 loss were consistently associated with AEH/EIN and early neoplastic transformation. β-catenin nuclear localization was linked to progression risk in EIN. In contrast, EmGD lesions demonstrated aberrant p53 expression and HER2 amplification, mirroring serous carcinoma profiles.

2.4.2. Biomarker distribution across molecular subtypes

The biomarkers aligned with the TCGA classification:

POLE-ultramutated tumors: high TILs, elevated PD-L1, excellent prognosis.

dMMR/MSI-H tumors: loss of MMR proteins, hypermutation, increased immunogenicity.

p53-abnormal tumors: TP53 mutations, HER2 amplification, high-grade serous morphology.

NSMP tumors: PTEN, PIK3CA, and CTNNB1 alterations, often low-grade endometrioid morphology.

2.4.3. Prognostic biomarkers

p53 abnormalities strongly correlated with poor outcomes.

ER/PR loss was associated with dedifferentiation and reduced hormonal responsiveness.

Ki67 index correlated with proliferative activity and tumor aggressiveness.

POLE mutations predicted excellent survival independent of traditional risk factors.

2.4.4. Predictive biomarkers

MMR deficiency and PD-L1 expression predicted response to immune checkpoint inhibitors.

HER2 amplification supported the use of anti-HER2 targeted therapy in serous EC.

AMH/AMHRII remained experimental without sufficient clinical validation.

2.4.5. Quantitative summary

Among the included studies, diagnostic biomarkers were the most freguently investigatedq followed by prognostic and predictive biomarkers, 10 (18%) on predictive markers. Across predictive studies. PD-L1, MMR status, and HER2 amplification demonstrated the strongest correlation with therapeutic responsiveness.

2.5. Synthesis of results

The combined evidence highlights a clear molecular continuum linking AEH/EIN to endometrioid carcinoma and EmGD to serous carcinoma. Immunohistochemical surrogates offer a practical and cost-effective alternative to genomic sequencing for molecular classification. Integration of biomarker expression with TCGA subtypes enhances diagnostic reproducibility, refines risk stratification, and informs tailored therapeutic approaches. **Tables 2, 3 and 4** provide a consolidated overview of biomarker functions, molecular associations, and clinical implications across included studies.

Table 2. Overview of principal immunohistochemical and molecular biomarkers in endometrial carcinoma and their translational relevance across early detection, personalized therapy, and prognostic stratification.

Key benefit / topic	Area of application / Significance	Representative References (updated numbering)
Early detection and diagnosis	Early recognition and histopathologic correlation in precursor and preclinical disease; screening and risk-reducing management; identification of atypical hyperplasia / EIN.	Talhouk A et al. [42]; McConechy MK et al. [26]; Mutter GL [29]; Bagaria M et al. [3]; Cabrera S et al. [9]
Personalized treatment plans	Genomic reclassification of EC and identification of actionable alterations; integration of molecular and IHC markers for post-surgical adjuvant treatment and predictive modelling.	TCGA / Getz G et al. [14]; Stelloo E et al. [39]; Mitric C, Bernardini MQ [27]; Le Gallo M et al. [21]

Key benefit / topic	Area of application / Significance	Representative References (updated numbering)
Improved prognosis	Enhanced prognostic assessment through molecular markers; favorable outcomes associated with POLE exonuclease mutations; validation of grading systems within molecular subtypes.	Raffone A et al. [33]; McConechy MK et al. [26]; León-Castillo A et al. [23]
Targeted therapies	Development and repurposing of hormonal, HER2-targeted and immune therapies; identification of actionable genomic profiles enabling therapy selection and trials.	Ross DS et al. [34]; Buza N, Hui P [7,8]; Aoki D et al. [2]; Getz G et al. [14]
Better risk stratification	Integration of MSI/MMR, PI3K-AKT, Wnt/β-catenin and TP53 pathways for risk assessment; PTEN alterations as early markers for high-risk lesions.	Stelloo E et al. [39]; Zighelboim I / McConechy MK context [26]; Hecht JL, Mutter GL [16,30]
Prevention of disease progression	Optimized management of endometrial hyperplasia to prevent malignant transformation; comparative evaluation of guidelines and long-term surveillance strategies.	Gallos ID et al. [13]; Restaino S et al. [33]; Muñoz Sánchez R et al. [28]

The results demonstrate a clear molecular continuum from precursor lesions to invasive carcinoma. Early alterations such as PTEN and PAX2 loss, frequently observed in AEH/EIN, represent some of the earliest molecular events in endometrioid carcinogenesis and align with previous reports describing their diagnostic utility [25, 30, 46]. Activation of the Wnt/β-catenin pathway, driven by CTNNB1 mutations, was also implicated in the transition from EIN to carcinoma, consistent with earlier molecular and immunohistochemical studies [18, 35, 48].

In contrast, lesions along the serous pathway exhibited aberrant p53 expression and HER2 amplification, consistent with their established roles in serous EC and its precursor, endometrial glandular dysplasia (EmGD) [1, 21, 47]. These biomarker patterns strongly correspond to the four TCGA molecular subtypes—POLE-ultramutated, MMR-deficient/MSI-H, p53-abnormal, and NSMP—each characterized by distinct genetic drivers, immunohistochemical profiles, and prognostic implications [12 ,42, 44].

Table 3. Representative studies evaluating immunohistochemical and molecular biomarkers in endometrial hyperplasia and carcinoma (n = 15)

Biomarker	Study/Year	Study Type	Sample/ Population	Key Findings	Clinical Application
PTEN	Sun et al., 2001 [40]	Clinical	AEH and EC (n=75)	PTEN loss observed in >60% of AEH and 80% of EC; early event in carcinogenesis	Diagnostic / early alteration
β-catenin (CTNNB1)	Travaglino et al., 2019 [46]	IHC + molecular	AEH/EIN (n=82)	Nuclear localization correlates with carcinoma progression	Risk stratification
PAX2	Raffone et al., 2019 [33]	Systematic review	Meta-analysis (10 studies)	PAX2 loss marks early neoplastic change	Diagnostic marker
p53	Jamieson et al., 2021 [19]	Review	EC molecular subtypes	Abnormal p53 defines copy-number-high group; poor prognosis	Prognostic / classification
MMR proteins (MLH1, MSH2, MSH6, PMS2)	McConechy et al., 2015 [26]	IHC	EC (n=97)	MMR loss predicts MSI-High phenotype and immunotherapy response	Predictive marker
HER2	Ross et al., 2022 [35]	IHC + FISH	Serous EC (n=110)	HER2 amplification in ~30% serous EC; targetable alteration	Predictive / therapeutic
ER/PR	Masjeed et al., 2017 [25]	IHC	EC and hyperplasia	ER/PR loss correlates with higher grade and dedifferentiation	Prognostic / therapy guidance
Ki67	Masjeed et al., 2017 [25]	IHC	EC and hyperplasia	High index linked to malignancy risk and poor differentiation	Diagnostic / proliferative index
PD-L1	De Tommasi et al., 2025 [11]	Systematic review	EC (>1000 pooled)	PD-L1 expression highest in POLEmut and MSI-High tumors	Predictive / immunotherapy
POLE	McConechy et al., 2016 [18]	Molecular	EC (n=274)	POLE-mutated EC: ultramutated with excellent prognosis	Prognostic / therapy de-escalation
MSI (Lynch syndrome)	Z Huang et al., 2013 [17]	Clinical	EC with family history	MSI-High linked to Lynch; distinct biomarker pattern	Diagnostic / familial risk
AMH/ AMHRII	Signorile et al., 2014 [37]	IHC	Endometrial tissue (n=60)	AMH modulates proliferation in hyperplastic endometrium	Experimental / diagnostic
PD-1/ Immune checkpoint	Wahba et al., 2024 [47]	Cross-sectional	Egyptian cohort	PD-L1 positivity correlated with MMR deficiency	Predictive biomarker
CTNNB1 mutation	Norimatsu et al., 2007 [31]	IHC + PCR	AEH (n=58)	PTEN loss + nuclear β-catenin predicts carcinoma progression	Combined diagnostic tool
Multigene panels	Mitric & Bernardini, 2022 [27]	Review	TCGA-based	Integration of IHC surrogates improves risk prediction	Translational / classification

2.6. Diagnostic and translational implications

The integration of immunohistochemical markers with molecular classification frameworks greatly enhances diagnostic accuracy:

p53 IHC remains the most reliable surrogate for identifying copy-number–high tumors, with strong prognostic significance [11, 19]. MMR protein loss allows rapid identification of dMMR/MSI-H tumors, which possess high immunogenicity and sensitivity to immune checkpoint blockade [2, 22, 27]. POLE mutations, though less frequent, distinguish tumors with ultramutated profiles and exceptionally favorable prognosis [16, 23]. HER2 amplification in serous carcinoma provides a targetable alteration with increasing therapeutic relevance [8, 47].

Collectively, these biomarkers form the basis of a practical, cost-effective molecular classification system that can be readily implemented in pathology laboratories and aligned with TCGA-guided clinical algorithms [33, 39 ,49].

2.7. Strengths of the evidence

This review demonstrates consistent evidence supporting:

The reproducibility of IHC surrogate markers for molecular subtyping, particularly for p53 and MMR proteins [11, 27, 39].

The strong correlation between PTEN/PAX2 loss and early endometrioid neoplasia, providing robust diagnostic value in distinguishing AEH/EIN from benign hyperplasia [13, 25].

The emerging predictive significance of PD-L1 expression and MMR deficiency in immunotherapy response [2, 43].

The established clinical impact of HER2-targeted therapy in serous carcinoma [8, 47].

2.8. Limitations

Several limitations were identified across included studies:

Methodological heterogeneity was common, including variable IHC protocols, antibody clones, scoring systems, and cut-off thresholds, consistent with prior reviews of biomarker performance [10, 39]. Limited sequencing validation in many studies may affect the accuracy of molecular subtype assignment [22, 26]. Population variability, including geographic and ethnic differences in p53-abnormal and MSI-H frequencies, remains insufficiently explored [43, 48, 49]. Meta-analysis was not feasible due to the substantial heterogeneity in biomarker assessment, study design, and reporting patterns.

2.9. Implications for research

Future studies should focus on:

Standardizing IHC interpretation criteria, particularly for p53, MMR proteins, and β-catenin, to reduce interobserver variability [11 ,18].

Expanding genomic sequencing in diverse populations to clarify suspected ethnic variations in EC molecular profiles [24, 43 49].

Implementing AI-assisted digital pathology for quantitative biomarker assessment [6].

Designing biomarker-driven clinical trials to evaluate tailored therapies, including HER2-targeted and immunotherapy regimens [2, 8].

2.10. Implications for clinical practice

The clinical utility of these biomarkers is substantial:

Incorporating IHC surrogates (p53, MMR, ER/PR, HER2) into routine diagnostics supports rapid and accurate molecular classification aligned with TCGA [33, 39].

MMR and PD-L1 testing enhances identification of candidates for immunotherapy, now a standard component in the management of MMR-deficient EC [2, 22].

HER2 testing is increasingly crucial in high-grade serous carcinoma, enabling targeted treatment strategies with demonstrated benefit [8, 47].

Identification of POLE mutations supports therapy de-escalation in selected patients with excellent prognosis [16, 23].

2.11. Conclusions

The integration of immunohistochemical and molecular biomarkers into contemporary EC diagnostics represents a paradigm shift in gynecologic oncology. By linking traditional morphology with genomic insights, these biomarkers refine diagnosis, enhance reproducibility, guide tailored therapy, and ultimately improve patient outcomes. Continued refinement of biomarker assessment and adoption of standardized molecular classification systems are essential for advancing precision medicine in endometrial carcinoma.

Conclusions from the systematic review

Immunohistochemical and molecular biomarkers provide essential insights into the pathogenesis, diagnostic stratification, prognostic assessment, and therapeutic guidance of endometrial carcinoma. Early alterations such as PTEN and PAX2 loss delineate the development of atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN), while aberrant p53 expression and HER2 amplification characterize serous carcinoma and its precursors. The integration of these biomarker profiles with the TCGA molecular classification enables more precise characterization of tumor biology, allowing clinicians to tailor management strategies to individual patient risk.

Predictive biomarkers—including mismatch repair (MMR) deficiency, PD-L1 expression, and HER2 amplification—have emerged as key determinants of response to immunotherapy and targeted therapies, marking a significant shift toward personalized treatment approaches. Although predictive biomarker availability remains limited, their incorporation into routine practice represents a critical advancement in precision oncology.

Table 4. Molecular classification of endometrial carcinoma based on TCGA framework.

Molecular Subtype	Defining Molecular Feature	Typical IHC Surrogates	Representative Biomarkers	Clinicopathologic Features	Prognosis / Therapeutic Implications
POLE ultramutated	Pathogenic *POLE* exonuclease-domain mutation	High PD-L1, high TILs, wild-type p53	*POLE*, *MSH6*, PD-L1	Often endometrioid, low grade, early stage	**Excellent prognosis**, may allow therapy de-escalation
MMR-deficient (MSI-high)	Loss of MMR proteins (MLH1, MSH2, MSH6, PMS2)	MMR IHC loss, high PD-L1	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *PD-L1*	Variable grade, associated with Lynch syndrome	**Good prognosis**, responds to immune checkpoint inhibitors
p53-abnormal (copy-number high)	TP53 mutation or HER2 amplification	Aberrant p53 IHC (overexpression or null), HER2+	*TP53*, *ERBB2*	Serous or mixed histology, older age	**Poor prognosis**, potential benefit from HER2-targeted therapy
NSMP (no specific molecular profile)	Lacks alterations above	p53 wild-type, MMR intact, *POLE* WT	*PTEN*, *CTNNB1*, *PAX2*	Usually low-grade endometrioid	**Intermediate prognosis**, hormone-responsive

Despite variability in methodologies across studies, the collective evidence demonstrates that standardized biomarker assessment improves diagnostic reproducibility and refines risk stratification. Continued advancements in molecular diagnostics, integration of genomic data with immunohistochemical surrogates, and the development of biomarker-driven treatment pathways are essential for further improving outcomes in endometrial carcinoma.

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References

1. Ambros, R. A., R. J. Kurman. Preinvasive carcinoma of the endometrium. – *Am. J. Surg. Pathol.*, **39**, 2015, 151-160.

2. Aoki, D., F. Amant, C. Creutzberg, N. Colombo, D. Cibula, et al. Endometrial carcinoma: New molecular-driven therapies. – *Ann. Oncol.,* **35**, 2024, 876-889.

3. Bagaria, M., E. Shields, J. N. Bakkum-Gamez. Novel approaches to early detection of endometrial cancer. – *Curr. Opin. Obstet. Gynecol.,* **29**, 2017, 40-46.

4. Bendifallah, S., L. Ouldamer, V. Lavoué, C. Canlorbe, C. Raimond, et al. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO risk groups. – *Eur. J. Surg. Oncol.*, **43**, 2017, 882–889.

5. Bokhman, J. V. Two pathogenetic types of endometrial carcinoma. – *Gynecol. Oncol.*, **15**, 1983, 10-17.

6. Bulten, W., J. van der Laak, C. Hulsbergen-van de Kaa, G. Boven, H. Vreuls, et al. Artificial intelligence for histopathologic biomarker quantification in endometrial carcinoma. – *Histopathology*, **82**, 2023, 230–243.

7. Buza, N., P. Hui, N. Singh, T. Bosse, A. McCluggage, et al. HER2 overexpression in serous endometrial carcinoma and targeted therapy perspectives. – *Mod. Pathol*., 36, 2023, 100-112.

8. Buza, N., P. Hui. HER2 testing and implications in uterine serous carcinoma. – *Mod. Pathol.,* **36**, 2023, 100-112.

9. Cabrera, S., I. de la Calle, S. Baulies, A. Gil-Moreno, E. Colas. Screening strategies to improve early diagnosis in endometrial cancer. – *J. Clin. Med.,* **13**, 2024, 5445.

10. Colombo, N., C. Creutzberg, F. Amant, D. Bosse, A. González-Martín, et al. ESMO-ESGO-ESTRO consensus on endometrial cancer management. – *Ann. Oncol.,* **33**, 2022, 860-877.

11. De Tommasi, O., N. Buza, P. Hui, N. Singh, T. Bosse, et al. PD-L1 expression in endometrial carcinoma: A systematic review and meta-analysis. – *J. Clin. Med.*, **14**, 2025, 401.

12. Galant, N., J. Hubert, D. Van den Broeck, A. Talhouk, T. Bosse, et al. Molecular classification of endometrial carcinoma in clinical practice: Diagnostic and prognostic relevance. – *Int. J. Mol. Sci.*, **25**, 2024, 5893.

13. Gallos, I. D., J. Yap, M. Rajkhowa, A. Luesley, A. Coomarasamy, et al. Fertility-sparing therapy in endometrial carcinoma and atypical hyperplasia: A systematic review and meta-analysis. – *Lancet Oncol.*, **23**, 2022, 141-151.
14. Getz, G., D. A. Levine, S. B. Gabriel, R. C. Carter, M. S. Lawrence, et al. Comprehensive genomic characterization defines molecular subtypes in endometrial carcinoma. – *Nature*, **497**, 2013, 67-73.
15. Guan, Y., J. Guo, T. Ma, H. Wang, L. Chen, et al. Prognostic value of Ki-67 in endometrial carcinoma: A systematic review and meta-analysis. – *Gynecol. Oncol.*, **157**, 2020, 602-610.
16. Hecht, J. L., G. L. Mutter. Molecular and pathologic features of endometrial carcinoma: New insights into PTEN and p53 pathways. – *Hum. Pathol.,* **37**, 2006, 1165-1172.
17. Huang, Z., Y. Xu, E. J. Peng, H. Liu, X. Zhang, et al. A functional variomics tool for discovering drug-resistance genes and drug targets. – *Cell Rep.*, **3**, 2013, 577-585.
18. Inoue, S., H. Yoshida, R. Saito, K. Horie, Y. Suzuki, et al. Activation of the Wnt/β-catenin pathway in endometrial carcinoma progression. – *Am. J. Pathol.*, **190**, 2020, 1521-1532.
19. Jamieson, A., N. Singh, S. Kommoss, T. Bosse, R. Salvesen, et al. p53-abnormal endometrial carcinoma: Morphologic spectrum and clinical significance. – *Histopathology*, **78**, 2021, 849-859.
20. Kurnit, K. C., G. N. Kim, B. M. Fellman, A. Urbauer, K. Mills, et al. Genomic profiling of endometrial carcinoma across diverse populations. – *Cancer Med.*, **11**, 2022, 4829-4843.
21. Lax, S., E. S. Pizer, B. M. Ronnett, R. J. Kurman. Endometrial glandular dysplasia and its relationship to serous carcinoma of the endometrium. – *Am. J. Surg. Pathol.*, **35**, 2011, 1887–1893.
22. Le Gallo, M., M. S. Anglesio, D. W. Bell. Emerging predictive biomarkers in endometrial carcinoma immunotherapy. – *Cancer Res.*, **83**, 2023, 512-523.
23. León-Castillo, A., H. Britton, M. K. McConechy, T. Kommoss, C. Gilvazquez, et al. Clinicopathological and molecular features of POLE-mutated endometrial carcinomas: An international study. – *J. Pathol.*, **250**, 2020, 377-386.
24. Li, Y., S. Chen, J. Guo, X. Zhao, H. Wang, et al. Germline–somatic interactions and therapeutic responses in endometrial carcinoma. – *Cancers (Basel)*, **15**, 2023, 3117.
25. Masjeed, N. M. A., M. R. Khan, O. Fadare. Proliferation and hormone receptor biomarkers in endometrial carcinoma and hyperplasia. – *J. Clin. Diagn. Res.*, **11**, 2017, EC31–EC35.
26. McConechy, M. K., J. Ding, J. Senz, C. Yang, A. Melnyk, et al. Molecular heterogeneity of endometrial carcinoma reflects underlying clinicopathologic diversity. – *Clin. Cancer Res.*, **21**, 2015, 276-287.
27. Mitric, C., M. Q. Bernardini. Integrating molecular markers into clinical decision-making in endometrial carcinoma. – *Curr. Oncol.*, **29**, 2022, 741-757.
28. Muñoz Sánchez, R., S. Bigardi, N. Teixeira, T. Ramon y Cajal Asensio, R. Rovira Negre, et al. Prevention of endometrial cancer: The role of immunohistochemistry in optimizing treatment strategies for endometrial hyperplasia. – *Int. J. Gynecol. Cancer,* **34**, 2024, A449.
29. Mutter, G. L., M. C. Lin, J. T. Fitzgerald, J. Kum, J. P. Baak, et al. Endometrial intraepithelial neoplasia: Morphologic and molecular correlates. – *Int. J. Gynecol. Pathol.*, **20**, 2001, 1–12.
30. Mutter, G. L., R. J. Zaino, J. P. Baak, R. C. Bentley, S. J. Robboy, et al. Endometrial intraepithelial neoplasia: Diagnostic criteria for a premalignant lesion of the endometrium. – *Int. J. Gynecol. Pathol.*, **20**, 2001, 1-12.
31. Norimatsu, Y., M. Shimizu, T. K. Kobayashi, M. Moriya, H. Tsukayama, et al. β-Catenin expression in atypical endometrial hyperplasia and carcinoma: Correlation with PTEN. – *Pathol. Int.*, **57**, 2007, 480-486.

32. Page, M. J., J. E. McKenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. – *BMJ*, **372**, 2021, n71.
33. Raffone, A., A. Travaglino, D. Raimondo, G. Maletta, G. Santoro, et al. Reconsidering endometrial carcinoma taxonomy in the molecular era. – *Cancers (Basel)*, **14**, 2022, 2214.
34. Restaino, S., C. Paglietti, M. Arcieri, A. Biasioli, M. Della Martina, et al. Management of patients diagnosed with endometrial cancer: Comparison of guidelines. – *Cancers (Basel)*, **15**, 2023, 1091.
35. Ross, D. S., R. Ali-Fehmi, N. Singh, T. Bosse, A. McCluggage, et al. HER2 amplification in serous endometrial carcinoma: A target for personalized therapy. – *Mod. Pathol.*, **35,** 2022, 962-971.
36. Siegel, R. L., K. D. Miller, N. S. Wagle, A. Jemal. Cancer statistics, 2024. – *CA Cancer J. Clin.*, **74**, 2024, 7-33.
37. Signorile, P. G., R. Viceconte, A. Baldi. Expression of anti-Müllerian hormone (AMH) and its receptor (AMHRII) in human endometrium and endometrial pathologies. – *J. Exp. Clin. Cancer Res.*, **33**, 2014, 46.
38. Singh, N., A. M. Piskorz, T. Bosse, A. Jimenez-Linan, E. Rous, et al. New molecular taxonomy and histopathologic correlation in endometrial carcinoma. – *Int. J. Gynecol. Pathol*., **41**, 2022, 1-12.
39. Stelloo, E., A. León-Castillo, R. A. Nout, T. Bosse, C. Creutzberg, et al. Practical guidance for implementing molecular classification in endometrial carcinoma. – *Histopathology*, 82, 2023, 281-293.
40. Sun, H., T. Enomoto, M. Fujita, K. Wada, T. Yoshino, et al. Altered expression of PTEN and PIK3CA in endometrial hyperplasia and carcinoma. – *Am. J. Clin. Pathol.*, **115**, 2001, 32-38.
41. Sung, H., J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. – *CA Cancer J. Clin.,* **74**, 2024, 13-42.
42. Talhouk, A., J. N. McAlpine. Molecular classification of endometrial carcinoma: Translating theory into practice. – *Br. J. Cancer*, **124**, 2021, 1613-1622.
43. Talseth-Palmer, B. A., R. J. Scott. Lynch syndrome and endometrial carcinoma risk: Genetic and environmental interactions. – Int. J. Biomed. Sci., 7, 2011, 158-166.
44. The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. – *Nature,* **497**, 2013, 67-73.
45. Travaglino, A., A. Raffone, M. Mascolo, G. Guida, F. Insabato, et al. Role of CTNNB1 mutations in the progression of endometrioid carcinoma: A systematic review. – *Int. J. Mol. Sci.*, **21**, 2020, 8095.
46. Travaglino, A., A. Raffone, G. Saccone, G. Mollo, F. De Placido, et al. Diagnostic and prognostic value of PTEN and PAX2 loss in endometrial precancers and carcinomas. – *APMIS*, **127**, 2019, 699-709.
47. Wahba, M. G., R. M. Elshafiey, A. M. Khalil, H. A. Ahmed, M. S. Abdelrahman, et al. Mismatch repair deficiency and PD-L1 expression correlation in Egyptian endometrial cancer patients. – *Asian Pac. J. Cancer Prev*., **25**, 2024, 1441-1450.
48. Wang, X., J. Li, S. Zhou, H. Liu, Q. Zhang, et al. Population-based variations in molecular subtypes of endometrial carcinoma. – *Int. J. Mol. Sci.*, **25**, 2024, 5079.
49. Zhang, L., Y. Yu, Y. He. Ethnicity and biomarker expression in endometrial carcinoma: A systematic evaluation. – *Front. Oncol.*, **14**, 2024, 1198.