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Molecular Classification and Emerging Targeted Therapy in Endometrial Cancer

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Abstract

Recent advances in molecular studies, especially genome-wide analyses, have revealed the landscape of genomic alterations present in endometrial carcinomas, and have provided valuable insight into the pathogenesis of this disease. The current challenges are in developing a molecular-morphological classification system to enhance traditional pathologic diagnosis and in determining the optimal approach to using this new information to guide clinical management. Molecular assays may be particularly beneficial in allowing the earlier detection of endometrial cancer or precursor lesions and in guiding personalized treatment approaches. In this review, we describe the current molecular landscape of endometrial cancers, efforts underway to incorporate molecular alterations into the current classification systems, and the development of diagnostic tools for the early detection of endometrial cancer. Finally, we present opportunities for using these data to tailor therapeutic strategies. A comprehensive understanding of the molecular alterations responsible for the origination, relapse, and resistance patterns of this disease will ultimately improve outcomes for patients with endometrial cancer.

Keywords

endometrial cancer; molecular classification; targeted therapy

Introduction

Uterine cancer is the most common cancer of the female reproductive organs in the United States, of which endometrial carcinomas account for more than 90% of cases [1, 2]. The

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incidence of uterine cancer is increasing at an alarming rate with an estimated 63,230 new cases in the United States in 2018 compared to 47,130 in 2012 [2, 3]. Endometrial cancer is one of the cancer types in the US in which clinical outcome is related to health disparity [4, 5]. Most patients diagnosed with endometrial cancer are postmenopausal with a median age at diagnosis of 60 years [1]. However, up to 14% of cases occur in premenopausal women [6], largely as a consequence of elevated body mass index (BMI) [7] which has been increasing in the US over the past two decades [8, 9]. Five-year survival rates for endometrial cancer vary according to stage at diagnosis. In patients with tumors localized to the uterus the 5-year survival rate is 95%, but decreases dramatically when the disease has escaped the uterus, with rates of 69% in patients with regional metastasis and 17% in those with distant metastatic disease [10]. Most endometrial cancers are sporadic, though some hereditary cases are caused by germline mutations, predominantly in mismatch repair (MMR) genes [11]. Understanding the molecular alterations involved in endometrial cancer provides an opportunity to (1) improve upon the current histologic classification system, (2) enhance diagnostic testing modalities, and (3) personalize treatments through the incorporation of targeted therapies. Here, we highlight from a clinical perspective, the implications of emerging molecular characteristics on classification of subtypes, development of diagnostic testing, and therapeutic options.

Current pathologic classification of endometrial cancer

Historically, the first subtype classification of endometrial carcinoma, as proposed by Bokhman in 1983, distinguished between Type I and Type II endometrial cancers based on clinical and hormonal features [12]. Today, the histologic classification of endometrial cancers is predicated on tumor morphology and tumor grade (based on glandular architecture and nuclear grade). The genetic profiling of different histologic subtypes has led to the understanding that they can be distinguished by defining early driver mutations, though overlap in genetic profiles exists [13].

Endometrial carcinomas are histologically classified according to the World Health Organization (WHO) classification system, and are divided into the following subgroups: endometrioid, serous, clear cell, mixed cell adenocarcinoma, and other relatively rare types including mucinous adenocarcinoma, neuroendocrine tumors (further divided to small cell, large cell carcinoma, or carcinoid tumor), dedifferentiated carcinoma and undifferentiated carcinoma. Figure 1 illustrates the approximate proportions of each major subtype of endometrial cancer. Figure 2 shows the gross and microscopic appearance of subtypes based on the WHO histological classification of uterine tumors.

Endometrioid endometrial carcinoma (EEC) accounts for 70 to 80% of all endometrial cancers [14]. Tumor grade is an important prognostic feature and grade 3 EEC are highly aggressive, accounting for a large proportion of endometrial cancer-related deaths [15]. Uterine serous carcinoma is the second most common histologic subtype, accounting for 10% of all endometrial cancers. It is highly aggressive and associated with early development of extrauterine disease at advanced stage (45% of serous carcinomas versus 9% of grade 1–2 endometrioid carcinomas are diagnosed at stage III or IV) [16, 17]. Endometrial clear cell carcinoma (ECCC) accounts for less than 6% of all endometrial

cancer [18]. While ECCC has typical features of Type II tumors — it is not hormone related, it is associated with atrophic endometrium, and it usually exhibits aggressive behavior and poor prognosis [19], it also shares characteristics of Type I endometrioid tumors with respect to immunohistochemical and molecular profiles [19, 20]. Carcinosarcomas, formerly known as malignant mixed Mullerian tumors (MMMTs), are composed of both high-grade carcinomatous and sarcomatous elements [21]. While classified as a mixed epithelial and mesenchymal tumor under the WHO system, the clinical risk factors and behaviors of carcinosarcomas are more similar to epithelial endometrial cancers than to sarcomas, and thus are staged and treated as high-grade endometrial cancers [22–25].

Limitations of the current classification systems

Classification by histology provides important prognostic information and is useful in determining appropriate surgical and adjuvant therapy. However, the current classification system could be improved through the incorporation of molecular determinants [26, 27].

There is frequently overlap between histologic subtypes and grade determination complicating clinical decision making. Grade 3 endometrioid carcinomas can be difficult to distinguish from serous carcinomas. Because of the propensity of serous carcinomas to metastasize early, chemotherapy is favored for treatment of early stage serous carcinomas, while radiation may be considered for similar stage grade 3 endometrioid carcinomas [22, 28]. Thus, correctly identifying the subtype greatly influences clinical care. Similarly, the clinical approach to treatment of a high-grade neuroendocrine carcinoma differs from the approach to treatment of an undifferentiated endometrial carcinoma despite histologic overlap [29]. Furthermore, grade 3 endometrioid cancers frequently share grade 1 endometrioid immunostaining patterns such as high cyclin D1 expression and low HER2 expression, but may exhibit aggressive nuclear features, lymphovascular invasion, and reduced hormone receptor expression [12]. Incorporation of molecular determinants to distinguish grade or subtype has the potential to simplify classification and clarify treatment approaches.

Histologic classification is further hampered by significant interobserver variability, which leads to inconsistent clinical approaches from center to center, and creates challenges in histologic stratification for clinical trials based on local pathology review [30–34]. While the application of rigorous criteria may limit interobserver variability, it is unlikely to completely resolve this issue. However, inclusion of precise molecular characterization has the potential to ensure consistency in diagnosis.

Characterization of endometrial cancers using immunohistochemical markers including p53, PTEN, ER, PR, and others has been helpful in differentiating between subtypes. Molecular features and genetic alterations associated with the major clinical-histologic categories further refine this distinction (Table 1). For example, significant genetic alterations seen in uterine serous carcinoma and endometrioid carcinoma can be helpful to differentiate these similar histologic types of endometrial cancer (Figure 3). Recently, advances in molecular characterization techniques, such as next-generation sequencing, have led to a deeper understanding of the molecular alterations that drive the pathogenesis of endometrial cancer. The incorporation of molecular classification into the standard histologic classification

schema has the potential to more precisely define the various subtypes of endometrial cancer and to guide development and use of molecular diagnostic techniques and targeted therapies. It will, of course, be essential to demonstrate that these techniques result in improved diagnostic accuracy and clinical outcomes in a cost-effective manner.

Molecular Classification

In 2013, The Cancer Genome Atlas (TCGA) Research Network reported a large scale, comprehensive, and integrated genomic analysis of 373 endometrial carcinomas. The study entailed whole exome sequence analysis, transcriptome sequence analysis, genomic copy number analysis, protein array analysis, microsatellite stability testing, and methylation profiling. The analyses identified four categories of endometrial carcinomas with distinct clinical, pathologic, and molecular features: *POLE* (ultra-mutated) (7%), microsatellite instability (MSI)/hypermutated (28%), copy number low/microsatellite stable (39%), and serous-like/copy number high (26%) [35]. These TCGA subgroups and associated molecular alterations correlate with and subdivide histologic subgroups of endometrial carcinomas (Figure 1).

POLE ultra-mutated is a subgroup characterized by somatic mutations in the polymerase epsilon DNA polymerase (*POLE*) exonuclease domain and its mutation results in a remarkably high mutation rate (232×10^{-6} mutations per Mb). The *POLE* ultra-mutated subgroup is composed of low-grade and high-grade endometrioid carcinomas. Interestingly, despite a high proportion of grade 3 endometrioid tumors in this subgroup, cancers in the ultra-mutated subgroup, irrespective of tumor grade, showed excellent prognosis with no recurrences [35, 36]. Similarly, a cohort of *POLE*-mutated endometrial carcinomas showed favorable prognosis despite a significant proportion exhibiting high-grade histology, morphologic heterogeneity, severe nuclear atypia, and *TP53* mutations [37, 38].

MSI hypermutation originates from deficiencies in the DNA mismatch repair (MMR) system. In the TCGA study, the majority of tumors in the MSI cluster showed decreased MLH1 mRNA expression secondary to promoter methylation, an indication of somatic loss of expression. Similar to the *POLE* subgroup, the MSI subgroup was composed exclusively of endometrioid tumors of grades 1–3. Common mutations in the MSI subgroup include *ARID5B* mutations, *PTEN* mutations, and mutations in the phosphatidylinositol-3-kinase family genes including *PIK3CA* and *PIK3R1* [35].

The TCGA study also identified two distinct molecular subgroups based on copy number alterations: a copy number (CN) low subgroup and a CN high subgroup. The CN low group is also called microsatellite stable, and includes more than half of low-grade endometrioid tumors. Conversely, almost all serous carcinoma (97.7%) and the majority of mixed type carcinomas (75%) belong to the CN high subgroup. These findings are consistent with the known aneuploidy and unstable chromosomal DNA typical of serous carcinomas [39–41]. In general, tumors in the CN high subgroup exhibit the least favorable prognosis among the four molecular subgroups [42, 43].

These molecular analyses not only offer new insights into the molecular determinants of the various types of endometrial cancer but also provide a gateway for using molecular

classification in combination with histopathologic features in routine pathology practice. While the TCGA study provided a comprehensive molecular analysis of endometrial cancers, there are practical limitations to using this approach in routine practice. To be clinically useful, the methodologies used in a molecular classification system need to be feasible, reproducible, and cost effective [44].

The Leiden/Trans PORTEC and Vancouver/ProMisE Studies

Two studies, Leiden/Trans PORTEC and Vancouver/ProMisE, have evaluated approaches to generating practical and feasible molecular classification systems. Although the subgroups of these two studies are not identical to the TCGA study, they integrate similar molecular alterations, assigning molecular classification according to MSI status, *POLE* mutation, and *TP53* mutation/p53 expression [44]. The PORTEC study defined four prognostic subgroups: *TP53*-mutant, microsatellite instability (MSI), *POLE*-mutant, and no specific molecular profile (NSMP) by testing p53 expression/*TP53* mutation, MMR gene expression by IHC, and Sanger sequencing for *POLE* hotspot mutations [45, 46]. The *p53* group exhibited unfavorable prognosis compared to the other three groups, while the *POLE*-mutant group showed the most favorable prognosis [46].

Separately, the Proactive Molecular Risk classification tool for Endometrial cancers (ProMisE) [47] aimed to provide more accurate diagnosis in endometrial biopsy or curettage before hysterectomy. This approach entailed MSH6 and PMS2 immunohistochemistry (IHC), *POLE* sequencing, and p53 IHC [44]. Tumors in the *POLE* subgroup had the most favorable prognosis, while those with abnormal p53 showed the worst [48]. This observation is similar to findings in the PORTEC studies [45, 46]. Importantly, molecular analysis of biopsy and curettage specimens accurately predicted the molecular characteristics of the final uterine specimen.

The molecular classification schema described in these recent studies represent significant refinements in the diagnosis and prognosis of endometrial neoplasms. Current efforts are underway to identify the best combination of molecular markers to be used in a diagnostic panel, and to illuminate the clinical impact of incorporating molecular classification in routine pathology reports. It will be essential to validate that use improves outcomes for endometrial cancer patients in prospective clinical trials.

Early Detection of Endometrial cancer

The development of a molecular classification system will not only improve routine pathologic practice but has the potential to enhance early diagnostic approaches. Increased sensitivity and improving costs of next generation sequencing make these approaches potentially feasible in the near term.

The PapSEEK Test is being developed to identify early endometrial cancer prior to development of symptoms or advanced stage. The strategy capitalizes on the finding that epithelial cells and their DNA are shed from uterine lining or fallopian tubes and migrate to the endocervical mucosa where they can be collected by cervical cytobrush. While the Pap test is generally not successful at detecting endometrial and ovarian cancers [49, 50], the advantage of the PapSEEK test is the use of ultrasensitive next generation sequencing to

detect tumor DNA with cancer driving alterations from early ovarian and endometrial cancer lesions even when cells are not available for histologic assessment [51]. In the initial proof-of-concept study, a panel of 12 genes including *PTEN*, *PIK3CA*, *KRAS*, *FBXW7*, *CTNNB1*, *BRAF*, and *TP53*, which are commonly mutated in endometrial and ovarian cancers, were examined using whole-exome sequencing of liquid-based Pap smear samples from patients with endometrial or ovarian cancer. This approach was able to detect endometrial and ovarian cancer with a 100% and 41% sensitivity, respectively, even in the very early stages of disease.

The PapSEEK test is undergoing further refinement to improve sensitivity and specificity through the incorporation of a greater number of genes sequenced and using an improved sampling approach (Tao brush) [52]. The Tao brush is an intrauterine sampling tool that can acquire samples closer to endometrial or ovarian lesions than can be obtained by Pap brush providing improved sampling capability. Detection of mutations in 18 genes and tests for aneuploidy were performed on DNA samples purified from plasma, Pap brush samples, and Tao brush samples from patients with endometrial cancer. Of 382 patients sampled by Pap brush, 81% tested positive, whereas of 123 patients sampled by Tao brush 93% tested positive. The most commonly mutated genes detected in Pap brush and Tao brush samples were similar, and notably included *PTEN*, *TP53*, *PIK3CA*, *PIK3R1*, *CTNNB1*, *KRAS*, *FGFR2*, *POLE*, and *PPP2R1A*.

Further efforts are underway to increase the sensitivity/specificity of the PapSEEK test and validate its use as for early detection of endometrial and ovarian cancer, especially in high-risk women.

Molecular Alterations Identify Potential Targeted Therapies

Molecular testing to personalize therapeutic approach is becoming more commonplace. Multiple targeted therapies have been evaluated for the treatment of endometrial cancer in recent years, and some have recently received FDA approval. Common alterations in molecular signaling pathways of endometrial cancers have well recognized functional effects on cellular DNA, cell proliferation, and cell invasion (Figure 4). These provide potential targeted approaches for the treatment of endometrial cancer.

Endocrine Therapy.—Endocrine therapy is often considered for the treatment of recurrent metastatic endometrial cancer or for initial therapy in patients for whom cytoreductive surgery and cytotoxic chemotherapy is not feasible. A recent meta-analysis showed modest response rates to endocrine therapy in endometrial cancer [53]. Characteristics favorable for response to endocrine therapy include Grade 1 or 2 endometrioid tumors, expression of estrogen receptor (ER) and progesterone receptor (PR), and low disease burden [54]. ER/PR expression is an often used indicator for endocrine therapy, however tumors with negative ER/PR expression may also respond to endocrine therapy [55]. Quantitative assessment of nuclear hormone receptor expression and response to therapy have not been as well determined as in breast cancer. This will be necessary to more effectively guide the use of endocrine therapy. In addition, mutations in *ESR1* (the gene encoding ERalpha) conferring constitutive activity are emerging as resistance

mechanisms to endocrine therapy in gynecologic malignancies, similar to the emergence of these mutations in endocrine resistant breast cancer [56].

Targeting HER2/Neu.—*ERBB2* oncogene amplification and overexpression of its encoded proteins (HER2/Neu) are significantly associated with uterine serous carcinoma, and are considered a negative prognostic indicator [57–59]. Under investigation is trastuzumab, a humanized monoclonal antibody against HER2/Neu, which has been associated with improved outcomes in recurrent, metastatic, or progressive uterine serous carcinomas [60–62]. Recently, a multi-institution prospective randomized phase II clinical trial showed improved progression-free survival with the addition of trastuzumab to paclitaxel/carboplatin-based chemotherapy [63]. Ongoing efforts are focused on developing a consensus HER2 scoring methodology to differentiate unique HER2/Neu features and testing algorithms for HER2-positive endometrial tumors [64].

Immune Checkpoint Inhibitors.—Immune checkpoint inhibitor, anti-PD-1 monoclonal antibody, has been in the research spotlight because of early successes in treating several types of cancers [65–68]. Pembrolizumab, an anti-PD-1 drug, has received FDA approval for the treatment of recurrent MMR-deficient or MSI-high tumors based on impressive response [69, 70]. MMR-deficiency and MSI-high status are associated with increased somatic mutations and higher neoantigen loads leading to increased tumor infiltration by cytotoxic T cells. Tumors harboring *POLE* mutations are also expected to have favorable responses due to the ultra-high mutation burden [71].

Targeting PI3K-AKT-mTOR Pathway.—The phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signal pathways are commonly altered in endometrial cancers leading to aberrant cell proliferation, increased protein synthesis, and angiogenesis [72]. mTOR inhibitors such as everolimus, temsirolimus, and ridaforolimus have shown modest clinical efficacy for endometrial cancer and continue to be investigated [73–78]. Combinations of mTOR inhibitors and other agents (e.g., temsirolimus and bevacizumab) have shown some activity but are also associated with significant toxicity [79]. Recently, the GOG 3007 study showed that a combination of everolimus and letrozole improves progression-free survival especially for chemo-naïve recurrent endometrial cancer [80]. Widespread application of these agents as standard of care for endometrial cancers will depend on final assessment of toxicity and tolerance.

Developmental Therapeutics for ARID1A Mutated Tumors.—ARID1A (AT-rich interactive domain 1A, aka BAF250A) is a member of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex [81]. *ARID1A* is the most commonly mutated gene among all members of chromatin remodeling genes, and inactivating *ARID1A* mutations can frequently be detected in a wide spectrum of human malignancies, particularly in endometrium-derived carcinomas [82, 83]. Inactivating *ARID1A* mutations are commonly detected in endometrioid endometrial carcinomas and are associated with worse prognosis [84]. Immunohistochemical analysis has demonstrated that the frequency of loss of ARID1A expression (presumably due to mutations) is associated with tumor progression from complex atypical hyperplasia to endometrioid carcinoma [85, 86].

ARID1A mutation can be used as a biomarker for identifying early stage cancer or for assessing new therapies. Preliminary data has shown that loss of *ARID1A* expression in endometrial biopsies (or curettage) from cases in which complex atypical hyperplasia was present may predict the presence of concurrent endometrioid endometrial cancer in the subsequent hysterectomy specimens [87]. *ARID1A* mutation may also sensitize cancer cells to *EZH2* inhibitor therapy because of synthetic lethality [88]. Similarly, *ARID1A* mutation can sensitize tumor cells to *PARP* inhibitor and conventional chemotherapeutic drugs because of its role in DNA damage repair [89]. These recent findings are being evaluated in clinical trials to determine their clinical benefit for patients with endometrial carcinomas.

Conclusions

Since publication of the TCGA data in 2013 [35], there have been extensive efforts toward incorporating molecular testing into routine clinical histologic diagnostic evaluation [30]. Although there is no current consensus on which tests to perform, it is clear that certain molecular tests, such as the evaluation of mismatch repair, *POLE*, and *HER2*, are important because of the potential efficacy of immune checkpoint inhibitors and other targeted therapies. Ongoing efforts are aimed at illuminating the clinical benefit of molecular testing alone or in combination with conventional morphology-based diagnostics, and at improving characterization of specific molecular genetic alterations for targeted therapy. In addition to driving selection of personalized therapy, these tests will be useful as prognostic tools and for the development of early detection methods. Over the next few years, a comprehensive understanding of the molecular patterns of the origin, relapse, and resistance of endometrial cancer is likely to emerge and promises improved outcomes for patients with endometrial cancer.

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Fig. 1. Associations of histological and TCGA classifications in endometrial cancer.

The outer circle shows the histological types of endometrial carcinoma. Seromucinous is a rare histological type and not shown. The inner circle shows the molecular classification of endometrioid and serous tumors based on subgroups identified in TCGA: *POLE* ultra-mutated group, MSI hypermutated group, copy number (CN) low and high groups. TCGA did not analyze clear cell carcinoma, carcinosarcoma, or poorly differentiated tumors. The outer boxes list various molecular signaling pathways altered in endometrial cancer. CCC, clear cell carcinoma; HG, high grade; LG, low grade; MMT, malignant mixed Mullerian tumor; N/A, not applicable.

Fig. 2. Gross and microscopic (H&E staining) appearances of different histological types of endometrial carcinoma.

2A. Endometrioid type tumor usually present with elongated nuclei and some degree of glandular or villoglandular structures. Glandular differentiation and the degree of cellular components are used to differentiate low grade and high grade endometrioid tumors. 2B. Carcinosarcoma has a mixture of malignant epithelial and mesenchymal components. Macroscopically, carcinosarcoma demonstrates necrotic and hemorrhagic neoplasms that occupy the endometrial cavity. Histologically, this biphasic tumor is composed of malignant epithelial glandular features and undifferentiated high-grade sarcoma elements. 2C. Serous type carcinoma is usually characterized by a papillary architecture both histologically and grossly. 2D. Tumor cells of clear cell carcinoma are filled with glycogen and thus have the appearance of being surrounded by a “clear” halo.

Fig. 3. Gene mutations in serous and endometrioid endometrial cancers. Distinct molecular genetic alterations in three major cancer genes (*ARID1A*, *TP53*, *CCNE1*) in uterine serous carcinoma and endometrioid carcinoma are shown. The majority of serous cases harbor *TP53* mutations and/or *CCNE1* locus amplification, while *ARID1A* mutations are rare. In endometrioid carcinomas, the reverse pattern is observed; these carcinomas are characterized by frequent *ARID1A* mutations and rare or no *TP53* mutations and *CCNE1* amplification. Each column represents a case. (*red*) Genetic alteration present; (*green*) genetic alteration absent.

Fig. 4. Common alterations of genes in endometrial carcinomas.

Several mechanisms can lead to carcinogenesis and metastasis, including inhibiting apoptosis, inducing cell proliferation, enhancing TERT transcription, and interfering with DNA repair. *ARID1A*, *PTEN*, *KRAS*, *CTNNB1*, and MMR molecular pathways exclusively affect endometrioid tumor whereas serous tumors more commonly harbor alterations in *TP53*, *HER2*, *p16*, *CCNE1*, and *FBXW7*. *ARID1A*, AT-rich interaction domain 1A; *CCNE1*, cyclin E1; *CTNNB1*, Catenin beta-1; *FBXW7*, F-box/WD repeat-containing protein 7; *HER2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *PI3K*, phosphatidylinositol 3- kinase; *PTEN*, phosphatase and tensin homolog; *TERT*, Telomerase reverse transcriptase; *TP53*, cellular tumor antigen 53.

This figure is modified from ScienceSlides Online (<http://www.scienceslides.com/BH41/common-alterations-in-endometrial-carcinoma-subtypes#>).

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Table 1.

Characteristics of endometrial carcinoma by histology.

	LG-Endometrioid	HG-Endometrioid	Serous	Clear Cell
Precancerous Lesion	Atypical endometrial hyperplasia	Atypical endometrial hyperplasia	Serous endometrial intraepithelial carcinoma	Unknown
Mutated Genes	<i>ARID1A, PTEN, KRAS, PIK3CA, CTNNB1, MLH1, MSH2, MSH6, PMS2</i>	<i>ARID1A, PTEN, KRAS, PIK3CA, CTNNB1, MLH1, MSH2, MSH6, PMS2, TP53</i>	<i>TP53, FBXW7, CCNE1, HER2, p16</i>	<i>TP53, PTEN, ARID1A, PIK3CA</i>
Molecular Pathway Alterations in TCGA data	<i>POLE</i> ultra-mutated, MSI hypermutated, Copy number low	<i>POLE</i> ultra-mutated, MSI hypermutated, Copy number high	Copy number high	N/A

ARID1A, AT-rich interaction domain 1A; *CCNE1*, cyclin E1; *CTNNB1*, Catenin beta-1; *FBXW7*, F-box/WD repeat-containing protein 7; *HER2*, human epidermal growth factor receptor 2; HG, high-grade; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LG, low-grade; *MLH1*, mutL homolog 1; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; N/A, not applicable; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; *PMS2*, PMS1 homolog 2; *PTEN*, phosphatase and tensin homolog; *TP53*, cellular tumor antigen 53.