The Journal of Pathology, Invited Review

Endometrial carcinoma: molecular subtypes, precursors and the role of pathology in early diagnosis

Jutta Huvila[1,2], Jennifer Pors[2], Emily F. Thompson[2], C. Blake Gilks[2]*

[1]Department of Pathology, University of Turku, Turku, 20520, Finland

[2]Department of Pathology and Laboratory Medicine, Vancouver General Hospital and University of British Columbia, Vancouver, BC, Canada

*Correspondence to:

C. Blake Gilks MD, FRCPC, Rm 1435, 1st Floor JPPN, Department of Pathology, Vancouver General Hospital, 855 West 12th Ave, Vancouver, BC, V5Z 1M9, Canada.

E-mail: Blake.Gilks@vch.ca

Running Title : Endometrial carcinoma precursors

The authors declare no conflicts of interest

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/path.5608

Abstract

Endometrial carcinoma (EC) is classified into a wide range of morphological variants; this list has expanded over the past decade with the inclusion of mesonephric-like and de-differentiated carcinoma as EC variants in the fifth edition of the WHO Classification of Female Genital Tumours, and recognition that carcinosarcoma is a biphasic carcinoma rather than a sarcoma. Each EC variant has distinct molecular abnormalities, including TCGA-based molecular subtypes, allowing further subclassification and adding complexity. In contrast to this rapid progress in understanding EC, there are only two recognized EC precursor lesions: endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (EAH/EIN) and serous intraepithelial carcinoma, a situation that has not changed for many years. Diagnosis of EC precursors is a cornerstone of surgical pathology practice, with early diagnosis contributing to the relatively favorable prognosis of EC. In this review we relate the precursor lesions to each of the EC morphological variants and molecular subtypes, discuss how successful early diagnosis is for each variant/molecular subtype and how it might be improved, and identify knowledge gaps where there is insufficient understanding of EC histogenesis.

Endometrial carcinoma (EC) is the most common cancer of the female reproductive organs in the developed world, the fourth most common cancer in women in Canada, the UK, and the USA, after breast, lung, and colorectal [1–3]. Although many EC patients are cured with surgery alone, there are significant numbers of women with more aggressive variants of EC for whom the prognosis remains poor. The main clinical challenges include risk stratification based on the diagnostic biopsy to guide the extent of surgery, and risk stratification/predictive biomarker assessment post-hysterectomy to determine the need for and type of adjuvant treatment [4].

Carcinoma of the uterus was first subclassified based on site of origin into those tumors involving the uterine corpus and arising from the endometrium, and those arising in the cervix [5]. The former were subclassified in 1983 by Bokhman who recognized two types of EC based on clinical and pathological features; Type I ECs were more common, related to excess unopposed estrogenic stimulation of the endometrium, and were mostly endometrioid histotype and of lower grade. The prognosis of patients with Type I EC was favorable, with greater than 85% 5-year disease free survival rate. In contrast, Type II ECs were high grade tumors of clinically aggressive histotypes (e.g., serous, clear cell, although it should be noted that within this "non-endometrioid" category not all clear cell carcinomas behave in an aggressive fashion). Type II ECs were associated with a poor response to hormonal therapy and relatively poor outcomes[6,7]. This categorization system was a major conceptual advance, but Type I/Type II classification identified loose constellations of cases illustrating biological truths, rather than specific diagnoses; although there are prototypical examples of Type I and Type II EC, too many ECs have features that are not readily classified as one or the other with certainty. The category of grade 3 endometrioid carcinoma, for example, has been considered Type I or Type II [8,9].

In 2013 The Cancer Genome Atlas (TCGA) identified four molecular subtypes of EC based on genomic features [10]. These molecular subtypes differ from each other with respect to molecular abnormalities, hereditary risk factors, environmental risk factors, prognosis, and response to treatment [11,12]. Furthermore, clinically applicable surrogate markers for the four molecular subtypes have been independently developed by two different groups of investigators [13–16]; as a result, molecular subtype can be diagnosed in practice with a high degree of interobserver reproducibility [17], and a diagnosis based on a biopsy specimen shows excellent correlation with the molecular classification based on the subsequent hysterectomy specimen[18–21].

The relationships between TCGA-based molecular subtypes and histotypes are shown in Figure 1 and Table 1 [10,13,15,16,19,22–34] , and the four molecular subtypes are described below. It should be noted that there may be publication bias in the cases included in Table 1, such that they may not be representative of a population-based case series. We have chosen to not include mixed EC in the figure as most so-called mixed carcinomas are examples of morphological mimicry rather than a true admixture of different tumor types [35].

***POLE*mut, ultramutated group** – These copy-number stable ECs feature pathogenic mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*), a gene involved in DNA replication and repair [36–39]. These EC have one of the highest somatic mutation frequencies of any solid tumor, frequently exceeding 100 mutations per megabase (Mb). *POLE*mut EC are most often, but not exclusively, of endometrioid histotype. They may show intratumoural morphological heterogeneity and ambiguous morphology, with features of both endometrioid and serous histotypes. Women with *POLE*mut ECs tend to be younger, with normal BMI, and are associated with a favorable prognosis despite often having high-risk pathologic features such as high tumor grade and extensive LVSI (>96% 5 year survival, confirmed across multiple studies) [40–43].

MMRd, hypermutated/microsatellite unstable group – These tumors have low levels of somatic copy number alterations but a very high mutational burden secondary to dysfunctional mismatch repair (MMRd) proteins i.e. MLH1, PMS2, MSH2, or MSH6 [44]. Epigenetic silencing of MLH1 is responsible for the majority of this subgroup but both somatic and germline mutations in any of the mismatch repair genes will lead to a high mutational frequency (>10 mut/Mb). These EC occur across a wide age range (younger in patients with Lynch Syndrome than in sporadic cases) and are not associated with an increased BMI. They are predominantly endometrioid histotype and are often higher grade. There is FDA approval of PD-1/PD-L1-inhibitors for this molecular subtype of EC, in the setting of recurrent or advanced disease, when there are no other treatment options[45–47].

NSMP (no specific molecular profile) group – These EC are generally genomically stable, with low levels of somatic copy number alterations [48], and are MMR-proficient, *POLE* wildtype and show wild type-pattern p53 immunoreactivity/wild type *TP53* on sequencing. This group encompasses mostly endometrioid tumors with high levels of estrogen and progesterone receptor (ER, PR) expression. Mutations in exon 3 of *CTNNB1*

are associated with a worse prognosis in NSMP EC [49]. This molecular subtype is associated with increased BMI.

p53abn, serous-like group – EC in this molecular subgroup have high somatic copy number alterations, similar to high grade serous tubo-ovarian and basal-like breast carcinomas. Abnormal p53 immunostaining/*TP53* mutations are the hallmarks of this molecular subtype, and also high-grade serous tubo-ovarian and basal-like breast carcinomas. In contrast to serous tubo-ovarian and basal-like breast carcinomas, however, p53abn EC have recurrent mutations in *PIK3CA*, *FBXW7* and *PPP2R1A* [10]; they are less likely to have mutations in *BRCA1* or *BRCA2* compared to tubo-ovarian high-grade serous carcinoma [10,50,51]. HER2 amplification occurs in ~20% of CN-high ECs and a proportion of CN-high ECs have homologous recombination deficiency [51,52]. A large majority of serous carcinomas and carcinosarcomas are of this molecular subtype, but it also includes most EC of mixed histology, and a minority of high-grade endometrioid EC (Table 1). Although only accounting for 15% of EC, this molecular subtype accounts for 50-70% of EC-associated mortality [10,13–15,19]. Patients with this molecular subtype are older, and it is not associated with increased BMI. The PORTEC 3 clinical trial results suggest that patients with p53abn ECs have superior outcomes when treated with chemotherapy in addition to radiation, as compared to radiotherapy alone [12]. It has become clear that EC is too heterogeneous a disease to be classified using a simple binary system, as more than 30% of EC are of MMRd or *POLE*mut molecular subtypes, which do not correspond exclusively to either Type I or Type II [25,26,53].

Endometrial Biopsy Performance in Diagnosis of Endometrial Carcinoma

Endometrial biopsy and curetting specimens are one of the most common gynecological pathology specimen types. For the purposes of this discussion we will consider biopsy and curettage specimens to be equivalent, given their equivalent diagnostic performance in the diagnosis of EC, and will hereafter refer to them as "biopsy/biopsies". With a markedly reduced role of endometrial biopsy in the assessment of patients with infertility [54], most endometrial biopsies are taken for investigation of abnormal bleeding in peri- or post-menopausal women, in order to rule out EC or a precursor lesion. In a review of >22,000 endometrial biopsies from our region, there were 172 that were negative for carcinoma or a precursor from patients who subsequently developed EC within 5 years of the negative biopsy [55]. The sensitivity of endometrial biopsy, based on this study, was 89%, a figure

unchanged from a study performed more than 15 years previously [56]. This is probably a conservative estimate of the sensitivity as some lesions may have truly been absent at the time of biopsy and developed in the interval between biopsy and hysterectomy, but as this was less than a year in a majority of the cases, it is unlikely to explain most of the lack of sensitivity. Thus, endometrial biopsy is a good but not perfect test for the diagnosis of EC, with false negative results in approximately 10% of patients with EC. There remain patients who present with advanced stage EC and these disproportionately consist of patients with p53abn EC, as noted previously. This suggests that the use of endometrial biopsy as a tool for early diagnosis of EC i.e. at low stage, based on biopsy of women with abnormal bleeding, is more effective in some subtypes of EC than others; in particular early diagnosis, while the norm in low-grade endometrioid NSMP carcinomas, is less likely in the other molecular subtypes (Table 2). As for the case series included in Table 1, there may be publication bias in the cases included in Table 2, such that they are not representative of a population-based series of EC. The goal of reducing mortality due to any carcinoma is based on one or more elements of the triad of prevention, early detection and more effective treatment. In the case of EC, early detection has been possible for many patients, but it is worth considering why it has not been more successful and if there are opportunities for improvement, in order to mitigate the impact of the increasing incidence of EC.

Precursors of Endometrial Carcinoma

Recognition of EC precursors and their accurate diagnosis on biopsy or curetting specimens is important because of the opportunity for early diagnosis and cure before progression to EC. Two morphological precursor lesions of EC are recognized:

1. **Endometrial atypical hyperplasia/Endometrioid intraepithelial neoplasia (EAH/EIN)** is characterized by a clonal proliferation of endometrial glands lined by atypical cells, with a predominance of glands over stroma (Figure 2A) [57]. Atypical hyperplasia is associated with unopposed estrogenic stimulation of the endometrium and acquisition of mutations in *PTEN*, *KRAS*; *PIK3CA*, *CTNNB1* and/or *ARID1A* [57]. EAH/EIN is the precursor lesion of almost all endometrioid carcinomas and a subset of serous carcinomas [58]. The mutational profile of EAH/EIN and the concurrent EC is highly concordant [18,59–62] in the majority of cases, however, Li et al. showed that 5 out of 30 EAH/EIC cases with concurrent EEC the EAH/EIC and EC shared less then 5% of the mutations identified, indicating clonality but with a high degree of divergence [62].

2. **Serous intraepithelial carcinoma (SEIC)** is characterized by preexisting endometrial glands lined by markedly atypical glandular epithelial cells in the absence of invasive disease. These epithelial cells show cytological features typical of serous carcinoma i.e. nucleomegaly and pleomorphism, and are associated with a high proliferative index (Figure 2B-C) [63–65]. As the name implies, this lesion is the precursor of some invasive serous carcinomas, but the exact percentage of cases that arise from it is not known as serous EC can also arise through progression of a morphologically low-grade lesion i.e. EAH/EIN, with genetic features of endometrioid EC e.g. *PTEN* loss. One hypothesis is that the SEIC is preceded by a sequence similar to that of tubo-ovarian high-grade serous carcinoma i.e. endometrial p53 signature lesion and glandular dysplasia followed by SEIC [66–68], analogous to the p53 signature, serous tubal intraepithelial lesion (STIL) and serous tubal intraepithelial carcinoma (STIC). The term SEIC is not used by many pathologists because such lesions, which are apparently confined to the endometrium without endometrial or myometrial invasion, can be associated with extra-uterine spread; thus the alternative diagnosis of "early serous carcinoma" has been proposed [63,65].

Although only two EC precursors are well characterized, it is entirely possible that additional precursor lesions, especially precursors of some of the less studied molecular subtypes/histotypes, such as *POLE*mut, MMRd, clear cell carcinoma, or mesonephric-like carcinoma may be described with further study. Just as a dualistic model of EC was an oversimplification, so to the description of only two precursor lesions may prove to be insufficient. We also devote little attention in this review to the phenomenon of tumor progression, whereby loss of MMR expression or abnormal (mutant pattern) p53 expression occurs after tumor initiation; this phenomenon is seen in practice as subclonal p53abn or MMRd expression, with part of the tumor showing wildtype p53 expression or intact MMR expression, adjacent to a contiguous area of p53abn or MMRd, respectively. Subclonal MMRd staining is predominantly observed in the context of *MLH1* hypermethylation [69], and subclonal p53 staining is frequently encountered in ECs known to carry high mutational burdens (MMRd, *POLE*mut), where *TP53* mutation is a secondary event and not associated with an adverse prognosis (so called 'multiple classifier' ECs) [70].

Morphological Features of the Endometrial Carcinoma Precursors Associated with the Four Molecular Subtypes

Very little data on the TCGA-based molecular subtype classification of EC precursor lesions is available. In recent work comparing resolving and progressing EAH/EIN and comparing EAH/EIN and subsequent carcinoma, Russo *et al.* identified NSMP, MMRd and p53abn EAH/EIN lesions [61,71]. Evidence of clonal evolution has been demonstrated in whole-exome sequencing studies of paired EAH/EIN and concurrent EC (mostly of NSMP and MMRd molecular subtypes [62].

A. **p53abn**: This is the prototypical Type II EC and accounts for a large majority of serous EC. The precursor lesion can be SEIC, but some p53abn EC progress from low-grade EC and there may be coexisting EAH/EIN, especially in younger patients [59]. In these latter tumors the acquisition of *TP53* mutations can be an early event i.e. present in the low-grade areas, or it can occur later and only be seen in the high-grade serous component (Figure 2D-E).

B. **MMRd**: These carcinomas are mostly of endometrioid histotype and there can be co-existing EAH/EIN as the precursor lesion [60]. There is identical loss of MMR protein(s) in the EAH/EIN as in the associated carcinoma in most but not all cases (Figure 2F). In one study of more than 100 EAH/EIN, fewer than 5% were MMRd; thus, MMRd is much more commonly identified in EC than in the precursor lesion, suggesting that there is rapid transit through the *in situ* phase in these genomically unstable tumors [60]. This is similar to the situation in vulvar squamous cell carcinoma, where purely in situ lesions are predominantly HPV-associated while invasive vulvar squamous cell carcinoma is predominantly HPV-independent, an observation attributable, at least in part, to the more rapid progression of HPV-independent VIN [72].

C. **NSMP**: These are prototypical Type I EC, arising from EAH/EIN, which may persist for years before progressing to invasive carcinoma, and may be treated with hormonal therapy i.e. progestins [73]. Progression from AEH/EIN to EC is associated with the acquisition of driver mutations [62].

D. ***POLE*mut**: The histogenesis of this molecular subtype is the least understood. EAH/EIN has been described in association with *POLE*mut EC (6/43 cases in one study) [74] and there is a single study demonstrating the presence of POLE mutations in EAH/EIN adjacent to EC [75], but there are no studies on the presence of *POLE*

mutations in isolated EAH/EIN. The low frequency of associated precursor lesions identified with *POLE*mut EC suggests that this molecular subtype may be associated with a rapid transit through the phase of EAH/EIN, due to the high mutation rate.

Rare Endometrial Carcinoma Histotypes: molecular subtypes and precursor lesions

Most of the work on molecular characterization of EC and its precursors has focused on the most common histotypes, i.e. endometrioid and serous carcinomas. In the following section we discuss rare EC histotypes, including mesonephric-like and de-differentiated, which are now included in the fifth edition of the WHO Classification of Female Genital Tract [57], focusing on their molecular abnormalities and (purported) precursor lesions.

Clear Cell Carcinoma

Clear cell EC is an uncommon histotype, comprising <5% of EC and patients are usually older, postmenopausal women [33,76]. Clear cell carcinomas can be of any of the four molecular subtypes. *POLE*mut clear cell carcinomas have the most favorable prognosis while p53abn clear cell carcinomas are associated with aggressive behavior i.e. the behavior of clear cell carcinoma is similar to that of non-clear cell EC of these molecular subtypes [26,77,78]. NSMP clear cell ECs, however, differ from NSMP endometrioid carcinomas, as they are associated with a worse prognosis [26]. Tumors that show mixed clear cell and endometrioid components are MMRd in most cases [35] whereas MMRd pure clear cell carcinomas are uncommon [26,32].

To date, data on precursor lesions of clear cell carcinoma remain scarce. Kurman *et al.* identified a putative precursor lesion, described as isolated glands or surface epithelium displaying cytoplasmic clarity and/or eosinophilia with varying degrees of nuclear atypia, in approximately half of pure clear cell carcinomas [79]. In later work, an intraepithelial carcinoma-like growth pattern was identified in 20% of clear cell EC adjacent to the invasive tumor [76] (Figure 2G-H). Clear cell carcinomas have been described to be associated with an endometrial polyp [76,80]. As well as an intraepithelial carcinoma-like precursor, we have seen NSMP clear cell EC associated with atypical glands with low-grade cytological features. Although the morphological appearance is consistent with EAH/EIN, the cells are ER negative, and this may also be a precursor of clear cell EC (Figure 2I-J).

Undifferentiated and Dedifferentiated Endometrial Carcinoma

Undifferentiated carcinoma is a highly aggressive EC subtype that lacks all patterns of differentiation and consists of monotonous cancer cells growing in a sheet-like pattern. Most express epithelial antigens (e.g. cytokeratin) but often focally/weakly. Dedifferentiated carcinomas are composed of FIGO grade 1 or 2 endometrioid EC adjacent to areas of undifferentiated carcinoma. This category of tumors is the least well understood of the major EC histotypes, as it was only recently described [81–83].

The most common molecular subtype of undifferentiated and dedifferentiated carcinomas is MMRd, accounting for 37% and 43% respectively [22,27–30]. *POLE*mut undifferentiated carcinomas are rare whereas nearly one third of the dedifferentiated carcinomas harbour a *POLE* mutation. Most of the *POLE*mut dedifferentiated carcinomas came from one study, which could also reflect the challenges of histomorphological classification of *POLE*mut tumors [16]. p53abn has been reported to account for 7% and 28% of dedifferentiated and undifferentiated carcinomas, respectively. This difference is concerning and it is possible that some p53abn "undifferentiated carcinomas" are better classified as solid pattern serous or high-grade endometrioid carcinoma of p53abn molecular subtype. Undifferentiated and dedifferentiated carcinomas often have mutations in genes encoding proteins of the SWI/SNF complex [29,84]. There is not a molecular marker or panel that is considered diagnostic of dedifferentiated/undifferentiated EC, which hampers research on this uncommon tumor type, as the reported case series may not be comparable.

The precursor of undifferentiated and dedifferentiated carcinomas is thought to be low-grade carcinoma that, in the case of undifferentiated carcinoma, has been overgrown by the undifferentiated component (Figure 2K-L).

Carcinosarcoma

Carcinosarcoma is an uncommon, aggressive, biphasic neoplasm that accounts for <5% of ECs. Carcinosarcomas contain both epithelial and mesenchymal cell types that share mutation profiles, indicating a carcinoma origin with metaplastic conversion due to EMT [85]. While a large majority of carcinosarcomas are of the p53abn molecular subtype, they can also be of the other three molecular subtypes of EC, including MMRd [85–87]. In TCGA, over 90% of carcinosarcomas harbor a *TP53* mutation [85]. Some carcinosarcomas share mutational profiles with the endometrioid lineage e.g. *PTEN* mutation, indicating that, like serous carcinoma, an alternative route of carcinogenesis is *via* a low-grade endometrioid carcinoma and its precursors. [85,88].

Mesonephric-like Endometrial Carcinoma

Mesonephric-like carcinoma is a rare and aggressive EC histotype [89–91]. They characteristically show a variety of histologic patterns, including tubular, ductal, papillary, solid, spindled, retiform, glomeruloid, and sex-cord like [90,92].

Although few studies have examined the molecular profile of these rare neoplasms, all available data suggests that they are of NSMP molecular subtype. To our knowledge, all cases of mesonephric-like carcinoma of the endometrium reported in the literature are *TP53* wildtype (by molecular or immunohistochemical analysis) [89,90,92–94], MMR-proficient (by immunohistochemical analysis) [95], and *POLE* wildtype [89]. Like NSMP clear cell carcinoma, mesonephric-like EC (all of which are NSMP) have a worse prognosis than NSMP endometrioid carcinoma [89,96,97].

Unlike mesonephric carcinoma of the uterine cervix, mesonephric neoplasms of the uterine corpus do not appear to be associated with mesonephric remnants/hyperplasia [90,92,98]. Furthermore, they appear to arise in the endometrium rather than the myometrium [92], and have considerable molecular overlap with endometrioid adenocarcinoma (including *PIK3CA* and *ARID1A* mutations) [94,99]. Mixed carcinoma, consisting of both mesonephric-like and endometrioid components, has been reported, suggesting the possibility that mesonephric-like carcinomas may arise from Mullerian origins, with subsequent mesonephric transdifferentiation [85].

Knowledge Gaps and Opportunities

Progression to carcinoma can be prevented by early detection of precursor lesions of EC. The relationships between the two EC precursor lesions, EAH/EIN and SEIC, and the molecular subtypes and histotypes of EC are depicted in Figure 3. How can diagnosis of EC precursor lesions be optimized to effect earlier diagnosis and improve outcomes? The current approach of endometrial biopsy based on symptoms (irregular perimenopausal bleeding or postmenopausal bleeding) works relatively well only in the detection of EAH/EIN as a precursor of Type I/low-grade endometrioid/NSMP EC. Patients with EAH/EIN have a uniformly favorable prognosis and young patients may be treated conservatively with hormonal therapy and preservation of fertility. Even when there has been progression to carcinoma, most low-grade endometrioid/NSMP EC are low stage and cured by surgery alone. As noted previously, EAH/EIN associated with MMR loss is rarely diagnosed except when adjacent to carcinoma, and the same appears to be true for EAH/EIN associated with *POLE*mut EC, suggesting that EAH/EIN associated with these

molecular subtypes, with their resulting high mutation rate, progress rapidly. In addition, there are no data on whether *POLE*mut or MMRd EAH/EIN are as responsive to the more common NSMP EAH/EIN treatments, and thus these patients might not be candidates for conservative treatments. Similarly, early diagnosis of SEIC is rare; isolated SEIC, without associated invasive carcinoma, is reported in only a few small case series, suggesting that SEIC is not consistently associated with post-menopausal bleeding that would trigger a biopsy, and thus it may routinely go undetected until invasive carcinoma develops. The precursor lesions of clear cell carcinoma, carcinosarcoma, dedifferentiated/undifferentiated carcinoma and mesonephric-like carcinoma are not well characterized, but given their aggressive behavior and the paucity of descriptions of precursor lesions adjacent to these carcinomas, the study of precursors will be challenging and the prospect for early detection, at a pre-invasive point in their natural history, is unlikely.

In a review of a large series of endometrial biopsies reported as negative, from patients who subsequently were diagnosed with EC, we found that there were no cases of SEIC that had been missed on these earlier biopsies, and only a handful of cases of EAH/EIN, indicating that the lack of sensitivity of endometrial biopsy (only 90% sensitivity) [55] is attributable to sampling rather than misinterpretation errors. Of the carcinomas with negative earlier biopsy in this series, 7.7% were serous carcinomas and the remaining endometrioid EC; thus it appears that focusing on improved pathologist diagnosis of EAH/EIN or SEIC for early diagnosis is unlikely to impact on mortality due to EC; as noted previously, EC mortality is mostly attributable to p53abn and MMRd EC, and uncommon histotypes that tend to only become symptomatic when there has been development of more advanced disease.

Conclusions

Only two EC precursor lesions have been well characterized: EAH/EIN and SEIC. These correspond to the classic precursor lesions of Type I and Type II EC respectively, but can also give rise to a wide range of EC histotypes and molecular subtypes. Only a small number of studies have examined the molecular subtype characteristics of EAH/EIN and SEIC, especially when diagnosed as an early lesion, without associated carcinoma. The precursor lesions associated with rare EC histotypes are not well characterized and warrant further study.

The apparently rapid transit through the precursor lesion to invasive (and often advanced stage) carcinoma means that diagnosis of MMRd or p53abn EC at the precursor stage is rare, and our current approach of endometrial biopsy based on symptoms is unlikely to impact on

the outcomes of patients with these EC molecular subtypes. Similarly, uncommon EC histotypes such as mesonephric-like, clear cell, dedifferentiated/undifferentiated and carcinosarcoma are not consistently detected as low stage disease based the current approach. As these less common molecular subtypes and histotypes collectively account for most EC mortality, alternative approaches to prevention or early detection will be needed to significantly reduce EC mortality. One possible approach is to look for key EC driver gene mutations in cervical cytology or intrauterine brush samples [100]. Such an approach, while promising, will have to take into account the presence of such mutations in normal endometrium [101], and the low disease prevalence, which will make screening difficult.

JH, ET and JP generated the first draft of this manuscript and provided all photomicrographs. JH generated the figures that are not photomicrographs and the Tables. All authors participated in revising the manuscript into its final state.

No specific ethical approval was received for this review, but it was conducted in accord with the ethical guidelines for research of the University of British Columbia.

Figure Legends

Figure 1. The relationship between histotype (top row), and molecular subtype (bottom row) in endometrial carcinoma. The thickness of the lines correlates with percent of tumors of each histotype that are of the corresponding molecular subtype.
Abbreviations: MMRd: mismatch repair deficient, NSMP: no specific molecular profile, abn: abnormal, mut: mutated, EEC: endometrioid endometrial carcinoma, CCC: clear cell carcinoma, SIEC: serous intraepithelial endometrial carcinoma, SEC: serous endometrial carcinoma, DDEC: dedifferentiated endometrial carcinoma, UDEC: undifferentiated endometrial carcinoma, CS: carcinosarcoma, Gr: grade

Figure 2. (A) Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia, with glandular crowding and cytological atypia. Note the abrupt change in cytological features from the benign glands on the left (arrow) (H&E). **(B-C)** Serous intraepithelial carcinoma (SEIC) involving an endometrial polyp, with pre-existing glands lined by markedly atypical cells **(B)** (H&E), that show mutant pattern p53 immunostaining, with nuclear overexpression **(C)**. **(D-E)** p53abn endometrial carcinoma with a low-grade component on the right and a high-grade component on the left **(D)** (H&E). Mutant pattern p53 (overexpression) is seen in the high-grade but not the low-grade component **(E)**. Note that in some such carcinomas both the low-grade and high-grade component show mutant pattern p53 staining. **(F)** MMRd endometrial carcinoma showing MSH6 loss of expression in both the carcinoma (bottom) and EAH/EIN (top). **(G-J)** Clear cell carcinoma **(G)** with adjacent atypical glandular proliferation (glandular crowding and mild cytological atypia **(H)**. Another clear cell carcinoma showing transition to endometrioid glands with mild cytological atypia (arrow) **(I)**; there is loss of ER expression in the atypical endometrioid glands with patchy expression in the associated clear cell carcinoma **(J)**. (**K-L)** Dedifferentiated endometrial carcinoma with loss of ARID1A expression in both the low-grade **(K)** and high-grade **(L)** components.

Figure 3. Proposed histogenesis of endometrial carcinoma from benign endometrium to carcinoma. A proposed model for endometrial cancer histogenesis is shown, with likely progression between lesions depicted(solid line). The dashed line depicts possible progression from NSMP to p53abn by an acquired *TP53* mutation. The tumor histology and molecular subtypes (*POLE*mut, MMRd, NSMP, p53abn) are indicated within each box.

Abbreviations: EAH/EIN: Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia, mut: mutation, MMRd: mismatch repair deficient, NSMP: no specific molecular profile, abn: abnormal, EC: endometrial carcinoma, EEC: endometrioid endometrial carcinoma, CCC: clear cell carcinoma, SIEC: serous intraepithelial endometrial carcinoma, SEC: serous endometrial carcinoma, DDEC: dedifferentiated endometrial carcinoma, UDEC: undifferentiated endometrial carcinoma, CS: carcinosarcoma

Table 1. Relationship between endometrial carcinoma histotype and molecular subtype

		***POLE*mut**		**MMRd**		**NSMP**		**p53abn**	
	Total	n	%	n	%	n	%	n	%
EEC grade 1-2	2515	150	6.0 %	720	28.6 %	1515	60.2 %	130	5.2 %
EEC grade 3	900	107	11.9 %	342	38.0 %	252	28.0 %	199	22.1 %
CCC	61	1	1.6 %	6	9.8 %	31	50.8 %	23	37.7 %
SEC	122	0	0.0 %	3	2.5 %	6	4.9 %	113	92.6 %
CS	244	13	5.3 %	30	12.3 %	23	9.4 %	178	73.0 %
UDEC	60	4	6.7 %	22	36.7 %	17	28.3 %	17	28.3 %
DDEC	28	8	28.6 %	12	42.9 %	6	21.4 %	2	7.1 %
mixed/NEEC	187	11	5.9 %	31	16.6 %	18	9.6 %	127	67.9 %
Total	4117	294	7.1 %	1166	28.3 %	1868	45.4 %	789	19.2 %

References: [10,13,15,16,19,22–34]. Abbreviations: *POLE*mut: pathogenic mutation in the exonuclease domain of *POLE*, MMRd: mismatch repair deficient, NSMP: no specific molecular profile, abn: abnormal, EEC: endometrioid endometrial carcinoma, CCC: clear cell carcinoma, SEC: serous endometrial carcinoma, DDEC: dedifferentiated endometrial carcinoma, UDEC: undifferentiated endometrial carcinoma, CS: carcinosarcoma.

Table 2. Relationship between molecular subtype and endometrial carcinoma stage at presentation

		***POLE*mut**		**MMRd**		**NSMP**		**p53abn**	
Stage		n	%	n	%	n	%	n	%
I	687	78	94.0 %	170	73.6 %	358	83.6 %	81	48.8 %
II-IV	221	5	6.0 %	61	26.4 %	70	16.4 %	85	51.2 %
total	908	83	9.1 %	231	25.4 %	428	47.1 %	166	18.3 %

References[13,15,19]. Abbreviations: MMRd: mismatch repair deficient, NSMP: no specific molecular profile, abn: abnormal, mut: mutated

References

[1] Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2016. [Internet]. [Accessed July 19, 2020]: Available from http://www.cancer.ca/statistics

[2] Ten most common cancers in females [Internet]. [Accessed Nov 15, 2020]: Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Two

[3] Common Cancer Types [Internet]. [Accessed Nov 15, 2020]: Available from https://www.cancer.gov/types/common-cancers

[4] Wan YL, Beverley-Stevenson R, Carlisle D *et al.* Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions. *Gynecol Oncol* 2016; **143:** 287-293.

[5] Karamanou M, Tsoucalas G, Laios K *et al.* Uterine cancer in the writings of Byzantine physicians. *J BUON* 2015; **20:** 1645-1648.

[6] Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983; **15:** 10-17.

[7] Brinton LA, Felix AS, McMeekin DS *et al.* Etiologic heterogeneity in endometrial cancer: evidence from a Gynecologic Oncology Group trial. *Gynecol Oncol* 2013; **129:** 277-284.

[8] Voss MA, Ganesan R, Ludeman L *et al.* Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer-a clinical and pathological evaluation. *Gynecol Oncol* 2012; **124:** 15-20.

[9] Zannoni GF, Vellone VG, Arena V *et al.* Does high-grade endometrioid carcinoma (grade 3 FIGO) belong to type I or type II endometrial cancer? A clinical-pathological and immunohistochemical study. *Virchows Arch* 2010; **457:** 27-34.

[10] Kandoth C, Schultz N, Cherniack AD *et al.* Integrated genomic characterization of endometrial carcinoma. *Nature* 2013; **497:** 67-73.

[11] McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. *J Pathol* 2018; **244**: 538-549.

[12] Leon-Castillo A, de Boer SM, Powell ME *et al.* Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. *J Clin Oncol* 2020; **38:** 3388-3397.

[13] Talhouk A, McConechy MK, Leung S *et al.* A clinically applicable molecular-based classification for endometrial cancers. *Br J Cancer* 2015; **113:** 299-310.

[14] Stelloo E, Nout RA, Osse EM *et al.* Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer - combined analysis of PORTEC cohorts. *Clin Cancer Res* 2016; **22:** 4215-4224.

[15] Talhouk A, McConechy MK, Leung S *et al.* Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. *Cancer* 2017; **123:** 802-813.

[16] Hoang LN, Kinloch MA, Leo JM *et al.* Interobserver agreement in endometrial carcinoma histotype diagnosis varies depending on the cancer genome atlas (TCGA)-based molecular subgroup. *Am J Surg Pathol* 2017; **41:** 245-252.

[17] Plotkin A, Kuzeljevic B, De Villa V *et al.* Interlaboratory concordance of ProMisE molecular classification of endometrial carcinoma based on endometrial biopsy specimens. *Int J Gynecol Pathol* 2020; **39:** 537-545.
[18] Abdulfatah E, Wakeling E, Sakr S *et al.* Molecular classification of endometrial carcinoma applied to endometrial biopsy specimens: Towards early personalized patient management. *Gynecol Oncol* 2019; **154**: 467-474.
[19] Kommoss S, McConechy MK, Kommoss F *et al.* Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol* 2018; **29:** 1180-1188.
[20] Stelloo E, Nout RA, Naves LC *et al.* High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma. *Gynecol Oncol* 2014; **133:** 197-204.
[21] Talhouk A, Hoang LN, McConechy MK *et al.* Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment. *Gynecol Oncol* 2016; **143:** 46-53.
[22] Prendergast EN, Holman LL, Liu AY *et al.* Comprehensive genomic profiling of recurrent endometrial cancer: Implications for selection of systemic therapy. *Gynecol Oncol* 2019; **154:** 461-466.
[23] Travaglino A, Raffone A, Gencarelli A *et al.* TCGA classification of endometrial cancer: the place of carcinosarcoma. *Pathol Oncol Res* 2020; **26:** 2067-2073.
[24] Stelloo E, Bosse T, Nout RA *et al.* Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Mod Pathol* 2015; **28**: 836-44.
[25] Thompson E, Leung S, Lum A *et al.* Abstract #1202 Endometrial carcinoma molecular subtype is associated with pathologic and prognostic indices:
Findings from a national study. *Mod Pathol* 2020; **33:** 1002-1163.
[26] Kim SR, Cloutier BT, Leung S *et al.* Molecular subtypes of clear cell carcinoma of the endometrium: Opportunities for prognostic and predictive stratification. *Gynecol Oncol* 2020; **158:** 3-11.
[27] Espinosa I, Lee CH, D'Angelo E *et al.* Undifferentiated and dedifferentiated endometrial carcinomas with POLE exonuclease domain mutations have a favorable prognosis. *Am J Surg Pathol* 2017; **41:** 1121-1128.
[28] Hoang LN, Lee YS, Karnezis AN *et al.* Immunophenotypic features of dedifferentiated endometrial carcinoma - insights from BRG1/INI1-deficient tumours. *Histopathology* 2016; **69:** 560-9.
[29] Köbel M, Hoang LN, Tessier-Cloutier B *et al.* Undifferentiated endometrial carcinomas show frequent loss of core switch/sucrose nonfermentable complex proteins. *Am J Surg Pathol* 2018; **42:** 76-83.
[30] Rosa-Rosa JM, Leskelä S, Cristóbal-Lana E *et al.* Molecular genetic heterogeneity in undifferentiated endometrial carcinomas. *Mod Pathol* 2016; **29:** 1390-1398.
[31] Cosgrove CM, Tritchler DL, Cohn DE *et al.* An NRG Oncology/GOG study of molecular classification for risk prediction in endometrioid endometrial cancer. *Gynecol Oncol* 2018; **148:** 174-180.
[32] Baniak N, Fadare O, Köbel M *et al.* Targeted molecular and immunohistochemical analyses of endometrial clear cell carcinoma show that POLE mutations and DNA mismatch repair protein deficiencies are uncommon. *Am J Surg Pathol* 2019; **43:** 531-537.

[33] DeLair DF, Burke KA, Selenica P *et al.* The genetic landscape of endometrial clear cell carcinomas. *J Pathol* 2017; **243:** 230-241.
[34] Le Gallo M, Rudd ML, Urick ME *et al.* Somatic mutation profiles of clear cell endometrial tumors revealed by whole exome and targeted gene sequencing. *Cancer* 2017; **123:** 3261-3268.
[35] Köbel M, Meng B, Hoang LN *et al.* Molecular analysis of mixed endometrial carcinomas shows clonality in most cases. *Am J Surg Pathol* 2016; **40**: 166-180.
[36] Shevelev IV, Hübscher U. The 3' 5' exonucleases. *Nat Rev Mol Cell Biol* 2002; **3:** 364-376.
[37] Rayner E, van Gool IC, Palles C *et al.* A panoply of errors: polymerase proofreading domain mutations in cancer. *Nat Rev Cancer* 2016; **16:** 71-81.
[38] Henninger EE, Pursell ZF. DNA polymerase ε and its roles in genome stability. *IUBMB Life* 2014; **66:** 339-351.
[39] Church DN, Briggs SE, Palles C *et al.* DNA polymerase ε and δ exonuclease domain mutations in endometrial cancer. *Hum Mol Genet* 2013; **22:** 2820-2828.
[40] Church DN, Stelloo E, Nout RA *et al.* Prognostic significance of POLE proofreading mutations in endometrial cancer. *J Natl Cancer Inst* 2015; **107**: 402.
[41] McConechy MK, Talhouk A, Leung S *et al.* Endometrial carcinomas with POLE exonuclease domain mutations have a favorable prognosis. *Clin Cancer Res* 2016; **22:** 2865-2873.
[42] Meng B, Hoang LN, McIntyre JB *et al.* POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. *Gynecol Oncol* 2014; **134:** 15-19.
[43] Stasenko M, Tunnage I, Ashley CW *et al.* Clinical outcomes of patients with POLE mutated endometrioid endometrial cancer. *Gynecol Oncol* 2020; **156:** 194-202.
[44] McConechy MK, Talhouk A, Li-Chang HH *et al.* Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. *Gynecol Oncol* 2015; **137:** 306-310.
[45] FDA approves first cancer treatment for any solid tumor with a specific genetic feature [Internet]. [Accessed May 2, 2020]: Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication
[46] Le DT, Uram JN, Wang H *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; **372:** 2509-2520.
[47] Talhouk A, Derocher H, Schmidt P *et al.* Molecular subtype not immune response drives outcomes in endometrial carcinoma. *Clin Cancer Res* 2019; **25:** 2537-2548.
[48] Proctor L, Pradhan M, Leung S *et al.* Assessment of DNA ploidy in the ProMisE molecular subgroups of endometrial cancer. *Gynecol Oncol* 2017; **146:** 596-602.
[49] Kurnit KC, Kim GN, Fellman BM *et al.* CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. *Mod Pathol* 2017; **30:** 1032-1041.
[50] Smith ES, Da Cruz Paula A, Cadoo KA *et al.* Endometrial cancers in BRCA1 or BRCA2 germline mutation carriers: Assessment of homologous recombination DNA repair defects. *JCO Precis Oncol* 2019; **3:** PO.19.00103.
[51] de Jonge MM, Auguste A, van Wijk LM *et al.* Frequent homologous recombination deficiency in high-grade endometrial carcinomas. *Clin Cancer Res* 2019; **25:** 1087-1097.

[52] Ashley CW, Da Cruz Paula A, Kumar R *et al.* Analysis of mutational signatures in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. *Gynecol Oncol* 2019; **152:** 11-19.
[53] Travaglino A, Raffone A, Mollo A *et al.* TCGA molecular subgroups and FIGO grade in endometrial endometrioid carcinoma. *Arch Gynecol Obstet* 2020; **301:** 1117-1125.
[54] Practice COTASFRM. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril* 2015; **103:** e44-50.
[55] Taraboanta C, Britton H, Plotkin A *et al.* Performance characteristics of endometrial sampling in diagnosis of endometrial carcinoma. *Int J Gynecol Pathol* 2020; **39:** 19-25.
[56] Clark TJ, Mann CH, Shah N *et al.* Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *BJOG* 2002; **109:** 313-321.
[57] Female genital tumours [Internet]. *WHO classification of tumours series, 5th ed; vol 4* [Accessed 18th July, 2020]: Available from https://tumourclassification.iarc.who.int/chapters/34
[58] Conlon N, Da Cruz Paula A, Ashley CW *et al.* Endometrial carcinomas with a "serous" component in young women are enriched for DNA mismatch repair deficiency, Lynch syndrome, and POLE exonuclease domain mutations. *Am J Surg Pathol* 2020; **44:** 641-648.
[59] Sherman ME, Bur ME, Kurman RJ. p53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. *Hum Pathol* 1995; **26:** 1268-1274.
[60] Lucas E, Chen H, Molberg K *et al.* Mismatch repair protein expression in endometrioid intraepithelial neoplasia/atypical hyperplasia: Should we screen for Lynch syndrome in precancerous lesions. *Int J Gynecol Pathol* 2019; **38:** 533-542.
[61] Russo M, Broach J, Sheldon K *et al.* Clonal evolution in paired endometrial intraepithelial neoplasia/atypical hyperplasia and endometrioid adenocarcinoma. *Hum Pathol* 2017; **67:** 69-77.
[62] Li L, Yue P, Song Q *et al.* Genome-wide mutation analysis in precancerous lesions of endometrial carcinoma. *J Pathol* 2020; **253:** 119-128.
[63] Baergen RN, Warren CD, Isacson C, Ellenson LH. Early uterine serous carcinoma: clonal origin of extrauterine disease. *Int J Gynecol Pathol* 2001; **20:** 214-219.
[64] Pathiraja P, Dhar S, Haldar K. Serous endometrial intraepithelial carcinoma: a case series and literature review. *Cancer Manag Res* 2013; **5:** 117-122.
[65] Wheeler DT, Bell KA, Kurman RJ, Sherman ME. Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. *Am J Surg Pathol* 2000; **24:** 797-806.
[66] Zhang X, Liang SX, Jia L *et al.* Molecular identification of "latent precancers" for endometrial serous carcinoma in benign-appearing endometrium. *Am J Pathol* 2009; **174:** 2000-2006.
[67] Zheng W, Xiang L, Fadare O, Kong B. A proposed model for endometrial serous carcinogenesis. *Am J Surg Pathol* 2011; **35:** e1-e14.
[68] Fadare O, Zheng W. Insights into endometrial serous carcinogenesis and progression. *Int J Clin Exp Pathol* 2009; **2:** 411-432.
[69] Watkins JC, Nucci MR, Ritterhouse LL *et al.* Unusual mismatch repair immunohistochemical patterns in endometrial carcinoma. *Am J Surg Pathol* 2016; **40:** 909-916.

[70] León-Castillo A, Gilvazquez E, Nout R *et al.* Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. *J Pathol* 2020; **250:** 312-322.
[71] Russo M, Newell JM, Budurlean L *et al.* Mutational profile of endometrial hyperplasia and risk of progression to endometrioid adenocarcinoma. *Cancer* 2020; **126:** 2775-2783.
[72] Singh N, Piskorz AM, Bosse T *et al.* p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. *J Pathol* 2020; **250:** 336-345.
[73] Williams AT, Ganesan R. Role of the pathologist in assessing response to treatment of ovarian and endometrial cancers. *Histopathology* 2020; **76:** 93-101.
[74] Bakhsh S, Kinloch M, Hoang LN *et al.* Histopathological features of endometrial carcinomas associated with POLE mutations: implications for decisions about adjuvant therapy. *Histopathology* 2016; **68:** 916-924.
[75] Temko D, Van Gool IC, Rayner E *et al.* Somatic POLE exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response. *J Pathol* 2018; **245:** 283-296.
[76] Fadare O, Zheng W, Crispens MA *et al.* Morphologic and other clinicopathologic features of endometrial clear cell carcinoma: a comprehensive analysis of 50 rigorously classified cases. *Am J Cancer Res* 2013; **3:** 70-95.
[77] Hoang LN, McConechy MK, Meng B *et al.* Targeted mutation analysis of endometrial clear cell carcinoma. *Histopathology* 2015; **66:** 664-674.
[78] Travaglino A, Raffone A, Mascolo M *et al.* Clear cell endometrial carcinoma and the TCGA classification. *Histopathology* 2020; **76:** 336-338.
[79] Fadare O, Liang SX, Ulukus EC *et al.* Precursors of endometrial clear cell carcinoma. *Am J Surg Pathol* 2006; **30:** 1519-1530.
[80] Ishida M, Iwai M, Yoshida K *et al.* Clear cell adenocarcinoma present exclusively within endometrial polyp: report of two cases. *Int J Clin Exp Pathol* 2014; 7: 1757-1763.
[81] Broaddus RR, Lynch HT, Chen LM *et al.* Pathologic features of endometrial carcinoma associated with HNPCC: a comparison with sporadic endometrial carcinoma. *Cancer* 2006; **106:** 87-94.
[82] Kurman RJ. *WHO classification of tumours of female reproductive organs*. Lyon: International Agency for Research on Cancer, 2014.
[83] Murali R, Davidson B, Fadare O *et al.* High-grade endometrial carcinomas: Morphologic and immunohistochemical features, diagnostic challenges and recommendations. *Int J Gynecol Pathol* 2019; **38 Suppl 1:** S40-S63.
[84] Karnezis AN, Hoang LN, Coatham M *et al.* Loss of switch/sucrose non-fermenting complex protein expression is associated with dedifferentiation in endometrial carcinomas. *Mod Pathol* 2016; **29:** 302-314.
[85] Cherniack AD, Shen H, Walter V *et al.* Integrated molecular characterization of uterine carcinosarcoma. *Cancer Cell* 2017; **31:** 411-423.
[86] Gotoh O, Sugiyama Y, Takazawa Y *et al.* Clinically relevant molecular subtypes and genomic alteration-independent differentiation in gynecologic carcinosarcoma. *Nat Commun* 2019; **10:** 4965.
[87] Segura SE, Pedra Nobre S, Hussein YR *et al.* DNA mismatch repair-deficient endometrial carcinosarcomas portend distinct clinical, morphologic, and molecular

features compared with traditional carcinosarcomas. *Am J Surg Pathol* 2020; **44:** 1573-1579.

[88] McConechy MK, Ding J, Cheang MC *et al.* Use of mutation profiles to refine the classification of endometrial carcinomas. *J Pathol* 2012; **228:** 20-30.

[89] Horn LC, Höhn AK, Krücken I *et al.* Mesonephric-like adenocarcinomas of the uterine corpus: report of a case series and review of the literature indicating poor prognosis for this subtype of endometrial adenocarcinoma. *J Cancer Res Clin Oncol* 2020; **146:** 971-983.

[90] Na K, Kim HS. Clinicopathologic and molecular characteristics of mesonephric adenocarcinoma arising from the uterine body. *Am J Surg Pathol* 2019; **43:** 12-25.

[91] Kolin DL, Costigan DC, Dong F *et al.* A combined morphologic and molecular approach to retrospectively identify KRAS-mutated mesonephric-like adenocarcinomas of the endometrium. *Am J Surg Pathol* 2019; **43:** 389-398.

[92] McFarland M, Quick CM, McCluggage WG. Hormone receptor-negative, thyroid transcription factor 1-positive uterine and ovarian adenocarcinomas: report of a series of mesonephric-like adenocarcinomas. *Histopathology* 2016; **68:** 1013-1020.

[93] Pors J, Segura S, Cheng A *et al.* Napsin-A and AMACR are superior to HNF-1β in distinguishing between mesonephric carcinomas and clear cell carcinomas of the gynecologic tract. *Appl Immunohistochem Mol Morphol* 2019; **28:** 593-601.

[94] Mirkovic J, McFarland M, Garcia E *et al.* Targeted genomic profiling reveals recurrent KRAS mutations in mesonephric-like adenocarcinomas of the female genital tract. *Am J Surg Pathol* 2018; **42:** 227-233.

[95] Patel V, Kipp B, Schoolmeester JK. Corded and hyalinized mesonephric-like adenocarcinoma of the uterine corpus: report of a case mimicking endometrioid carcinoma. *Hum Pathol* 2019; **86:** 243-248.

[96] Pors J, Segura S, Chiu DS *et al.* Clinicopathologic characteristics of mesonephric carcinomas in the gynecologic tract: A multi-institutional study. *Am J Surg Pathol* 2020; doi: 10.1097/PAS.0000000000001612. Online ahead of print.

[97] Euscher ED, Bassett R, Duose DY *et al.* Mesonephric-like carcinoma of the endometrium: A subset of endometrial carcinoma with an aggressive behavior. *Am J Surg Pathol* 2020; **44:** 429-443.

[98] Pors J, Cheng A, Leo JM *et al.* A Comparison of GATA3, TTF1, CD10, and calretinin in identifying mesonephric and mesonephric-like carcinomas of the gynecologic tract. *Am J Surg Pathol* 2018; **42:** 1596-1606.

[99] Yano M, Shintani D, Katoh T *et al.* Coexistence of endometrial mesonephric-like adenocarcinoma and endometrioid carcinoma suggests a Müllerian duct lineage: a case report. *Diagn Pathol* 2019; **14:** 54.

[100] Wang Y, Li L, Douville C *et al.* Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. *Sci Transl Med* 2018; **10:** eaap8793

[101] Lac V, Nazeran TM, Tessier-Cloutier B *et al.* Oncogenic mutations in histologically normal endometrium: the new normal. *J Pathol* 2019; **249:** 173-181.