Guideline Resource Unit
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Endometrial Carcinoma

Effective Date: June, 2025

Background

Endometrial carcinoma is the seventh most common gynecological cancer in women in North America and fifth most common in Alberta.[1] Globally it is the sixth most common female cancer, with a prediction that it will be the second most common female cancer by 2040.[2] The prevalence of endometrial carcinoma is increasing by almost 2% per year in women younger than 50 and by 1% per year in older women.[3] An estimated 8,600 Canadian women will be diagnosed with endometrial carcinoma in 2024 and 1,600 will die from it.[3] In Alberta, the annual prevalence increased by 56% from 386 cases in 2008 to 603 in 2016, during a time where the population grew by 17% with 850 cases in 2023.[4] Over 95% of cases are in women over the age of 45 with over 80% being diagnosed as stage 1 and 2. Overall 5-year survival for early-stage endometrial carcinoma is approximately 80% with advanced cancers only have a survival of 15-17%.

Traditionally, endometrial cancers were broadly categorized into type I and type II. The former are linked to excess estrogen with a favourable prognosis compared to latter are believed to be hormone independent with worse outcomes.[5] Amongst these types, there are several histotypes of endometrial carcinoma. These include (1) endometrioid carcinoma (EEC), of low grade (grades 1 and 2) or high grade (grade 3); (2) serous carcinoma (ESC); (3) carcinosarcoma (CS); (4) clear cell carcinoma (ECCC); (5) undifferentiated or dedifferentiated carcinoma (DDEC, UEC); and other rare types, such as (7) mesonephric-like (MA); and (8) gastrointestinal mucinous type carcinomas. These histotypes differ with respect to frequency, clinical presentation and molecular subtypes (Table 1) [4,6,7]. The primary issue with this historical classification system was its challenge in clinical practice. Both grade and histotype assignment in endometrial carcinoma have been shown to have poor reproducibility among pathologists. The inconsistent diagnoses have also led to biologically diverse tumours being grouped together in trials and treatment pathways.

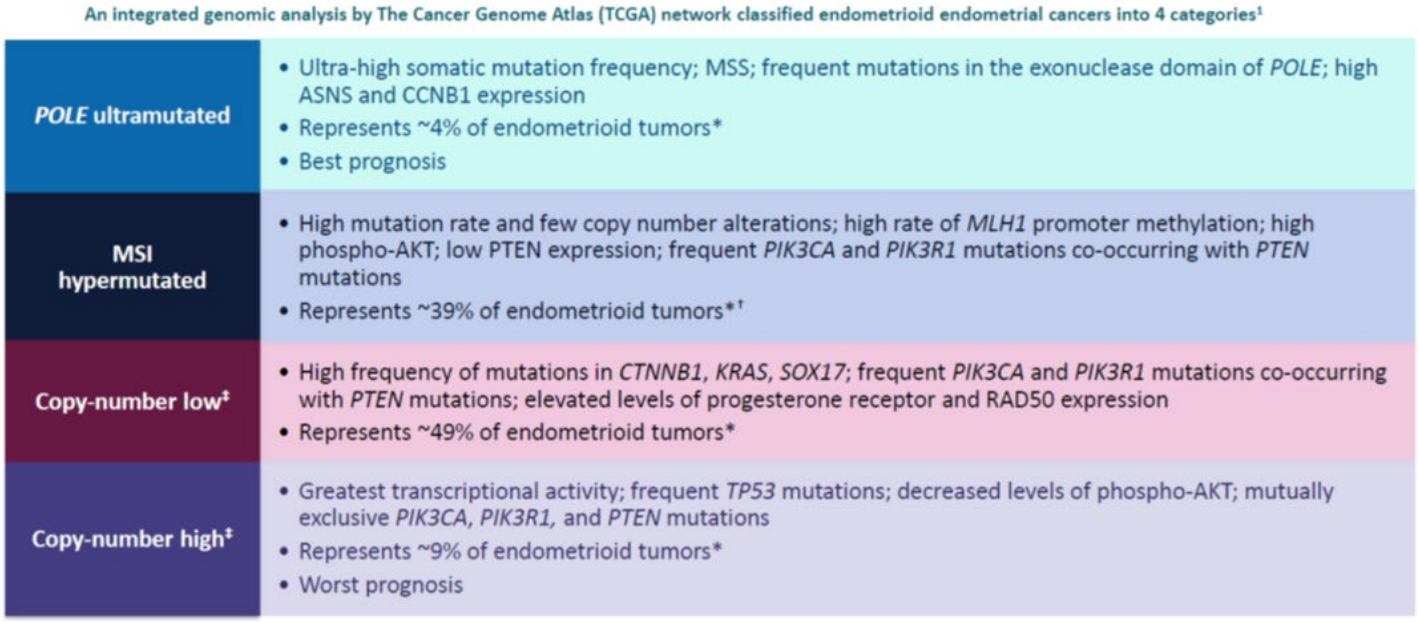
Table 1: Clinical and molecular features of main endometrial carcinoma histotypes[4,6]

	EEC1/2	EEC3	ESC	CS	ECCC	DDEC/UEC	Total
Frequency	75%	9%	5%	4%	3%	3%	
Mean age in years	64	65	72	71	71	68	65
Proportion of stage I	87%	81%	80%	50%	44%	44%	82%
Proportion of sLVSI	12%	31%	13%	58%	0	56%	16%
POLEmut	4%	15%	*	*	*	4%	5%
MMRd	24%	27%	*	*	*	66%	27%
NSMP	71%	31%	*	*	41%	22%	53%
P53abn	<1%	27%	100%	100%	59%	8%	15%

sLVSI = substantial lymphvascular invasion

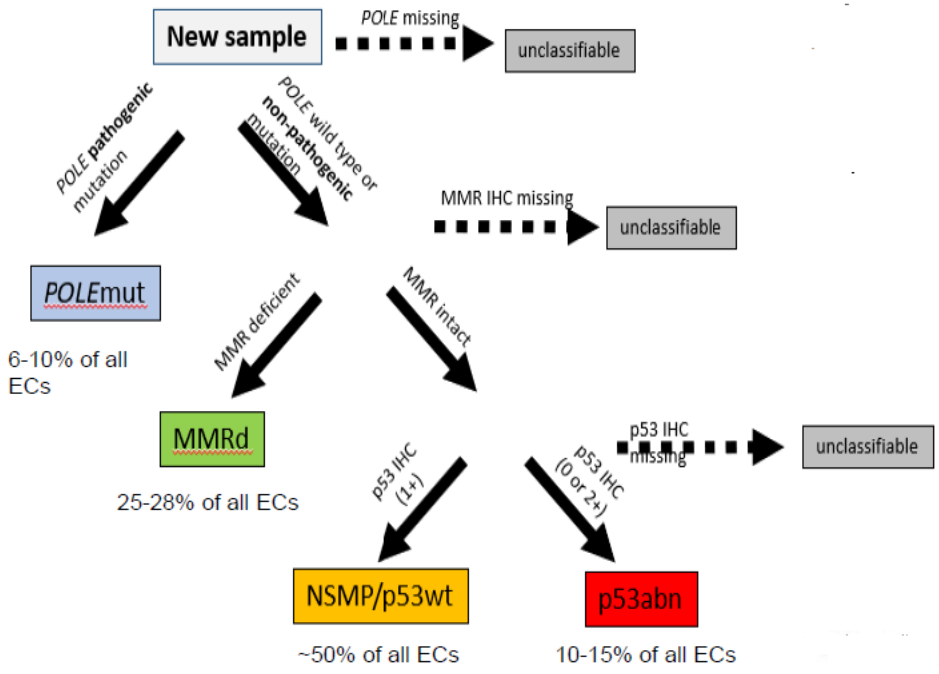
To address this issue, four molecular subtypes were established in 2013 through The Cancer Genome Atlas (TCGA): POLE-mutated (POLEmut), MMR-deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP).

Figure 1: Molecular Classification of Endometrial Cancer[8]



Following this, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was developed and validated as a practical classification system that mirrored the survival curves from the TCGA and identified molecular subtypes through clinically feasible assays. Molecular subtyping provides a more objective and reproducible classification system compared to traditional histologic evaluation[8]. The integration of histotype with molecular subtype provides a robust classification with greater prognostic value than molecular subtyping or histotyping alone. The largest prognostic discrimination of molecular subtyping is seen in endometrioid carcinomas. Molecular subtyping can also be a diagnostic aide as certain molecular subtypes (POLEmut and MMRd) are largely restricted to endometrioid histotype. The added prognostic and therapeutic value has led the WHO to recommend molecular testing where feasible.

Figure 2: ProMise (Proactive Molecular risk classifier for Endometrial cancer)[8,9]



Because of the rare occurrence (~5%) of multiple classifier (cases with more than one molecular subtype abnormality), molecular subtype classification follows a hierarchical decision tree. For example, a case with more than 1 molecular classifier such as POLEmut and p53abn should be classified as either POLEmut because abnormal p53 is likely a passenger event.

Molecular Subtypes:

POLE mut : The POLE gene helps in the prevention of cancer. This gene encodes the catalytic subunit of DNA polymerase epsilon. The DNA polymerase epsilon is a member of the DNA polymerase family of enzymes composed of subunits POLE, POLE2, POLE3 and POLE4.This enzyme has a role in DNA repair and chromosomal DNA replication. It plays an essential role in maintaining a low mutational rate in DNA replication

POLE mut endometrial cancers have a high tumour mutation burden, tumour neoantigen production and tumour infiltrating T cells. Prognosis is generally excellent, and studies are ongoing to validate de-escalation of adjuvant treatments in these patients. Only pathogenic tier1/tier2 *POLE* mutations are clinically relevant[10]. However, this is a changing field and the interpretation of variants of uncertain significance require molecular expertise and integration of other data variables such as level of tumour mutation burden.

MMRd: MMR system repairs DNA errors which occur during replication. Defects in this system can lead to genetic instability and an increased risk of cancer. MMRd can be caused by sporadic MLH1 promoter hypermethylation, somatic or germline mutations in the main MMR genes (MLH1, PMS2,

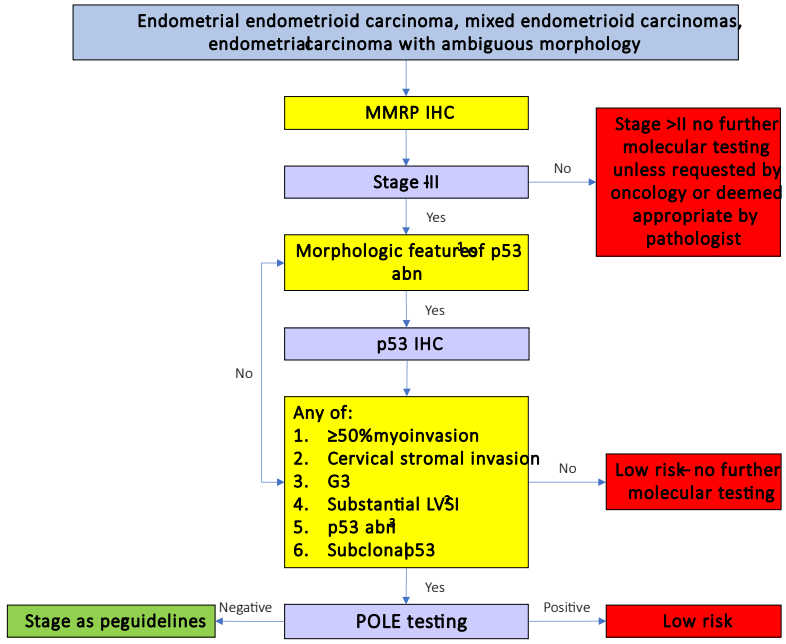
MSH2 or MHS6). The detection of a germline mutation in MLH1, PMS2, MSH2 or MHS6 confirms underlying Lynch syndrome.

NSMP/p53 wt: Cases without alterations in POLR, MMR and p53 are designated as no specific molecular subtype. They include a heterogeneous group of histotypes (ER positive endometrioid and ER-negative clear cell, mesonephric, and other rare endometrial carcinomas). NSMP cases are generally low risk [11,12]. Adverse prognostic factors are non-endometrioid histotype, grade 3 or ER negativity. ER negativity largely overlaps with non-endometrioid histotype and grade 3; ER negative EEC1/2 are uncommon (<1%). The definition of ER negative varies across studies. ER+ EEC1/2 NSMP have a with a 5-year disease specific death rate of only 1.6% versus 23% in NSMP cases of non-endometrioid histotype, grade 3 or ER negative[13,14].

P53abn: p53abnormal tumours include a heterogeneous group of histotypes such as endometrioid (usually grade 3), serous, carcinosarcoma and clear cell carcinoma. A diagnosis of p53 abnormal EEC1/2 is uncommon and may be acceptable in the context of limited subclonal abnormal p53 (10-50%) or bland nuclear features but this will likely require gynecopathology subspecialty confirmation. A specific issue is the classification of subclonal p53 abnormalities. According to the above multiple classifier decision tree and a recent study[15], only POLE wild type and MMRp tumours with >10% subclonal abnormal p53 should be classified as p53 abnormal. TP53 mutations can also be detected by next generation sequencing, however, the classification of cases as p53abn versus subclonal based on TP53 sequencing data (i.e. variant allelic frequency) is currently not established. While both assays are generally considered complimentary, p53 IHC is the currently validated method to assess subclonal p53 abnormalities. PORTEC 3 data and retrospective studies show improved outcomes in p53abn ECs with chemoradiation vs radiation alone even in Stage I, and even in non-serous p53abn ECs.

In Alberta, selective molecular testing (unrelated to ancillary diagnostic testing) is recommended for endometrial carcinoma samples (Figure 3).[4,15,16]

Figure 3: Selection of Endometrial Carcinomas for Molecular Testing [4,15,16]



[1]Tumor giant cells
Pleomorphism
Smudged chromatin
Atypical mitoses
Nucleoli

[2]5 or more involved vessels

[3]1. Strong nuclear staining in >80% of tumor cells
2. Absent nuclear staining in tumor cells with positive internal control
3. Cytoplasmic staining in tumor cells
4. ≥10% of tumor cells showing abnormal p53 immunohistochemistry confirmed on hysterectomy

Kang et al. Selection of endometrial carcinomas for p53 IHC based on nuclear features. JPathol Clin Res. 2022. 8:19-32.

Huvila et al. Subclonal p53 immunostaining in the diagnosis of endometrial carcinoma molecular subtype. Histopathology. 2023.

Betella et al. Int J Gynecol Cancer. 2022. Jun 22.

The underlying principle for selected (versus universal) molecular testing is whether the testing result will ultimately change patient management. Further, to steward resources the test should have a likely yield (i.e. >1% chance of detection). Following this, to screen for Lynch syndrome, endometrioid carcinomas or carcinomas with mixed or ambiguous morphology are subjected to a 2-marker MMR IHC testing (PMS2/MSH6), to detect p53 abnormal endometrial endometrioid carcinomas, p53 IHC should be performed in cases showing above mentioned nuclear features at a low threshold. POLE mutation testing via the APL Cancer Biomarker Comprehensive DNA panel is performed based on clinical risk factors that put a patient in the ESGO 2021 intermediate or high intermediate risk groups. In addition, to exclude possible double classifiers, endometrial endometrioid carcinomas that show abnormal or subclonal abnormal p53 IHC should be subjected to POLE mutation testing.

In 2023 FIGO proposed a new staging system that incorporates pathological parameters (non-aggressive/aggressive histotypes, extent of lymphovascular space invasion) and molecular information (molecular subtype: POLE-mutated or p53abn) into this new staging system. [17]

While these features are not without merit (e.g. risk factors for “synchronous endometrial and ovarian endometrioid carcinomas) and have been developed from the for risk assignment in the ESGO 2021 guidelines for management of endometrial carcinoma [18], transferring them into a staging system has been met with some resistance[17,19,20]. For example, the grouping of EEC3 with aggressive histotypes without consideration of molecular subtype may lead to overtreatment.

The College of American Pathologist still lists the FIGO 2009 classification, as well as the FIGO 2023 classification.

Table 2: FIGO 2023 Classification[17]

2023 Figo Stage	*Defining Criteria*
IA1	non-aggressive histological type limited to the endometrium or an endometrial polyp
IA2	non-aggressive histological type involving <50% myometrium, with no/focal LVSI
IA3	low-grade EEC limited to the uterus and ovary
$IAm_{POLEmut}$	*POLEmut EC, confined to the uterine corpus or with cervical extension, regardless of LVSI or histological type*
IB	non-aggressive histological type involving ≥50% myometrium, and with no/focal LVSI
IC	aggressive histological type limited to the endometrium or an endometrial polyp
IIA	non-aggressive histological type with invasion of the cervical stroma
IIB	non-aggressive histological type with substantial LVSI
IIC	aggressive histological type with any myometrial infiltration
$IICm_{p53abn}$	*p53abn EC, confined to the uterine corpus with any myometrial infiltration, with or without cervical invasion, and regardless of LVSI or histological type*
IIIA1	spread to ovary or fallopian tube (except if it meets the Stage IA3 criteria)
IIIA2	involvement of uterine subserosa/serosa
IIIB1	metastasis or direct spread to the vagina and/or the parametria
IIIB2	metastasis to the pelvic peritoneum

Guideline Questions

1. What is the pathological subclassification of endometrial carcinoma?
2. What predictive biomarkers are used to inform treatment decisions?
3. What is the recommended management of early endometrial cancer?
4. What is the recommended management for advanced and recurrent endometrial cancer?
5. What is the role of adjuvant therapy in endometrial cancer?
6. How are immunotherapy toxicities managed for patients with endometrial cancer?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to March 2024. The following guidelines were reviewed and information included where relevant: the National Comprehensive Cancer Network (NCCN) guidelines,[21] the American Society of Clinical Oncology (ASCO) guidelines, European Society for Medical Oncology (ESMO)[22] guidelines, Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines,[23] the Society of Gynecologic Oncology (SGO),[24] and the American College of Radiology.[25]

Target Population

The recommendations outlined in this guideline apply to women with endometrial carcinoma (EC). This guideline does not cover leiomyosarcoma and endometrial stromal sarcoma, which should be staged as uterine sarcomas. For recommendations on the management of uterine sarcomas, please refer to the Alberta Health Services guideline, *Uterine Sarcoma*.

Recommendations

Pathological Subclassification of Endometrial Carcinomas

- Histotype should be assessed for all EC specimens. It is acknowledged that this might not always be possible especially in the biopsy setting and a diagnosis of high-grade endometrial carcinoma; describing features and ancillary results is acceptable. This is also acceptable in the hysterectomy setting pending molecular results.
- Molecular subtype should be assessed on selected cases as per selection for molecular testing flow chart (Figure 3).
- Molecular subtype will be assessed by 3 tests: p53 immunohistochemistry (IHC), PMS2/MSH6 IHC followed by MLH1 or MSH6 IHC if the partner is abnormal, and next generation sequencing for POLE.
- Molecular subtype can only be reported if all 3 tests have been performed due to the possibility of double classifiers. If only some of the tests have been performed, individual test results should be reported, and a provisional molecular subtype label can be given (designated as provisional).
- Double classifier: presence of pathogenic POLE mutation (associated with high TMB) determines POLEmut (even in the presence of MMRd or p53abn), absence of POLE mutation and presence of MMR deficiency determines MMRd even in the presence of p53abn (often subclonal), absence of POLE mutation, absence of MMR deficiency and presence of p53 abn (even as subclonal if >10%) determines p53 abn. Absence of all 3 alterations determines NSMP

- P53 IHC will be reported as normal/wild type, abnormal (presumed to be clonal, with description of the abnormal pattern) or abnormal subclonal (the latter describing the abnormal pattern and an estimate of the % distribution).
- Histotype and molecular subtype are interrelated (see Table 1). For example, ESC should always be p53 abnormal in a clonal manner (not subclonal). Molecular subtype is most important within EEC3.
- MMRd and POLEmut strongly support endometrioid histotype (including its descendants, i.e. DDEC/UEC).
- Grade as defined by FIGO and WHO only applies to endometrioid histotypes. WHO2020 and ESGO2021 support a binary grouping into low-grade (EEC1 and EEC2) versus high-grade (EEC3).
- Grade and molecular subtype are interrelated. For example, EEC1/2 are only exceptionally p53abn (see below). Significant nuclear atypia >50% tumor cells justify upgrade by one level (i.e. from low to high-grade).
- Subclonal abnormal p53 IHC most likely occurs in a POLEmut and/or MMRd context, in which it has no significance. However, if POLE mutation is not detected or MMR is proficient, subclonal abnormal p53 in distribution of >10% determines p53abn molecular subtype.
- Significant nuclear atypia is associated with p53abn, hence, the % distribution of p53abn can be used to judge whether the 50% cut-off is reached. Subclonal p53abn molecular subtype >50% generally are EEC3.
- Prospects: grade may only be relevant in EC NSMP
- Lymphovascular invasion (LVSI) should be reported (absent/focal/substantial) on all hysterectomy specimens containing endometrial carcinoma. The precise cut-off for substantial LVSI is changing and following the College of American Pathologists guidelines is recommended.
- If only sentinel lymph node dissection (LND) is performed, a sentinel lymph node protocol may be applied.

Lynch Syndrome

Lynch syndrome screening is recommended for all patients with newly diagnosed endometrioid carcinoma. This syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes. Almost all of these mutations are loss of function mutations, leading to absence of MMR protein expression.

- It is recommended to use IHC to identify tumours with MMR deficiency.
- MSI testing can be considered in equivocal cases.
- There are no current recommendations on how to classify MMR subclonal cases, subclonality with % should be recorded.
- For cases with absent MLH1/PMS2, MLH1 hypermethylation testing should be reflexibly ordered, as hypermethylation suggests a somatic event and genetic referral is not required.
- For all other abnormal findings genetic referral is necessary, namely, absence of MLH1/PMS2 without MLH1 hypermethylation, and absence of PMS2, MSH2, or MSH6.
- Although isolated subclonal PMS2, MSH2 and MSH6 loss is conceptionally not compatible with Lynch syndrome, consideration should be given to possibly refer these cases to genetic testing.

Combined subclonal loss (e.g. subclonal MSH6 loss in a case with MLH1 promoter hypermethylation and MLH1/PMS2 loss) is considered secondary and does not require genetic testing.

- Note: greatly reduced MSH6 staining (focal positivity in <10% of tumor cells with significantly weaker intensity as the internal control of normal cells) has been observed in cases of Lynch syndrome, this should be reported as equivocal or abnormal (not normal or sublonal) and result in recommendation of genetic referral.
- Patients with significant personal or family history suggestive of hereditary cancer syndromes should be considered for genetic referral regardless of normal screening studies (Appendix B).

Lynch Syndrome and Genetic Counselling

- Lynch syndrome is a hereditary cancer condition associated with increased risk for colorectal and endometrial cancers, and variable risk for other cancers. It is an autosomal dominant condition caused by pathogenic variants in a mismatch repair gene (MMR). Lynch syndrome accounts for 2-5% of colon cancer and 2-3% of endometrial cancer. Previously, it was called hereditary nonpolyposis colorectal cancer syndrome, or HNPCC.

Table 3: Cancer Risks (to age 80) for Female Patients[26]

Cancer site	MLH1	MSH2	MSH6	PMS2
Any Lynch cancer	80.2%	83.4%	55.2%	40.1%
Colorectal	48.3%	42.6%	17.3%	8.5%
Endometrial	37.2%	44.1%	45.7%	21.2%
Gastric	4.3%	4.0%	0.7%	*
Ovarian	8.0%	13.4%	6.3%	2.5%
Ureter/kidney	2.9%	19.5%	3.9%	*
Bladder	4.8%	9.4%	2.6%	*
Breast	12.4%	15.5%	15.1%	12.4%
Brain	1.4%	2.2%	1.2%	*
Small bowel	4.5%	3.7%	0.6%	2.1%
Pancreas	3.7%	3.5%	2.2%	*
Bile duct/gallbladder	1.5%	2.4%	*	*

Screening and Prevention Recommendations for Lynch Syndrome

Annual Pelvic Examination:

- There is no proven effective screening strategy for early detection of endometrial or ovarian cancer:
    - Endometrial biopsy +/- US every 1-2 years is not recommended for the diagnosis of endometrial cancer.
    - Ovarian cancer screening is not recommended as the benefit of screening (e.g. transvaginal ultrasound and serum CA-125) has not been proven. Prophylactic bilateral salpingo-oophorectomy may be considered.
- Patients should be given the opportunity to discuss fertility and contraceptive needs with a specialist.
- Risk reducing hysterectomy and BSO can be discussed after age 40 following completion of childbearing. Timing should be individualized based on personal risk (Higher risk for MLH1, MSH6, MSH2. Insufficient evidence for MSH6 but can be considered. PMS2 age 50).
- All women who undergo hysterectomy-BSO should be offered estrogen-only HRT until natural age of menopause (age 51 or older) or in consultation with specialist.

Predictive Biomarker Testing HER2/ERBB2 for Endometrial Serous Carcinoma (ESC)

Criteria for Testing:

- HER2 testing should be ordered on select patients with recurrent or advanced (stage III and IV) endometrial serous carcinomas in which additional targeted combination therapy with trastuzumab or other HER2 targeted medication is being considered.
- Eligible tumours include pure endometrial serous carcinomas and mixed serous carcinomas with no minimum requirement on the percentage of serous carcinoma in the mixed serous carcinoma group.
- Given the heterogeneity of HER2, testing should be performed on all available tissue specimens. This often includes biopsy samples and hysterectomy specimens at initial diagnosis and time of recurrence.

Scoring of HER2:

Scoring is performed in accordance with the 2023 College of American Pathologists (CAP) for reporting results of biomarker testing of specimens from patients with carcinoma. The outline of the algorithm used in that testing protocol is listed in the table in the appendix at the end.

- The overall HER2 status is regarded as positive if any specimen is HER2 positive by immunohistochemistry or ISH since published literature to date suggests that HER2-positive endometrial serous carcinomas frequently show significant intratumoral heterogeneity.
- In mixed serous carcinomas, scoring is performed on the serous component.

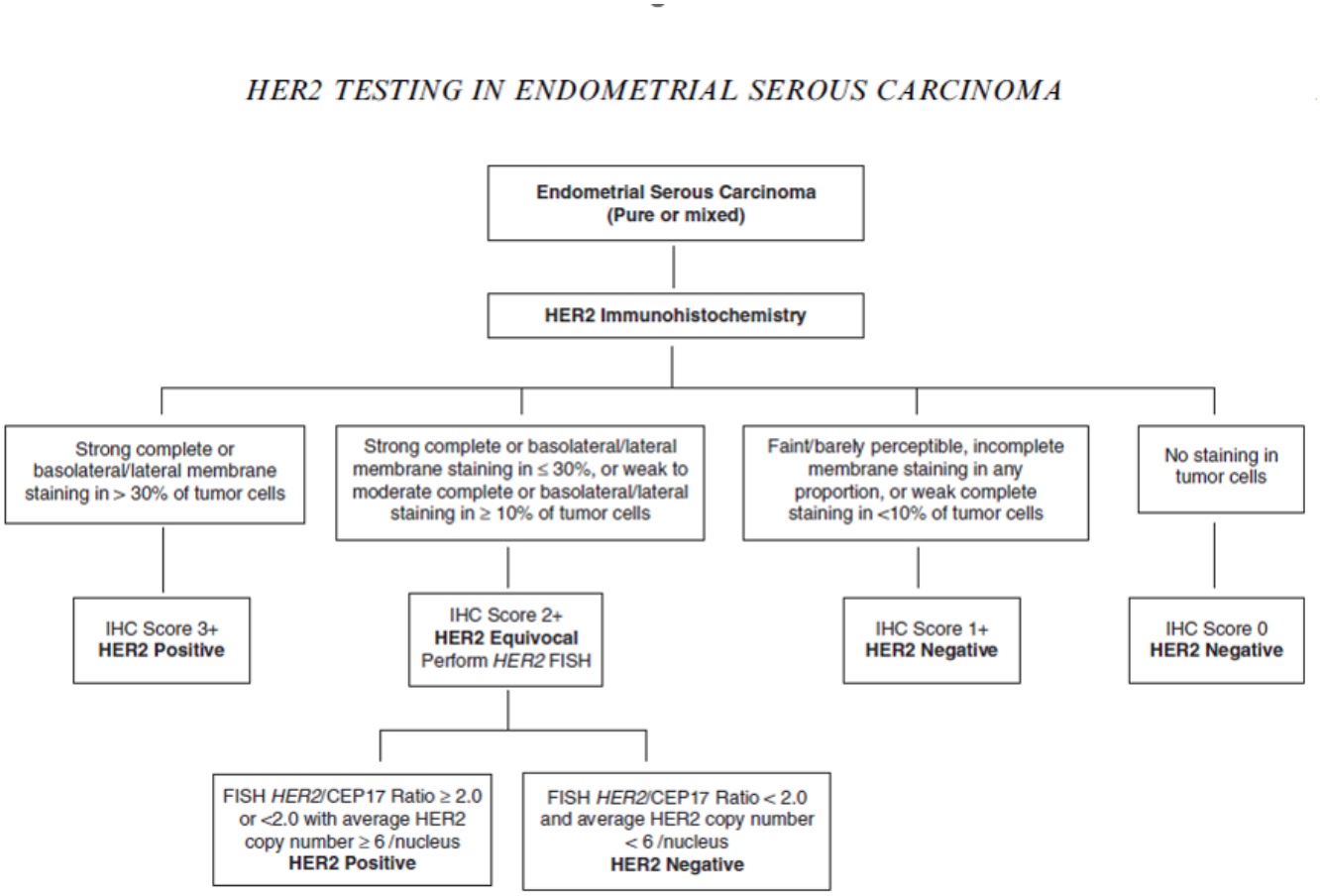
Additional Notes:

Scoring protocols for carcinosarcomas have not been formalized yet. Thus, while this is a tumour type that some published recommendations suggest HER2 testing on, it is not clear how the testing

algorithm applies to this tumour type yet. In particular, if the scoring should be performed only on the carcinomatous component of the tumour or only on carcinosarcomas that have a serious or p53 mutated carcinomatous component.

Testing of endometrial carcinomas, all histologic subtypes, for eligibility for treatment with trastuzumab deruxtecan has not been approved in Canada currently. In the United States such testing utilizes HER2 scoring systems in accordance with ASCO/CAP scoring guidelines of gastric carcinomas.

Figure 4: Algorithm for HER2 Scoring in Endometrial Serous Carcinoma[27]



- Endometrial Serous Carcinoma – Any endometrial serous carcinoma or endometrial carcinoma that has a mixed endometrial serous carcinoma regardless of percentage of serous component.
    - Drug: Trastuzumab and carboplatin and paclitaxel- recurrent or advanced stage (stage III/IV in prior FIGO staging system). Score - serous component using ASCO-CAP endometrial serous guideline. *Currently funded and operational in province.*

- Endometrial Carcinoma - All histologic types
    - Drug: Trastuzumab deruxtecan (T-DXd). Advanced disease with at least one prior treatment. *Currently not funded in the province.*

- Endometrial Carcinosarcomas - In patients with advanced or recurrent carcinosarcomas which are MMRd the recommendations are a combination of carboplatin with paclitaxel and dostarlimab.

- Drug: Trastuzumab and carboplatin and paclitaxel. Recurrent or advanced stage carcinosarcomas.There may be a role for trastuzumab in the recurrent or advanced setting. There is, however, uncertainty in scoring for HER2.
- Score: the epithelial component using ASCO-CAP Endometrial Serous guidelines or does one score both components or score only if the epithelial component is Serous

Currently trastuzamab is NOT funded in the province for carcinosarcomas, and trastuzumab deruxtecan (T-Dxd) is not funded in the province for gynecologic oncology indications.

Surgery:

All patients should be referred to a gynecologic oncologist for comprehensive continuing care as they are trained to decide and provide appropriate individualized treatment. Additionally, a full staging procedure with minimally invasive surgery can be offered with evidence to suggest that high volume centers have better long-term outcomes.

- Hysterectomy with bilateral salpingo-oophorectomy is the standard surgical procedure in early-stage EC.
- For patients of reproductive age, the discussion of bilateral oophorectomy is individualized and should be discussed with a gynecologic oncologist.
- Minimally invasive surgery (laparoscopic or robotic) is the recommended approach in stage I EC including patients with high-risk endometrial carcinoma.
- In low-risk EC, systematic LND is not recommended however in intermediate and high-risk group, LND is recommended to guide surgical staging and adjuvant therapy.
- AEH – Hyst + BSO +/- LND
- EEC1/EEC2 Hyst + BSO +/- LND
- EEC3 Hyst +BSO + pelvic LND +/- PA LND
- ESC, EEC3p53abn, CS, ECCC, DDEC/UEC Hyst + BSO + pelvic LND + PA LND +/- Omentectomy
- Alternative – sentinel LNDs instead of full LND[28]

Adjuvant Treatment Recommendations

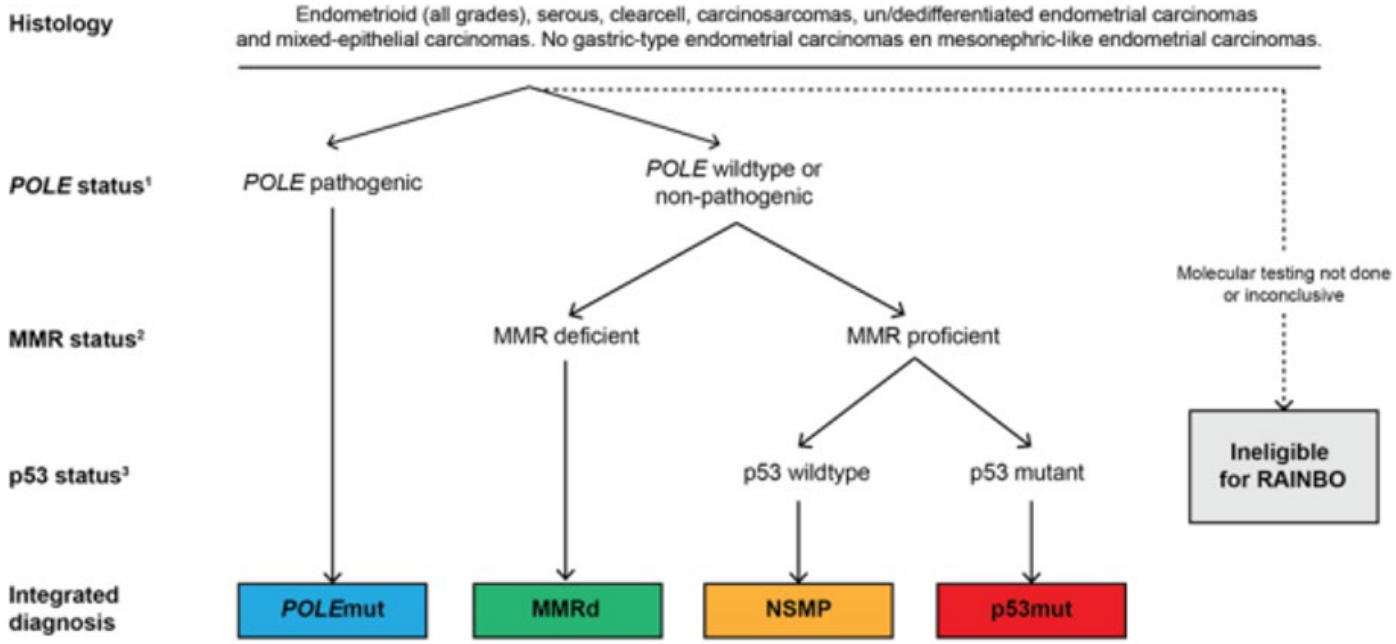
Stage I&II

EEC POLEmut:

Endometrial carcinomas of POLEmut molecular subtype should be considered for treatment de-escalation (via enrolment onto clinical trial EN.10-/Rainbo Blue, or PORTEC3) regardless of other risk factors.

Prior to inclusion in RAINBO (EN.10) trial, complete molecular classification must be performed on an EC specimen. This can be either the tumour-containing hysterectomy specimen or the preoperative endometrial biopsy specimen.[29] Molecular classification includes mutational status assessment of the exonuclease domain of DNA polymerase epsilon (POLE), MMR-IHC and p53-IHC or TP53 sequencing (Figure 5). [29]

Figure 5: Endometrial Cancer Molecular Classification for Inclusion in the RAINBO Program



EEC1/2 molecular subtype unknown or NSMP or EEC1/2 MMRd:[4] [6]

The majority (67%) of EEC1/2 patients will present with stage IA with no LVSI.

- Stage IA: No adjuvant treatment required, but may be an option in some situations.
- Stage IB: Adjuvant VBT is recommended.
- Stage II: Adjuvant pelvic EBRT is recommended +/- VBT, but adjuvant VBT alone (instead of EBRT) may be considered in lower-risk contexts.
- sLVSI: Adjuvant EBRT should be considered.

Treatment should be individualized, depending on tumour factors like: grade 2, LVSI status, tumour size, age > 65 years, polyp-confined disease, nodal isolated tumour cells (N0(i+)). Patient-level considerations may also come to bear, such as treatment-related toxicity, and treatment/follow-up logistics.

EEC3 molecular subtype unknown or NSMP:

- Stage IA: No or focal LVSI, adjuvant VBT is recommended.
- Stage IB or II or sLVSI: Adjuvant pelvic EBRT is recommended, +/- VBT for stage II.
  Addition (concomitant and/or sequential) of chemotherapy to EBRT could be considered, especially for G3 and/or substantial LVSI. If G3 MMRd stage I/II, chemotherapy with pembrolizumab could be considered. However, pembrolizumab has not received approval in Alberta for this indication yet.

Treatment should be individualized, depending on treatment factors like: LVSI status, unknown/unsampled nodal status (pNx) or isolated tumor cells (N0(i+)), tumour size, age > 65 years, polyp-confined disease. Patient-level considerations may also come to bear, such as treatment-related toxicity, and treatment/follow-up logistics.

ESC, EEC3p53abn, CS, ECCC, DDEC/UEC, mesonephric, gastric-intestinal, neuroendocrine:

- Adjuvant chemotherapy is recommended.
- Adjuvant RT is recommended, EBRT and/or VBT individualized to tumor risk factors and patient considerations.
- Participation in clinical trials is strongly encouraged, especially for rare types

For cases where myometrial invasion is absent, limited data available; may consider chemotherapy and pelvic EBRT and/or VBT in p53 tumors confined to a polyp.

Stage III

Approximately 20% of all patients with endometrial cancer will present with a stage III disease.

- If MMRd then recommendation for combination of chemotherapy and immunotherapy (dostarlimab).
- If MMRp then recommendation of adjuvant treatment with combined chemotherapy and radiation
- Please see note below on dostarlimab.
- Adjuvant pelvic EBRT +/- VBT; may consider nodal boost for suspected involved (unresected) nodes.

Stage IV

Approximately 10% of all patients with endometrial cancer will present with a stage IV disease.

Treatment with dostarlimab + carboplatin-paclitaxel will be reimbursed in adult patients with MMRd or MSI-H primary advanced or recurrent endometrial cancer not amenable to curative therapy who meet ≥ 1 of the following criteria: [30]

- Have primary stage III or IV endometrial cancer.
- Have a first recurrence and have not previously received systemic anticancer therapy in advanced disease.
- Have received prior neoadjuvant or adjuvant systemic anticancer therapy and a first recurrence at a minimum of 6 months after completion of treatment.

Patients should have good performance status (ECOG 0-1).

Patients must not have any of the following:

- First recurrence within 6 months. of completing neoadjuvant or adjuvant systemic therapy.
- Prior therapy with anti-PD-1, anti-PD-L1, or anti-PD-L2 drug for advanced disease.
- Uncontrolled brain metastasis.

Discontinuation should be based on a combination of clinical and radiological progression and/or significant adverse events potentially related to dostarlimab + carboplatin-paclitaxel.

Dostarlimab will be reimbursed for a maximum of 3 years (i.e., 500 mg q 3 wks. [cycles 1 to 6] and 1,000 mg q 6 wks. [cycle 7 and thereafter]).

Dostarlimab + carboplatin-paclitaxel will only be reimbursed when started as a combination. [30]

Tumour-directed palliative RT may be considered for symptom control, and in some situations also for local tumor control. RT volumes, dose, and fractionation should take into consideration factors like: treatment aims, toxicity concerns, logistical burden on patients, any ongoing or upcoming systemic therapy, and patient preferences. See more information in appendix A

Unresectable or metastatic microsatellite instability-high or mismatch repair deficient endometrial cancer

- Pembrolizumab for the treatment of adult patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient endometrial cancer whose tumours have progressed following prior therapy or who are intolerant of prior therapy and who have no satisfactory alternative treatment options, as monotherapy.[31] Patients must not have had any prior treatment with a PD-1 or PD-L1 inhibitor. Pembrolizumab will be reimbursed for maximum of 18 cycles or 2 years whichever is longer. The dosing schedule for this monotherapy **is either 2 mg/kg to a maximum of 200 mg every 3 weeks or 4 mg/kg to a maximum of 400 mg every 6 weeks."**
- When feasible, and with acceptable morbidity, cytoreductive surgery to a maximal surgical extent should be considered in stage III and IV.

Recommended chemotherapy: Four to six cycles of carboplatin (AUC 5-6) with paclitaxel at 175 mg/m2 every 21 days for six cycles. In the case of hypersensitivity to paclitaxel, nab-paclitaxel (Abraxane) 260 mg/m^2 should be considered.

Recommended hormone therapy: The recommended medications are medroxyprogesterone (Progestin) 200 mg daily or megestrol (Megace) 160 mg daily.

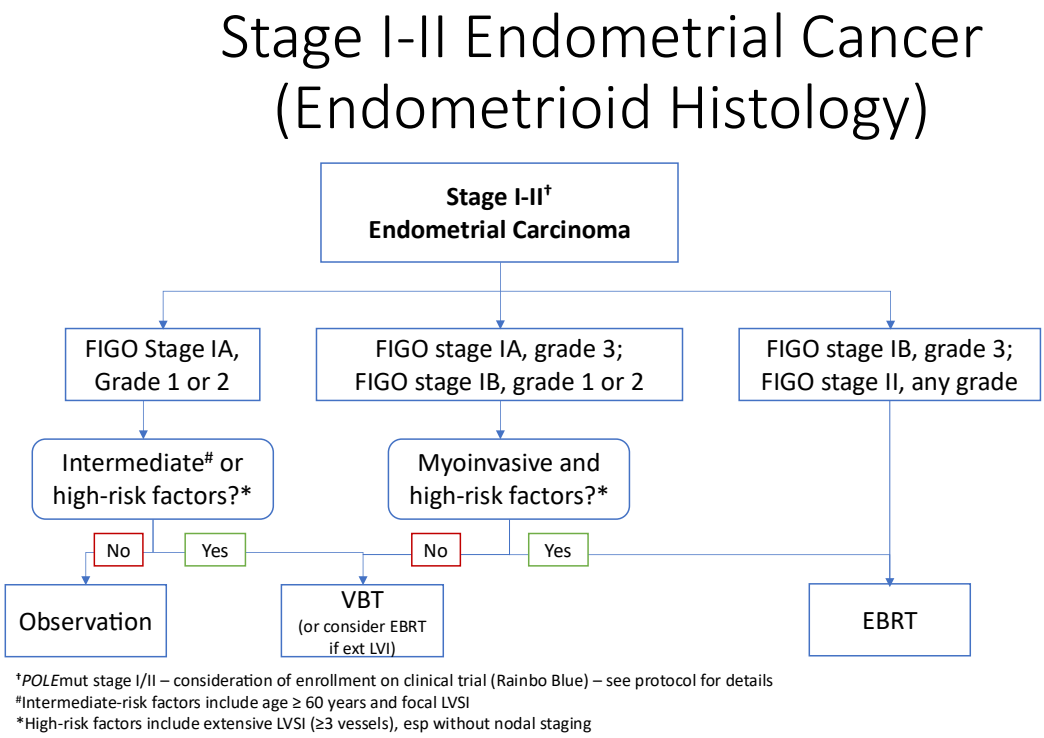
Molecular marker influence on adjuvant RT and systemic therapy:

- For patients with endometrial cancer considering adjuvant therapy, molecular testing is recommended.
- For patients with myoinvasive FIGO stage IA-IIIC2 TP53 mutated endometrial cancer, chemotherapy and RT are conditionally recommended.
- For patients with FIGO IIIC2 mismatch repair deficiency endometrial cancer, RT with chemotherapy is recommended.
- For patients with FIGO stage IIIC2 POLE mutant tumours, RT with chemotherapy is conditionally recommended.

RT technical notes :

- For patients with endometrial carcinoma undergoing adjuvant EBRT, VMAT is recommended to reduce acute and late toxicity.
- For patients with endometrial carcinoma undergoing adjuvant EBRT using VMAT, final PTV should take into account organ motion, which may include creation of a vaginal ITV structure. Daily 3D image-guidance is recommended, such as CBCT, with standardized processes in place for treatment verification and/or adaptation.
- For patients with endometrial carcinoma undergoing adjuvant EBRT, a dose of 45 Gy in 25 fractions is recommended for microscopic disease targets; simultaneous integrated boost (SIB) may be considered in the 50-65 Gy EQD2 range to address margin concerns and/or gross nodal disease.
- For patients with endometrial carcinoma undergoing adjuvant vaginal brachytherapy alone, treating the proximal vagina (at least 3 cm) is recommended, dose regimen and prescription may be guided by contemporary protocols (e.g. PORTEC-4a).
- For patients with endometrial carcinoma with close or positive margins, postoperative RT is recommended; boost may be delivered as focal pelvic SIB or VBT, depending on location/extent of the margin of concern, anatomic factors, and dosimetric considerations.

Figure 6: Endometrioid Histology



Advanced or Recurrent Disease

Recurrence may be symptomatic or asymptomatic so the type of treatment will depend on the location, extent of disease, previous management and the patient's preferences. The recurrence rate for early stage I and II endometrial cancer is approximately 15 -20%. Of these recurrences, 50% are local (vaginal vault), 25% are distal with 25% having a combination of local and distant metastasis. We recommend all patients be presented at multidisciplinary tumour board conference to review management strategies.

Isolated Locoregional Recurrence

- For local and/or regional recurrence in the absence of previous radiation, salvage intent radiotherapy may be possible.
- Surgical management with pelvic exenteration can be considered in the absence of distant disease in those who have previously received radiotherapy.
- For vaginal/supravaginal recurrence (no prior RT): Pelvic EBRT is recommended, with boost delivered via image-guided intracavitary +/- interstitial brachytherapy where technically feasible. SIB boost may be considered in some situations.
- In case of superficial tumours, brachytherapy alone can be considered.
- In cases of isolated recurrence after prior VBT, salvage RT may be possible, depending on tumour, anatomic, and toxicity considerations.

Extra-Pelvic/Distant Recurrence

- For patients with recurrent endometrial cancer not amenable to radiotherapy or surgery, treatment options vary depending on previous treatment and MMR status.
- First line therapy in the upfront treatment setting includes a combination of carboplatin and paclitaxel.
- MMRd:Patients who have progressed after first line chemotherapy, treatment with immune checkpoint inhibitors (dostarlimab or pembrolizumab) have demonstrated high response rates and improved survival outcomes.[32,33]
- MMRp: Patients who have progressed after first line chemotherapy, treatment with combination of pembrolizumab and lenvatinib has shown to improve survival.[34]
- There is no consensus on the starting dose of lenvatinib. Consideration of toxicity and patients tolerance should be made prior to starting treatment.
- For some oligometastasis or oligoprogression scenarios, high-dose local RT (e.g. SBRT) may be considered for local control purposes. Clinical appropriateness and technical feasibility should be determined in a multidisciplinary approach.

Immunotherapy:

- It is recommended that pembrolizumab or dostarlimab can be used to treat advanced endometrial cancers, if surgery or radiation are not feasible options.
- Dostarlimab can be used to treat advanced or recurrent endometrial cancer, in combination with chemotherapy as first treatment (and then as single agent maintenance treatment), if the cancer cells have a defect in a mismatch repair gene (dMMR) or a high level of microsatellite instability (MSI-H).

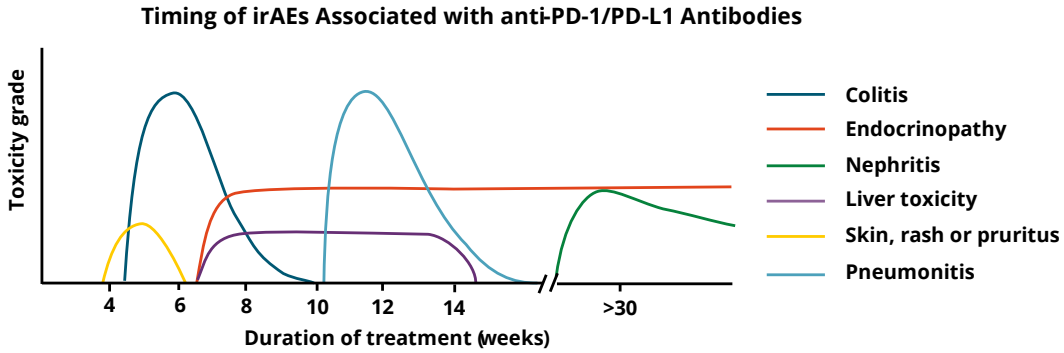
- Dostarlimab (500 mg every 3 weeks (Q3W) from cycle 1 through cycle 6 followed by 1,000mg monotherapy every 6 weeks (Q6W), beginning at cycle 7 Day 1 until progression of disease (PD), unacceptable toxicity, or up to 3 years or pembrolizumab (200 mg every 3 weeks or 400mg every 6 weeks up to 2 years) can be recommended by itself after systemic treatment (and if surgery and radiation are not good options), in MMRd tumours.
- Patients with recurrent advanced MMRp endometrial cancer, who have failed chemotherapy, can be considered for a combination of pembrolizumab and lenvatinib.
- Side effects: Most irAEs associated with anti-PD-1 antibody use occur within the first 6 months of treatment, but late-onset irAEs can occur. [35]
- Other side effects: Feeling tired or weak, fever, cough, nausea, itching, skin rash, loss of appetite, muscle or joint pain, shortness of breath, constipation or diarrhea.

Table 4: Timing of irAEs[35]

Timing of irAEs Associated with anti-PD-1/PD-L1 Antibodies	
Toxicity	Duration of treatment (weeks)
Colitis	Occurs between 4 and 8 weeks after first infusion
Endocrinopathy	Typically emerges between 6 and 14 weeks of treatment
Nephritis	Start after 20 weeks
Liver Toxicity	Emerges between 6 and 14 weeks with a median time of onset of 8 weeks
Skin rash or Pruritus	4-6 weeks
Pneumonitis	ranging from 2 to 24 months

Figure 7. Timing of irAEs

- **Most irAEs associated with anti -PD-1 antibody use occur within the first 6 months of treatment**, but late-onset irAEs can occur



PD-1: programmed cell death-1; PD-L1: programmed cell death-ligand 1.
1. Martins F et al. Nat Rev Clin Oncol. 2019;16:56380.

Follow Up and Surveillance

- Patient counseling on potential recurrence symptoms could include but are not limited to discussion of:
    - unexplained vaginal bleeding or discharge
    - detection of a mass
    - abdominal distension
    - persistent pain, especially in the abdomen or pelvic region
    - fatigue
    - diarrhea, nausea or vomiting
    - persistent cough
    - swelling
    - weight loss
    - shortness of breath or chest pain

- Follow-up by the treating gynecologic oncologist, general gynecologist, or general practitioner (GP) could be based on the risk of recurrence. The majority of recurrences are symptomatic and occur within 5 years. A general examination, including complete history, speculum, and a pelvic-rectal examination, could be performed as follows:
    - Visits every 6 months for the first 2 years followed by follow-ups every yearly for 3 years. Follow-up should include a speculum examination and pelvic examination. Pap smear is not required – unless abnormal high grade cytology in the past.

Fertility Sparing Options

Fertility sparing treatment for endometrial can be considered in select patients, although it is not the standard of cancer. Patients should meet the following criteria:

- Well differentiated low grade endometrial carcinoma
- Disease limited to endometrium (preferred imaging with MRI)
- Absence of metastatic disease
- No contraindications to progestin therapy or pregnancy

Following completion of family planning, or failure of therapy (persistent disease after 12 – 24 months of therapy, hysterectomy and BSO are recommended. Appropriate counselling and surveillance are essential if conservative management is being considered.

The recommended treatment consistent of continuous based progestin therapy including intrauterine device (IUD), megestrol acetate, medroxyprogesterone. Monitoring with endometrial sampling (endometrial biopsy or D&C) is recommended every 3-6 months

Hormone Replacement Therapy for Hypoestrogenism

Patients with endometrial cancer following surgery with BSO become post-menopausal with an array of symptoms including but not limited to vasomotor symptoms, vaginal atrophy, osteoporosis and increased risk of cardiovascular disease. For postmenopausal patients and especially pre-menopausal patients prior to surgery, estrogen replacement therapy was believed to reverse some of these signs and symptoms. However, this treatment has usually been denied due to concerns of a higher risk of relapse with what is traditionally considered a hormone dependent cancer, However, retrospective trials and prospective trials in women with stage I or II disease have failed to demonstrate an increased risk

of recurrence of disease related death. For this reason, estrogen therapy remains controversial and remains individualized.[36]

- **Low-risk disease:** estrogen-replacement therapy can be considered in scenarios to decrease the risks of long-term health consequences. [37]
- **Intermediate-risk or high-risk disease:** nonhormonal interventions for menopausal symptoms should be considered first line. If symptoms remain uncontrolled, estrogen therapy can be considered in weighing the severity of symptoms and the risk of recurrence. [38]

Future Directions in Immunotherapy for Endometrial Cancer

Two trials, namely NRG018[33] and DUO-E[39] are being considered by the Canadian Drug Agency in the management of recurrent and advanced endometrial cancer. The results from RUBY 2 have not been published yet.

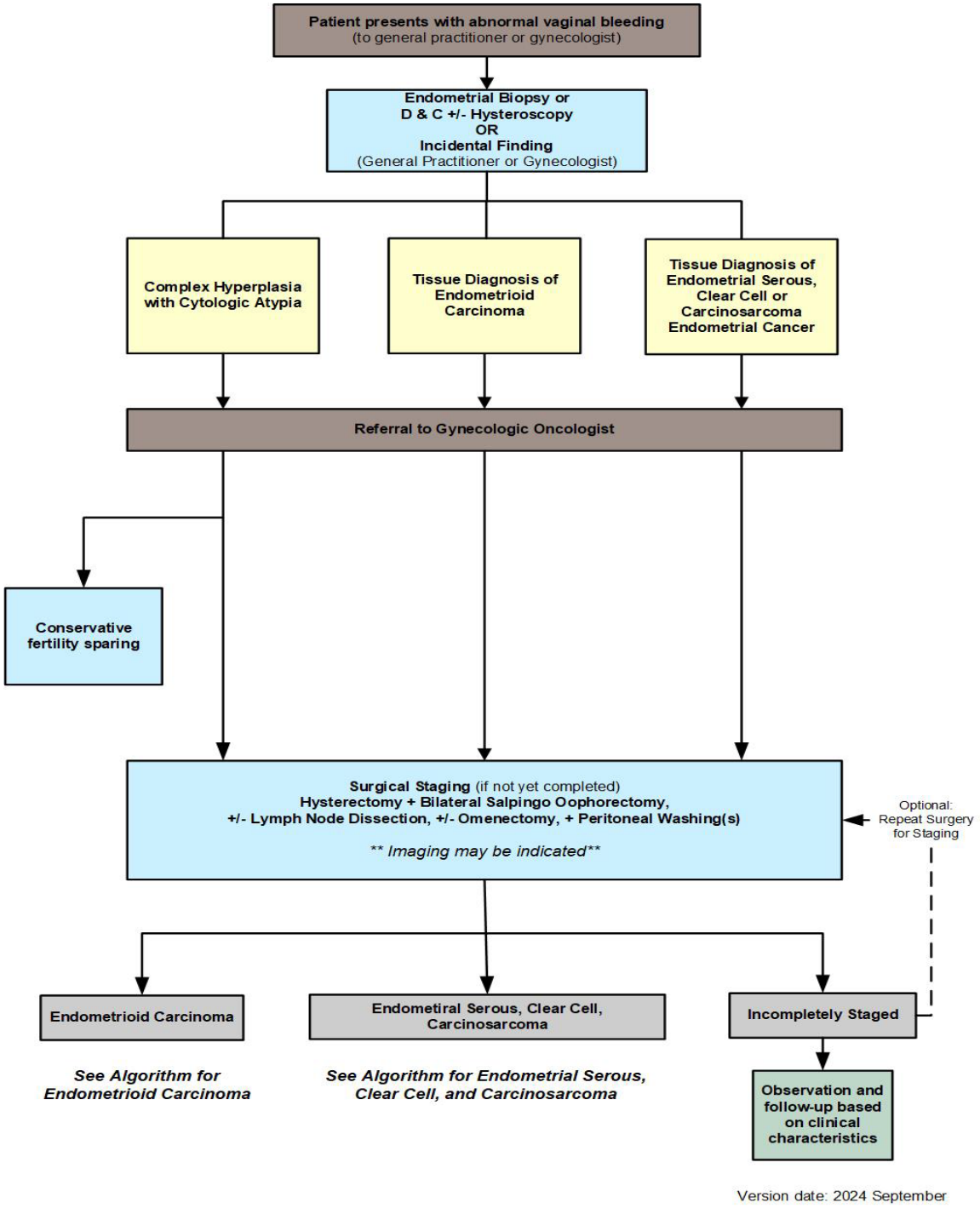
Table 5: Summary of Immunotherapy Trials:

Group	Chemotherapy	Maintenance	Trial
MMRd	Carboplatin + Paclitaxel + Dostarlimab	Dostarlimab	RUBY
	Carboplatin + Paclitaxel + Pembrolizumab	Pembrolizumab	NRG018
MMRp	Carboplatin + Paclitaxel + Pembrolizumab	Pembrolizumab	NRG018
	Carboplatin + Paclitaxel + Durvalumab	Durvalumab + Olaparib	DUO-E
	Carboplatin + Paclitaxel + Dostarlimab	Dostarlimab + Niraparib	RUBY Part 2

The data suggest that future treatments for MMRd patients will be standard chemotherapy with the addition of immunotherapy for those with advanced, recurrent or metastatic endometrial cancer.

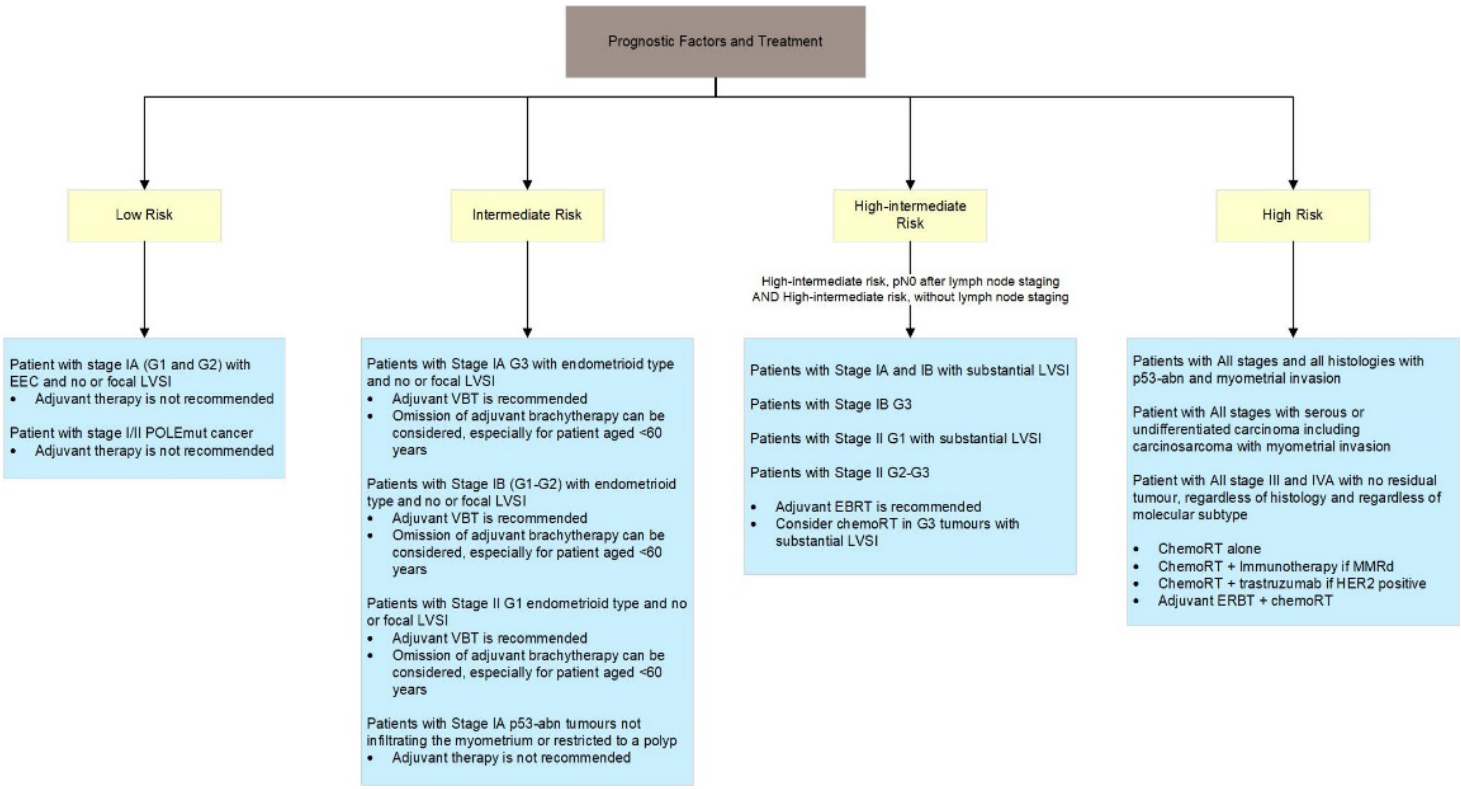
Final recommendations in the use of immunotherapy in combination with standard chemotherapy in newly diagnosed advanced or recurrent MMRp patients, in the province, are dependent on the CDA.

Treatment Algorithm

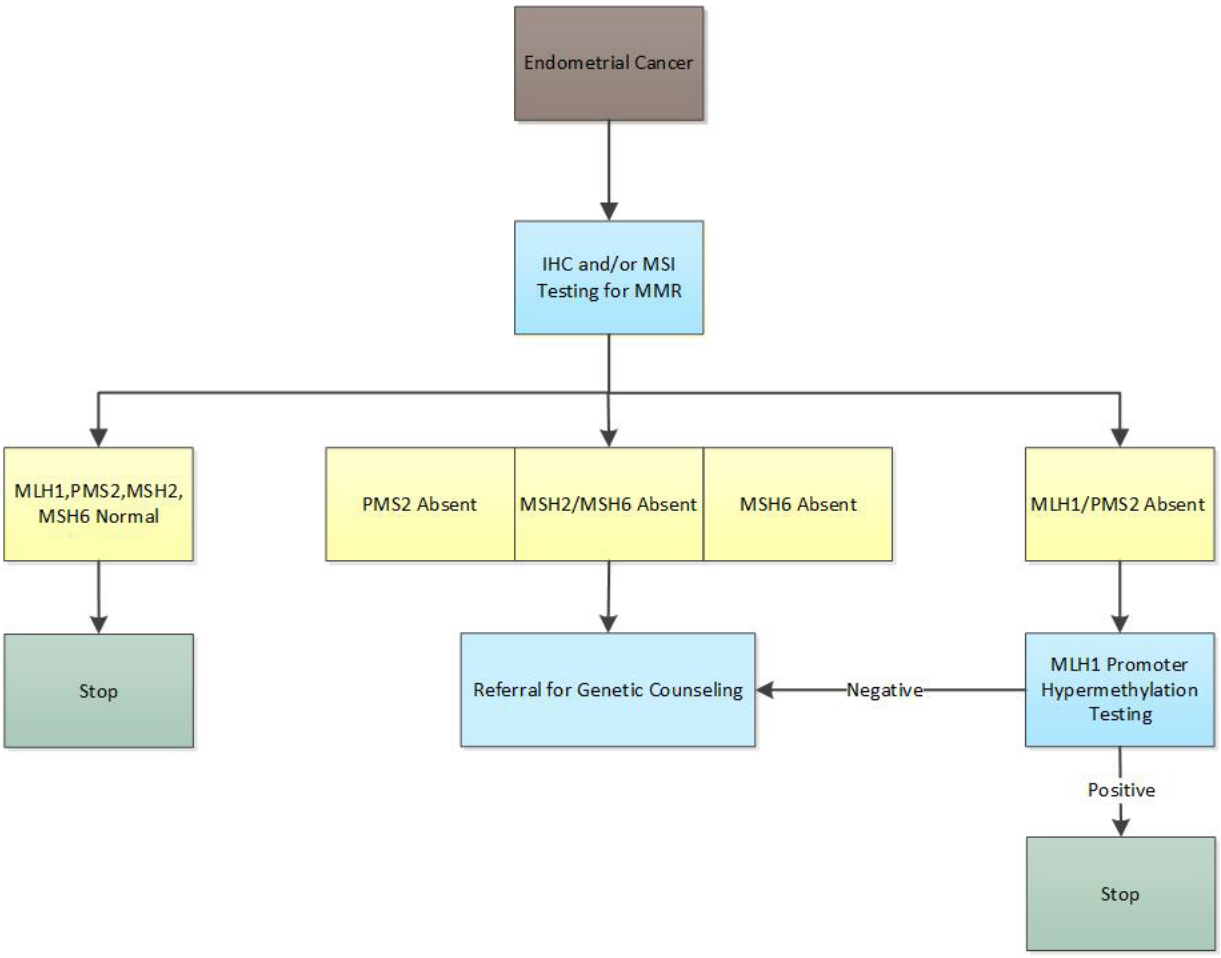


Appendix A

Prognostic Factors and Treatment: Treatment decision-making may consider additional tumor and patient-level factors, please see main text



Appendix B: Lynch Syndrome Screening



Version date: 2024 September

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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Gyne Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Gyne Tumour Team who were not involved in the guideline's development, including [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2016.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2026. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

EC; Endometrial Carcinoma; EEC; Endometrioid Carcinoma, (EEC); ESC; Serous Carcinoma, CS; carcinosarcoma, ECCC; clear cell carcinoma undifferentiated or dedifferentiated carcinoma, LVSI; Lymphovascular invasion, MA; mesonephric, ProMisE; Proactive Molecular Risk Classifier for Endometrial Cancer,

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gyne Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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Wendy Pak has nothing to disclose
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