Oncology Clinical Pathways
Uterine Cancer

November 2024 – V1.2024

Table of Contents

Uterine Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Gulf War and Post 9/11 Veterans

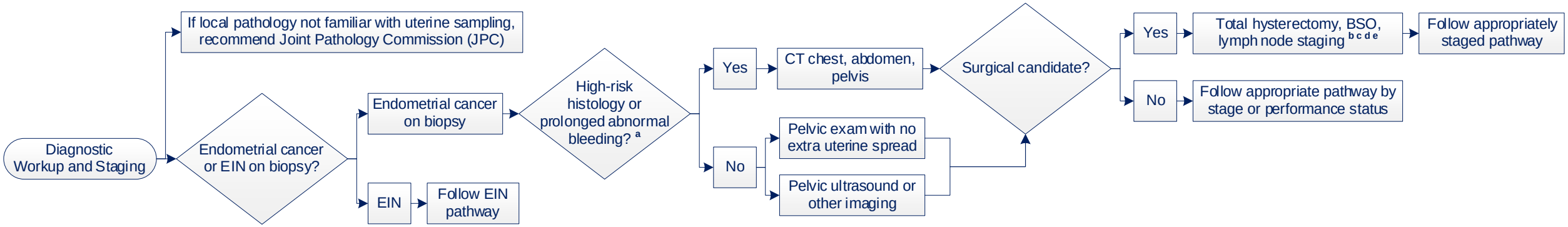
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Reproductive cancer of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Uterine Cancer – Diagnostic Workup and Staging



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **High-risk histology** grade 2-3 endometrioid, carcinosarcoma, clear cell carcinoma, serous carcinoma, mixed or undifferentiated carcinoma

[b] **Fertility-sparing surgery** fertility-sparing management is an option for some patients age ≤ 45 with grade 1 endometrioid endometrial cancer and no evidence of myometrial invasion or spread (see Fertility-Sparing pathway)

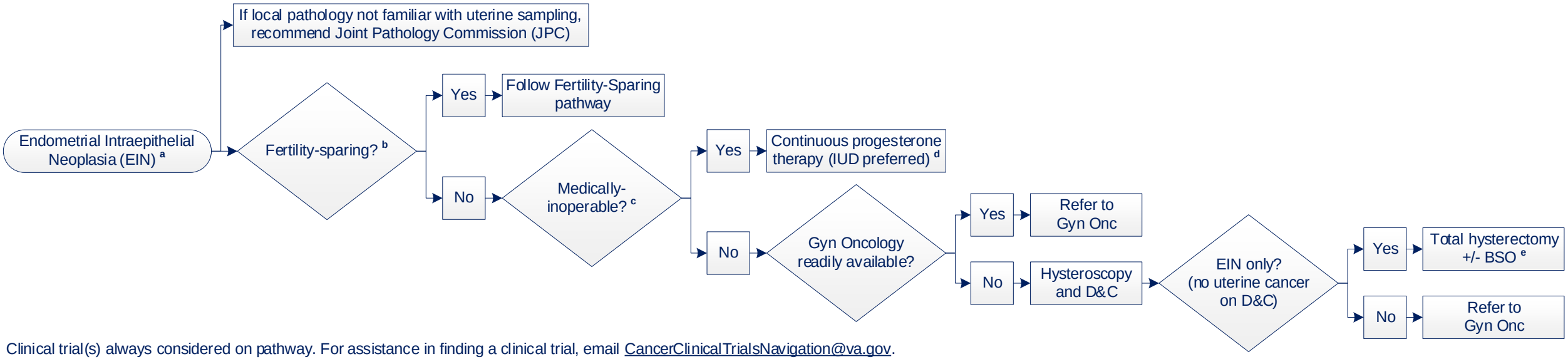
[c] **Surgery** by Gyn Oncologist is preferred

[d] **Minimally-invasive surgery and sentinel lymph node sampling** are preferred when technically feasible; omental biopsy and pelvic washings are recommended for high-grade histologies

[e] **Oophorectomy** may be omitted in select patients who are premenopausal with clinically early-stage (grade 1-2) endometrioid cancer, normal appearing ovaries, and no family history of Lynch Syndrome or other hereditary cancer syndrome

BSO bilateral salpingo-oophorectomy
EIN endometrial intraepithelial neoplasia

Uterine Cancer – Endometrial Intraepithelial Neoplasia (EIN)



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **EIN** consider genetic testing based on family history

[b] **Fertility-Sparing** means uterine preservation; treatment should only be recommended to patients with no contraindication to pregnancy or medical therapy; evaluation of inherited cancer risk and molecular testing is recommended alongside fertility-sparing management of uterine cancer (see Molecular Testing pathway)

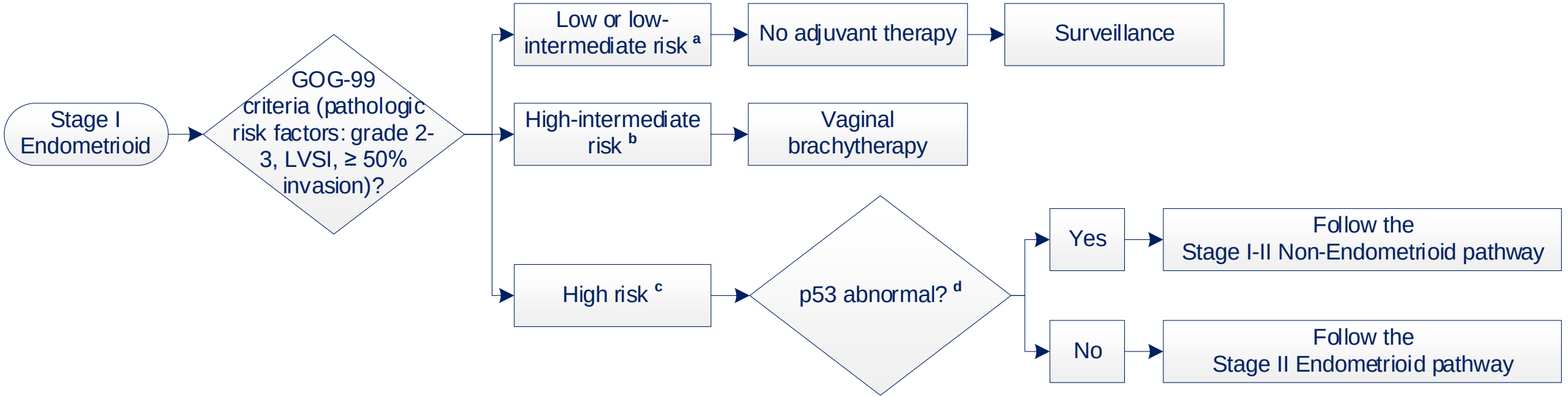
[c] **Medically-inoperable** recommend D&C for full uterine sampling to rule out uterine cancer if procedure and be performed in timely fashion and patient able to tolerate minor surgery

[d] **Continuous progesterone therapy** levonorgestrel IUD preferred, otherwise megestrol or medroxyprogesterone

[e] **Oophorectomy** may be omitted in select patients who are premenopausal with EIN or clinically early-stage (grade 1-2) endometrioid cancer, normal appearing ovaries, and no family history of Lynch Syndrome or other hereditary cancer syndrome

BSO bilateral salpingo-oophorectomy
D&C dilation and curettage
EIN endometrial intraepithelial neoplasia

Uterine Cancer – Stage I Endometrioid



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Low or low-intermediate risk** if stage IA, stage IB, or not meeting high-intermediate risk criteria

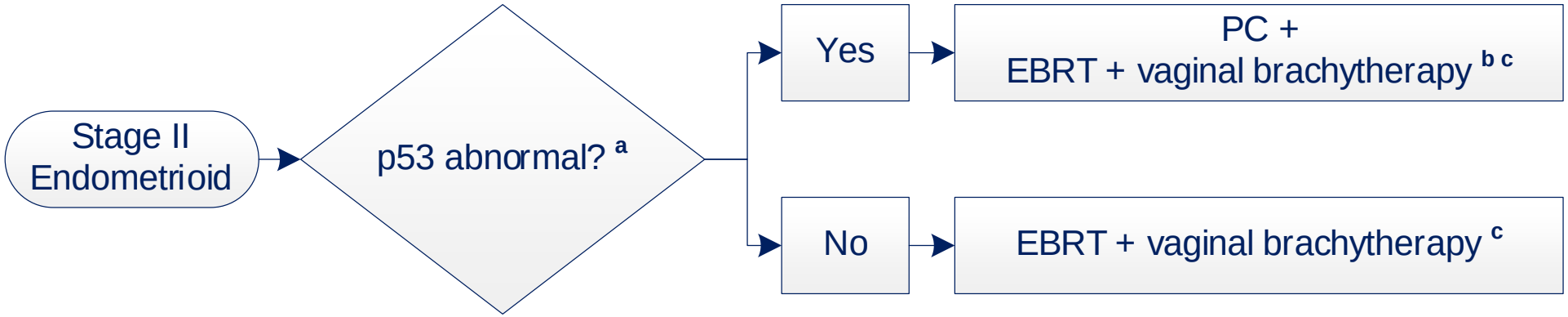
[b] **High-intermediate risk** if age 70 + 1 pathologic risk factor, age 50-69 + 2 pathologic risk factors, or age 18-49 + 3 pathologic risk factors

[c] **High risk** if stage I and more pathological risk factors than high-intermediate risk

[d] **p53 (by IHC) abnormal** lack of staining or upregulated is considered abnormal p53 pattern

IHC immunohistochemistry
LVSI lymphovascular space invasion

Uterine Cancer – Stage II Endometrioid



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

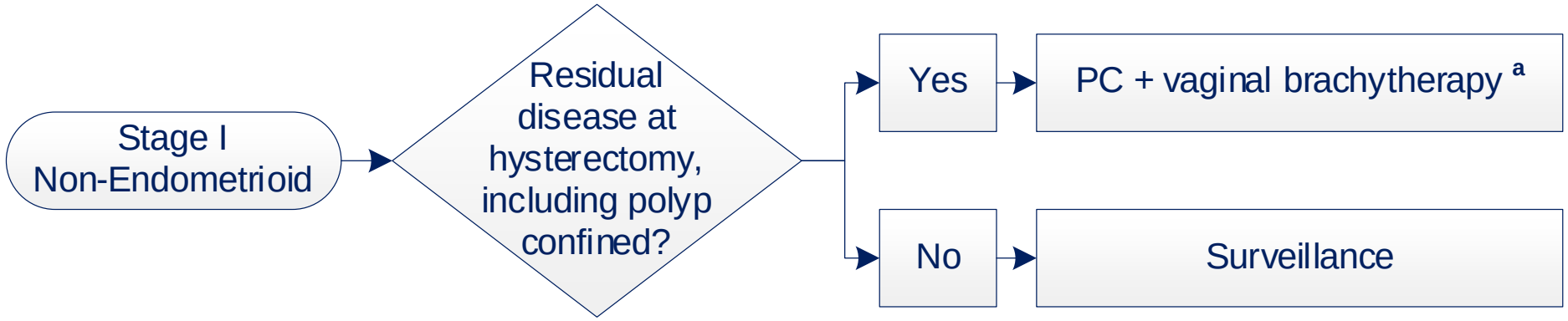
[a] **p53 (by IHC) abnormal** lack of staining or upregulated is considered abnormal p53 pattern

[b] **PC** every 3 weeks for 6 cycles

[c] **EBRT** IMRT/VMAT are preferred techniques when expertise is available

EBRT external beam radiation therapy
IHC immunohistochemistry
IMRT intensity-modulated radiation therapy
PC paclitaxel and carboplatin
VMAT volumetric modulated arc therapy

Uterine Cancer – Stage I Non-Endometrioid



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **PC** every 3 weeks for 6 cycles

PC paclitaxel and carboplatin

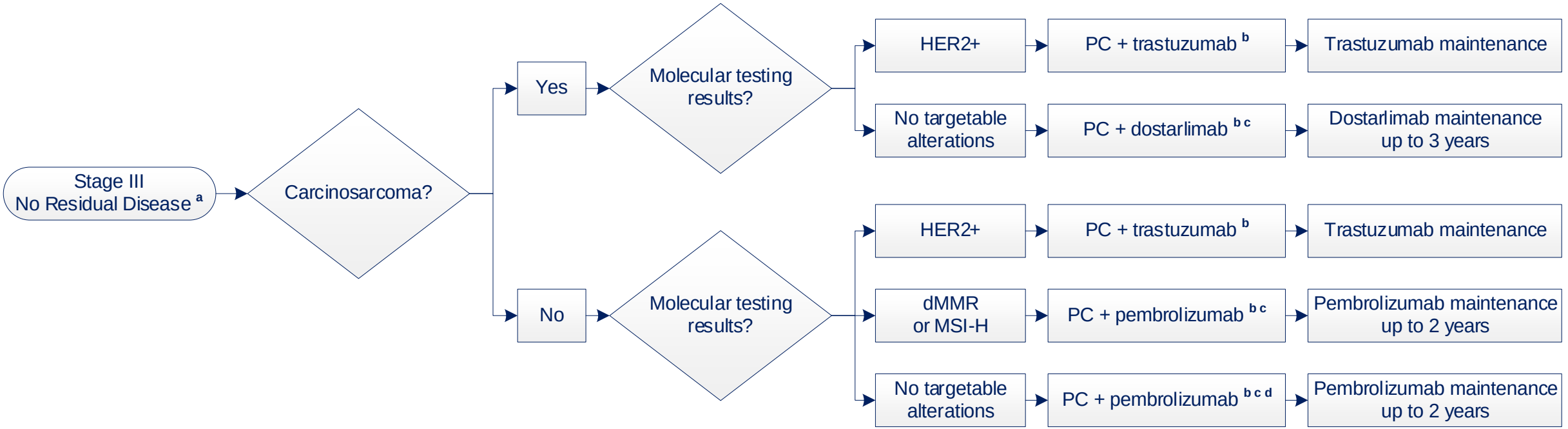
Uterine Cancer – Stage II Non-Endometrioid

Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **PC** every 3 weeks for 6 cycles

PC paclitaxel and carboplatin

Uterine Cancer – Stage III No Residual Disease



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Stage III No Residual Disease** also consider for patients whose only nodal disease is positive sentinel lymph nodes

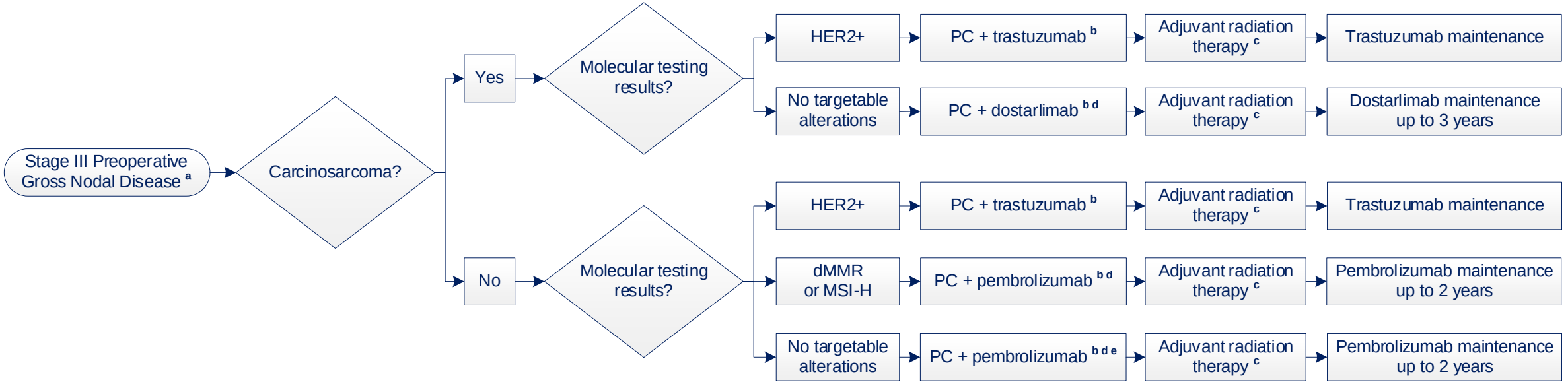
[b] **PC** every 3 weeks for 6 cycles

[c] **Dostarlimab + pembrolizumab** candidate for immunotherapy if patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent > 10mg/day), or prior allogeneic HSCT/solid organ transplant

[d] **No carcinosarcoma, no targetable alterations, PC** immunotherapy can be added at physician's discretion

PC paclitaxel and carboplatin

Uterine Cancer – Stage III Preoperative Gross Nodal Disease



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Stage III Preoperative Gross Nodal Disease** with radiographic evidence of lymph node involvement

[b] **PC** paclitaxel and carboplatin every 3 weeks for 6 cycles

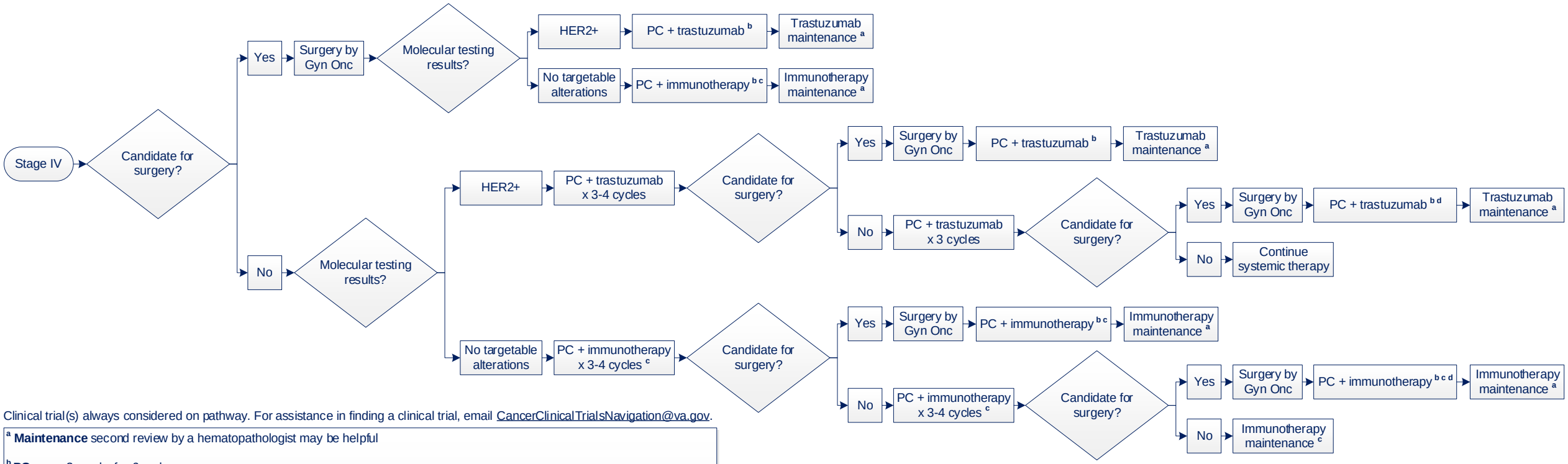
[c] **Adjuvant radiation therapy** most adjuvant radiation therapy will involve EBRT (IMRT/VMAT are preferred techniques when expertise is available) and vaginal brachytherapy following 6 cycles of chemotherapy

[d] **Dostarlimab + pembrolizumab** candidate for immunotherapy if patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent > 10mg/day), or prior allogeneic HSCT/solid organ transplant

[e] **No carcinosarcoma, no targetable alterations, PC** immunotherapy can be added at physician's discretion

EBRT external beam radiation therapy
IMRT intensity-modulated radiation therapy
PC paclitaxel and carboplatin
VMAT volumetric modulated arc therapy

Uterine Cancer – Stage IV



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Maintenance** second review by a hematopathologist may be helpful

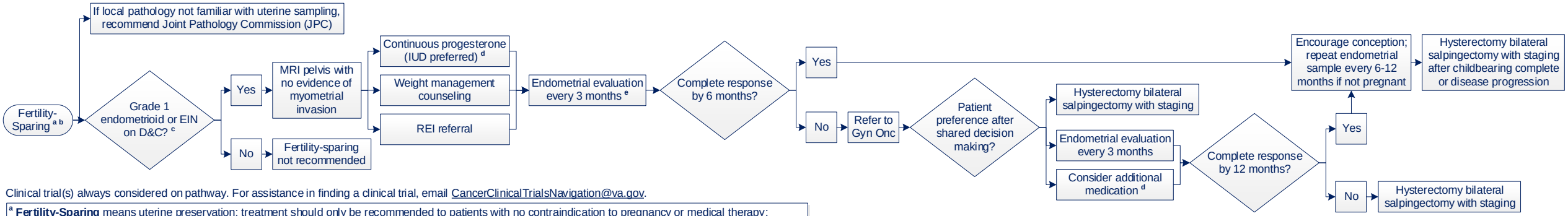
[b] **PC** every 3 weeks for 6 cycles

[c] **Immunotherapy** for carcinosarcoma, use dostarlimab; for other histologies, use pembrolizumab

[d] **Primary treatment** for most patients, first-line PC consists of 6-8 cycles

PC paclitaxel and carboplatin

Uterine Cancer – Fertility-Sparing



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Fertility-Sparing** means uterine preservation; treatment should only be recommended to patients with no contraindication to pregnancy or medical therapy; evaluation of inherited cancer risk and molecular testing is recommended alongside fertility-sparing management of uterine cancer (see Molecular Testing pathway)

[b] **Gyn Oncology** e-consult referral is appropriate at this time

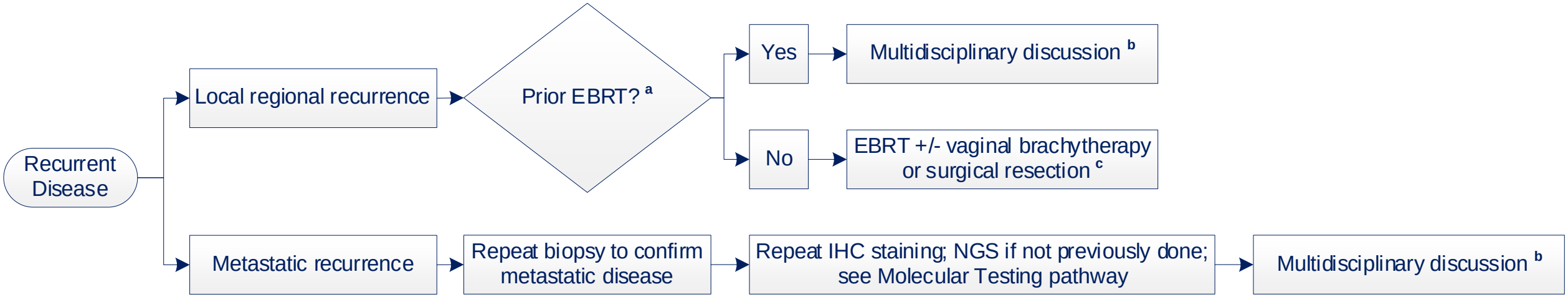
[c] **Grade 1 endometrioid or EIN** if endometrial biopsy performed, recommend D&C for full uterine sampling to confirm grade and histology

[d] **Continuous progesterone therapy** levonorgestrel IUD preferred, otherwise megestrol or medroxyprogesterone

[e] **Endometrial evaluation** can be endometrial biopsy or D&C

D&C dilation and curettage
EIN endometrial intraepithelial neoplasia
REI reproductive endocrinology and infertility

Uterine Cancer – Recurrent Disease



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

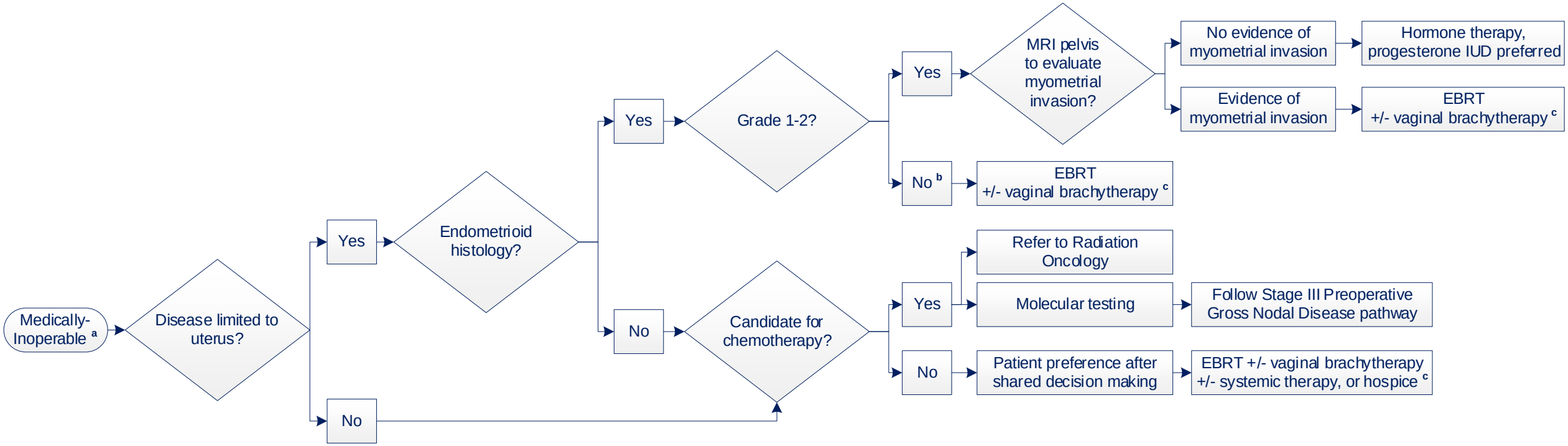
[a] **EBRT** IMRT/VMAT are preferred techniques when expertise is available

[b] **Multidisciplinary discussion** discuss at virtual tumor board (email NTOVirtualTumorBoards@va.gov); consider adding bevacizumab for clear cell histology

[c] **Surgical resection** consider interval since primary treatment and disease distribution

EBRT external beam radiation therapy
IHC immunohistochemistry
IMRT intensity-modulated radiation therapy
NGS next-generation sequencing
VMAT volumetric modulated arc therapy

Uterine Cancer – Medically-Inoperable



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

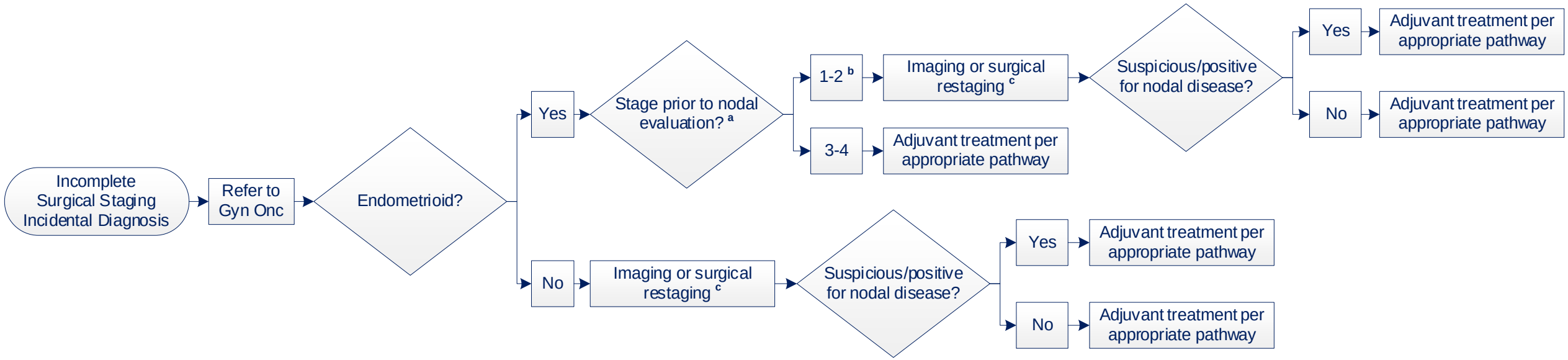
[a] **If grade 1-2 endometrioid uterine cancer** diagnosed upon endometrial biopsy, consider D&C for full uterine sampling to confirm grade and histology without delay if patient able to tolerate minor surgery

[b] **No grade 1-2** grade 3 endometrioid

[c] **EBRT** IMRT/VMAT are preferred techniques when expertise is available

D&C dilation and curettage
EBRT external beam radiation therapy
IMRT intensity-modulated radiation therapy
VMAT volumetric modulated arc therapy

Uterine Cancer – Incomplete Surgical Staging Incidental Diagnosis



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

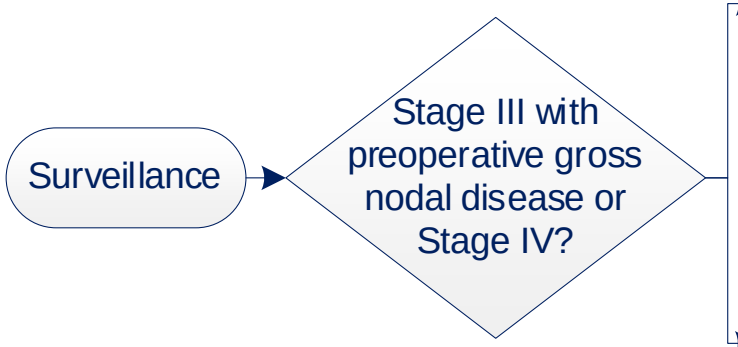
[a] **Stage prior to nodal evaluation** this includes myometrial invasion, involvement of fallopian tube / ovaries, cervical, vaginal or parametrial involvement, and other involved organs; this may include LVSI

[b] **Stage 1-2** discuss oophorectomy if patient diagnosed with hereditary cancer syndrome and ovaries not removed at time of original surgery

[c] **Imaging or surgical restaging** consider trachelectomy and removal of any residual uterine tissue if supra-cervical hysterectomy was performed

LVSI lymphovascular space invasion

Uterine Cancer – Surveillance



Yes

	Year 1-2	Year 3-5	After Year 5
Exam including pelvic and symptom review	Every 3 months [a b]	Every 6 months [a b]	Annually if no recurrence [a b]
CT chest, abdomen, pelvis	Annually	As clinically indicated	

No

	Year 1-2	Year 3-5	After Year 5
Exam including pelvic and symptom review	Every 3-6 months [a c]	Every 6-12 months [a c]	Annually if no recurrence [a]

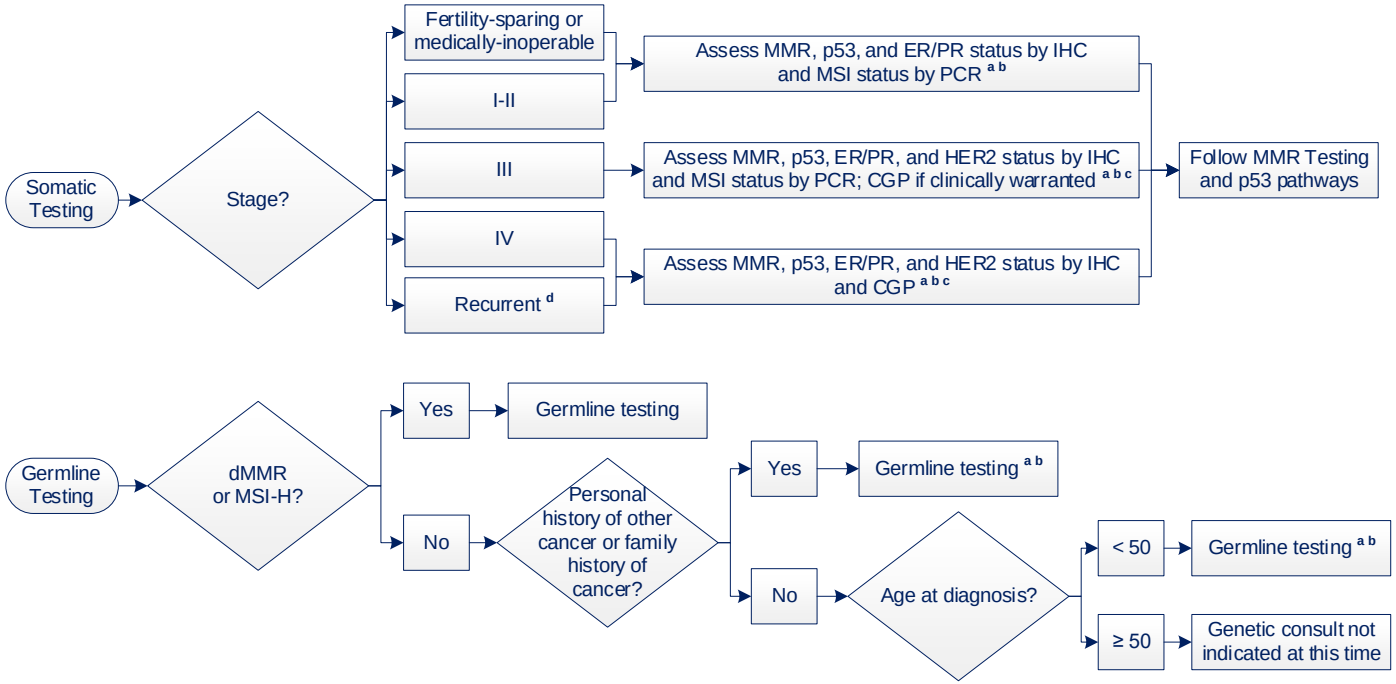
Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Imaging** as indicated by symptoms or examination findings suspicious for recurrence; CT chest, abdomen, pelvis preferred mode of imaging

[b] **CA125** if initially elevated

[c] **Stage I-III exam frequency** consider more frequent surveillance visits based on clinical judgment, e.g., p53 positive, grade 3

Uterine Cancer – Molecular Testing



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Lynch Testing** the diagnostic Lynch genetic testing algorithm depends on the pattern of MLH1, MSH2, MSH6, and PMS2 expression by IHC; diagnostic Lynch genetic testing should be performed if there is loss of MSH2, MSH6, MSH2/MSH6, or PMS2 expression by IHC; if there is loss of MLH1 expression by IHC, *MLH1* promoter hypermethylation testing should be performed; diagnostic Lynch genetic testing should be performed if *MLH1* is unmethylated in the context of MLH1 loss by IHC; a diagnostic Lynch genetic testing panel should include at minimum the following genes: *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*

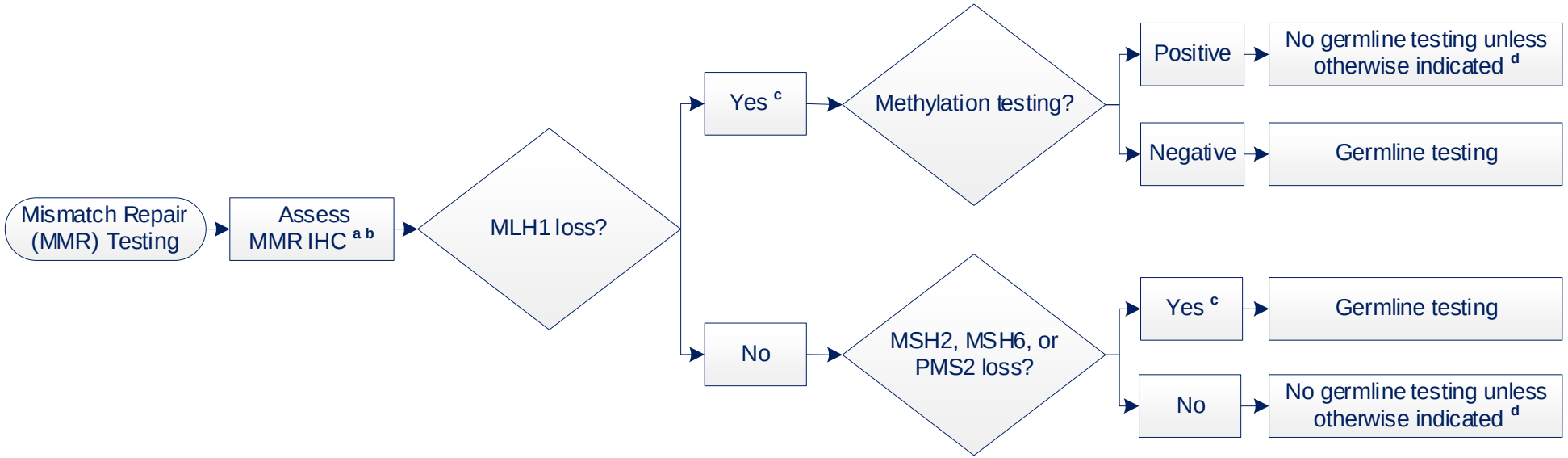
[b] **Germline Testing** consider germline testing beyond Lynch Testing based on family history or known hereditary cancer gene in family; Germline Testing for uterine cancer should include at the minimum the following genes: MLH1, MSH2, MSH6, PMS2, EPCAM, PTEN, POLD1, POLE, and BRCA½. Genetic testing is also recommended if personal history of other cancer or family history of cancer, or pathogenic or likely pathogenic variant in a gene associated with known hereditary cancer syndrome is present in the family member

[c] **HER2** per ASCO pathology guidelines; use HER2 scoring for breast cancer; for recurrent, use HER2 scoring for gastric cancer

[d] **Recurrent** any recurrent uterine cancer, any previous stage at diagnosis

CGP comprehensive genomic profiling
IHC immunohistochemistry
MSI microsatellite instability

Uterine Cancer – Mismatch Repair (MMR) Testing



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **MMR IHC** the diagnostic Lynch genetic testing algorithm depends on the pattern of MLH1, MSH2, MSH6, and PMS2 expression by IHC; diagnostic Lynch genetic testing should be performed if there is loss of MSH2, MSH6, MSH2/MSH6, or PMS2 expression by IHC; if there is loss of MLH1 expression by IHC, *MLH1* promoter hypermethylation testing should be performed; diagnostic Lynch genetic testing should be performed if *MLH1* is unmethylated in the context of MLH1 loss by IHC; a diagnostic Lynch genetic testing panel should include at minimum the following genes: *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*

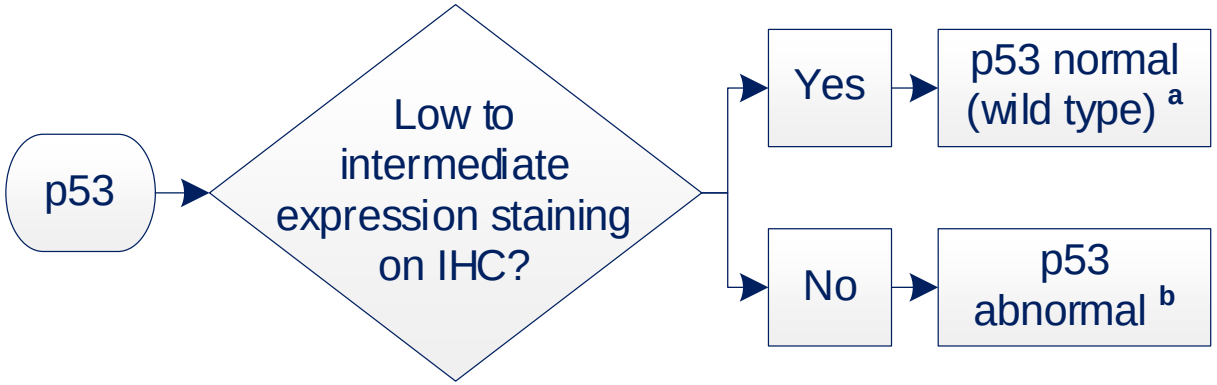
[b] **If IHC** not feasible, consider MSI testing;

[c] **Yes MLH1, MSH2, MSH6, or PMS2 loss** alone is sufficient to consider tumor to be dMMR

[d] **Germline Testing** consider germline testing beyond Lynch Testing based on family history or known hereditary cancer gene in family; Germline Testing for uterine cancer should include at the minimum the following genes: MLH1, MSH2, MSH6, PMS2, EPCAM, PTEN, POLD1, POLE, and BRCA½. Genetic testing is also recommended if personal history of other cancer or family history of cancer, or pathogenic or likely pathogenic variant in a gene associated with known hereditary cancer syndrome is present in the family member

IHC immunohistochemistry

Uterine Cancer – p53



Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **p53 normal** is also called p53 wild type

[b] **p53 (by IHC) abnormal** lack of staining or upregulated is considered abnormal p53 pattern

IHC immunohistochemistry

Uterine Cancer – HER2 Scoring

Breast Scoring per HER2 (IHC) used for new uterine cancer diagnosis	
Result	**Criteria**
Negative (Score 0)	No staining observed OR Complete membrane staining that is faint/barely perceptible and within ≤10% of tumor cells
Negative (Score 1+)	Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells
Equivocal (Score 2+)	Weak to moderate complete membrane staining in >10% of tumor cells OR Complete membrane staining that is intense but within ≤10% of tumor cells
Positive (Score 3+)	Complete membrane staining that is intense and >10% of tumor cells

Gastric Scoring per HER2 (IHC) used for recurrent uterine cancer [a]			
Score	**HER2 IHC Pattern in Surgical Specimen**	**HER2 IHC Pattern in Biopsy Specimen**	**HER2 Expression Assessment**
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or membranous reactivity in any cancer cells	Negative by IHC
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative by IHC
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Cancer cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal by IHC
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Cancer cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

Clinical trial(s) always considered on pathway. For assistance in finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **HER2 scoring** in cancer is rapidly evolving; lower HER2 scores may qualify for HER2-directed therapy

IHC immunohistochemistry

Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Uterine Carcinoma All Stages, All Histologies	IHC	MLH1, MSH2, MSH6, PMS2	Local VA or locally contracted vendor	No	Tumor Tissue
	IHC	TP53	Local VA or locally contracted vendor	No	Tumor Tissue
	IHC	ER, PR	Local VA or locally contracted vendor	No	Tumor Tissue
	PCR	Microsatellite instability (MSI) status by PCR*	Regional Testing Center (GLA)	Yes	Tumor Tissue AND Normal Tissue or Blood
	Methylation Testing	MLH1 promoter hypermethylation testing (in the setting of loss of MLH1 or PMS2 expression by IHC). Hypermethylation suggests somatic mutation. Unmethylated calls for Germline Lynch testing.	Local VA or locally contracted vendor	No	Tumor Tissue
Stage III/IV or Recurrent Carcinoma (any previous stage)	IHC	HER2 IHC with reflex to FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue
	FISH	HER2 FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue
	Somatic NGS	Comprehensive genomic profiling (CGP)	Tempus Foundation	Yes Yes	Tumor Tissue, Blood
Any stage or histology, MMR-deficient or MSI-H	Germline NGS	Germline Lynch NGS Panel* If full germline testing not performed, perform Germline Lynch testing if: 1) MSH2 or MSH6 loss by IHC; 2) MLH1 or PMS2 loss by IHC and MLH1 unmethylated; or 3) MSI-H without IHC testing and MLH1 unmethylated	Fulgent Genetics	Yes	Blood, Saliva
Age < 50 or Personal or Family History of Other Cancers	Germline NGS	Germline NGS panel for Uterine cancers**	Fulgent Genetics	Yes	Blood, Saliva

* For Uterine cancers, mismatch repair proficiency/deficiency is best determined by IHC; PCR can detect microsatellite instability (MSI-H), but a normal result (MSS or MSI-L) should always be confirmed by IHC

** Germline Lynch NGS panel should include at minimum the following genes: *EPCAM* (deletion), *MLH1, MSH2, MSH6,* and *PMS2*

*** VA Common Hereditary POC panel or Equivalent Germline Test; Full Germline NGS panel for uterine cancers should include at minimum the following genes: *EPCAM* (deletion), *MLH1, MSH2, MSH6, PMS2, PTEN, POLD1, POLE,* and *BRCA1/2;* For genetic online ordering, refer to CCGS page for further details