

The Role of the Pathologist in Hereditary GYN Cancer Screening

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Introduction

- BRCA1/2 syndromes
- Lynch syndrome
- Peutz-Jeghers syndrome
- Cowden syndrome
- Gorlin syndrome
- Li-Fraumeni syndrome
- Hereditary leiomyomatosis
- Tuberous sclerosis complex
- Dicer syndrome

Holman et al. Hematol Oncol Clin North Am 2012;26:13-29

Hereditary Breast-Ovarian Cancer (HBOC)

BRCA1

- Dominant inheritance pattern of susceptibility
- Mutation in 17q21 (>100 mutations)
- 85-90% lifetime risk of breast cancer
- 40 to 60% lifetime risk of ovarian cancer
- Possible gastric & pancreas cancer risk

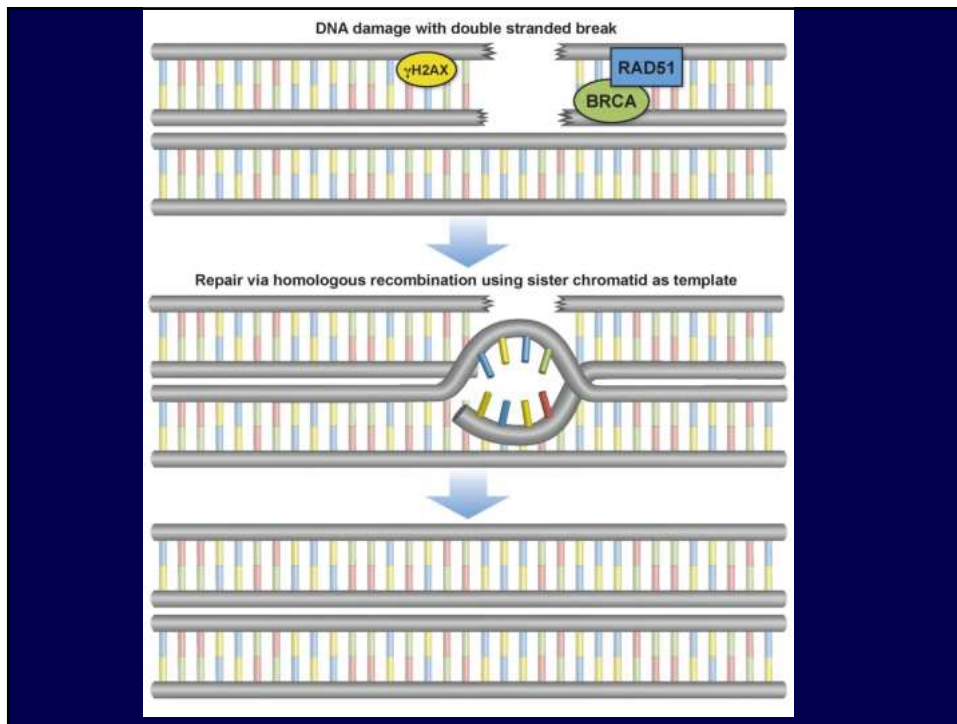
BRCA2

- Dominant inheritance pattern of susceptibility
- Mutation in 13q12-13
- 85-90% lifetime risk of breast cancer – including male
- 20% lifetime risk of ovarian cancer
- Possible prostate, pancreas, gastric cancer risk

Features of *BRCA1* vs. *BRCA2* Carriers

Mutation	Onset breast cancer	Onset ovarian cancer	Other malignancies
<i>BRCA 1</i>	Risk increases by age 40 y	Risk increases by age 36-39 y, with a 2-3% risk by age 40 y	Pancreatic, gastric, prostate, liver, cervix, uterine, colon
<i>BRCA2</i>	Risk increases by age 45 y	Risk increases by age 44-46, with 2-3% risk by age 50 y	Pancreatic, biliary, prostate, male breast cancer, melanoma

J Natl Cancer Inst 1999; 91:1310–1316
 J Natl Cancer Inst 2002; 94:1358–1365.



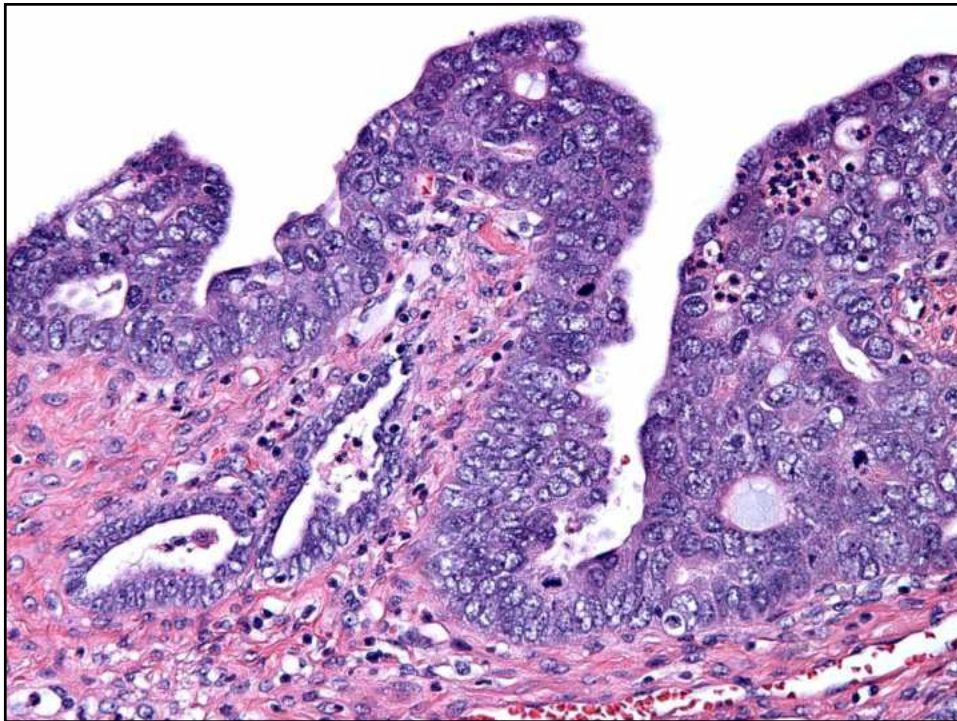
Hereditary Breast Ovarian Cancer: Current Recommendations

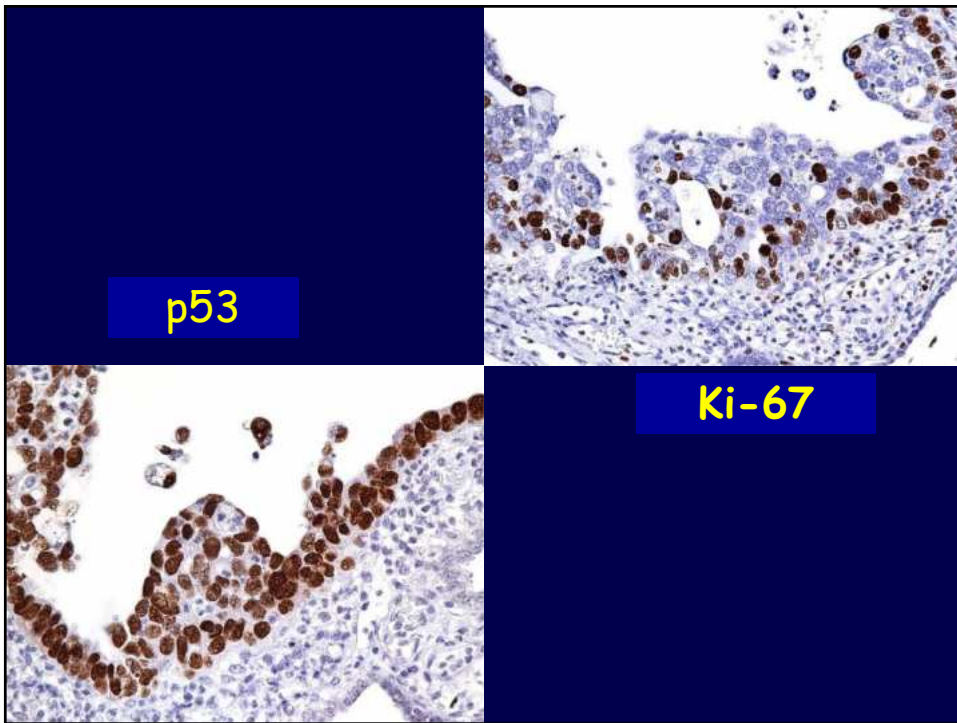
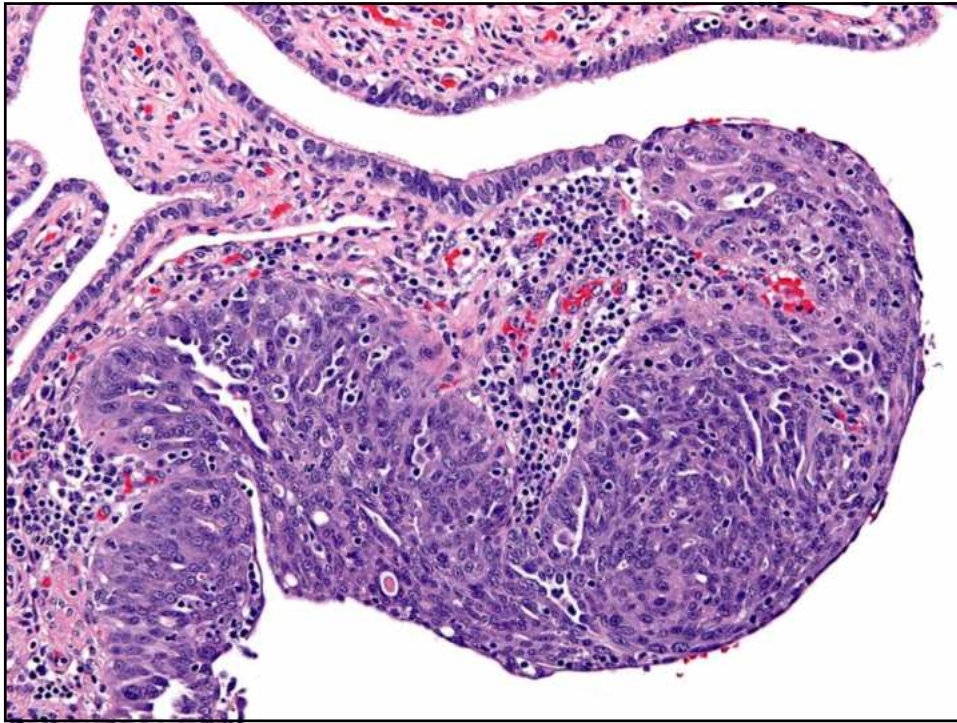
- Early screening (25 years of age)
- Risk reducing salpingo-oophorectomy (RRSO) at age 40

RRSO: BRCA Lessons

- High incidence of serous tubal intraepithelial serous carcinoma (STIC) in BRCA1/2
- STIC also seen in tubal mucosa from patients with ovarian & peritoneal high grade serous carcinoma
- STIC assoc with p53 mutations

Am J Surg Pathol 2001;25:1283-1289; Am J Surg Pathol 2006;30:230-231; Am J Surg Pathol 2007;31:161-169





Serous Tubal Intraepithelial Carcinoma

- Nuclear pleomorphism
- Increased nuclear/cytoplasmic ratio
- Increased proliferation
- Disorganized growth
- Nucleoli often present
- Typically fimbria or distal tube

Serous Tubal Intraepithelial Carcinoma

- 90% fimbria, 10% ampulla/isthmus
- Approx 10-20% bilateral
- Approx 20% multifocal

Am J Surg Pathol 2010;34:1407-16.

“Ovarian” Cancer: Possible Tubal Origin

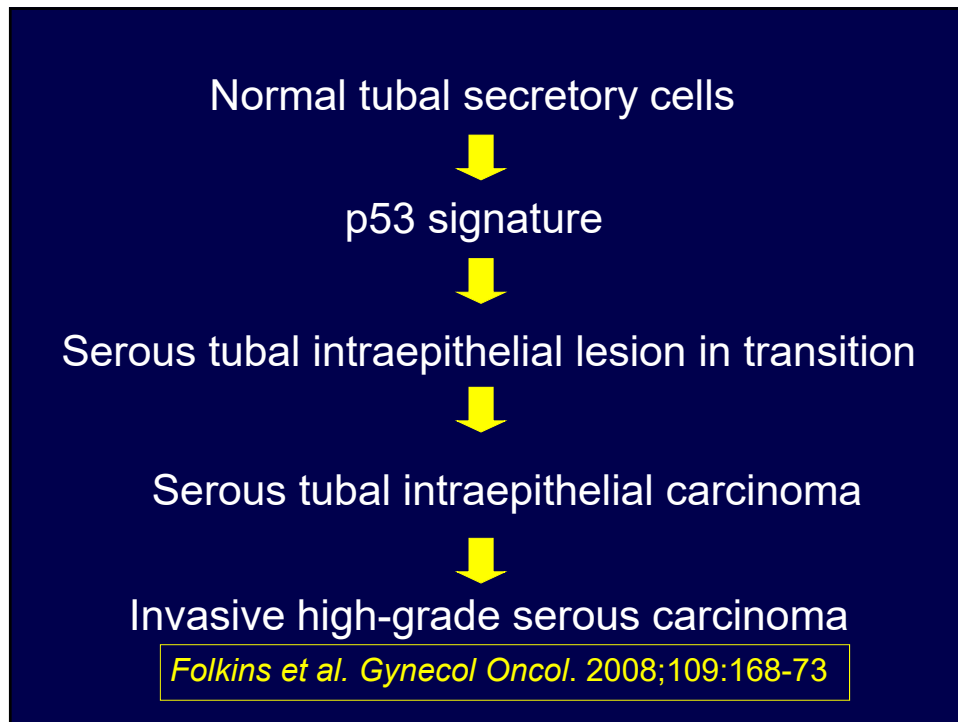
Study	Diagnosis	Cancer	STIC
Powell et al	BRCA	7/67 (10%)	57%
Finch et al	BRCA	7/159 (4%)	86%
Callahan et al	BRCA	7/100 (4%)	100%
Leeper et al	BRCA	5/30 (17%)	60%
Kindelberger et al	Ovary	All (43)	47%
Carlson et al	Peritoneum	All (19)	47%
Roh et al	Ovary	All (87)	36%

Gynecol Oncol 2009;113:391-396

Risk Factors For STIC In BRCA

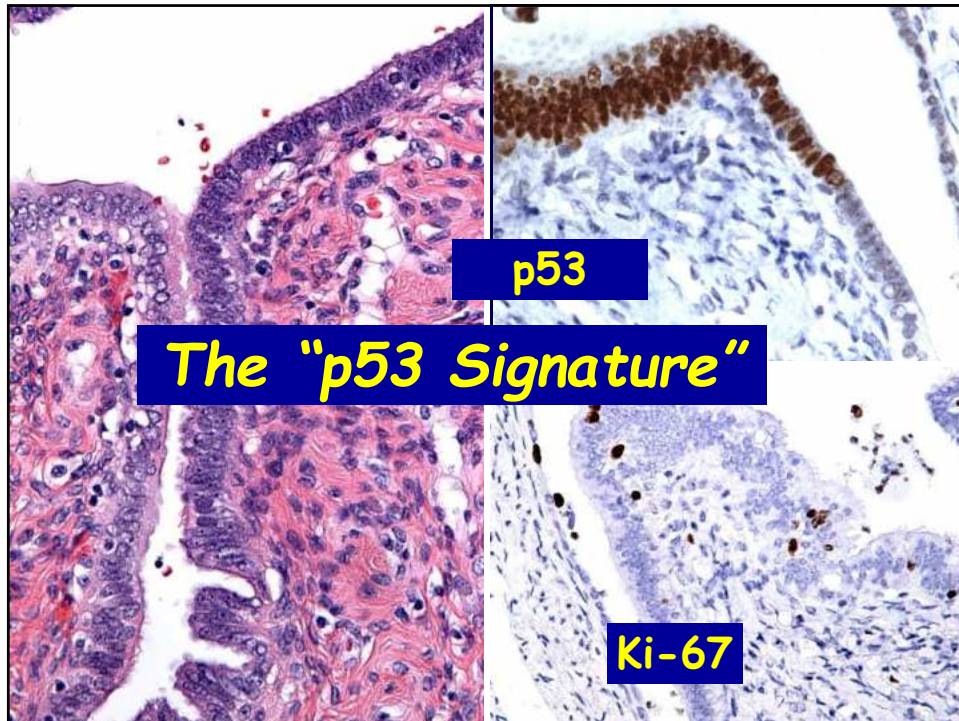
- Age: 5% <40 yrs vs 56% >60 yrs
- BMI: 18% <25 kg/mm² vs 31% >25 kg/mm²
- Oral contraceptive use:
 - 6 yrs OCP: Normal tubal mucosa
 - 4 yrs OCP: p53 signature
 - 2.7 yrs OCP: STIC

Vicus et al. Gynecol Oncol 2010;118:295-8



The p53 Signature: Possible Precursor Lesion

- Histologically “normal” tubal epithelium
- At least 12 consecutive p53 positive secretory cell nuclei
- “Normal” proliferative index (Ki-67)

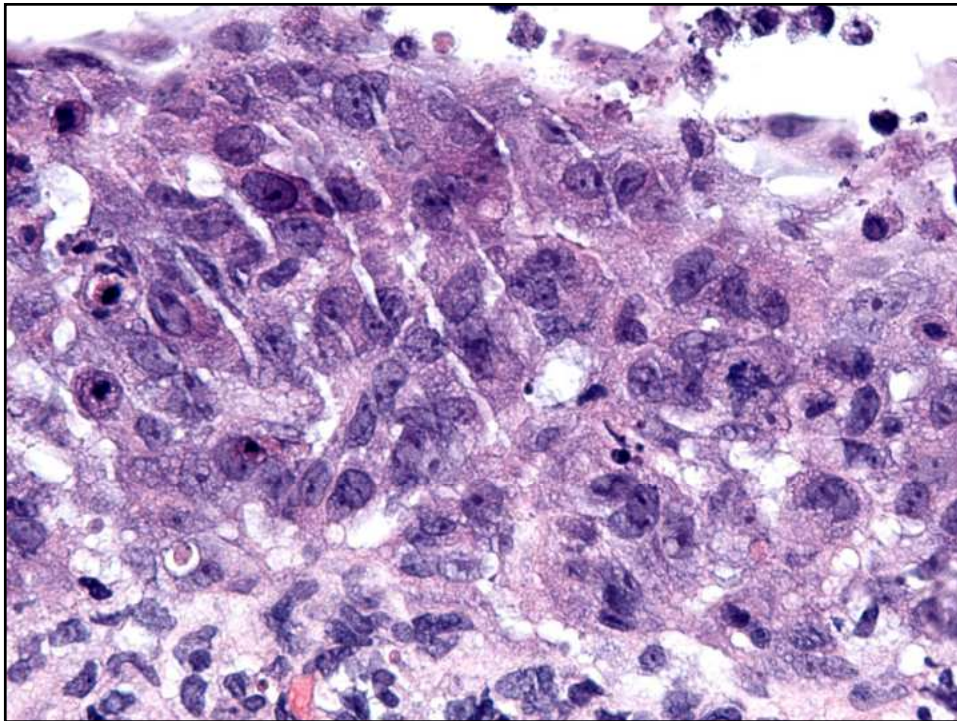


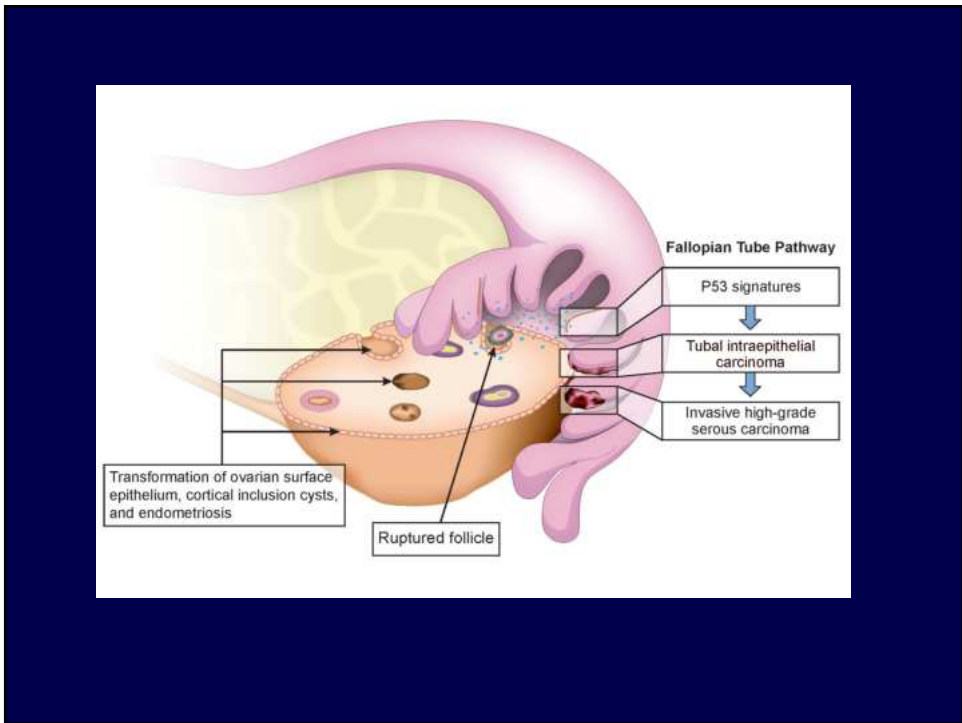
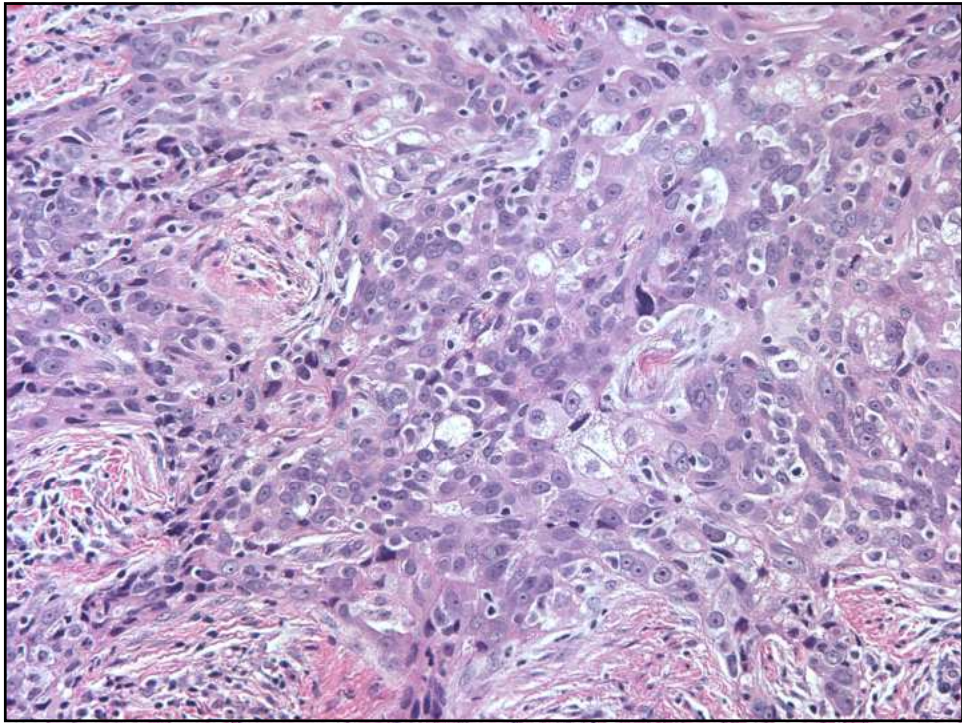
How Common Is p53 Signature?

	BRCA 1/2	Low Cancer Risk
Lee et al <i>J Pathol</i> 2007;211:26-35	10/41 (24%)	19/58 (33%)
Shaw et al <i>Mod Pathol</i> 2009;22:1133-8	19/176 (11%)	12/64 (19%)

Is Fallopian Tube Source of Ovarian & Peritoneal Carcinoma?

- Role of surface epithelium in ovarian carcinogenesis is largely circumstantial
- Epithelial inclusion cysts, peritoneal inclusion cysts are other strong contenders
- Tubal primary vs secondary involvement
- Role for “pelvic (nonuterine) serous carcinoma” or “mullerian (nonuterine) serous carcinoma”





Why Screen Ovarian Carcinoma for BRCA1/2?

- Risk of breast cancer
- Risk of BRCA1/2 in family members
- Tumor prognosis, treatment, response – PARP inhibitor therapy
- Chemoprevention

SGO Screening Criteria For BRCA1/2 (10%–15% Risk)

- Women with a personal history of breast and ovarian cancer
- Women with ovarian cancer and a first-, second-, or third-degree relative with breast cancer at ≤ 50 years or ovarian cancer at any age
- Ashkenazi Jewish women with ovarian cancer

Lancaster et al. Gynecol Oncol 2007;107:159–62.

SGO Screening Criteria For BRCA1/2 (20%–25% Risk)

- Women with breast cancer at ≤ 50 years and a first-, second-, or third-degree relative with ovarian cancer or male breast cancer
- Ashkenazi Jewish women with breast cancer at ≤ 40 years
- Women with a first- or second-degree relative with a BRCA mutation

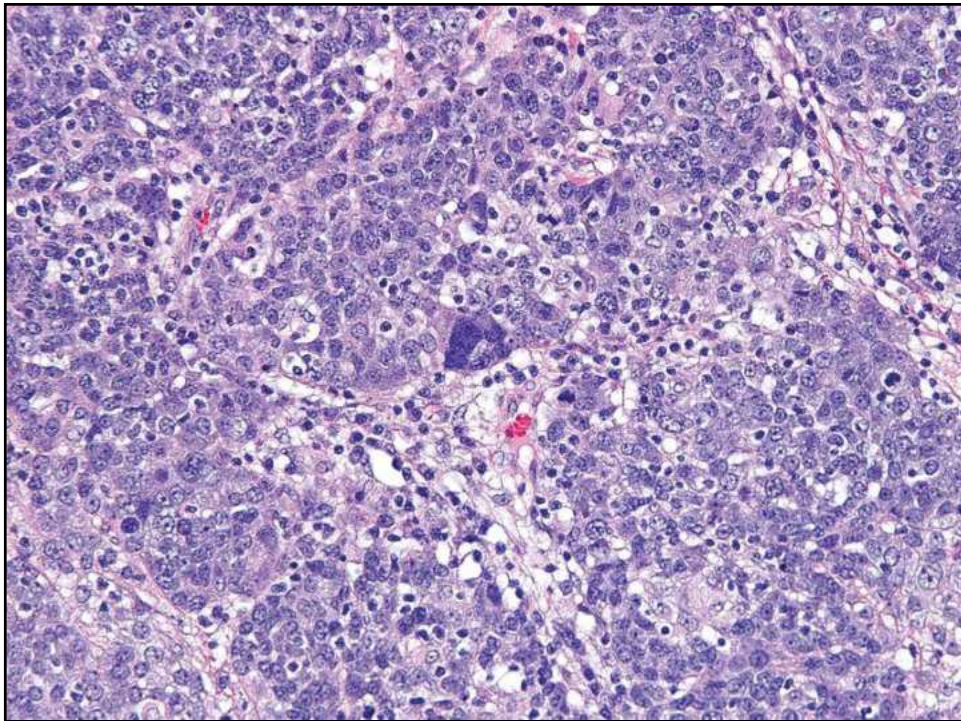
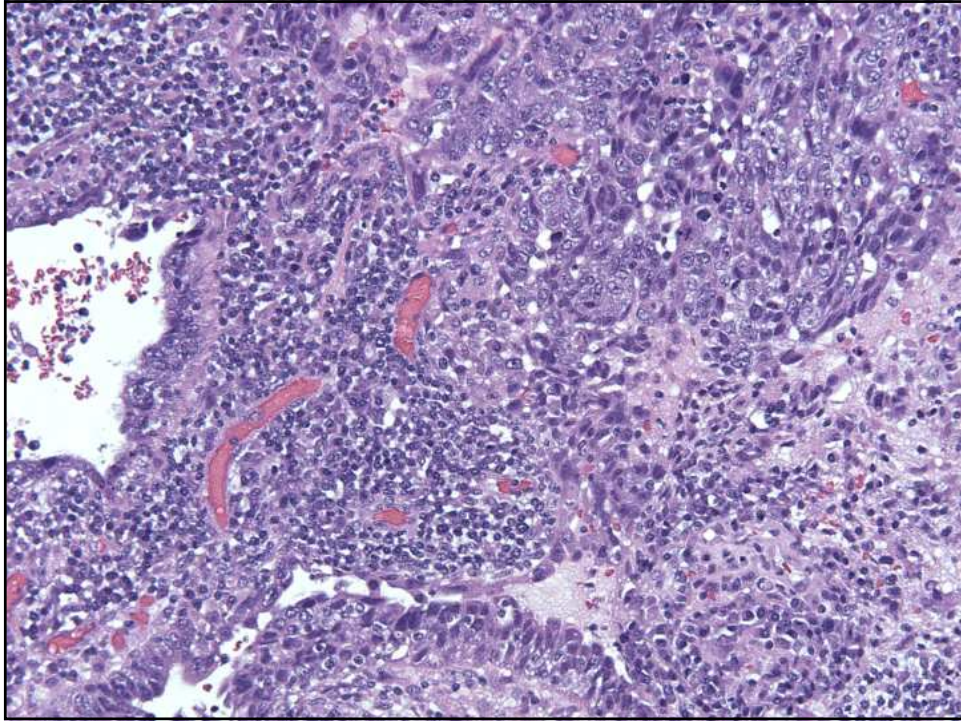
Lancaster et al. Gynecol Oncol 2007;107:159–62.

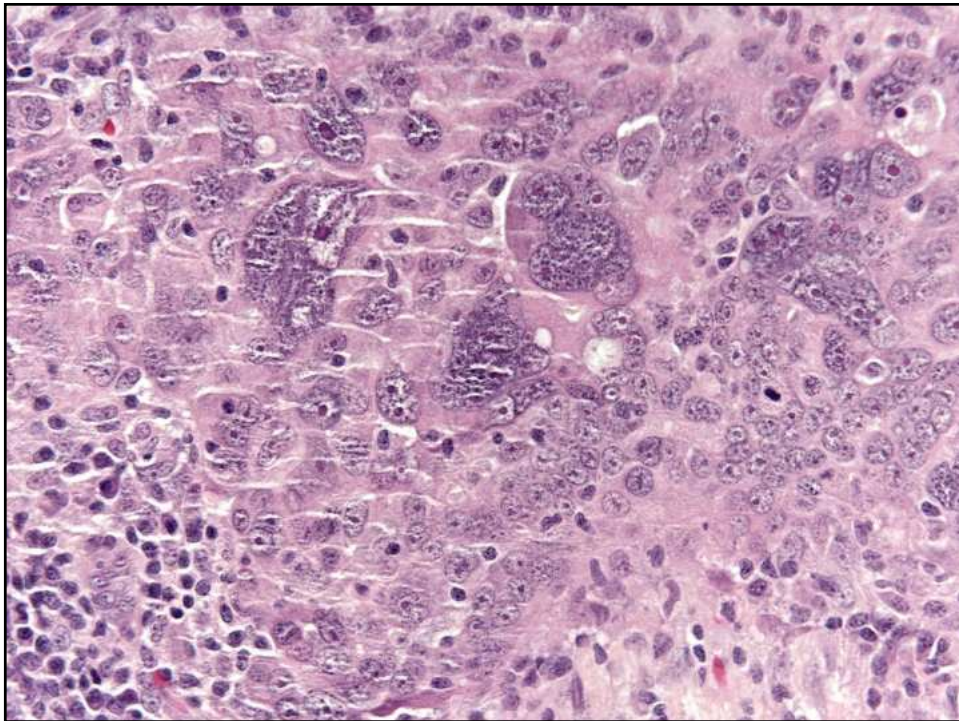
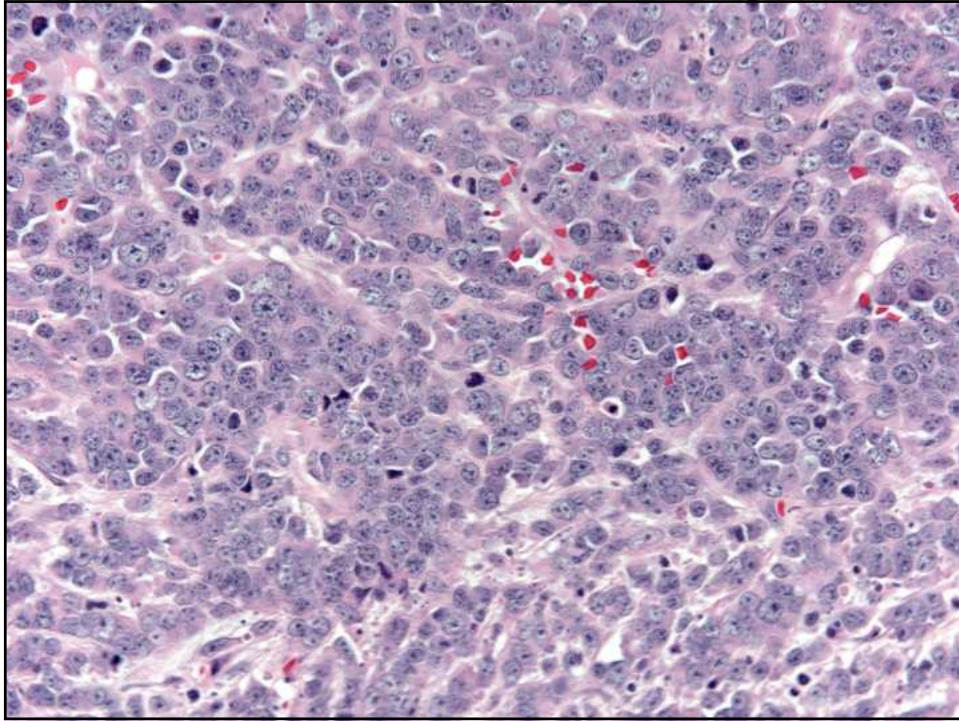
Tumor Morphology: BRCA-1 Hereditary “Ovarian” Cancer

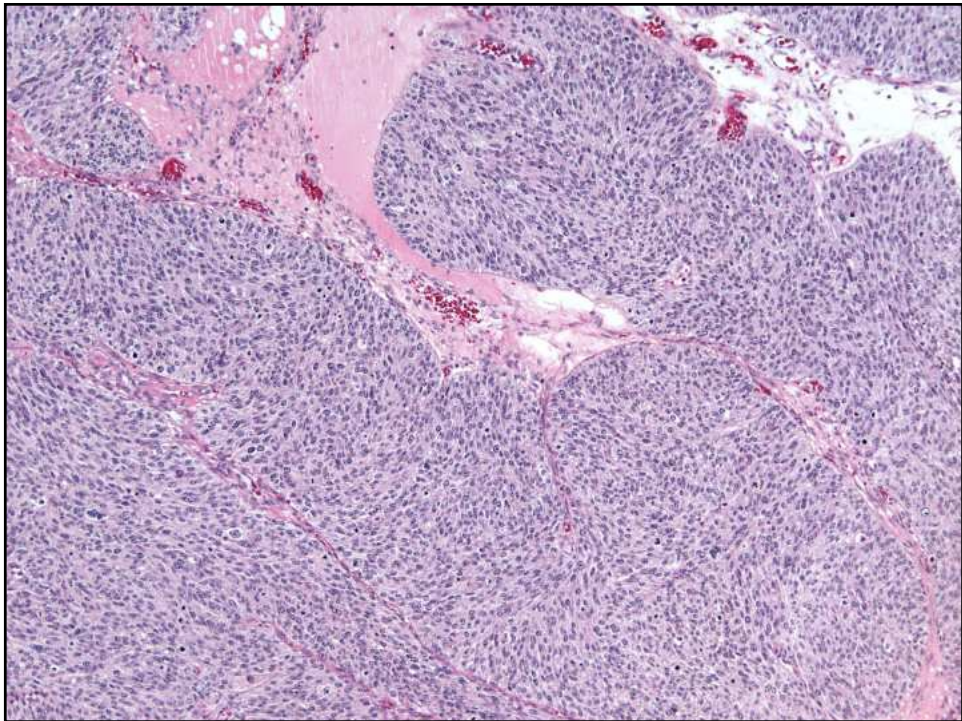
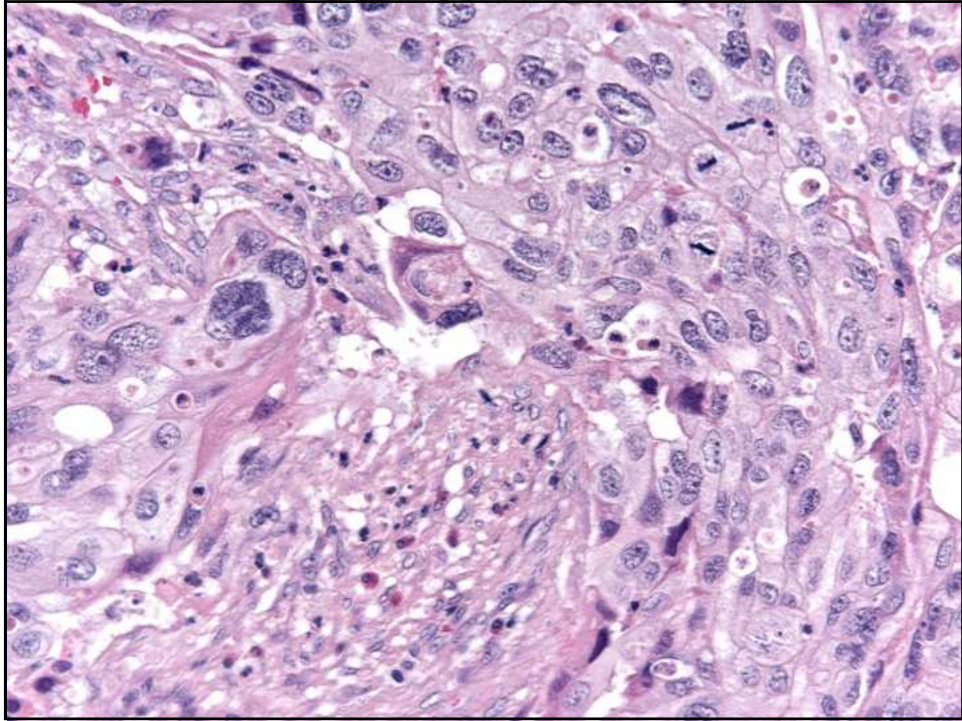
- High-grade serous, undifferentiated or pseudo-endometrioid (“SET”)
- Nuclear anaplasia
- High mitotic index
- Tumor intraepithelial lymphocytes (TILs)

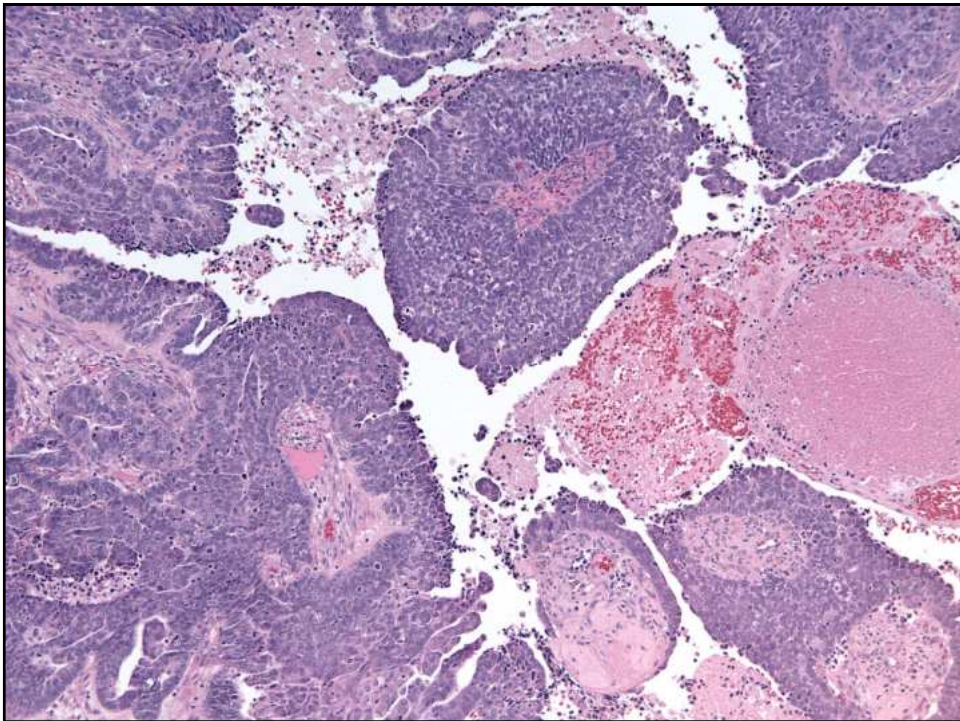
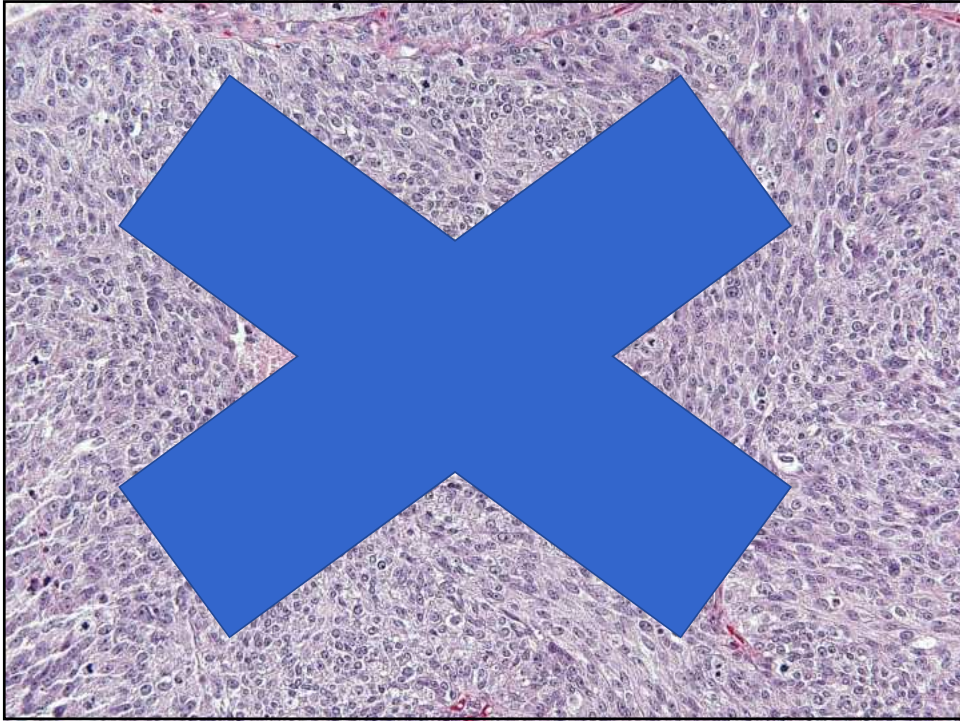
- p53 overexpression due to mutation

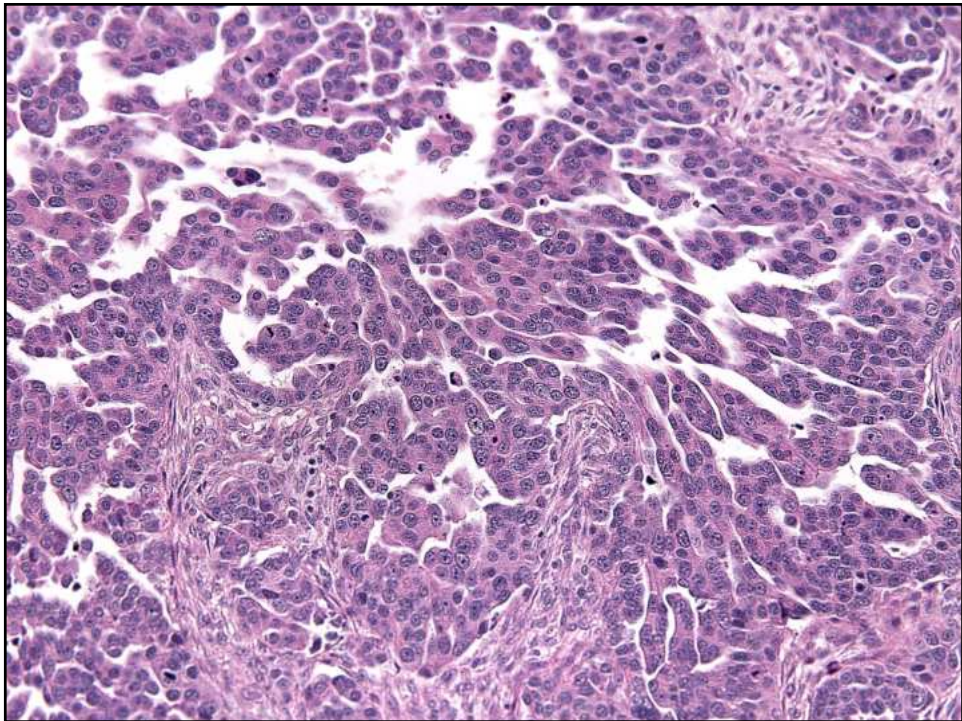
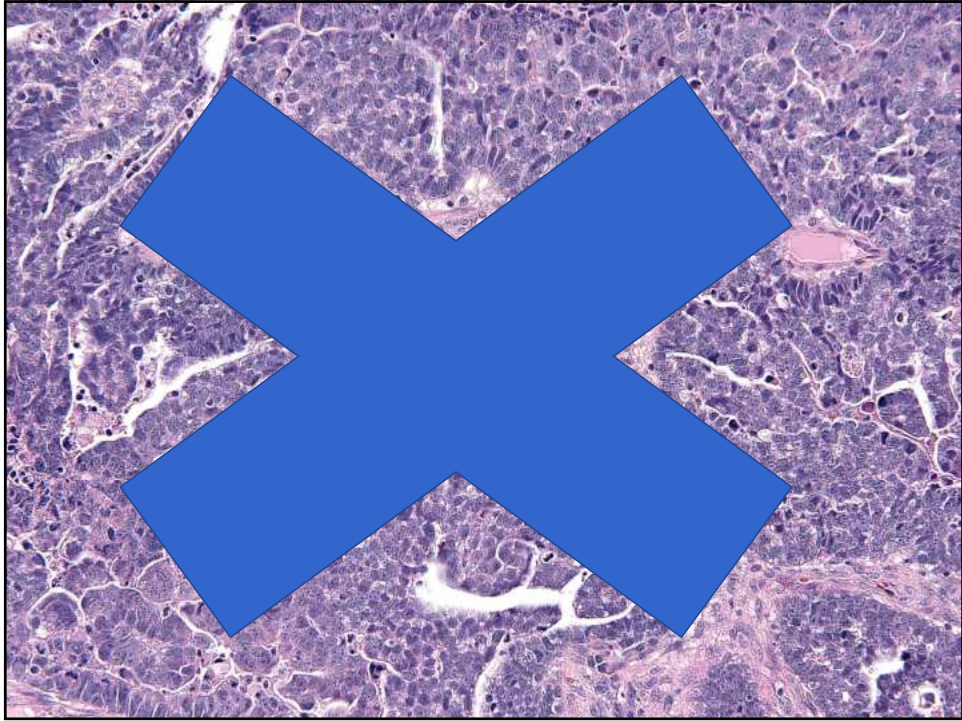
Fujiwara et al. Am J Surg Pathol 2012;36:1170-7
Soslow et al. Mod Pathol Mod Pathol 2012;25:625-36

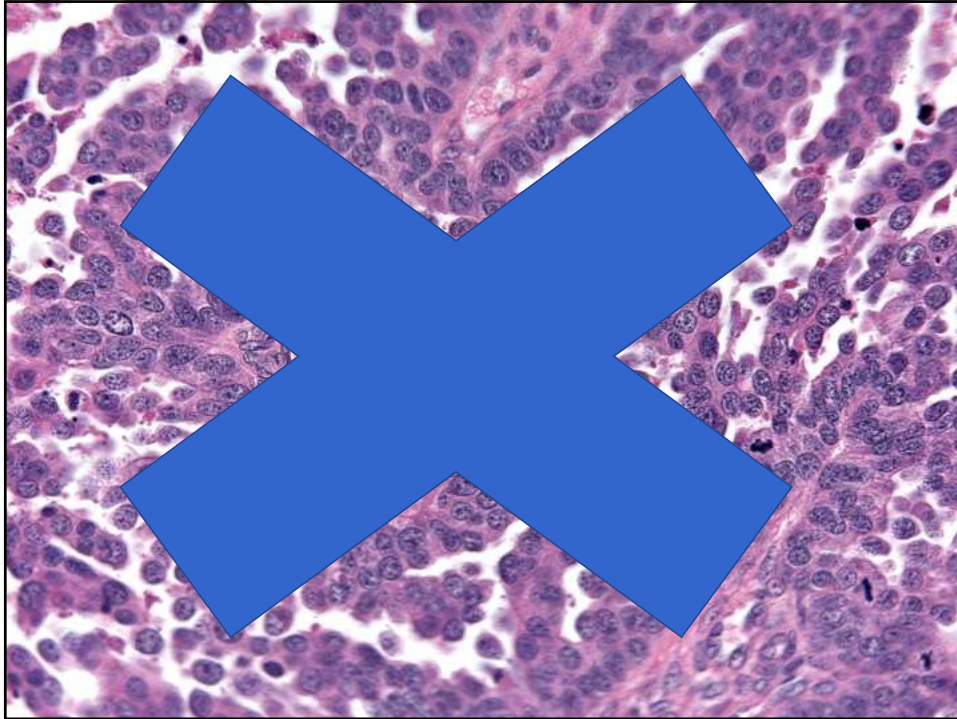












Predictive Value of “BRCA Histology”

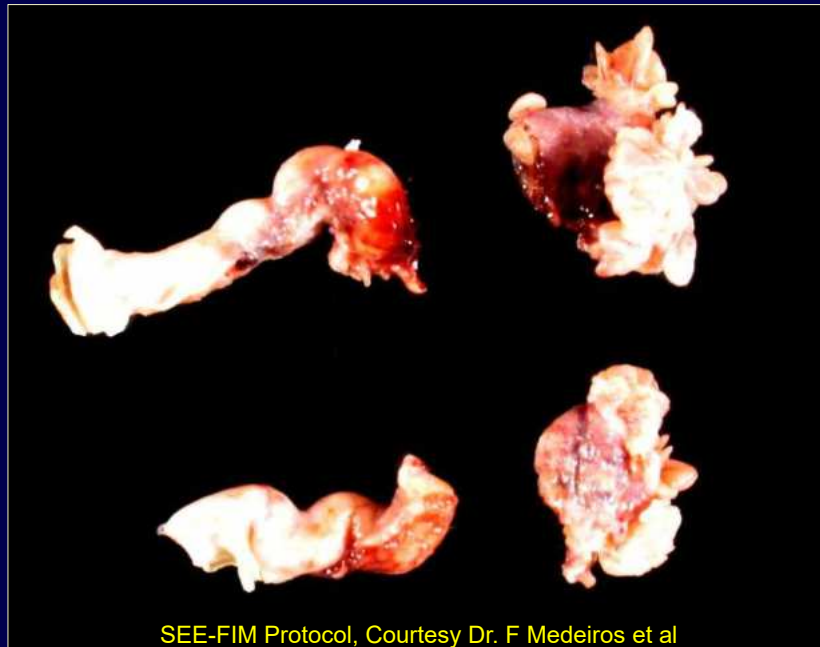
- Negative predictive value (>95%)
- Positive predictive value (26%)
- But high likelihood that tumor with “BRCA histology” is associated with BRCA germline mutation if fallopian tube is also involved (43%)

Fujiwara et al. Am J Surg Pathol 2012; 36:1170-7

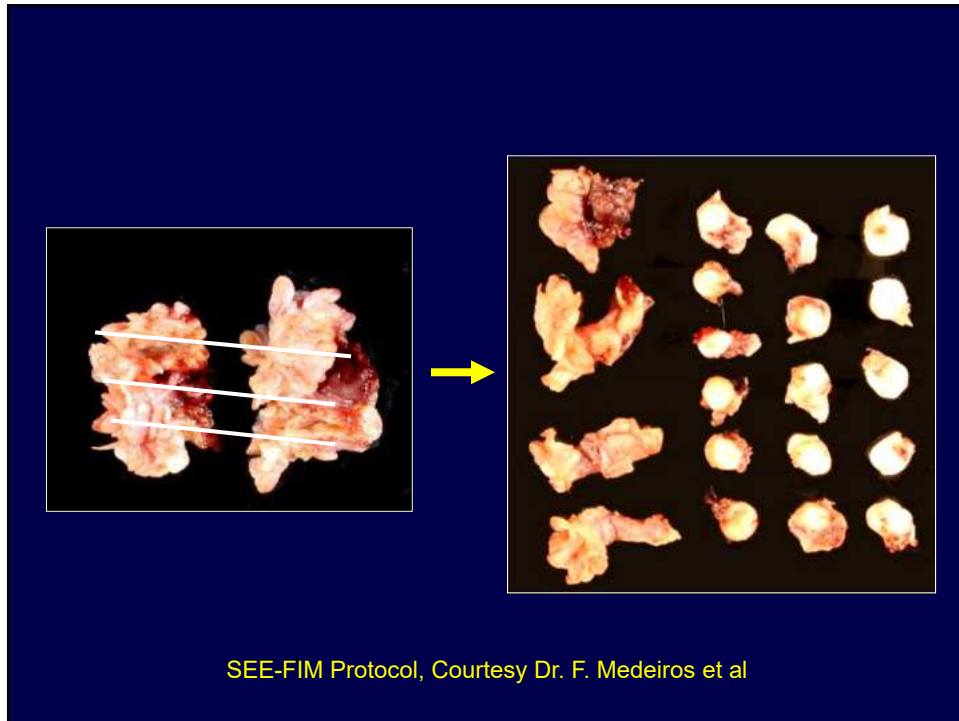
Fallopian Tube Surgical Pathology: Risk Reducing Salpingo-oophorectomy

- Serial sections of entire fallopian tube (longitudinal sections of fimbria) at 2-3 mm
- p53 mutation/expression is not a criterion for diagnosis of STIC! Diagnosis should be made using standard morphologic criteria

Virchows Arch 2007;450:25-29



SEE-FIM Protocol, Courtesy Dr. F Medeiros et al



Fallopian Tube Surgical Pathology: All Other

- Serial (longitudinal) sectioning of fimbria for routine sections of non-cancer hysterectomy; at least 1 section of fimbria
- Serial (longitudinal) sectioning of fimbria for routine sections of apparent uterine or ovarian serous carcinoma; at least 3 sections to include fimbria

Lynch Syndrome (HNPCC)

- Autosomal dominant mode of inheritance
- Predisposes to numerous malignancies – not just colon
- Often early age of onset
- One defective allele is inherited; 2nd “hit” happens during patient’s lifetime

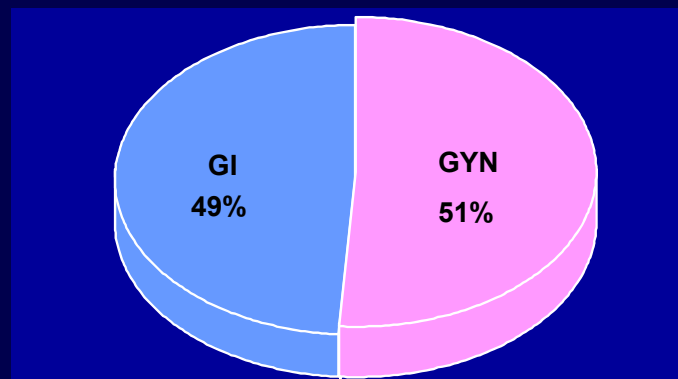
Lynch Syndrome (HNPCC) Lifetime Risk of Cancer in Women

- Endometrium 25-70%
- Colorectum 25-50%
- Ovary 10%
- Breast 11%
- Ureter and renal pelvis 10%
- Stomach 10%
- Pancreas 2%
- Small bowel 5%
- Biliary tract 2%
- Brain (usually glioblastoma as seen in Turcot syndrome) 4%
- Sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome

Lynch Syndrome (HNPCC)

- Due to germline mutations in mismatch repair (MMR) genes*
- 4 genes have been identified: *MSH2*, *MSH6*, *MLH1*, and *PMS2*
- Epigenetic methylation of *MLH1* can also lead to dysfunction - not part of Lynch Syndrome (HNPCC)***

Sentinel Cancer in Women with Lynch Syndrome



Lu et al. Obstet Gynecol 2005;105:569-574

Lynch Syndrome (HNPCC): Endometrial Cancer

	Endometrial Cancer	Colorectal Cancer
Age at presentation	>75% older than 50 years	35-45 years
MMR mutations	<i>MSH2</i> & <i>MSH6</i> > <i>MLH1</i>	<i>MLH1</i> & <i>MSH2</i> > <i>MSH6</i>
MSI-H	70%	95%

Why Screen Endometrial Carcinoma for Lynch Syndrome?

- Risk of second cancer 30% at 10 yrs, 50% at 15 yrs
- Risk of Lynch syndrome in family members
- Tumor prognosis, treatment, response to treatment
- Chemoprevention (?)

Risk of Carcinoma in Lynch Syndrome is MMR-Dependent

	Endometrial	Ovarian	Colorectal
MLH1	21%	4%	41%
MSH2	54%	29%	48%
MSH6	16%	1%	12%

Bonadona et al. JAMA 2011;305:2304-2310

Why Screen Endometrial Carcinoma for Lynch Syndrome?

20-year risk following diagnosis of endometrial cancer:

- Colorectal cancer 48%
- Kidney, renal pelvis or ureter cancer 11%
- Breast cancer 11%
- Bladder cancer 9%

J Natl Cancer Inst 2013;105:274-279

Tumor Topography

Westin SN, et al. J Clin Oncol 2008;26:5965-71

- 30% of lower uterine segment tumors are Lynch syndrome-associated
- LS-associated LUS tumors show overlapping morphologic and immunophenotypic features of endocervical and endometrial carcinoma

Tumor Topography

Offman S, et al. [Manuscript in Preparation]

- 11.5% (3/26) LUS vs 7.4% (23/312) corpus vs 6.2% (5/80) LUS & corpus are LS-associated
- LS-associated cancers show overlapping morphologic but not immunohistologic features of endocervical and endometrial carcinoma

Pathology of Lynch Syndrome Associated Endometrial Carcinomas

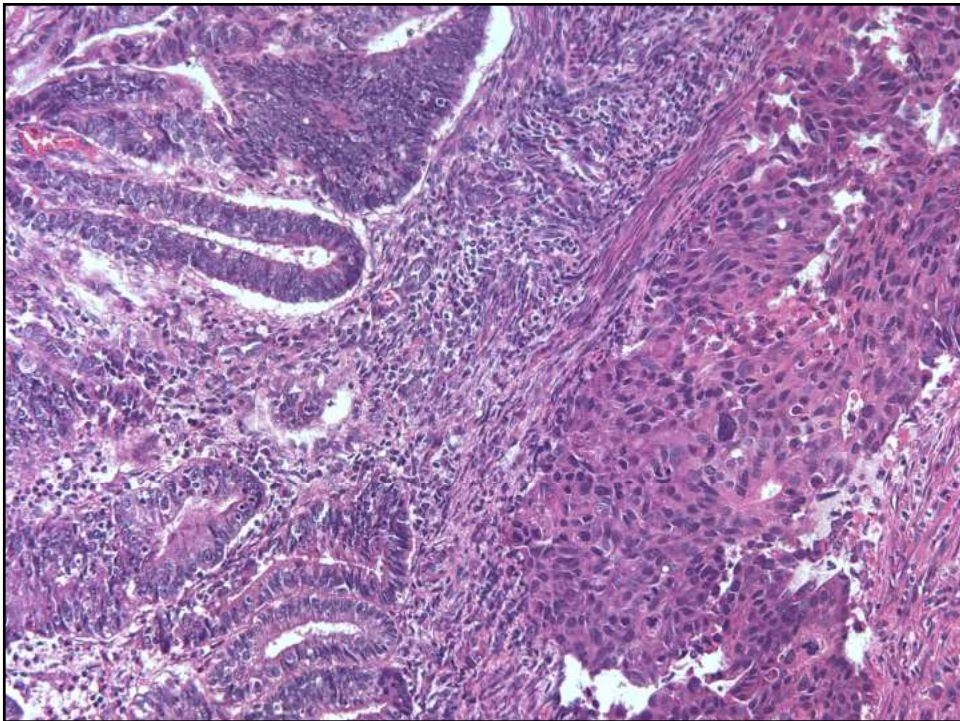
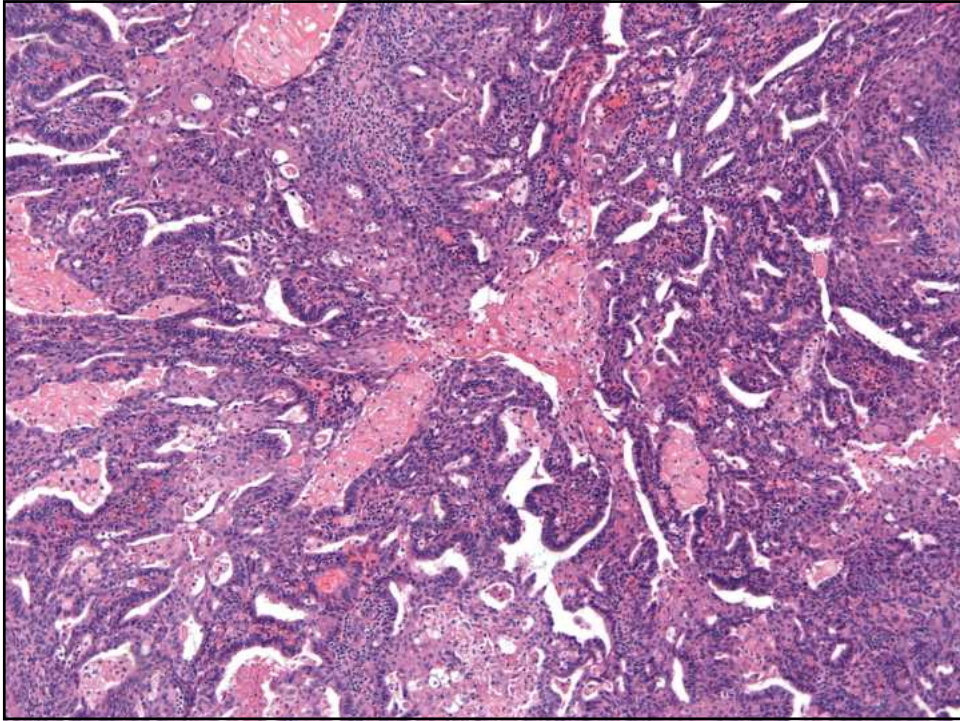
- Endometrioid carcinoma – 80% *
- Clear cell carcinoma – <5%
- Undifferentiated – <5%
- Carcinosarcoma (MMMT) – <5%
- Serous – <5%
- Mucinous – <5%

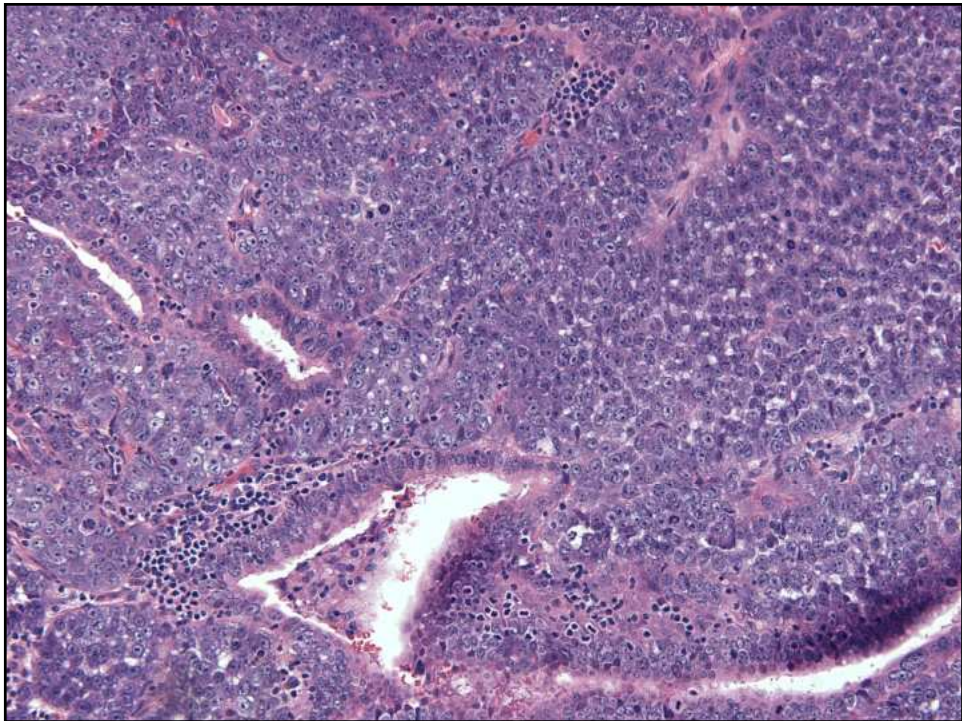
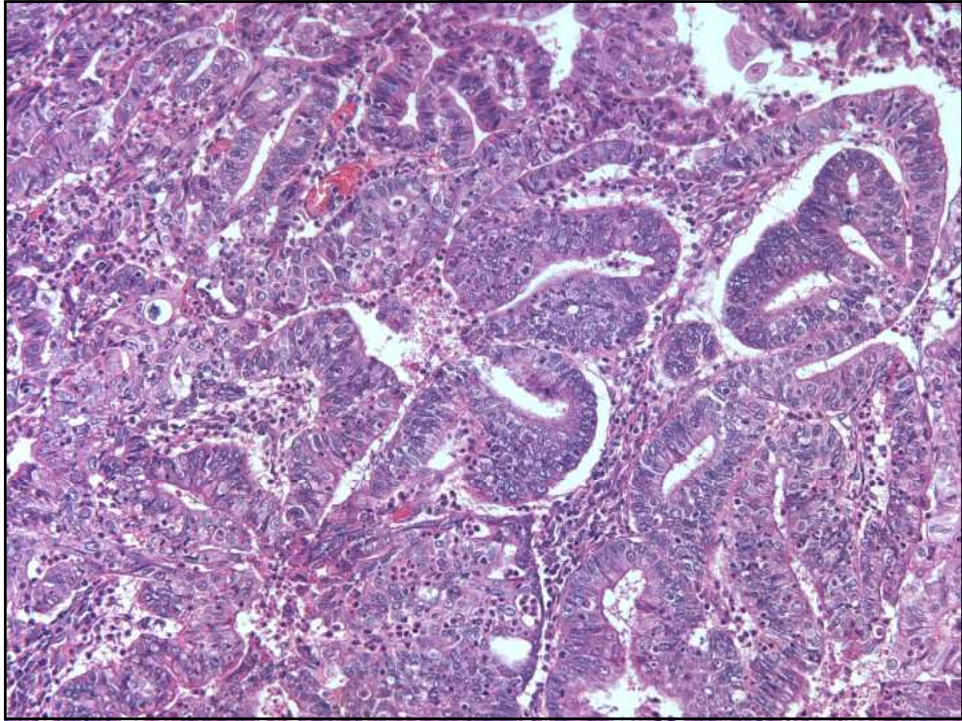
* May be mixed histology

Tumor Morphology: Endometrioid

- Peritumoral lymphocytes
- Tumor infiltrating lymphocytes (TILs)
- Dedifferentiated endometrial carcinomas
- Mixed patterns – e.g., endometrioid & mucinous

Shia et al. Hum Pathol 2008;39:116-25





Dedifferentiated Carcinoma

Combination of undifferentiated carcinoma with well to moderately differentiated endometrioid carcinoma

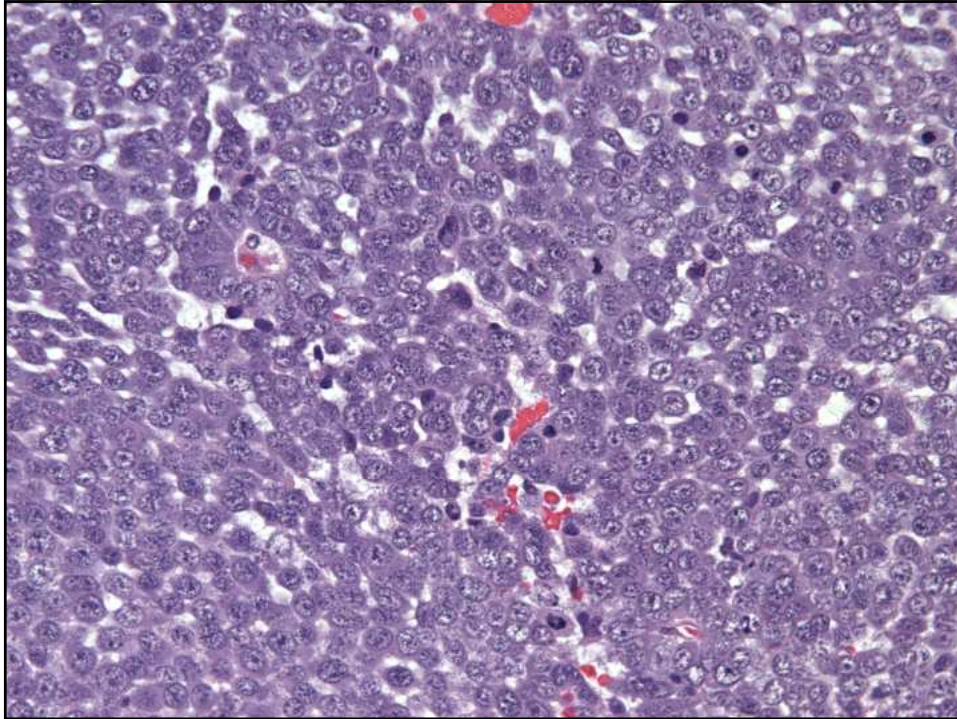
Silva et al. Int J Gynecol Pathol 2006;25:52-8

Undifferentiated Carcinoma

- Solid sheets without nests or glands
- Small, ovoid cells
- Usually monomorphic, but may have pleomorphic, rhabdoid cells
- Loss of keratin, EMA
- Absence of ER/PR common

- Poor outcome (21/22 DOD or AWD)

Altrabulsi et al. Am J Surg Pathol 2005;10:1316-21
Silva et al. Int J Gynecol Pathol 2006;25:52-8



How Many TILs?

- Few data
- M-S-K: More than 42 per 10 HPF
- Increased TILs not specific for Lynch syndrome
- 33% of sporadic hypermethylated endometrial cancer have increased TILs

Mills et al. Mod Pathol 2011; [Abstract]

Lynch Syndrome: Endometrial Cancer [Population Based Data]

- MSH2/MSH6 (24) >> MSH1/PMS2 (2)
- Approx 10% LUS
- Approx 33% TILs
- Grade 1 (48%) > Grade 2 (26%) or Grade 3 (26%)
- Almost 75% >50 years of age

*Mills et al. Am J Surg Pathol [In Press]
Leenen et al. Gynecol Oncol. 2012;125:414-20.*

Lynch Syndrome: Ovarian Cancer [Population-Based Data < 50 Years Of Age] (n=54)]

- MSH2 > MLH1
- Clear cell (3/4)
- Undifferentiated (1/4)
- Unilateral, organ-confined (3/4)
- Synchronous endometrial cancer (1/4)

Jensen et al. Am J Surg Pathol 2008;32:1029-1037

Lynch Syndrome: Ovarian Cancer [Registry Data]

- Most <50 years of age
- Most clear cell
- MSH2 > MLH1
- Unilateral, organ-confined (7/15)
- Synchronous endometrial cancer (4/15)

Ryan et al. Mod Pathol 2011;24:265A [Abstract]

Lynch Syndrome: Ovarian Cancer

- 10% dMMR
- Most endometrioid
- High association with concurrent endometrial cancer

Aysal et al. Am J Surg Pathol 2012;36:163-72

Lynch Syndrome: What About Cervix?

- No clear reported association (1 case report)
- Stanford study: 101 cervical/LUS adeno, including variants
- LUS adenocarcinoma in 2 LS patients:
 - Cervical: All 4 mismatch repair proteins intact
 - Endometrial: Loss of mismatch repair proteins

Mills et al. Int J Gynecol Pathol 2012

Screening For Lynch Syndrome

- Clinical
- Pathological
- Clinical & pathological
- All colorectal, endometrial, ovarian cancers

Amsterdam I Criteria

Three or more family members with confirmed diagnosis of colorectal cancer, one of whom is a first degree relative of the other two.

Two successive affected generations.

One or more colorectal cancers diagnosed under age 50 years

Familial adenomatous polyposis (FAP) has been excluded.

Vasen et al, Gastroenterology 1999

Amsterdam II Criteria

Three or more family members with LS/HNPCC-related cancers, one of whom is a first degree relative of the other two.

Two successive affected generations.

One or more of the LS/HNPCC-related cancers diagnosed under age 50 years

Familial adenomatous polyposis (FAP) has been excluded.

Vasen et al, Gastroenterology 1999

Revised Bethesda Criteria

Colorectal cancer diagnosed in a patient who is less than 50 years of age.

Presence of synchronous, metachronous colorectal, or other LS/HNPCC-associated tumors, regardless of age.

Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age.

Colorectal cancer diagnosed in one or more first-degree relatives with an LS/HNPCC-related tumor, with one of the cancers being diagnosed under age of 50 years.

Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Umar et al. J Natl Cancer Inst 2004

SGO Criteria (20-25% Risk)

Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria.

Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50.

Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50.

Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability or immunohistochemical loss of expression of MLH1, MSH2, MSH6 or PMS2).

Patients with first or second degree relative with a known mismatch repair gene mutation.

Lancaster, et al. Gynecol Oncol 2007

SGO Criteria (5-10% Risk)

Patients with endometrial or colorectal cancer diagnosed prior to age 50.

Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other LS/HNPCC associated tumor at any age.

Patients with endometrial or colorectal cancer and a first degree relative with LS/HNPCC associated tumor diagnosed prior to age 50.

Patients with colorectal or endometrial carcinoma diagnosed at any age with two or more first or second degree relatives with LS/HNPCC associated tumors, regardless of age.

Patients with a first or second degree relative that meets the above criteria.

Lancaster et al. Gynecol Oncol 2007

Screening for Lynch Syndrome in Endometrial Carcinoma Patients

- 58% met Amsterdam II criteria
- 36% met revised Bethesda guidelines
- 71% met SGO 20-25% screening criteria
- 93% met SGO 5-10% screening criteria

Ryan et al, Cancer 2012;118:681-8

Screening for Lynch Syndrome in Endometrial Carcinoma Patients

- Pathologic features noncontributory
 - Lower uterine segment origin
 - Tumor heterogeneity
 - Tumor infiltrating lymphocytes
 - Peritumoral lymphocytes

Ryan et al, Cancer 2012;118:681-8

Screening for Lynch Syndrome in Endometrial Carcinoma Patients

- Applied 6 pathologic criteria for testing endometrial cancer patients for Lynch syndrome
- IHC triage of patients with first degree relative with LS associated cancer most cost effective

Kwon et al, J Clin Oncol 2011;29:2247-52

Screening for Lynch Syndrome in Endometrial Carcinoma Patients

- All patients newly diagnosed with endometrial carcinoma tested for MMR by IHC followed by methylation
- Cost-effectiveness depends on patient follow up with genetic counselling & participation rate of at risk relatives

Mills et al. Am J Surg Pathol [In Press]

Screening for Lynch Syndrome in Ovarian Carcinoma Patients

- Non-serous histology
- Clear cell carcinoma, particularly in young patients
- Undifferentiated/dedifferentiated carcinoma
- Endometrioid or mixed histology - if clinically indicated

Screening for Lynch Syndrome in Ovarian Carcinoma Patients

- Synchronous endometrioid carcinomas of the uterus and ovary are NOT likely to be Lynch syndrome associated
- Synchronous uterine endometrioid and ovarian clear cell cancer exception

Diagnosis of Lynch Syndrome

Diagnosis of Lynch Syndrome

1. MMR gene mutation testing
2. MSI analysis by PCR
3. Immunohistochemistry for MMR proteins
4. *MLH1* promoter methylation

MMR Gene Mutation Testing

Requires consent and counseling
Expensive
Labor intensive
Specialized centers
Only definitive test to establish a diagnosis of Lynch syndrome
Not a screening test

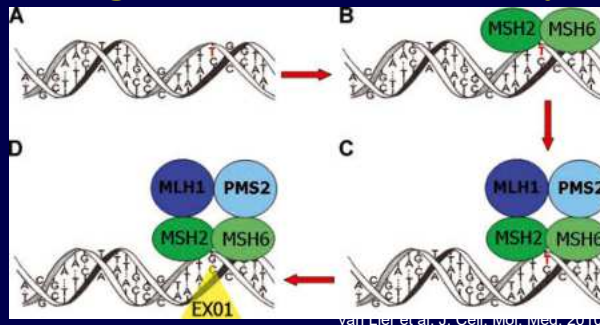
Lynch Syndrome: MSI Testing

- Microsatellites are repetitive sequences that are particularly vulnerable to error without functioning MMR system
- Microsatellite instability (MSI) can serve as a proxy for impaired MMR

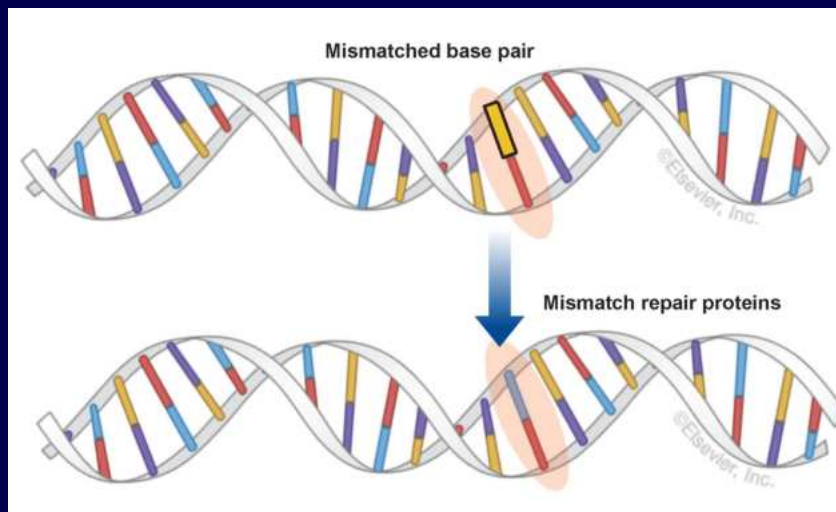
MSI Analysis

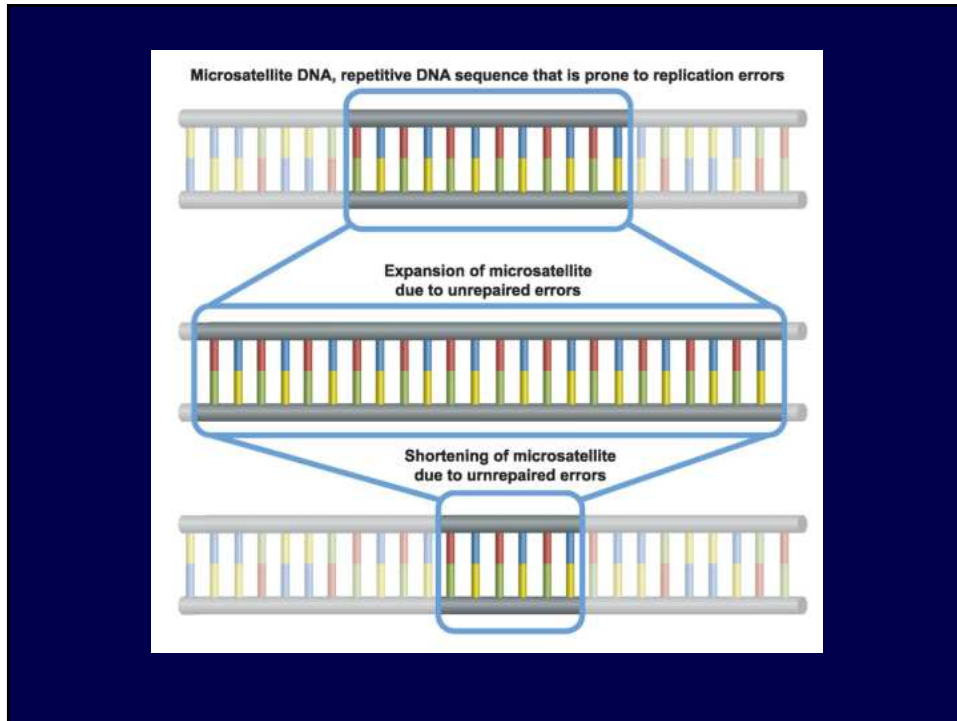
- PCR method
- 5 dinucleotide and mononucleotide markers
- 5 mononucleotide markers

Background: The MMR system



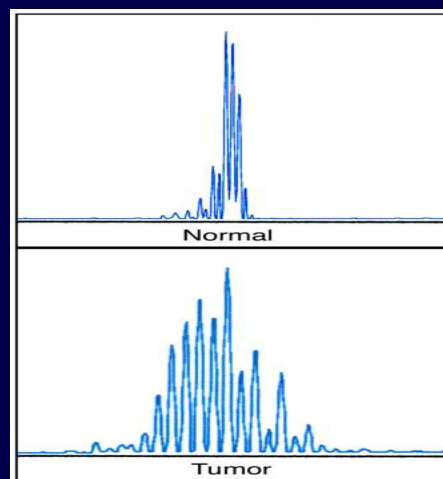
- During DNA replication, insertions or deletions of one or more nucleotides and single nucleotide mismatches may occur
- MSH2 and MSH6 form a heterodimer and recognize the mismatch
- MLH1 and PMS2 dimerize and bind to the MSH2-MSH6 complex
- The complex of four proteins activates an exonuclease to perform the DNA repair





Microsatellite Instability (MSI)

- Five mononucleotide microsatellite loci (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) (Promega fluorescent multiplex assay)
- Allelic profiles from the normal and malignant tissue are compared
- MSI-H = 2 or more abnormal profiles
- MSI-L = 1 abnormal profile
- MSS = no abnormal profile
- MSI-H vs MSI-S/MSI-L



MSI PCR Disadvantages

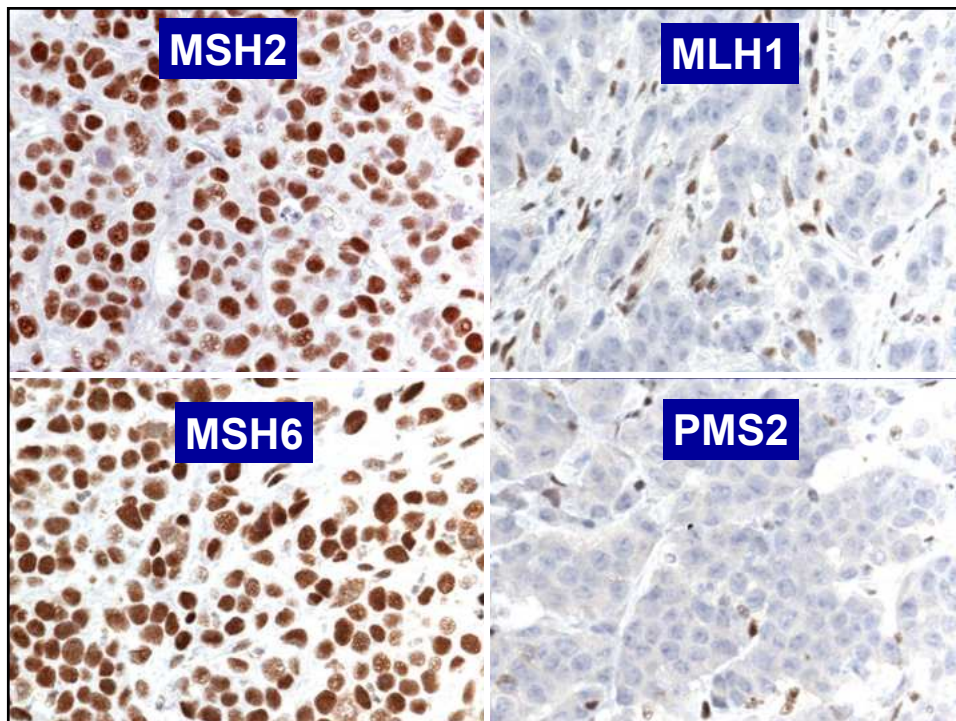
- Requires molecular laboratory set up
- Insufficient tumor cell nuclei may hinder test – esp problematic with colloid colorectal carcinomas
- May not identify MSH6 MMR protein deficient cases (MSS or MSI-L)
- Does not distinguish between genetic and epigenetic causes of MSI
- Does not identify specific MMR protein

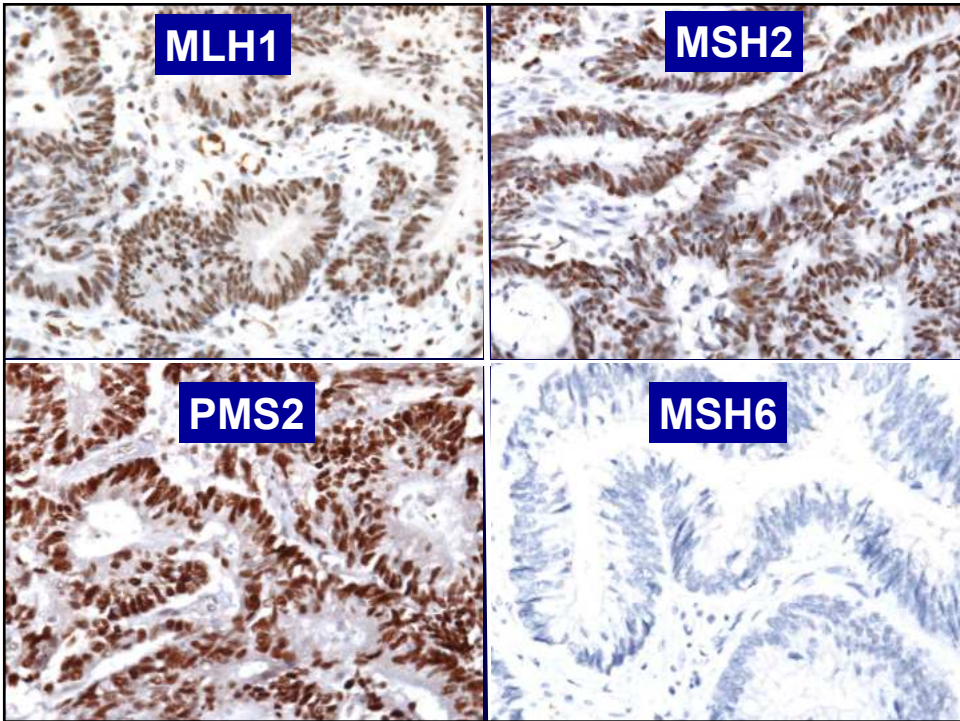
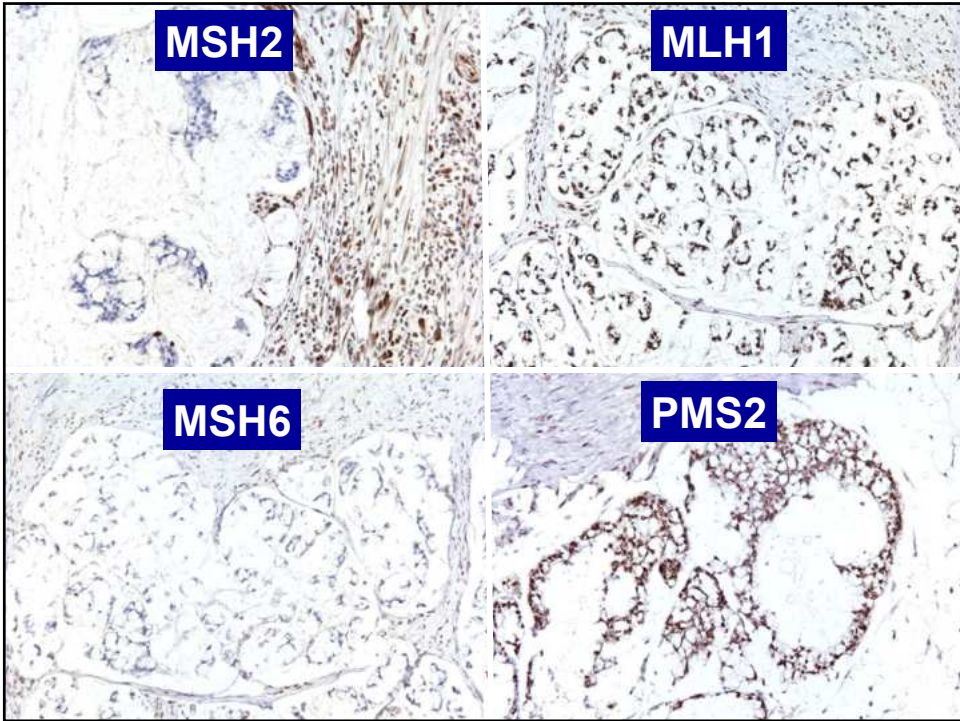
Mismatch Repair Protein (IHC)

- Mismatch repair protein expression is lost in nonfunctioning MMR
- IHC can detect specific MMR protein deficiency

Mismatch Repair Protein (IHC)

- MLH1, PMS2, MSH2, MSH6
 - MLH1 and PMS2 dimer: MLH1 is dominant
 - MSH2 and MSH6 dimer: MSH2 is dominant
- All 4 intact = MMR proficient (pMMR)
- Loss of 1 or 2 = MMR deficient (dMMR)
- Rarely, loss of >2 due to gene mutation and epigenetic methylation





IHC for DNA Mismatch Repair Proteins: Patterns of Loss

- 1. Loss of MLH1 and PMS2:** Epigenetic (MLH1 promoter methylation) or genetic (MLH1 mutation)
 - Need further studies to differentiate between the 2 (MLH1 promoter methylation)
- 2. Loss of PMS2 alone:** Lynch syndrome due to PMS2 mutation (rare)

IHC for DNA Mismatch Repair Proteins: Patterns of Loss

- 3. Loss of MSH2 and MSH6:** Lynch syndrome due to MSH2 mutation (rarely, mutation in EpCAM)
- 4. Loss of MSH6 alone:** Lynch syndrome due to MSH6 mutation

IHC for DNA Mismatch Repair Proteins: Advantages

- Familiar methodology
- Quick turn-around
- Relatively inexpensive
- MSH6 mutations may be MSI-L or MSS
- Can pinpoint genes of interest for sequencing
- Cost effective

Shia et al. J Mol Diagn 2008;10:293-300
Shia et al. Am J Surg Pathol 2009;33:1639-45
Resnick et al. Obstet Gynecol 2009;114:530-6

IHC for DNA Mismatch Repair Proteins: Disadvantages

- Numerous TILs may create false impression of intact MMR expression in tumor nuclei
- MSH6 may be heterogeneous – need to evaluate entire tumor
- Absence of internal positive control – if tumor nuclei negative, test can only be interpreted as equivocal
- Fixation dependent

Epigenetic Methylation in Colorectal Cancer: MLH1

- Common in colorectal carcinomas
- Occurs in left- and right-sided tumors
- Trend for older individuals
- Trend for females
- May show differential response to standard (5-FU) chemotherapy
- Can be detected by *BRAF* mutation

Epigenetic Methylation in Endometrial Cancer: MLH1

- Common in endometrial cancer
- Endometrioid & mixed endometrioid/mucinous histology; undifferentiated
- Average age: 65 years (range: 42-88)
- Majority (86%, 44/51) located in the uterine fundus
- Cannot be detected by *BRAF* mutation: must do promoter methylation analysis

Mills et al Mod Pathol 2011;24:260A [Abstract]

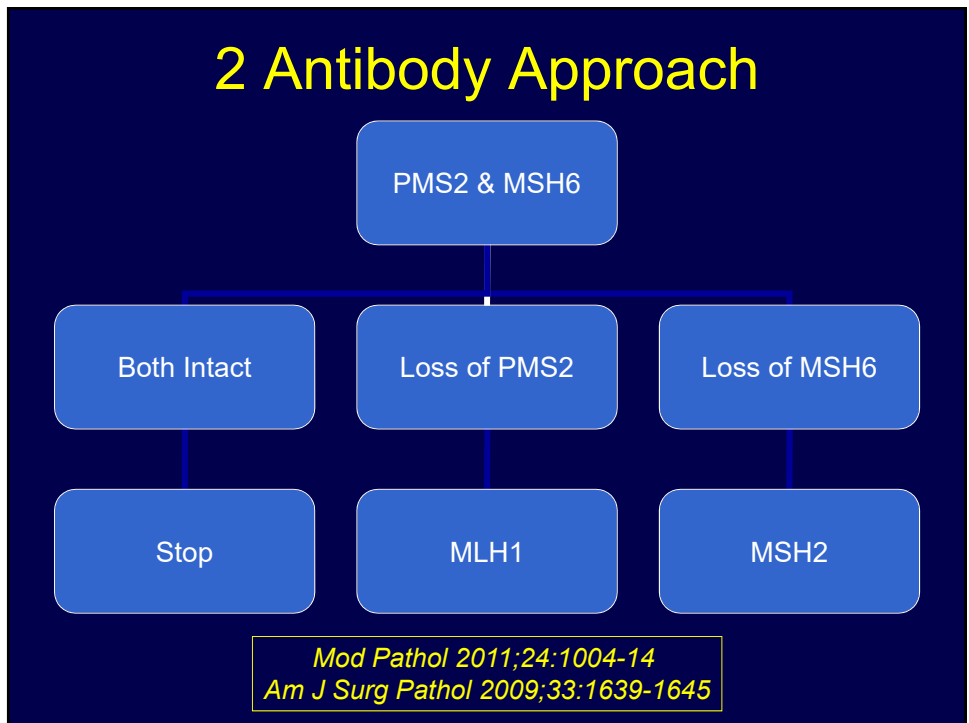
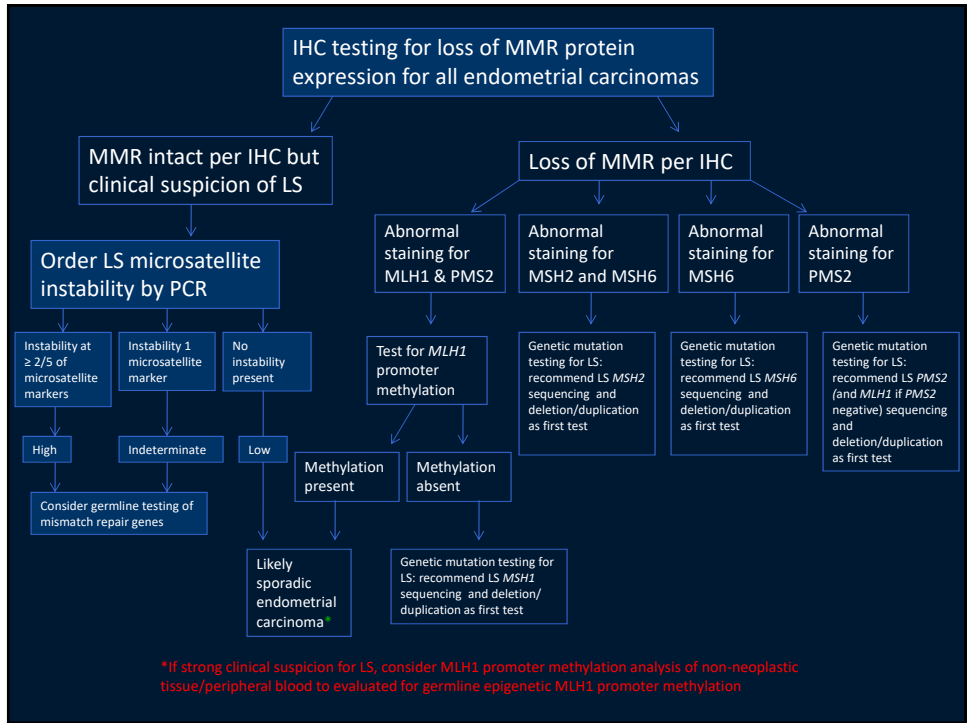
Epigenetic Methylation in Endometrial Cancer: MLH1

- Typically low grade, but may be higher stage
- Can have TILs (33%)
- Prognosis, response to therapy unknown
- Need large, long-term studies

Mills et al Mod Pathol 2011;24:260A [Abstract]

Reflex Testing

- Is consent needed to test with IHC? Short answer...no
- Assure all targeted patient samples are tested
- Assure all relevant patients are referred for counseling



2 Antibody Approach

- Effective for colon, endometrial, & sebaceous lesions
- Requires unequivocal positive internal control
- Despite promising results, most labs still performing 4 antibody panel

Mod Pathol 2011;24:1004-14
Am J Surg Pathol 2009;33:1639-1645

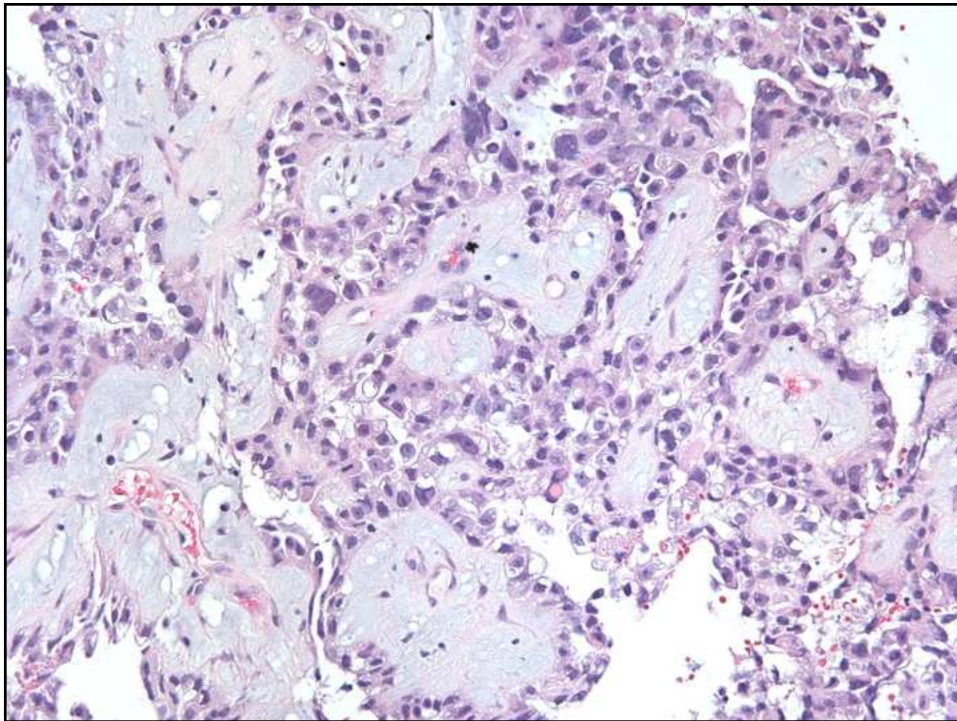
2 Antibody Approach

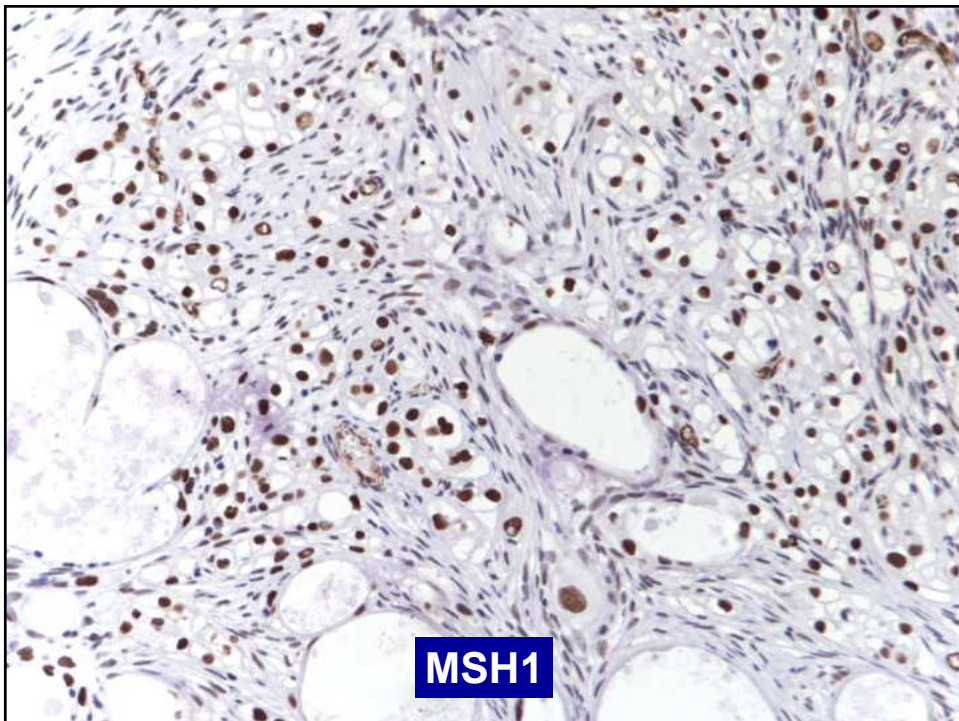
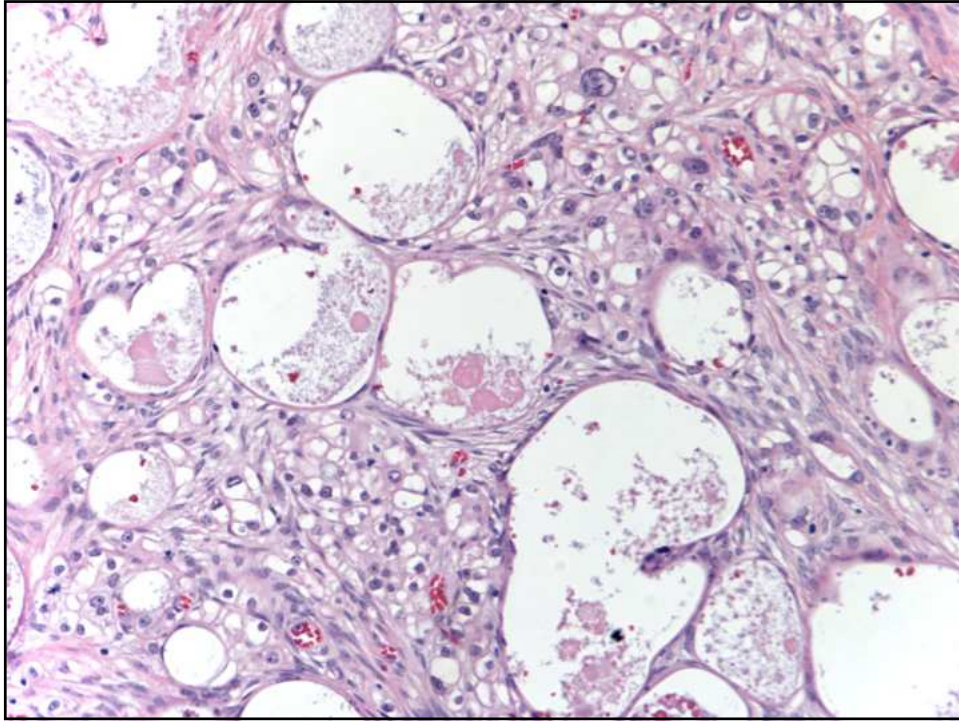
- May not be reliable in small samples due to heterogeneity in protein expression, esp. MSH6
- MSH2 deficiency may be due to mutation in EpCAM not MSH2 (11% colorectal cancer, 6% endometrial cancer)

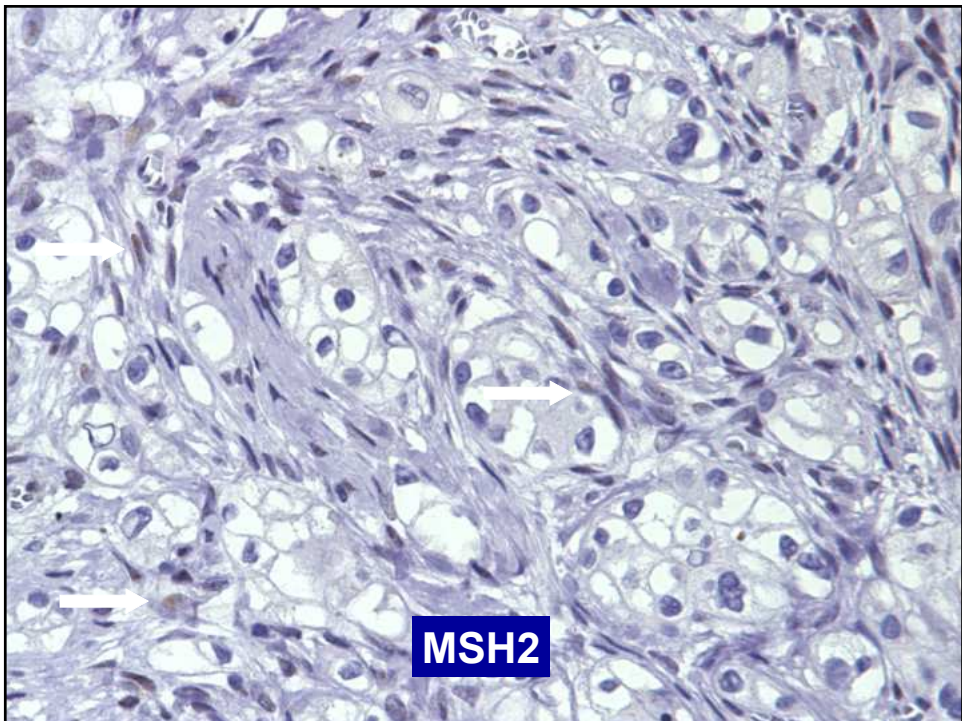
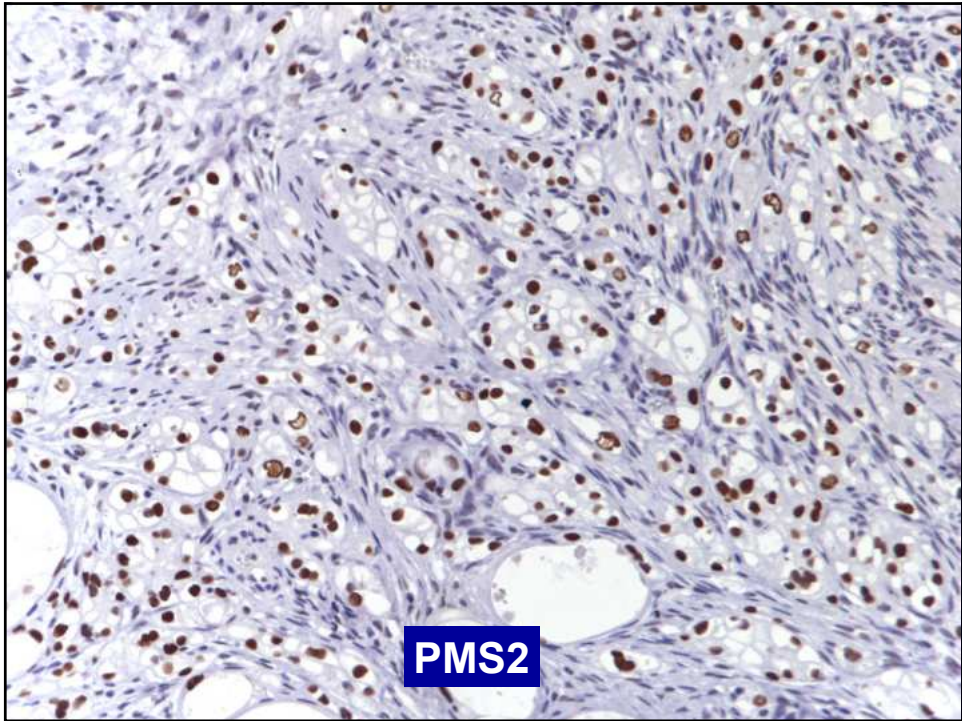
J Mol Diagn 2011;13:93-9
Mod Pathol 2013 [Abstract]

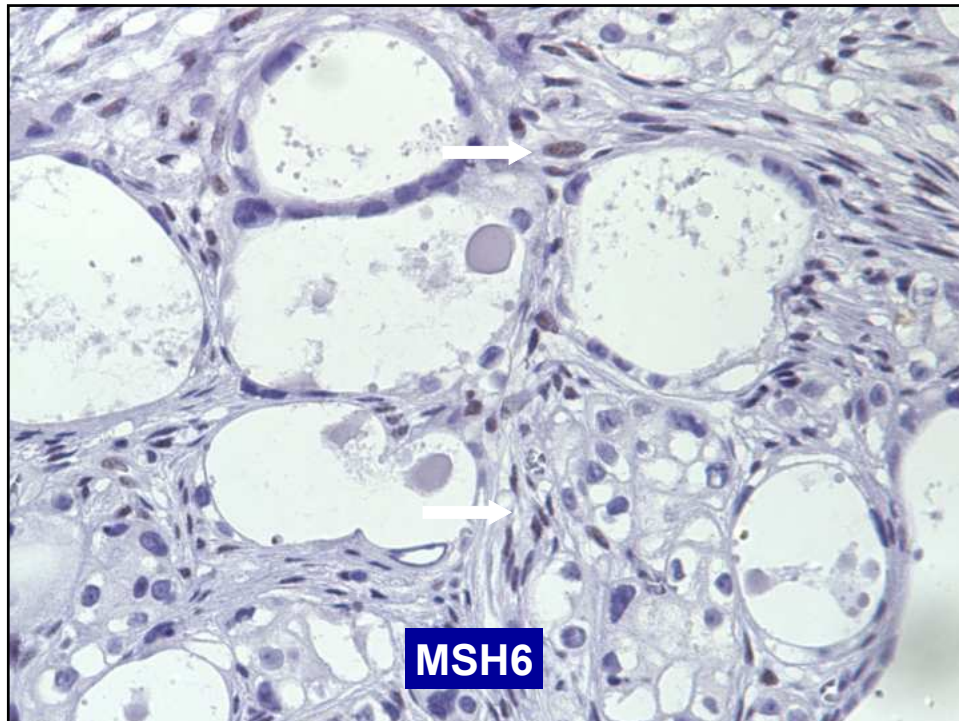
Case Presentation

- 42 year old woman with ovarian mass









Case Presentation

- Tumor board discussion by pathologist with recommendation for genetic counseling
- Follow up: positive family history of father with colorectal cancer, older sister with endometrial cancer
- Pt has germline mutation in MSH2

Surveillance for Gynecologic Tumors in Women with Lynch Syndrome

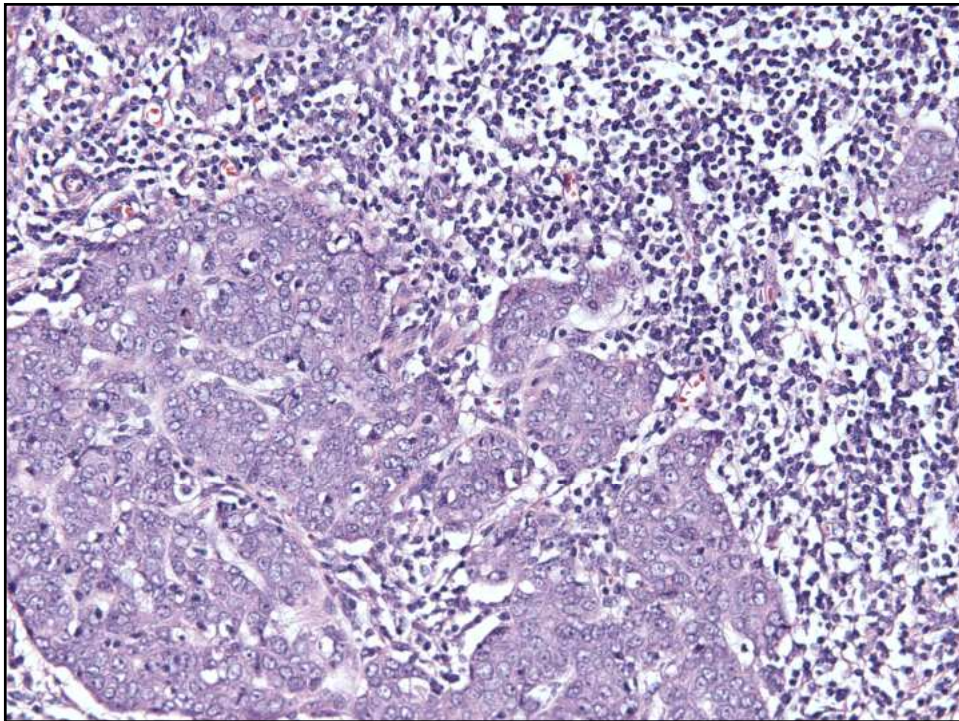
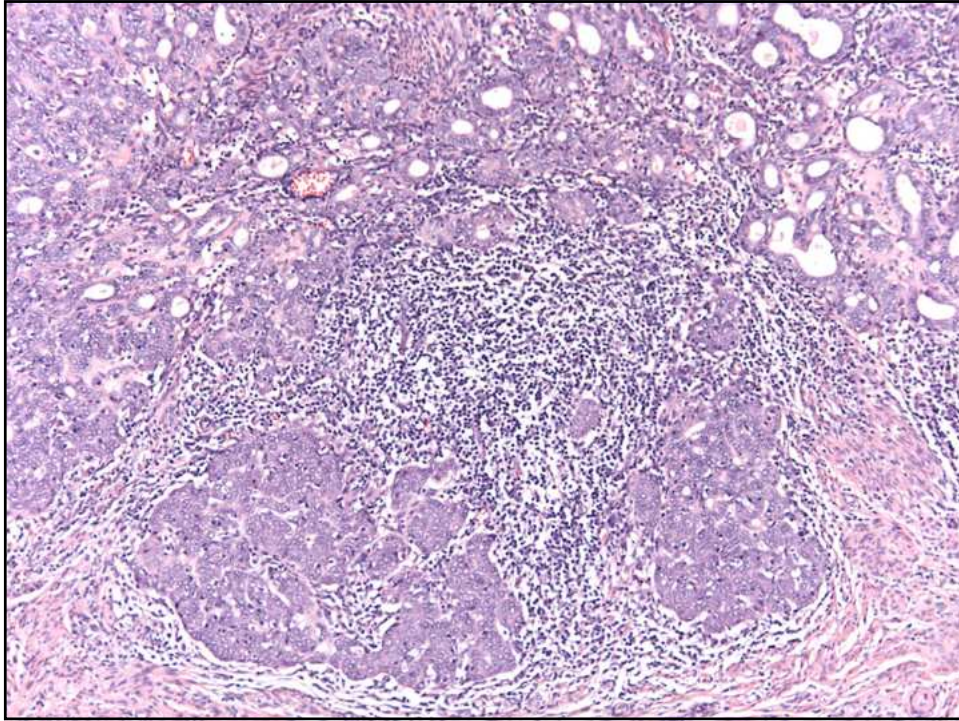
- Age 25-35 years
- Annual pelvic exam with pap smear
- Transvaginal and/or pelvic ultrasound
- Endometrial biopsy

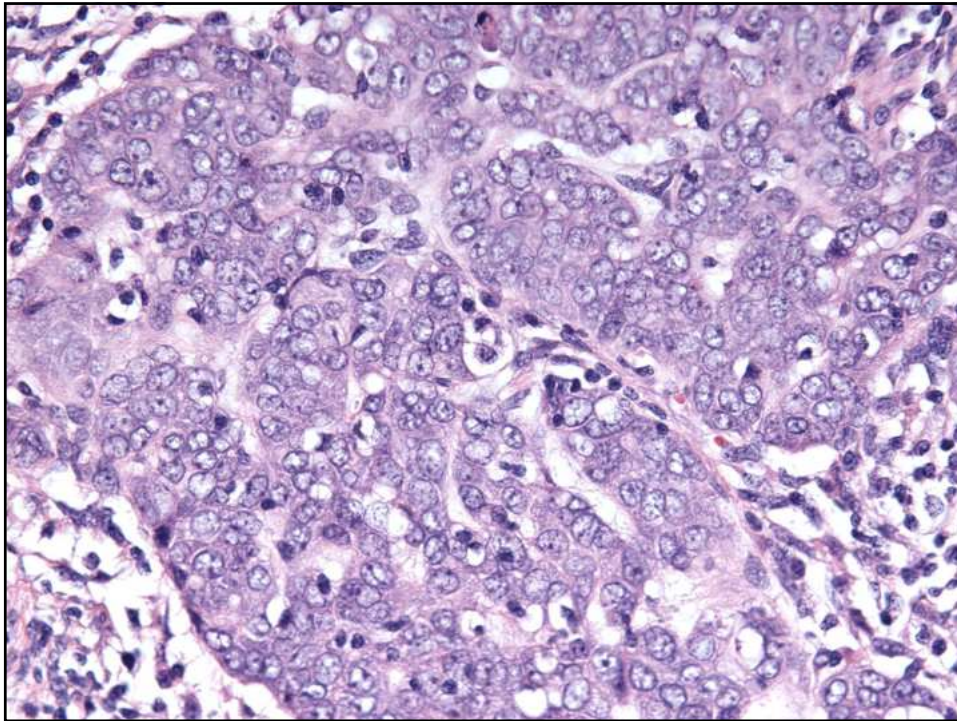
- Not shown to be effective

Risk Reducing Surgery in Lynch Syndrome

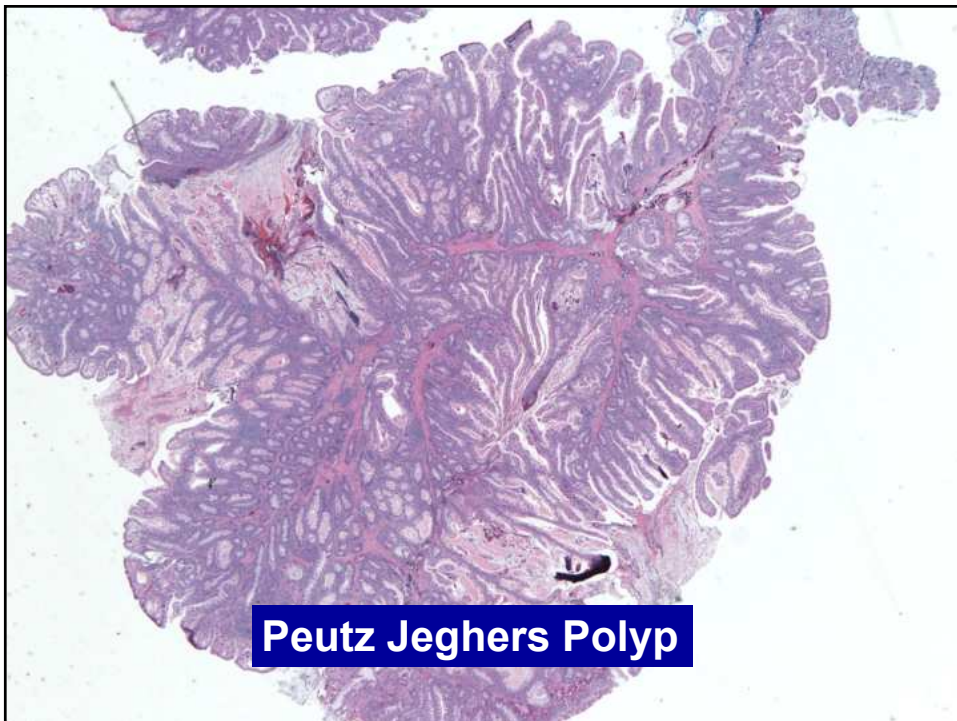
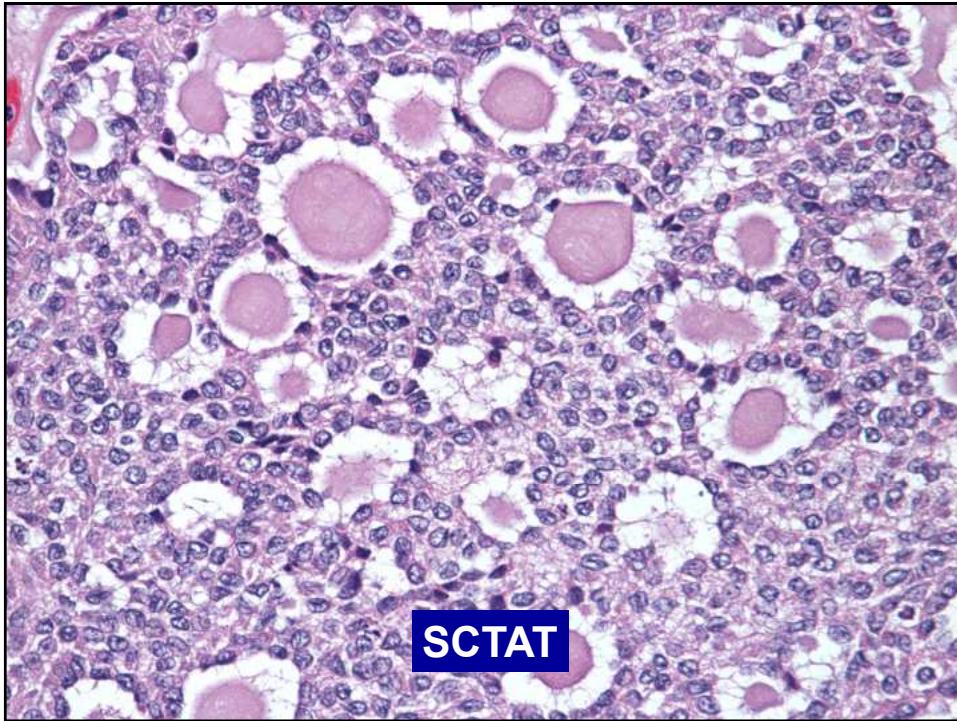
- Women who undergo prophylactic surgery do not develop cancer
- Consider risk reducing surgery in women with Lynch syndrome after the age of 35 years or once childbirth has been completed
- More effective and less expensive compared to surveillance
- Disadvantages: Surgical complications and surgical menopause

Am J Surg Pathol 2013;37:579-85

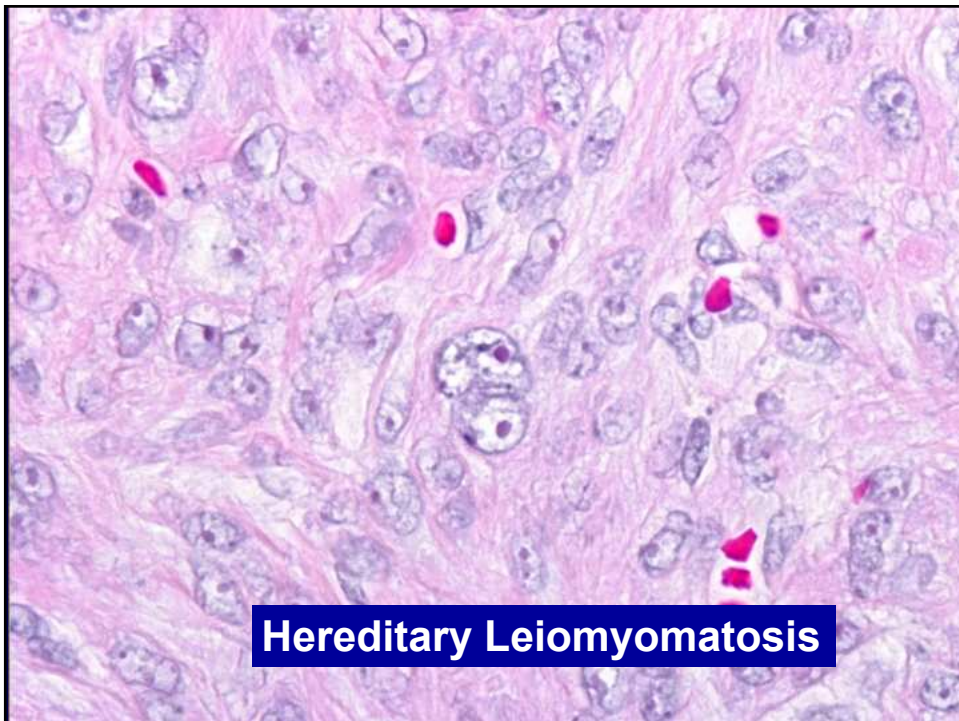
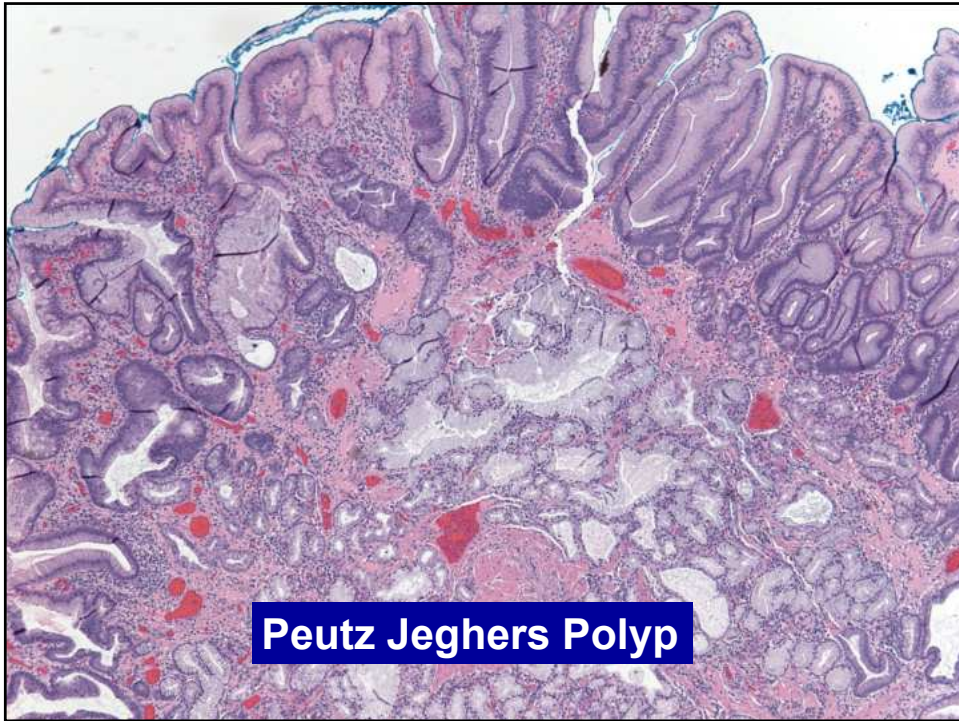




Syndrome	Gene	Gynecologic Tumors	Associated Tumors
Peutz-Jeghers syndrome	<i>STK11/LKB1</i>	Ovary: <ul style="list-style-type: none"> Sex cord stromal tumors (5-15% risk) Mostly sex cord tumor with annular tubules (SCTAT), small, bilateral, and calcified Cervix: <ul style="list-style-type: none"> Adenoma malignum (10% risk) 	<ul style="list-style-type: none"> Hamartomatous GI polyps Breast, GI, lung, pancreas, testis cancers
Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)	<i>Fumarate hydratase</i>	Uterus: <ul style="list-style-type: none"> Leiomyomas with prominent nucleoli and perinuclear halos, in young patients (present in most with syndrome) 	<ul style="list-style-type: none"> Renal cell carcinoma (15% risk) Cutaneous leiomyomas
Gorlin syndrome (Nevoid Basal Cell syndrome)	<i>PTCH</i>	Ovary: <ul style="list-style-type: none"> Fibromas, bilateral and calcified (2-25% risk) 	<ul style="list-style-type: none"> Basal cell carcinomas Odontogenic keratocysts Medulloblastomas
Cowden syndrome (PTEN Hamartoma Tumor syndrome)	<i>PTEN</i>	Uterus: <ul style="list-style-type: none"> Leiomyomas Endometrial carcinoma (5-19% risk) 	<ul style="list-style-type: none"> Hamartomas of GI tract, skin, mucous membranes, breast, thyroid, endometrium Breast (25-50% risk) and thyroid (3-10% risk) carcinomas

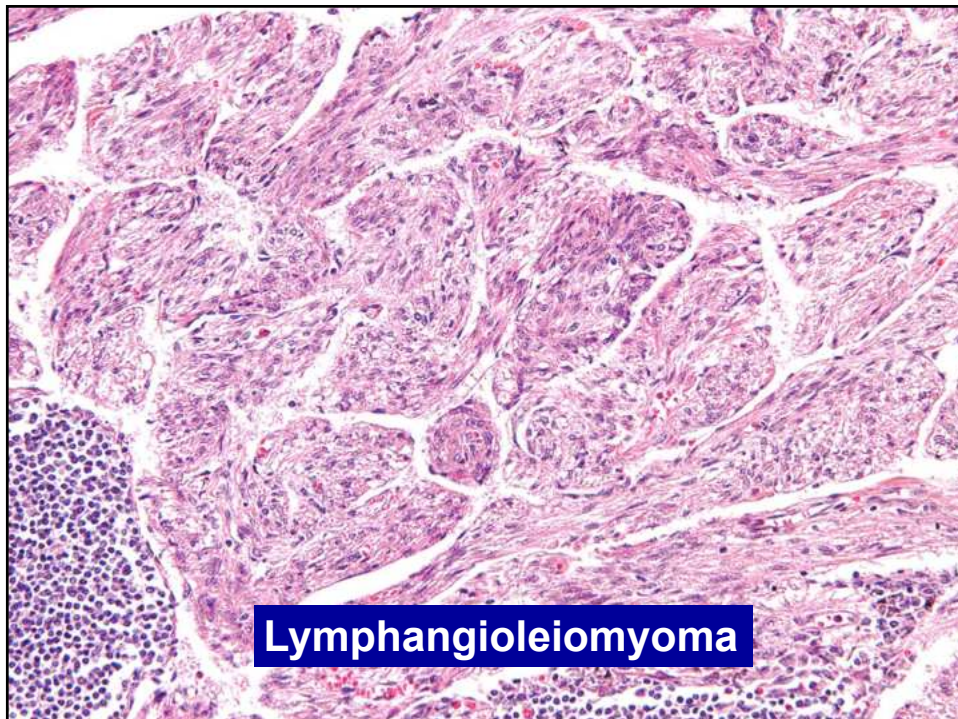


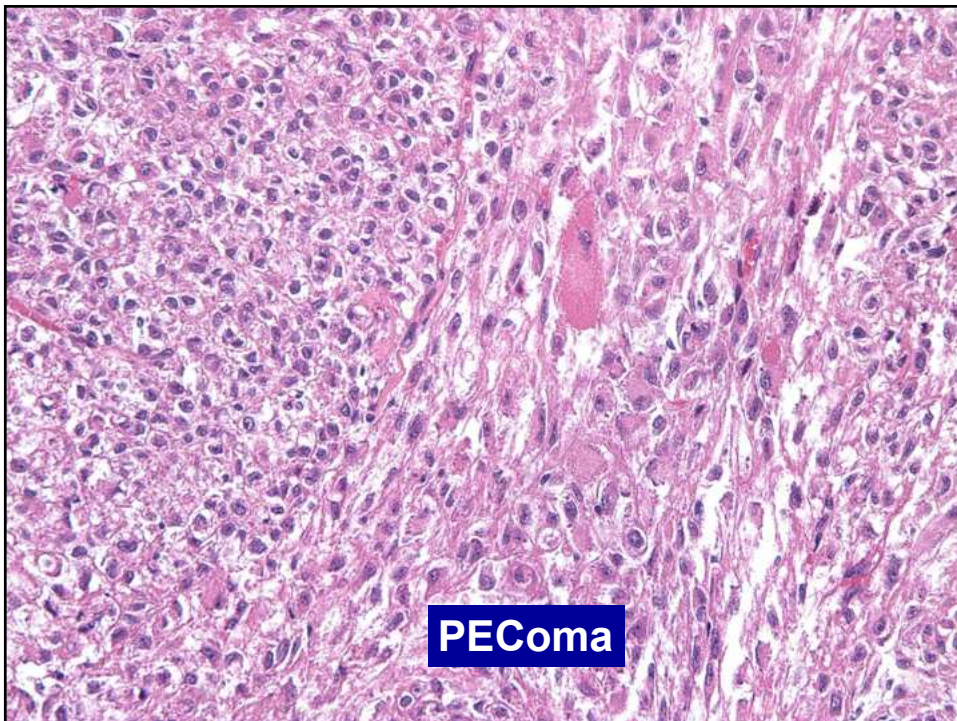
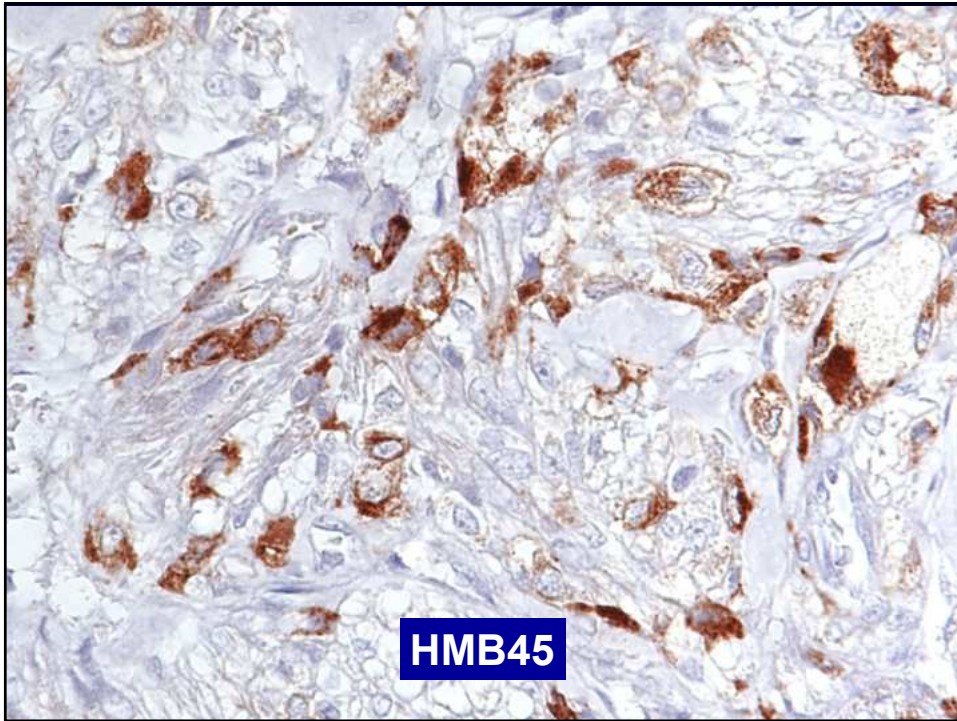




Tuberous Sclerosis Complex (TSC)

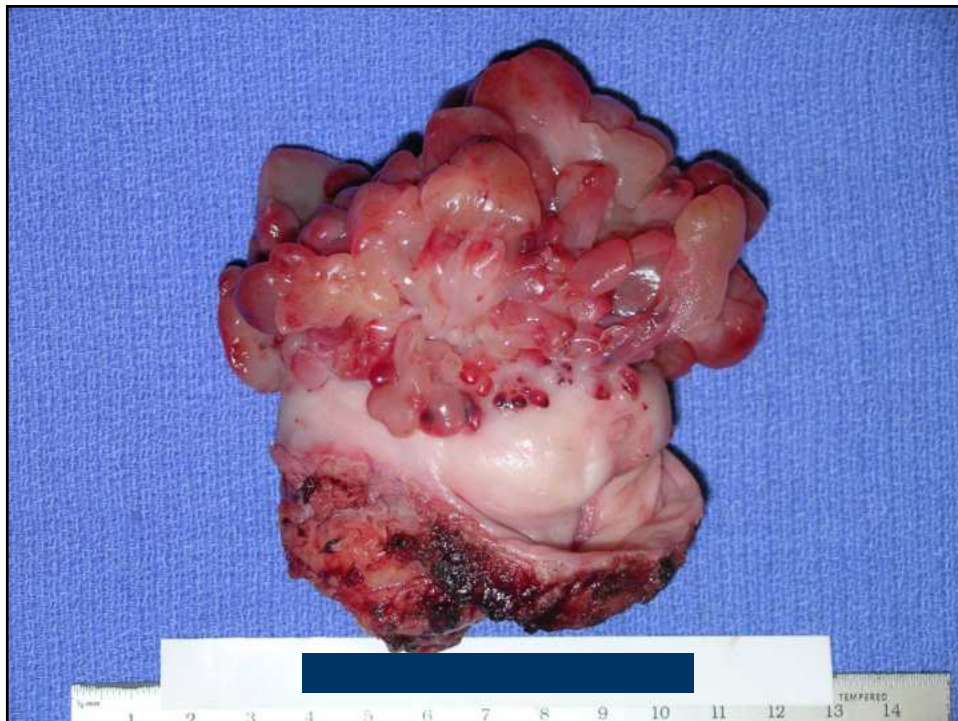
- Germline mutations in the *TSC1* or *TSC2* genes.
- Abnormalities of the skin, brain, kidney and lungs.
- **Lymphangiomyomatosis**, **angiomyolipoma** and **perivascular epithelioid cell tumors (PEComas)** that affect the gynecologic tract.

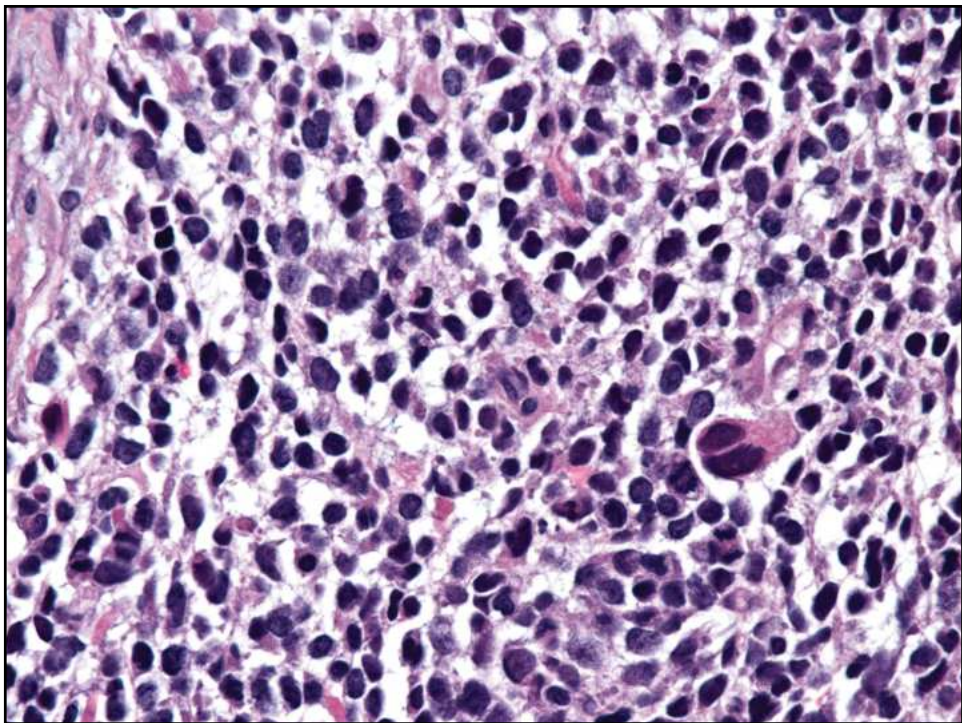
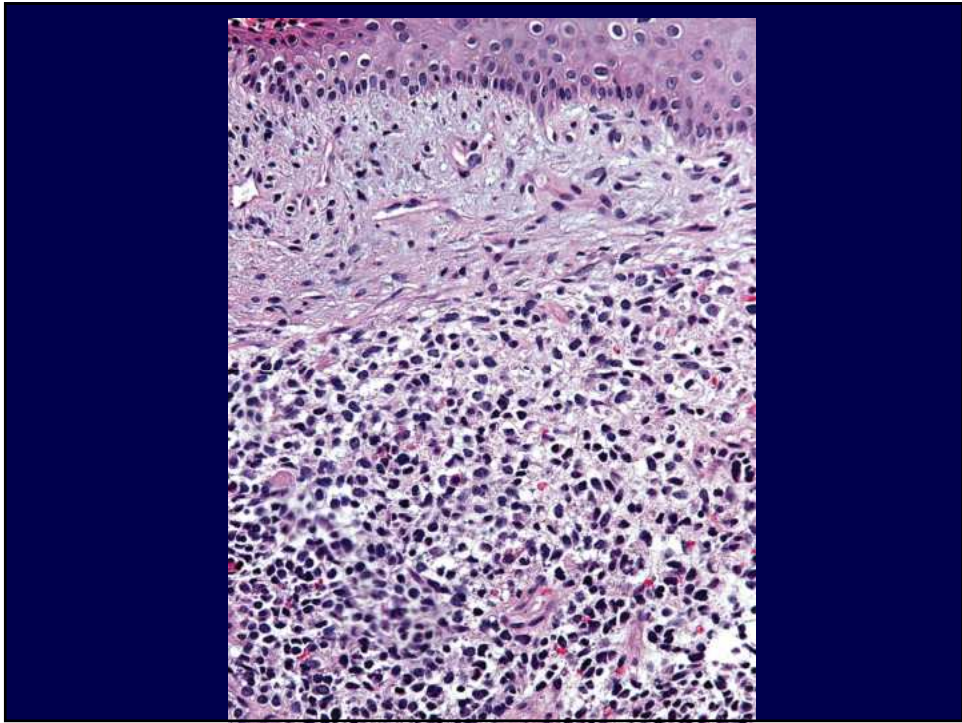


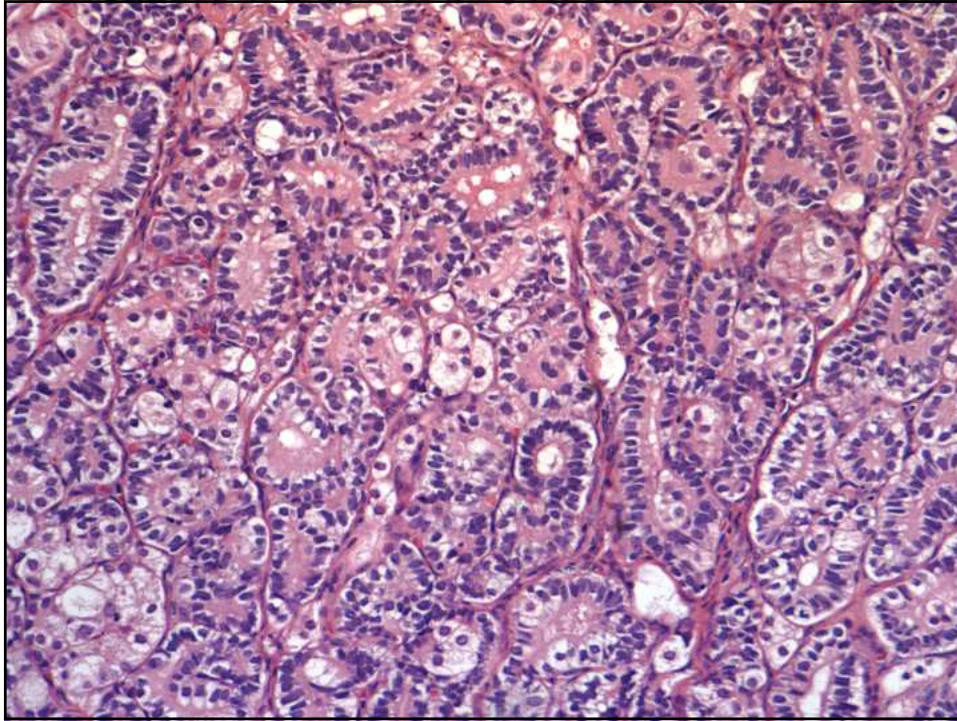


Dicer Syndrome

- Pleuropulmonary blastoma (PPB), cystic nephroma (CN), **ovarian sex cord-stromal tumors (Sertoli-Leydig cell tumor [SLCT]), embryonal rhabdomyosarcoma (especially involving cervix)** and/or multinodular goiter in children and/or young adults.
- Recommendations for screening unaffected mutation carriers are not yet established.







Summary

- BRCA1/2 syndromes
- Lynch syndrome
- Peutz-Jeghers syndrome
- Cowden syndrome
- Gorlin syndrome
- Li-Fraumeni syndrome
- Hereditary leiomyomatosis
- Tuberous sclerosis complex
- Dicer syndrome

