Gynecologic Cancer in Women with Lynch Syndrome

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Objective

1. To review the life-time risk of gynecologic cancer
2. To review potential symptoms of gynecologic cancer
3. To discuss data and controversies of screening for gynecologic cancer
4. To discuss data on risk-reducing surgery

Lynch Syndrome

- **Lynch Syndrome (LS) is an inherited cancer susceptibility syndrome**
- **Characterized by familial clustering of cancers (e.g. colorectal, endometrial)**
- **Autosomal dominant genetic defects in mismatch repair genes (MMR)**
    - ***MLH1, MSH2, MSH6, PMS2***
- **3-5% of unselected women with EC have LS[1,2]**

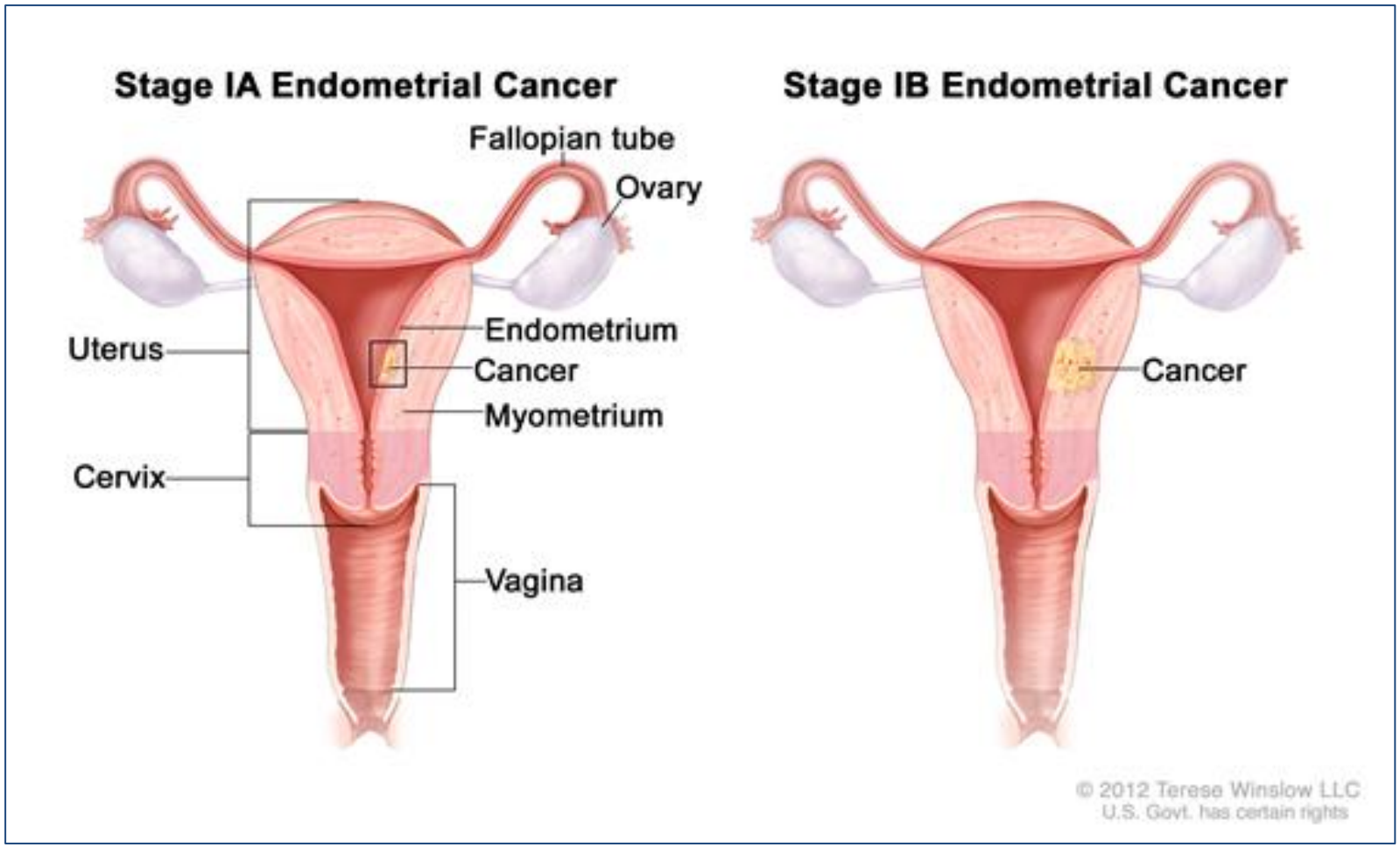
[1]Ferguson SE ASCO, 2013 [2]Hampel H. *et al. Cancer Res* 2007;

LS–Associated Lifetime Risk of Cancer

Cancer	General Population Risk	Lynch Syndrome	*MLH1* and *MSH2*	*MSH6*	*PMS2*
Colon	6%	40-50%	40-80%	10-22%	15-20%
Endometrium	2.7%	30-60%	25-60 %	16-26%	15%
Ovary	1.7%	12%	4-24%	1-11%	-

NCCN Guidelines Version 1.2013

Endometrial Cancer and LS



Endometrial Cancer and LS

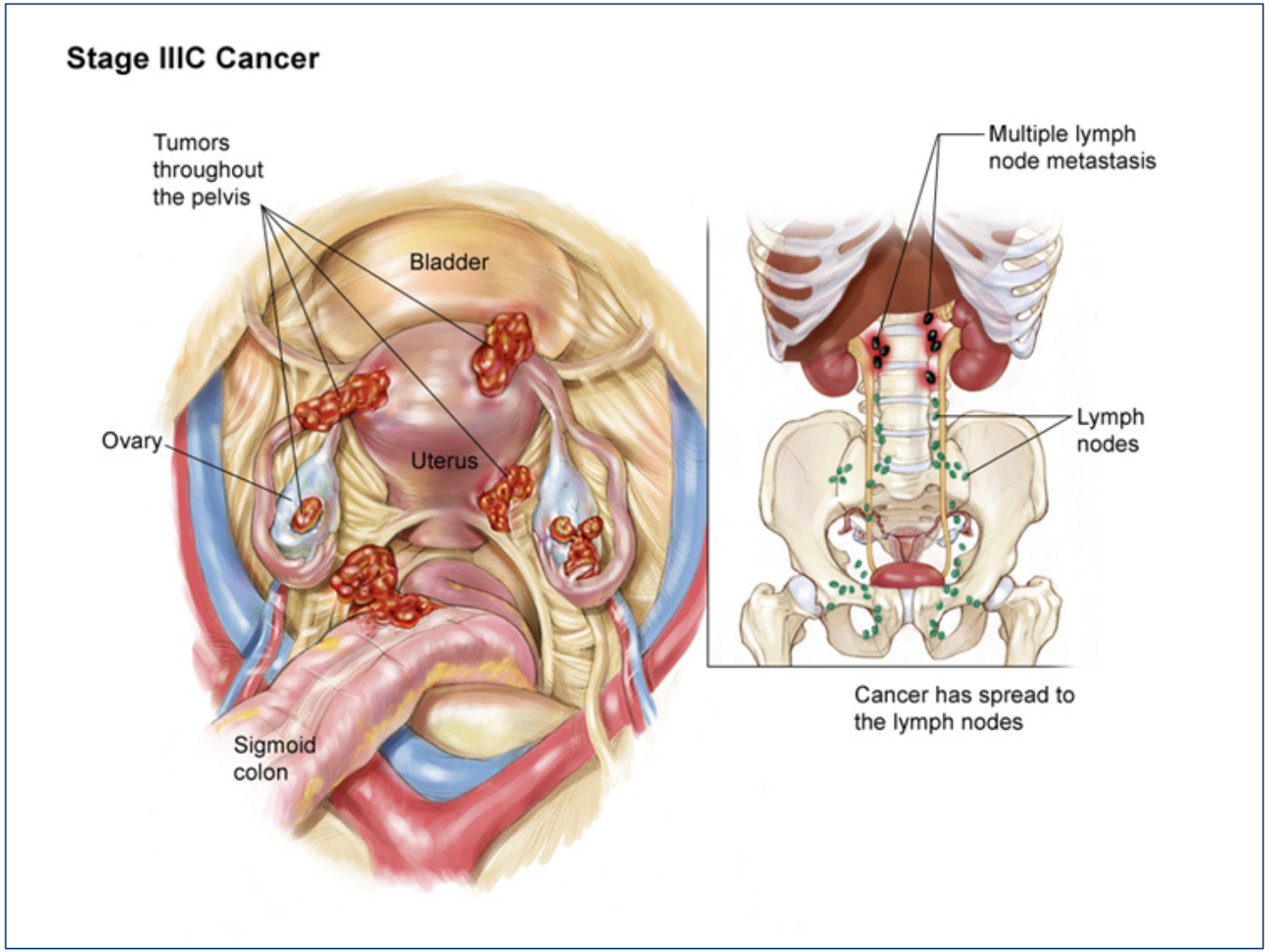
- EC is often the first cancer or "sentinel" cancer in LS[1]
- Significant lead time before 2nd cancer
- Opportunity to impact patient and family members with CRC screening and risk-reducing surgery[2,3]
- Difficult to identify women with EC at risk for LS:
  - Criteria for LS colorectal-based
  - Dependence on detailed family history
  - 2/3 with EC would not be identified[4,5]

[1]Lu *et al. Obstet Gynecol*, 2005, [2]Jarvinen *et a*l *Gastroenterology* 1995; [3]Schmeler *et al. NEJM* 2006; [4]Ferguson SE ASCO, 2013
[5]Hampel H. *et al. Cancer Res* 2007;.

Endometrial Cancer and LS

- Median age of developing EC significantly younger
  - median age late 40's compared to age 63
- Similar types of endometrial cancer as in sporadic EC
  - 20% high risk type of cancer; may require chemotherapy or radiation
- Similar stage distribution- 80% stage I
- Often associated with symptoms:
  - Postmenopausal bleeding
  - Bleeding between periods
  - Heavy periods
  - Irregular periods

Ovarian Cancer and LS



Ovarian Cancer and LS

- Median age of developing OV is significantly younger than
  - median age early 40's compared to early 60's
- Unlike sporadic or other cancer syndromes, different type of ovarian cancer: endometrioid, clear cell type
- Different stage distribution- 80% stage I (70% stage III/IV for sporadic)
- Often picked up incidentally at surgery for EC
- May have better prognosis than sporadic OC likely due to early stage at diagnosis
- May have more predictable progression from early stage to advanced stage compared to sporadic or *BRCA* OC

Gynecologic Symptoms that Need Investigation

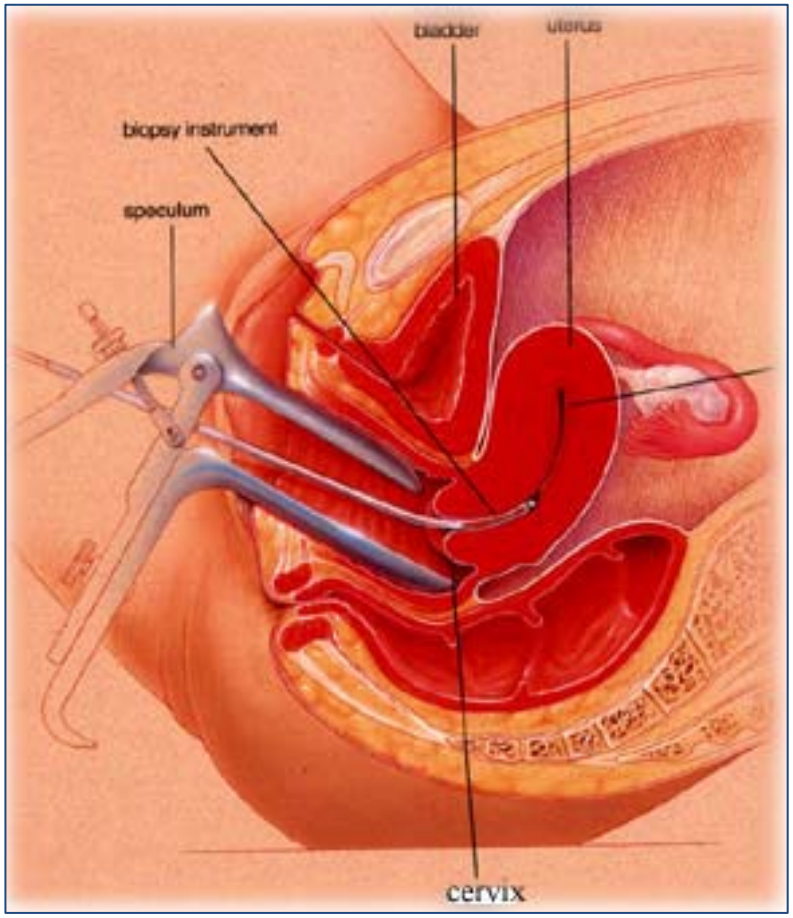
- **Endometrial**
  - Postmenopausal bleeding
  - Bleeding between periods
  - Heavy periods
  - Irregular periods
- **Ovarian** (symptoms almost daily for > 2-3 weeks)
  - Bloating
  - Pelvic or abdominal pain
  - Difficulty eating or feeling full quickly
  - Urinary symptoms (going often or having urgenc)

- These symptoms are non-specific and may be due to other non-cancer causes

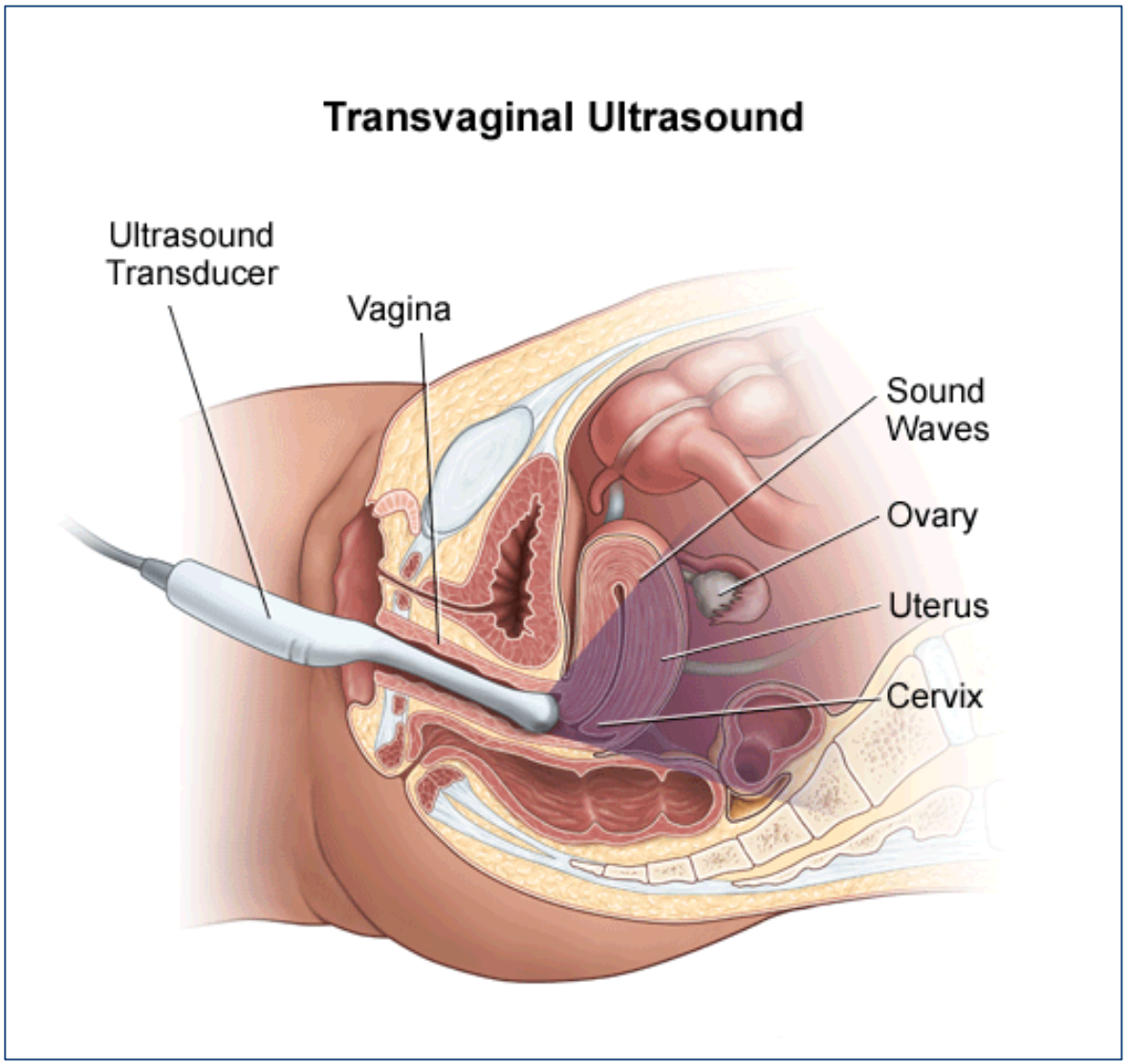
What Investigations Should be Performed for these Symptoms?

- **Abnormal or Postmenopausal Bleeding:**
  - **ENDOMETRIAL SAMPLE (in office biopsy preferred or D&C if no delay)**
  - **Ultrasound- but should not delay sampling of endometrium**
  - **Sometimes need to advocate for yourself to get to MD that can do these tests**
- **Bloating, abdominal/pelvic pain, difficulty eating or urinary symptoms:**
  - **ULTRASOUND- to assess ovaries/pelvis/abdomen**
  - **+/- CA 125 depending on ultrasound results**

In Office Endometrial Biopsy



Transvaginal Ultrasound



Screening for Gynecologic Cancer in Women with Lynch Syndrome

- Ideally want to find precancerous or very early cancerous lesions to minimize morbidity of treatment (requiring less extensive therapy) and decreasing mortality
- We have evidence that CRC screening in the general population and in individuals with LS decreases CRC-related deaths and morbidity (finding precancerous lesions)

Screening for Endometrial Cancer

- There is an early precancerous lesion and a step wise development from precancer to cancer for most types of endometrial cancer
- Therefore there is potential that screening could find these early lesions and offer benefit by minimizing treatment and preventing advanced cancer diagnosis

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Screening for Endometrial Cancer

- No data on EC screening in the general population to guide us:
  - Low prevalence of disease
  - High rate of PMB as an early symptom resulting in early stage of diagnosis with excellent prognosis
- Minimal data in women with LS:
  - Average age of women with EC are premenopausal so abnormal bleeding symptoms not as reliable
  - Higher prevalence of disease
  - May have benefit in this population but very few studies

Screening for Endometrial Cancer

- Only 2 prospective studies which looked at ultrasound with endometrial sampling:
  - Increased rate of precancer and cancer when endometrial sampling is added yearly
  - 66-100% of these lesions would be missed if ultrasound used alone
  - No data on whether lives will be saved or if women will undergo less treatment by participating in EC screening

Screening for Ovarian Cancer

- **Excellent evidence in the general population and in other high risk populations (*BRCA1/2* mutation carriers) that there is No Benefit of screening for OC with ultrasound and CA125**
- **Actual increase rate of complications secondary to investigating false positive test results**
- **These results likely due to the fact that:**
  - **Most present with advanced stage disease**
  - **No preclinical lesion identifiable with current screening methods**

Screening for Ovarian Cancer in Lynch Syndrome

- Is OC a different disease in LS?
  - Different histology
  - More present with early stage is there a longer preclinical stage
- Could there be a benefit in this population?
  - Lower prevalence of disease compared to BRCA1/2
  - Small # of women with LS
- Significant rate of interval cancers which may give false sense of security

Consensus Guidelines For Gynecologic Cancer Screening

- No evidence to support screening for EC however annual endometrial sampling is an option and often recommended
- May be circumstances where OC may be helpful but no evidence to support its benefit. Possible screening with transvaginal ultrasound and CA125

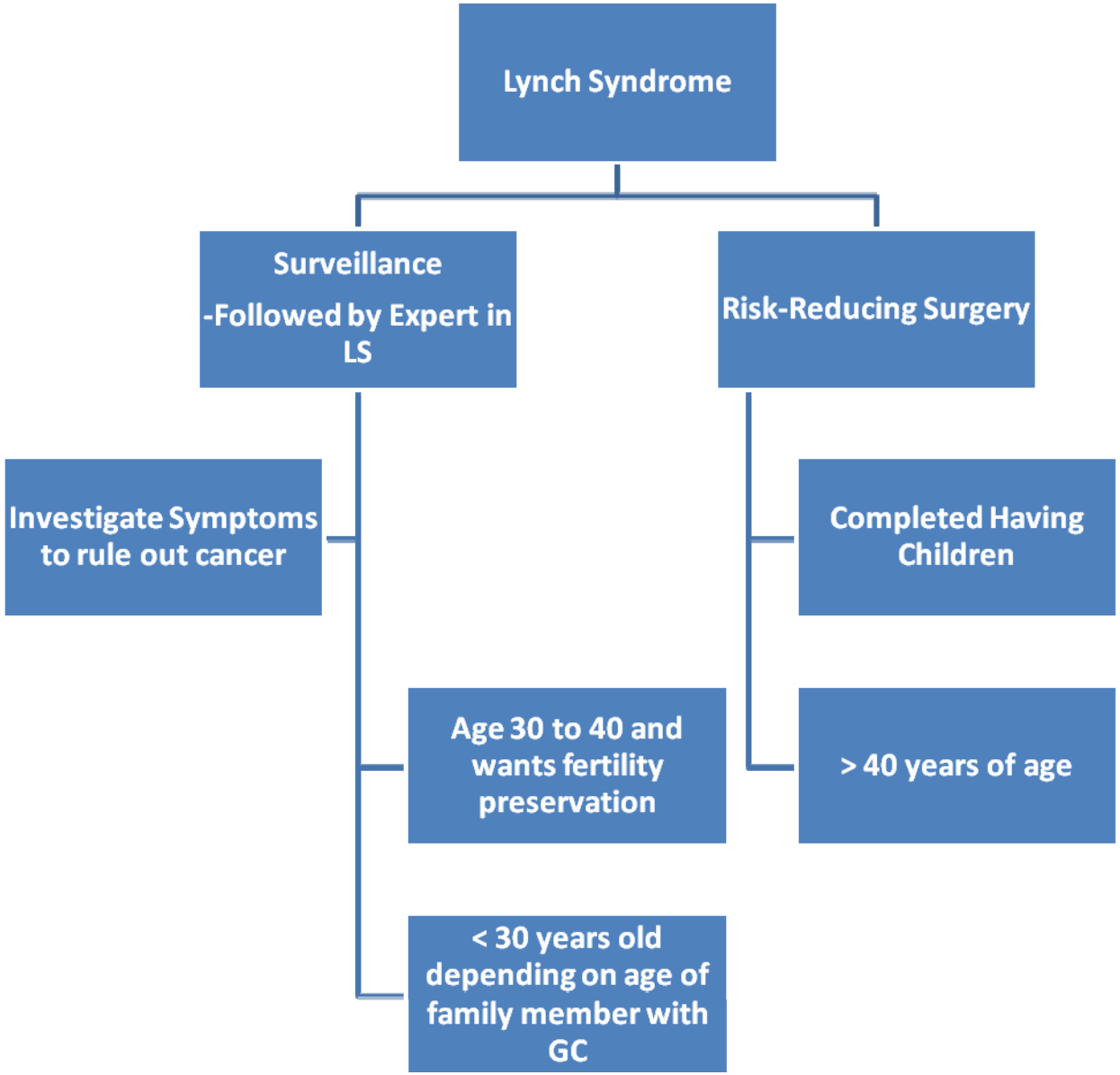
What Can Be Done to Prevent Gynecologic Cancer?

- Study that compared women who had risk-reducing surgery (removal ovaries and uterus) to those women who had not had surgery
- No cases of gynecologic cancer in those that had surgery
- 33% developed EC and 5% developed OC in the non-surgery group
- EC median age 46 years and OC median age 42 years

Risk-Reducing Surgery

- Strong recommendation that women undergo risk-reducing surgery when completed child-bearing
- Removal of uterus and ovaries by age 40 b/c cancer risk significantly increases after age 40
- Difficult to give recommendations based on specific mutation
- If no cancer history can replace hormones with estrogen until approximate age of natural menopause

Risk Reduction for Gynecologic Cancer



Conclusion

- All abnormal symptoms need to be investigated b/c of increased risk of EC/OC
- No documented benefit of routine surveillance for women with LS
- Good evidence that risk-reducing surgery (removal of ovaries and uterus) will prevent cancer
- Surveillance only as a temporary measure for those who have not completed child-bearing
- Hormone replacement can be given after risk-reducing surgery