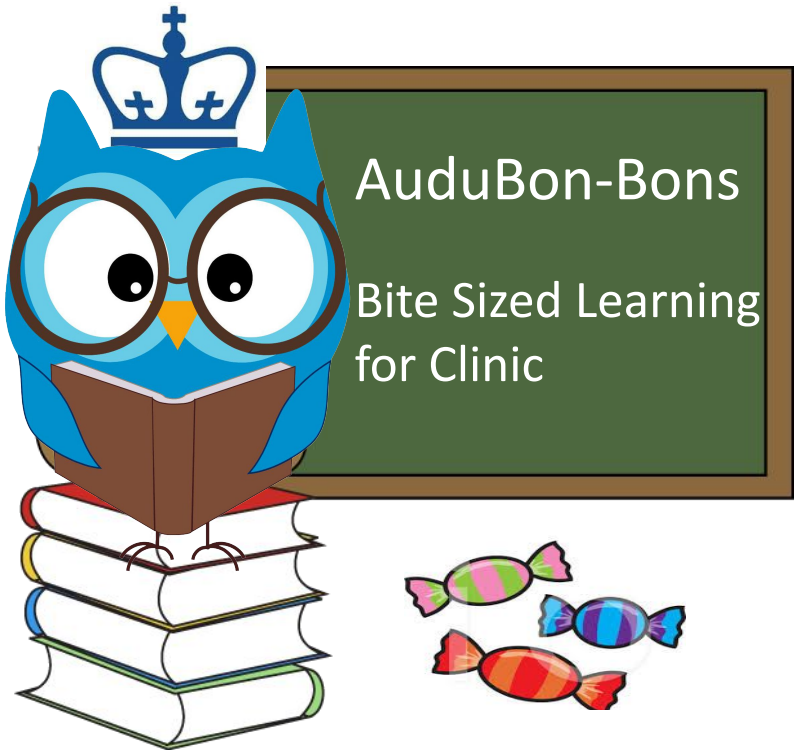
CANCER SYNDROMES: LYNCH SYNDROME



Week 5

Prepared by: **Stephanie Warsheski, MD**

Homework Assignment:

ACOG Practice Bulletin #147

Lynch Syndrome

LEARNING OBJECTIVES

- To review cancers associated with Lynch syndrome and their lifetime risk
- To be able to identify individuals at risk of Lynch syndrome through assessment of personal and family medical histories
- To feel comfortable counseling patients on screening and prevention strategies for at risk individuals in order to reduce morbidity and mortality

CASE VIGNETTE

- Ms. J.M., a 28 y.o. G0 woman presents to your office as a new patient for her annual well-woman exam.
  - She has no acute complaints.
  - She reports feelings of sadness and grief over the past few months due to the recent loss of her mother.

FOCUSED HISTORY

What elements of the patient's history are most relevant?

- OBHx: Nulliparous
- GYNHx: Regular menses. Denies h/o abnormal paps, STIs, fibroids, cysts. Reports 3 lifetime sexual partners. Not currently SA.
- PMHx/PSHX: Denies
- Meds: MVI
- Allergies: NKDA
- SocHx: Occasional ETOH. Denies use of tobacco or illicit drugs.
- **FamHx**: Mother deceased from endometrial cancer at 57 y.o., maternal grandmother deceased from glioblastoma at 48 y.o.

Box 1. Recommended Key Elements for Minimum Adequate Cancer Family History

Family history should be taken at diagnosis and updated periodically.

Key components should include information about the following:

- First-degree relatives: siblings, parents, children
- Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half-siblings
- Maternal and paternal sides
- Ashkenazi ancestry
- For each cancer case in the family, establish
  - Age at cancer diagnosis
  - Type of primary cancer

Modified with permission from Lu KH, Wood ME, Daniels M, Burke C, Ford J, Kauff ND, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. American Society of Clinical Oncology. J Clin Oncol 2014;32:833–40.

PERTINENT PHYSICAL EXAM FINDINGS

What elements of the patient's physical exam are most relevant?

- Vitals: BP 123/68, 145lbs, 5'4", BMI 24.9
- HEENT: No adenopathy, normal thyroid
- Breast: Symmetric, non-tender, no masses, no skin changes, no nipple changes or discharge, no LN
- Abd: Non-distended, soft, nontender
- Pelvic:
    - Vulva: NEFG, no lesions
    - Vagina: Pink, healthy mucosa, no discharge
    - Cervix: Nulliparous os, no lesions, no discharge, no CMT
    - Uterus: Small, AV, non-tender
    - Adnexa: No masses, non-tender

BACKGROUND

- Lynch syndrome was previously known as hereditary nonpolyposis colorectal cancer
- **Autosomal dominant** inherited cancer susceptibility syndrome
- Caused by **defects in the mismatch repair system**
  - Responsible for repairing single-base mismatches which occur during DNA replication
- Accounts for:
  - **Most cases of hereditary uterine and colon cancer**
  - **Second most common cause of inherited ovarian cancer**
- Population prevalence: 1 in 600 to 1 in 3,000 individuals

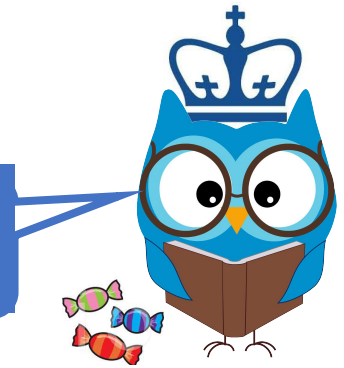
CANCERS ASSOCIATED WITH LYNCH SYNDROME

Table 1. Summary of Syndromes With Malignant Manifestations Associated With Breast and Ovarian Cancer

Syndrome	Breast Cancer	Ovarian Cancer	Endometrial Cancer	Colon Cancer	Other Types of Cancer
Hereditary breast and ovarian cancer	X	X			Pancreatic, prostate, and melanoma
Lynch		X	X	X	Gastric, ureteral, biliary, pancreatic, glioblastoma, renal pelvis
Li-Fraumeni	X			X	Sarcomas, brain, adrenocortical
Cowden	X		X	X	Benign mucocutaneous lesions, thyroid, gastrointestinal hamartomas
Peutz-Jeghers	X	X		X	Cervical adenoma malignum, gastrointestinal hamartomas, pancreatic, gastric, small bowel
Hereditary diffuse gastric cancer	X				Gastric, colorectal

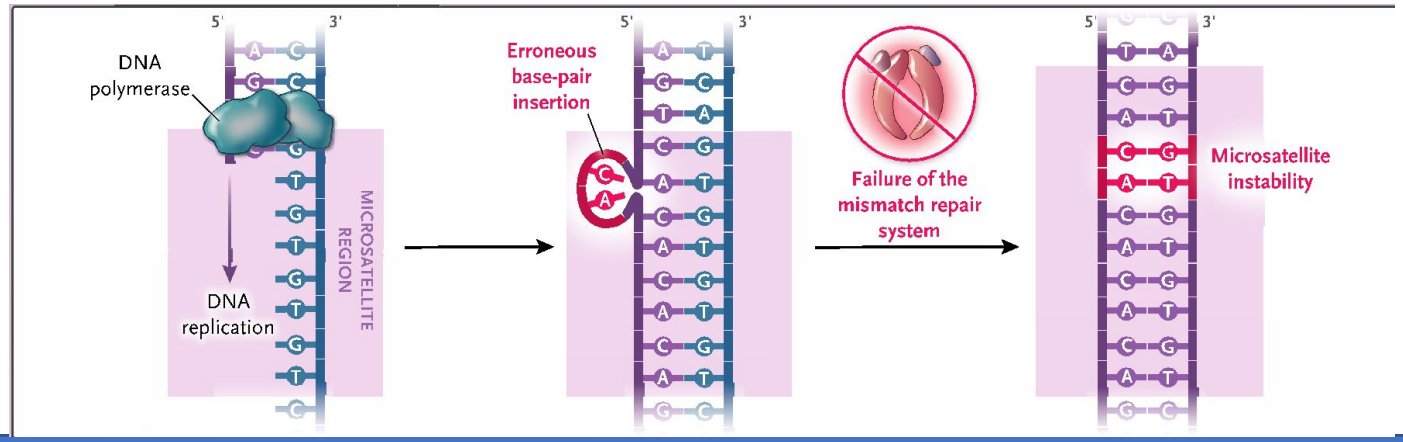
Data from National Comprehensive Cancer Network. Breast cancer: NCCN Evidence Blocks. Version 2.2019. NCCN Clinical Practice Guidelines in Oncology [after login]. For Washington [PA]: NCCN; 2019 *and* Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. Genet Med 2015;17:70–87.

The presence of Lynch syndrome increases the lifetime risk of colon cancer (52-82%), endometrial cancer (25-60%), and ovarian cancer (4-24%)



PATHOGENESIS

- Genetic instability caused by **defects in the mismatch repair (MMR) system poor repair of DNA replication errors**
  - Genetic instability is not limited to the coding region of genes, but affects the entire genome
  - The affected noncoding single nucleotide and dinucleotide repeats are called microsatellites microsatellite instability (MSI)
  - **Microsatellite instability is the reference-standard genetic feature of Lynch syndrome**
  - **Germ-line mutations of the MMR genes *MLH1, MSH2, MSH6,* and *PMS2* are diagnostic for Lynch syndrome**



DIAGNOSIS

- Ms. J.M. would like to know what her chances are of developing cancer sometime in her life. Should she be offered hereditary cancer risk assessment for Lynch syndrome?
  - **YES**. Referral to a genetic counselor is needed
  - Genetic risk assessment should be considered for:
    - Unaffected women who have a first-degree relative affected with endometrial or colorectal cancer diagnosed before age 60
    - Unaffected women with a pattern of repeated generations of Lynch syndrome-associated cancer, especially dxed at a young age (< 60y)

DIAGNOSIS

Table 1. Amsterdam II Criteria and Revised Bethesda Guidelines for Diagnosis of the Lynch Syndrome.

Amsterdam II criteria

1. Three or more relatives with histologically verified Lynch syndrome–associated cancer, one of whom is a first-degree relative of the other two*
2. Cancer involving at least two generations
3. One or more cancer cases diagnosed before 50 years of age

Revised Bethesda guidelines

1. Diagnosis of colorectal cancer or endometrial cancer in a patient younger than 50 years of age
2. Presence of synchronous colorectal cancers, metachronous colorectal cancers, or other Lynch syndrome–associated tumors, regardless of patient age
3. Diagnosis of colorectal cancer with a high frequency of microsatellite instability on the basis of histologic findings (Crohn's-like lymphocytic reaction, mucinous or signet-ring cell differentiation, or medullary growth pattern) in a patient younger than 60 years of age
4. Diagnosis of colorectal cancer in one or more first-degree relatives with a Lynch syndrome–related tumor, with one of the diagnoses occurring before 50 years of age
5. Diagnosis of colorectal cancer in two or more first- or second-degree relatives with Lynch syndrome–related tumors, regardless of patient age

* Lynch syndrome–associated tumors include cancers of the colon and rectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, and sebaceous glands, as well as keratoacanthomas.

A clinical diagnosis is suspected when a patient history and a family history fulfill the Amsterdam criteria. However, because only 50% of affected patients meet the Amsterdam criteria, the Bethesda guidelines were developed.

More recently, universal testing of all newly diagnosed colorectal cancers for deficient mismatch repair or microsatellite instability is recommended

EVALUATION

- Genetic risk assessment for Lynch syndrome includes:
  - Assessment of personal and family medical histories
  - ± tumor testing (using immunohistochemistry or MSI testing)
  - ± germline DNA testing

- Formal genetic risk counseling performed by someone with appropriate training and experience in cancer genetics and counseling is recommended.

EVALUATION

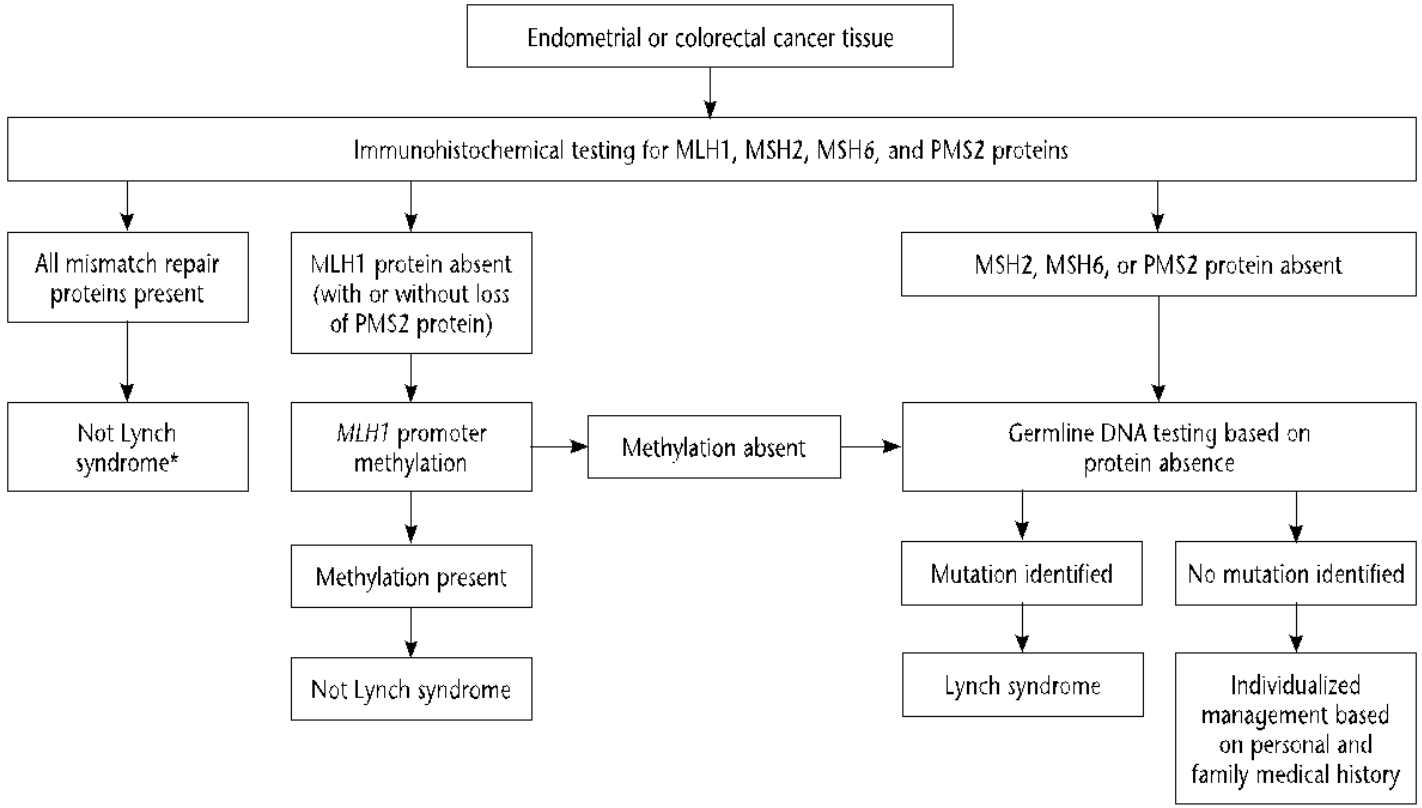


Fig. 1. Immunohistochemistry-based endometrial or colorectal tumor testing for mismatch repair gene expression to assess for the possibility of Lynch syndrome. ⇐

*The scenario in which the presence of all four mismatch repair proteins does not rule out Lynch syndrome is the relatively uncommon situation in which a deleterious mutation allows the production of a full-length but nonfunctional mismatch repair protein. Given this possibility, in the setting of a very high clinical suspicion of Lynch syndrome and normal immunohistochemical testing results, the tumor can be further evaluated by microsatellite instability testing.

MANAGEMENT – SCREENING AND SURVEILLANCE

- Ms. J.M. returns to your office after being diagnosed with Lynch syndrome. She would like to know what she can do during her life to help decrease her risk of complications of cancer.

Box 2. Screening and Surveillance Recommendations for Women With Lynch Syndrome

- Colonoscopy every 1–2 years, beginning at age 20–25 years, or 2–5 years before the earliest cancer diagnosis in the family, whichever is earlier
- Endometrial biopsy every 1–2 years, beginning at age 30–35 years
- Keeping a menstrual calendar and evaluating abnormal uterine bleeding

Int. J. Cancer: **120,** 821–824 (2006)

Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome

Laura Renkonen-Sinisalo[1], Ralf Bützow[2,3], Arto Leminen[3], Pentti Lehtovirta[3], Jukka-Pekka Mecklin[4] and Heikki J. Järvinen[1]*

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There is no consensus on ovarian cancer surveillance in women with Lynch syndrome.

MANAGEMENT – CHEMOPREVENTION

- Progestin-based contraception, including oral contraceptives, may be considered for chemoprevention of endometrial cancer in women with Lynch syndrome.
  - COCs can reduce endometrial cancer risk in the general population by 50%.
  - Progestin therapy is effective in treatment of endometrial hyperplasia and early endometrial cancer.
  - A short-term study using surrogate biomarkers in women with Lynch syndrome suggested that 150-mg depot medroxyprogesterone acetate as well as 30-micrograms ethinyl estradiol/0.3-mg norgestrel oral contraceptives demonstrated a decrease in endometrial proliferation.
- ASA 600mg daily for > 2 years may reduce the incidence of colorectal cancer.

MANAGEMENT – RISK-REDUCING SURGERY

- **Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option for women who have completed child bearing**
  - Should be discussed by early to mid-40's
    - Estimated **risk of endometrial cancer** by **age 40: 2 – 4%** and by **age 50: 8 – 17%**
    - Estimated **risk of ovarian cancer** by **age 40: 1 – 2%** and by **age 50: 3 – 7%**
  - **Risk reduction approaches 100%**
  - May be accomplished through vaginal or laparoscopic approaches
  - R/B/A of risk-reducing surgery, medical management of menopause and desire for future fertility can influence decision making.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

Kathleen M. Schmeler, M.D., Henry T. Lynch, M.D., Lee-may Chen, M.D., Mark F. Munsell, M.S., Pamela T. Soliman, M.D., Mary Beth Clark, M.S.W., Molly S. Daniels, M.S., Kristin G. White, B.S., Stephanie G. Boyd-Rogers, R.N., Peggy G. Conrad, M.S., Kathleen Y. Yang, M.D., Mary M. Rubin, Ph.D., Charlotte C. Sun, Dr.P.H., Brian M. Slomovitz, M.D., David M. Gershenson, M.D., and Karen H. Lu, M.D.

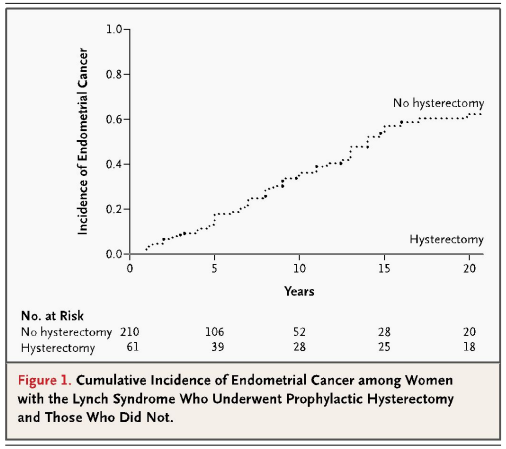

Figure 1. Cumulative Incidence of Endometrial Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Hysterectomy and Those Who Did Not.

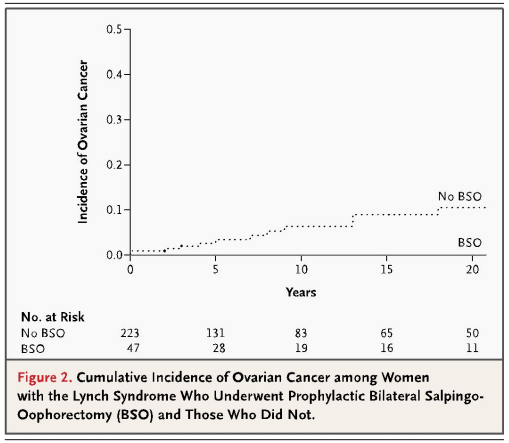

Figure 2. Cumulative Incidence of Ovarian Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Bilateral Salpingo-Oophorectomy (BSO) and Those Who Did Not.

SOCIAL DETERMINANTS OF HEALTH

- Despite similar rates of colorectal tumor analysis, minority patients are less likely to be recommended for genetic evaluation or to undergo germline testing for Lynch syndrome.
    - Negative predictive factors of a recommendation for genetic evaluation and genetic testing include:
        - African-American ethnicity
        - Older age
        - Advanced tumor stage
- These differences underscore the importance of provider recommendations, education and counseling in all patients regardless of race, age or disease severity.

EPIC .PHRASE

BBonLynchSyndrome

Description: Counseling for patients with Lynch syndrome

After a comprehensive personal and family history was obtained, the patient was deemed to be at increased risk for Lynch syndrome. She was referred for genetic counseling and testing. Testing confirmed diagnosis of Lynch syndrome. Cancers associated with Lynch syndrome were discussed including but not limited to the increased lifetime risk of colon cancer (52-82%), endometrial cancer (25-60%), and ovarian cancer (4-24%). She was then counseled on screening and prevention strategies in order to reduce morbidity and mortality. The following was recommended:

- Colonoscopy every 1 – 2 years, beginning at age 20 – 25 years, or 2 – 5 years before the earliest cancer diagnosis in the family, whichever is earlier
- Endometrial biopsy every 1 – 2 years, beginning at age 30 – 35 years
- Keeping a menstrual calendar for evaluation of abnormal uterine bleeding

Additionally, initiating of COCs and ASA for chemoprevention of endometrial and colorectal cancer, respectively, was discussed. Risk-reducing surgery with total hysterectomy and BSO was also discussed with the risk of both endometrial and ovarian cancers approaching 100%.

CODING AND BILLING

- Diagnostic Codes (ICD-10)
  - Z15.09 Genetic susceptibility to other malignant neoplasm

CODING AND BILLING – NEW PATIENT

HISTORY	EXAM	MEDICAL DIAGNOSIS MAKING	CODE	APPLICABLE GUIDELINES
Problem focused: - Chief complaint - HPI (1-3)	Problem focused: - 1 body system	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99201	- Personally provided - Primary care exception - Physicians at teaching hospitals
Expanded problem focused: - Chief complaint - HPI (1-3) - ROS (1-3)	Expanded problem focused: - Affected areas and others	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99202	- Personally provided - Primary care exception - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4) - ROS (2-9) - Past, family, social history (1)	Detailed: - 7 systems	Low: - Diagnosis: limited - Data: limited - Risk: low	99203	- Personally provided - Primary care exception - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Comprehensive: - 8 or more systems	Moderate: - Diagnosis: multiple - Data: moderate - Risk: moderate	99204	- Personally provided - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Comprehensive: - 8 or more systems	High: - Diagnosis: extended - Data: extended - Risk: high	99205	- Personally provided - Physicians at teaching hospitals

CODING AND BILLING – ESTABLISHED PATIENT

HISTORY	EXAM	MEDICAL DIAGNOSIS MAKING	CODE	APPLICABLE GUIDELINES
Expanded problem focused: - Chief complaint - HPI (1-3)	Problem focused: - 1 body system	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99212	- Personally provided - Primary care exception - Physicians at teaching hospitals
Expanded problem focused: - Chief complaint - HPI (1-3) - ROS (1)	Expanded problem focused: - Affected area and others	Low: - Diagnosis: limited - Data: limited - Risk: low	99213	- Personally provided - Primary care exception - Physicians at teaching hospitals
Detailed - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Detailed: - 7 systems	Moderate: - Diagnosis: multiple - Data: moderate - Risk: moderate	99214	- Personally provided - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (2)	Comprehensive: - 8 or more systems	High: - Diagnosis: extended - Data: extended - Risk: high	99215	- Personally provided - Physicians at teaching hospitals

EVIDENCE

- References

  - Cox et al. Lynch Syndrome: Genomics Update and Imaging Review. RadioGraphics 2018;38:483-499.
  - Hereditary cancer syndromes and risk assessment. ACOG Committee Opinion No. 793. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e143–9.
  - Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, et al. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res 2013;6:774–81.
  - Muller, C. et al. Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening. Clin Gastroenterol Hepatol. 2018 December ; 16(12): 1911–1918.
  - Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;124:1042–54.
  - Schmeler, K.M. et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261-9.
  - Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120:821–4.
  - Sinicrope, F.A. Lynch Syndrome-Associated Colorectal Cancer. N Engl J Med 2018;379:764-73.