Cancer Risks and Screening/Risk Reduction Recommendations for Individuals with Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, and EPCAM mutations)

- **Colorectal Cancer:**
  - **General population lifetime risk:** ~5%
  - **Lifetime risk for those with Lynch syndrome varies by gene**
    - MLH1 and MSH2: ~30-74%
    - MSH6: ~10-22%
    - PMS2: ~15-20%
  - **Increased risk of second primary colon cancer**
  - **Risk is higher for men than women**

  **Screening:**
  - MLH1 and MSH2: colonoscopy every 1-2 years starting at age 20-25 *
  - MSH6 and PMS2: colonoscopy every 1-2 years starting at age 25-30 *
  *Or 2-5 years younger than the youngest colorectal cancer in the family if diagnosed before age 25. However, this should be evaluated in the context of the individual’s personal and family history.

- **Risk reduction:**
  - Upon a diagnosis of colon cancer, consider the pros and cons of a more extensive resection (including total colectomy with ileorectal anastomosis) versus increased screening
  - **Preventive** colectomy (in the absence of a colon cancer diagnosis) is usually not recommended as screening with regular colonoscopies and removal of polyps is generally effective
  - Smoking and high body mass index (BMI) increase the risk of colorectal cancer; therefore, it is recommended that individuals refrain from smoking and maintain a healthy weight
  - There is some evidence to suggest that use of 600 mg of aspirin daily (2 adult aspirin per day) may reduce colorectal cancer risk; however, data are still limited and individual usage should be discussed in the context of the potential side effects

- **Gynecologic Cancer:**
  - **Endometrial (uterine) Cancer:**
    - **General population lifetime risk:** 2.7%
    - **Lifetime risk for those with Lynch syndrome varies by gene** *(risk also tends to increase significantly after starting menopause)*
      - MLH1 and MSH2: ~14-54%
      - MSH6: ~17-71%
      - PMS2: ~15%
Ovarian Cancer:
- General population life time risk: ~1.5%
- Lifetime risk for those with Lynch syndrome: ~4-20%
- Risk varies by gene with the order from highest to lowest risk being: MLH1 or MSH2 > MSH6 > PMS2

Screening:
- The efficacy of screening options for women with Lynch syndrome is unclear at this time. Therefore, we recommend you speak to your gynecologist to become better informed about the symptoms of endometrial and ovarian cancer (e.g. irregular vaginal bleeding, postmenopausal vaginal bleeding, pelvic pain, pressure, or bloating, trouble urinating or increased urination, pain during intercourse) and seek prompt medical care for any symptoms.
- Options for screening include: annual transvaginal ultrasound, endometrial biopsy, and CA125 tumor marker blood test starting by age 30-35 (or 5-10 years younger than the youngest diagnosis in the family, whichever is earlier). In premenopausal women, this screening should preferably take place between day 1-10 of the menstrual cycle.

Risk Reduction:
- Prophylactic total hysterectomy and bilateral salpingo-oophorectomy (removal of the uterus, ovaries, and fallopian tubes) is recommended at menopause or earlier based on family history. This has been shown to be highly effective.
- Oral contraceptives may be used for risk reduction although the efficacy is not known specifically among women with Lynch syndrome.

***Genetic counseling is particularly important as the cancer risks can vary greatly between the several genes associated with Lynch syndrome; one’s family history and environmental factors should also be taken into account when making a risk assessment and providing recommendations for management***

Data regarding the efficacy of screening for other cancers in individuals with Lynch syndrome are very limited and thus there are few standard screening recommendations for these cancers. In addition, the lifetime risks for many of these other cancers are relatively low, making it difficult to justify costly and/or invasive screening. The risks for other cancers may also be lower in individuals with a MSH6 or PMS2 mutation; however, data are limited and it is not possible to make gene-specific screening recommendations for other cancers at this time. Therefore, the benefits, limitations, risks and costs of the screening options must be weighed carefully for each individual.

**The general population lifetime risk for the following cancers is ~1.5% or less**
**Upper Gastrointestinal Tract (including stomach and small bowel/duodenum):**

- Lifetime risk of stomach cancer (intestinal type adenocarcinoma) is ~6-13%; risks are higher in countries with a higher background incidence of stomach cancer including Korea and Japan
- Lifetime risk of small bowel (small intestinal) cancer (mainly in duodenum and jejunum) is ~1-7%
- Baseline gastric biopsy to evaluate for *H. pylori* infection and pursue appropriate treatment if identified
- Upper endoscopy at the time of colonoscopy (with extended duodenoscopy to the distal duodenum or into the jejunum) and removal of polyps every 2-5 years beginning by age 30-35 (particularly in individuals with family members who have Lynch syndrome and a history of stomach cancer)
- Capsule endoscopy for small bowel screening every 2-3 years beginning by age 30-35, particularly in individuals with unexplained abdominal complaints or iron deficiency anemia, or in individuals with family members who have Lynch syndrome and history of small bowel cancer

**Urinary Tract (transitional cell carcinomas of the ureter and renal pelvis):**

- Lifetime risk is ~4-12%
- Risk is greater in men vs. women
- Risk varies by gene with risk higher in MSH2 than MLH1
- Annual urinalysis with cytology beginning at age 25-30; more extensive screening can be recommended to individuals with family members who have Lynch syndrome and a history of urinary tract cancers

**Pancreas and Hepatobiliary Tract (gallbladder and bile duct):**

- Pancreatic cancer lifetime risk is ~ 10%
- Hepatobiliary tract cancer lifetime risk is ~1.4-4%
- No current screening recommendations at this time (if any of the available screening options are being considered, endoscopic ultrasound [EUS] would likely be preferred as it can be used to visualize the hepatobiliary tract in addition to the pancreas)

**Brain/central nervous system:**

- Lifetime risk is ~1-4%
- Annual physical examination
- No additional screening recommendations have been made at this time
- **Sebaceous skin tumors and cancers:**

  - Increased risk (~1-9% lifetime risk) for sebaceous skin tumors and cancers including sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthomas
  - The combination of sebaceous skin tumors and internal cancers is sometimes referred to as Muir-Torre syndrome
  - Recent studies suggest that the rate of these tumors in individuals with Lynch syndrome is higher than previously recognized
  - Annual clinical skin examination by a dermatologist has been suggested for all individuals with Lynch syndrome

- Rarely, an individual inherits two mutations in the same Lynch syndrome gene, one from each parent. This causes a different hereditary syndrome known as Constitutional Mismatch Repair Deficiency (CMMR-D). Children with CMMR-D are at increased risk to develop brain tumors, leukemia and lymphoma, colon polyps, uterine and ovarian cancer and other rare pediatric cancers. For this reason individuals who are found to have a mutation in a gene associated with Lynch syndrome and are of reproductive age may wish to consider having their partner tested for mutations in that specific Lynch syndrome-associated gene. If both parents carry a mutation in the same Lynch syndrome-associated gene, there is a 25% risk that their children will have CMMR-D.
References:


