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# Efficacy in Screening Patients for Lynch Syndrome

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## Abstract

Lynch syndrome is an autosomal dominant syndrome caused by an inherited germline mutation of the MMR proteins. A mutation of any of the MMR proteins, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* increases the risk of developing cancer, specifically colorectal and endometrial cancer. Approximately 3% of colorectal cancers are associated with Lynch Syndrome (LS). Early identification of a patient's hereditary cancer risk offers the best outcome. To aid clinicians in the identification of a carrier of LS clinical guidelines and risk prediction models are used. In this analysis the Amsterdam II criteria and Revised Bethesda guidelines are compared to the more recent prediction models, PREMM, MMRpro and MMRpredict to identify if further tumor testing or germline sequences should be considered. A meta-analysis comparing clinical criteria to the prediction models produced results identifying the prediction models with both a specificity and sensitivity of >90% of predicting MMR protein mutations (Win, 2013). The performance of each model compared to Amsterdam or Bethesda guidelines was found to exceed the clinical criteria's ability to discriminate LS carriers from noncarriers (Katrinos, Balmana, & Syngal, 2013).

## What is Lynch Syndrome?

- Also known as hereditary nonpolyposis colorectal cancer (HNPCC)
- Malignant tumors associated with Lynch Syndrome progress more rapidly through stages and are commonly diagnosed at an earlier age.
- Cancer most commonly associated with LS is colorectal and endometrial.
- Affected individuals are also at an increased risk of developing other cancers: stomach, ovarian, biliary, and renal cancers.
- LS carcinomas are characterized by a progressive accumulation of genetic damage resulting in injury.
- Injury is detected through evidence of short tandem repeats of DNA, normally these should be of equal length, and referred to as microsatellites
- Microsatellite instability (MSI) refers to changes in 2 or more of the 5 microsatellite markers. MSI alone lacks specificity (limited screening tool)
- Immunohistochemistry (IHC), screens for mismatch repair proteins, identifying, *MLH1*, *MSH2*, *MSH6* and *PMS2*.
- An abnormal IHC implies at least one of the proteins is not expressed.
- IHC is an alternative screening tool, can be used in combination with MSI.

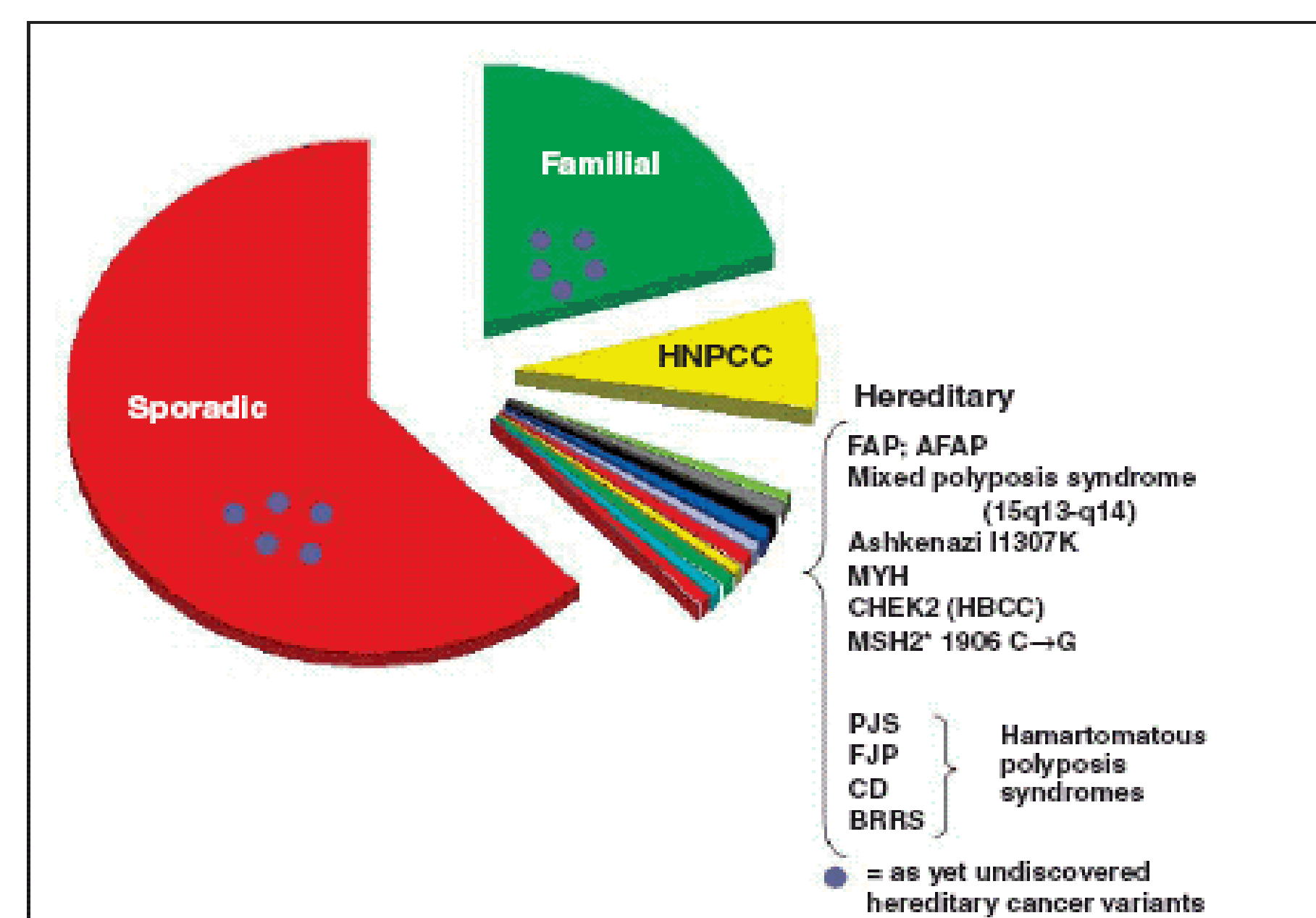
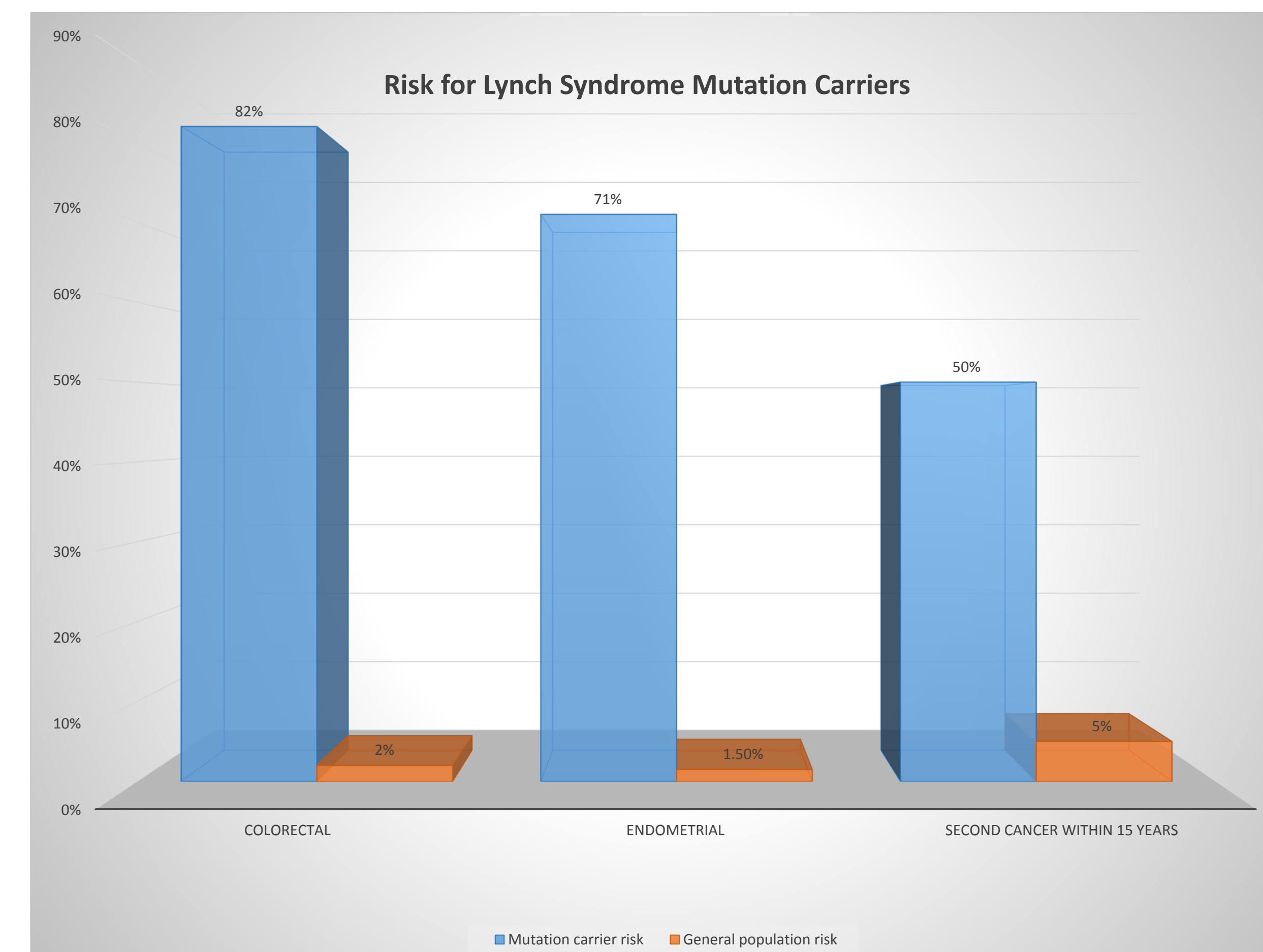


Figure 1: Colorectal Cancer and Heredity—Relative numbers of colorectal cancer cases that are considered sporadic, familial, or due to a recognized hereditary cancer syndrome. AFAP = attenuated familial adenomatous polyposis; BRRS = Bannayan-Ruvalcaba-Riley syndrome; CD = Cowden's disease; FAP = familial adenomatous polyposis; FJP = familial juvenile polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; PJS = Peutz-Jeghers syndrome. Reprinted, with permission, from Lynch et al.[2]



## Research Question

Does screening high risk patients with prediction models versus Amsterdam II or Revised Bethesda guidelines have a better probability of identifying Lynch Syndrome?

## Statement of Problem

- No standardized approach to screening patients for LS to determine if germline testing is appropriate.
- Germline testing is required to identify mutation carriers.
- Universal testing of all colorectal cancer is no longer done due to cost and low occurrence.
- When ever possible the 'proband' should be tested, and the tumor when available.

## Literature Review

- Clinical suspicion of LS was originally based on Amsterdam criteria, but was too stringent and only identifying 60% of patients. They were revised in 1998, increasing sensitivity to 80%.
- Bethesda guidelines were developed by the National Cancer Institute in the advent of molecular testing, revised in 2004.
- Revised Bethesda guidelines added indicators improving sensitivity, CI 86-92%, but specificity 49-58%.
- Prediction models were found to be sensitive and specific at >90% of predicting MMR gene mutation carriers.
- Kidambi et al. conducted a 6 year retrospective study that screened patients 'selectively'. CRC less than 60 years old, suggestive MSI histology or previous LS cancer. Selective screening was similar to the Revised Bethesda guidelines. These results were compared to that of 'universally' screening all colorectal cancers (2014).
- Amsterdam criteria and components of the Revised Bethesda guidelines are quite complex and are not designed to determine the likelihood of an individual carrying a genetic mutation (Katrinos, Balmana, & Syngal, 2013)
- Win et al., conducted a meta-analysis reviewing 12 criteria/guidelines, including the Amsterdam and Bethesda guidelines, and prediction models (2013)
- The values from the analysis for MMRpro was 0.80 with a 95% CI, MMRpredict was 0.81 with a 95% CI, and PREMM was 0.84 with a 95% CI (Win, 2013).
- Katrinos, et al. (2013) conducted a study comparing the PREMM model with MSI and IHC tumor testing. 1,868 unrelated patients with colorectal cancer were recruited through the Colon Cancer Family Registry. A univariate analysis was then conducted.
- Journal National Cancer Institute reported a study that was conducted to compare cost effectiveness of the two screening strategies, clinical criteria compared to that of prediction models, and all were followed by either IHC then germline testing or direct germline testing (Barzi, 2015).
- Predictive models in initial screening has comparable sensitivity to that of universal screening of all CRC with IHC, further stating that prediction models are effective in evaluating hereditary risk of Lynch syndrome and should be considered as a quality-of-care measure (Barzi, 2015).

## Discussion

- ❖ Katrinos, et al.(2013), indicated that PREMM, had better results of distinguishing mutation carriers from non-carriers in the entire cohort. Similarly, according to Katrinos, Balmana & Syngal (2013), the PREMM model selected 20% more individuals than the Revised Bethesda guidelines. With high-quality information a negative screening could eliminate the need to refer for molecular or genetic testing for Lynch Syndrome (Barzi, 2015).

There is ample evidence that each of the models have superior performance characteristics in terms of sensitivity, specificity, positive and negative predictive values to support the use of models over the existing clinical guidelines for the diagnosis and evaluation for Lynch syndrome. (Katrinos, Balmana, & Syngal, 2013, p. 7-8)

## Applicability to Clinical Practice

- “Red Flags” for patients who do not have cancer
- ✓ An individual or family history of the following:
  - ✓ 2 or more relatives with a Lynch syndrome (LS) cancer, one before the age of 50
  - ✓ 3 or more relatives with a LS cancer at any age.
  - ✓ A previously identified LS mutation in the family.
- ✓ Prediction models are indicated when the:
  - ✓ individual does not have colorectal cancer (CRC)
  - ✓ individual is without a family member with CRC or the family is unwilling to have tumor tested.

In clinical practice, a thorough personal and family history will remain clinician's best approach to screening for a hereditary cancer family risk. (Katrinos, Balmana & Synga 2013)

- ✓ Patients with a strong history suggestive of LS can be screened in office with use of the PREMM model.
- ✓ PREMM model prediction score can aid providers in guiding patients care.
- ✓ PREMM model can be utilized at <http://dana-farber.org/premm>
- ✓ A negative result on a prediction model could eliminate the need to refer for genetic counseling for germline sequencing.
- ✓ If the PREMM score is >5% the patient should be referred to genetic counseling.

- Patients identified with Lynch Syndrome mutation
  - ✓ Colonoscopy at age 20-25 years or 2-5 years earliest colon cancer if diagnosed <25 years of age.
  - ✓ Repeat colonoscopy every 1-2 years
  - ✓ Prophylactic hysterectomy and bilateral salpingo-oophorectomy for women who have completed childbearing.
  - ✓ Any dysfunctional uterine bleeding warrants work-up

## References

- Barzi, A., Sadeghi, S., Kattan, M., Meropol, N. (2015). Comparative effectiveness of screening strategies lynch syndrome. *Journal of National Cancer Institute*, 107(4). doi:10.1093/jnci/djv005
- Katrinos, F., Balmana, J., Syngal, S. (2013). Prediction models in Lynch syndrome. *Fam Cancer*, 12(2): 217-228. doi:10.1007/s10689-013-9632-0.
- Katrinos, F., et al. (2013). Comparison of the clinical prediction model PREMM and molecular testing for systematic identification of lynch syndrome in colorectal cancer. *Gut*, 62(2): 272-279. doi:10.1136/gutjnl-2011-301265
- Kidambi, T., Blanco, A., Myers, M. Conrad, P., Loranger, K., Terdiman, J. (2015) Selective versus universal screening for lynch syndrome: A six-year clinical experience. *Digestive Disease Science*, 60. 2463-2469. doi:10.1007/s10620-014-3234-z
- Win, A., MacInnis, R., Dowty, J., Jenkins, M. (2016). Criteria and prediction models for mismatch repair gene mutations: a review. *Journal of Medical Genetics*, 50: 785-793. doi.org/10.1136