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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, MMPreps, and MMPrepnext 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 gene mutation carriers. The performance of each model compared to Amsterdam and 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 (HNPPC)
- 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

Risk for Lynch Syndrome Mutation Carriers

Discussion

- Kantinos, et al. (2013), indicated that PREMM, led better results of distinguishing mutation carriers from non-carriers in the entire cohort. Similarly, according to Kantinos, Balmana, & Syngal (2013), the PREMM model selected 20% more individuals than the Revised Bethesda guidelines. With high-quality information a negative screening would 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 the models over the existing clinical guidelines for the diagnosis and evaluation for Lynch syndrome. (Katrinos, Balmana, & Syngal, 2013, p. 7-8)

References


Literature Review

- Clinical suspicion of LS was originally based on Amsterdam criteria, but was too stringent and only identifying 40% of patients. They were revised in 1998, increasing sensitivity to 80%. Bartholome 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 66-87%, but specifically 49-50%.
- Prediction models were found to be sensitive and specific at >90% of predicting MMR gene mutation carriers.
- Kulamb et al. conducted a 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 MMPreps was 0.81 with a 95% CI, MMPrep at 0.81 with a 95% CI, and PREMM was 0.84 with a 95% CI (Win, 2013).
- Kantinos et al. (2013) conducted a study comparing the PREMM model with MSI and IHC tumor testing. 1,686 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 the prediction models with both a specificity and sensitivity of >90% of predicting MMR gene mutation carriers.

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, & Syngal 2013)