FORCE
Facing Hereditary Cancer EMPOWERED

USPSTF New Topic Nomination

Submitted February 3, 2021

Topic Details: New Preventive Service Topic You Are Nominating

Lynch Syndrome-Related Cancers: Risk Assessment, Genetic Counseling, and Genetic Testing

Rationale for Topic: What category or categories does this service fall under?

Counseling
Screening

Primary Care Relevance: The preventive service must be provided in the primary care setting or referable from a primary care setting.

Referable from the Primary Care Setting

Public Health Impact (max 449 words)

Potentially harmful mutations of the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2 and EPCAM) are associated with increased risk of colorectal, endometrial, ovarian, gastric and other cancers[1]. Colorectal cancer is the third most common cancer and the second leading cause of cancer death[2]. In the general population, Lynch syndrome mutations occur in an estimated one in 279 people (or over 1 million Americans) and account for 3-5% of colorectal and endometrial cancer cases[3]. An individual's risk of colorectal cancer increases if they have a clinically significant mutation in one of the Lynch syndrome genes. Mutations in Lynch syndrome genes increase colorectal cancer risk to 10-61% by age 70 years[4-12] and endometrial cancer risk to 13-57%[5-10,12]. There are at least three validated screening tools to identify unaffected individuals at risk for Lynch syndrome based on their family history: Amsterdam II criteria[1,13], PREMM5[14] and the Colorectal Risk Assessment Tool[15]. The Amsterdam criteria are very sensitive in detecting Lynch syndrome but not very specific and are based on family history criteria known as the 3-2-1 rule; three cases of Lynch syndrome-associated cancers in at least two generations with one case diagnosed under age 50 and one case being a first-degree relative of the other two. The PREMM5 model is easy-to-use and available online at https://premm.dfci.harvard.edu. It considers first- and second-degree family history of colorectal, endometrial and other Lynch syndrome-associated cancers along with the earliest age of diagnosis to provide a likelihood percentage that an individual has a Lynch syndrome gene mutation. Anyone with $\geq$2.5% risk for having a mutation warrants referral to cancer genetics. The Colorectal Risk Assessment Tool, endorsed by the U.S. Multi-Society Task Force on Colorectal Cancer, includes four simple yes/no questions about family history to determine which patients should be referred for genetic counseling and consideration of genetic testing. With the new draft USPSTF colorectal cancer

screening guidelines for the general population recommending that screening begin at age 45 and repeat every 10 years for those at average risk, it is important to help primary care physicians identify high-risk patients who may need earlier, more frequent screening. A USPSTF recommendation that guides identification of patients at high risk for colorectal cancer based on family history and referral to genetic counseling would help fill this gap. With a prevalence of one in 279 individuals, Lynch syndrome mutations are more common than BRCA mutations so this would supplement the USPSTF BRCA-Related Cancer recommendation, facilitating the identification of more individuals at increased risk of cancer due to heredity and enabling them to adjust their cancer screening regimen as appropriate.

Potential Impact (max 120 words)

Diagnosis of Lynch syndrome (LS) in an asymptomatic individual allows participation in potentially life-saving cancer screening and prevention options. Surveillance with colonoscopy may reduce colorectal cancer incidence by over 65% among individuals with LS and eliminates deaths due to colorectal cancer[16]. Colonoscopy is recommended every 1-2 years beginning at age 20-25 (MLH1, MSH2, EPCAM) or 30-35 (MSH6, PMS2)[17]. LS carriers taking aspirin had reduced colorectal cancer risk (HR=.65, compared to placebo), while participants without an LS mutation did not[18]. Research shows that risk-reducing hysterectomy and bilateral salpingo-oophorectomy reduce risk for endometrial and ovarian cancer among women with LS[19]. Knowledge of a LS mutation enables cascade screening, potentially identifying additional family members who may benefit from awareness of increased cancer risk.

Supporting Documentation

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4. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J Natl Cancer Inst.* 2010;102(3):193-201.
5. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* 2011;305(22):2304-2310.
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13. Vasen H, Watson P, Mecklin J-P, Lynch H. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology.* 1999;116(6):1453-1456.
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15. Kastrinos F, Allen JI, Stockwell DH, et al. Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. *Am J Gastroenterol.* 2009;104(6):1508-1518.
16. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* 2000;118(5):829-834.
17. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). 2020 National Comprehensive Cancer Network, Inc.
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