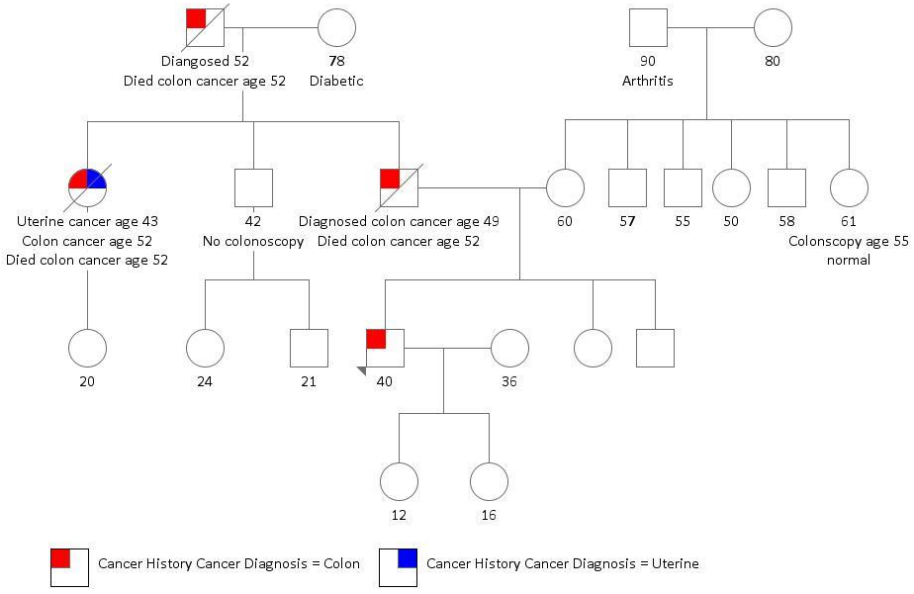
I. **Specialty/Professional Society**: National Cancer Institute
II. **Type of Use Case**: Family History
III. **Title**: Utilizing family history to identify Lynch Syndrome

Key Takeaways

- Recording a cancer family history is important to identify families with predisposition to cancer and guide an efficient, cost-effective genetic testing strategy.
- Lynch syndrome is an important cancer predisposition syndrome responsible for a significant proportion of cases of colorectal and endometrial cancers. Identification of a patient and family with Lynch syndrome allows the application of effective surveillance and preventive interventions.
- If a specific mutation has been identified in a family, then cascade testing of at risk family members should be restricted to the known mutation.

IV. **Clinical Scenario**: A 40 year old white male of Northern European ancestry on both the maternal and paternal lineage received a screening colonoscopy recommended by his primary care physician based a single first degree relative diagnosed with colon cancer before the age of 50. The colonoscopy identified a 20 mm elevated, nodular lesion in the descending colon that was biopsied. No polyps were seen. Diagnostic evaluation revealed a Stage 1 adenocarcinoma. He was referred to an oncologist for staging and treatment options. Per the American Society of Clinical Oncology guidelines, a cancer family history was obtained on all maternal and paternal first- and second-degree relatives recording age at cancer diagnosis, type of primary cancer and ethnicity[1]. His father was diagnosed with colon cancer at age 49 and died of the disease at age 52; he had a paternal aunt with endometrial cancer at age 43 and colon cancer at age 52 who died shortly after, and his paternal grandfather with colon cancer diagnosed at age 52 who died of the disease at age 53. Polyposis was not reported in affected relatives. There are no other family members with a cancer history. He reported no prior history of genetic testing in the family.

V. **Relevant Genomic Information**: The 3-generation pedigree reveals that the patient meets the Amsterdam II[2] criteria to make a clinical diagnosis of Lynch syndrome (Hereditary non-polyposis colorectal cancer syndrome). He also meets the Revised Bethesda Guidelines[3] for testing colorectal tumors for microsatellite instability (MSI).



Amsterdam Criteria II: As indicated in the pedigree there are least three affected relatives with an HNPCC-associated cancer (in this case colorectal and endometrial cancer); at least one is a first-degree relative of the other two; at least two successive generations are affected; at least one of the relatives with HNPCC-associated cancer diagnosed at age <50 years; and familial adenomatous polyposis coli has been excluded.

Revised Bethesda Guidelines: The patient is less than age 50 at CRC diagnosis, thereby meeting the Bethesda guidelines. He additionally meets the guideline by being diagnosed with colorectal cancer and having one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group Recommendations: Microsatellite instability (MSI) or immunohistochemical (IHC) testing of tumor tissue in all newly diagnosed patients with colorectal cancer (irrespective of age of diagnosis) may improve clinical outcomes for patients and their relatives through identification and removal of polyps prior to malignant transformation.

Given the high cost and complexity of germline testing, a step-wise approach to detect Lynch syndrome was employed[4]. His tumor underwent pre-screening with microsatellite instability (MSI) analysis demonstrating a high level of instability (MSI-H) phenotype. This instability indicated a failure of the DNA mismatch repair system to correct errors that are introduced during normal DNA replication. Tumor testing with DNA immunohistochemistry (IHC) demonstrated a loss of expression for the MSH2 protein, which is coded for by the *MSH2* gene, one of four DNA mismatch repair (MMR) genes implicated in Lynch syndrome.

VI. **Recommended Clinical Action**: Based on the MSI and IHC testing identifying a loss of MSH2, the decision was made to refer the patient for genetic counseling and molecular genetic testing. He underwent genetic counseling and after obtaining consent, had testing of the *MSH2* gene. He was found carry a known pathogenic mutation confirming the diagnosis of Lynch syndrome. With the assistance of a genetic counselor, the patient notified family members of the results and is undergoing management of the disease.

VII. **Suggested Practice-based Learning Activities:** Review up to 10 consecutive charts of patients with a new diagnosis of colorectal cancer to see if a cancer family history in paternal and maternal relatives extending to first- and second-degree relatives with primary cancer type and age of diagnosis was obtained and documented.

- If yes, assess if any of the family histories met the Amsterdam II or Revised Bethesda Guidelines. If this was done, review to see if appropriate follow-up was recommended and documented. If not done, use the criteria to see if a family history meets criteria necessitating follow-up
- If no, develop a process that insures that a family history is obtained, analyzed and documented for all patients newly diagnosed with colorectal cancer consistent with the published guidelines[1].

The same activity can be applied to women newly diagnosed with endometrial cancer, the second most common Lynch syndrome-associated tumor. There are guidelines published by the Society for Gynecologic Oncology[5].

VIII. **Family Implications**: Once a positive Lynch syndrome diagnosis has been identified, it is essential to complete cascade familial mutation (single-site) testing of first-degree relatives who

have a 50% probability of being a carrier of the mutation identified in the patient. At the present time because of privacy and confidentiality considerations it is recommended that the patient contact first-degree relatives, inform them of the risk and recommend they contact a genetic professional. Sequencing of the entire gene is not indicated since a familial mutation has been identified. After meeting with the genetic counselor, the proband's brother would like testing but does not have health insurance and the proband's sister has refused testing. A number of genetic testing laboratories have financial assistance programs for patients without insurance or those underinsured and various resources are available to provide free or low cost colonoscopies in those found to have Lynch syndrome. When a family member refuses testing, discussions about cancer screening as if they have Lynch syndrome should occur and be followed. Providing family members with opportunity to ask questions in the future allows time to consider their options and for them to change their mind. Should the sister have children, they should all be offered genetic testing once they become adults. Family members testing positive for mutations or alterations in MMR genes, *MLH1, MSH2, MSH6* and *PMS2*, should undergo routine colorectal cancer screening per national guidelines[6]. Female carriers should consult with their gynecologist and schedule annual gynecological surveillance screenings with a consideration of prophylactic surgery[8].

If testing for the familial mutation is negative, the patient should be counseled that their risk for developing colorectal cancer is the same as the general population risk and that screening should follow guidelines for the general population.

IX. **Supporting Evidence**: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP)[1] working group at the Center for Disease Control (CDC) has developed recommendations, and the National Comprehensive Cancer Network (NCCN)[6] Colon Cancer Panel has developed national guidelines on Lynch syndrome screening. Increasing evidence has led to EGAPP recommendations to offer genetic testing to all those newly diagnosed with colorectal or endometrial cancer (universal screening), due to the poor sensitivity of the Amsterdam and Bethesda diagnostic criteria which only identifies about half of Lynch syndrome patients due to their dependence on a strong family history of diagnosed cancer. The NCCN guidelines recommend 3 Lynch syndrome screening approaches: 1) all CRC patients; 2) CRC patients diagnosed <70 years and those 70 years and above who meet Bethesda guidelines 3) All endometrial cancer patients age 50 or below[6]. The US Multi-Society Task Force on Colorectal Cancer issued a guideline on the Genetic Evaluation and Management of Lynch Syndrome in July of 2014[7]. Guidelines for patients diagnosed with endometrial cancer are published by the Society for Gynecologic Oncology[5].

X. **References and Resources**

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