Review Article

The role of Creighton University's hereditary cancer center

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Abstract: Hereditary predisposition is a significant issue in gastrointestinal cancer. The most common hereditary colorectal cancer (CRC) syndrome is Lynch syndrome (LS), which we use as a model in this paper. A major problem is the identification and education of individuals at increased cancer risk due to a hereditary syndrome in their family. Extending the reach of care to a proband's first- and second-degree and even more distant relatives is a challenge. A dedicated hereditary cancer center (HCC) is in the position to aid in this effort across multiple hereditary cancer syndromes.

Keywords: Hereditary cancer; cancer genetics; familial cancer; Lynch syndrome (LS)

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Introduction

Creighton University's hereditary cancer center (HCC) registry is focused upon the collection and documentation of hereditary cancer families and subsequently identifying and educating patients at high hereditary cancer risk and/or those already affected with cancer regarding their cancer risk based on their position in the family pedigree and/or their genetic mutation status.

We will be using Lynch syndrome (LS) as a model, as it is the most common hereditary colorectal cancer (CRC) syndrome, accounting for 3-5% of the total number of CRC cases (1,2), making the annual estimate for LS-associated CRC in the United States 4,000-6,000, since the estimated CRC in the U.S. for 2015 is 132,700 (3). Those relatives who harbor a deleterious LS mutation can have a lifetime CRC risk of at least 74% (4). Women with LS mutations are at 40-60% lifetime risk of endometrial cancer, with approximately 2% of all endometrial cancer being LS-associated (5). Predisposition also exists for a variety of other cancers, including that of the ovary, stomach, small bowel, pancreato-biliary, upper urinary epithelial tract (uroepithelial), breast, prostate, adrenal cortical, and Muir-Torre syndrome spectrum of skin tumors (sebaceous adenomas, sebaceous carcinomas, keratoacanthomas), as well as brain (glioblastoma) in Turcot's syndrome (See *Table 1*).

Other gastrointestinal cancers with significant hereditary components are pancreatic cancer and diffuse gastric cancer. See *Table 2* for other hereditary CRC syndromes.

Collection of detailed and extended family histories is a core function of the HCC registry, accurately documenting the relationships of family members, cancer diagnoses with histological features, age(s) of cancer onset, surveillance and preventive surgical measures, and genetic test results. Accurate documentation of relationships of family members allows for risk assessment calculations for each bloodline family member based upon pedigree position as well as genetic risk based on individual genetic test results. The ability to quickly and accurately calculate pedigree and genetic risk assessments for all bloodline relatives in the family provides the opportunity to inform and educate family members about their cancer risk and recommend personalized screening/prevention plans. In addition, researchers have the ability to quickly identify eligible subjects for a wide variety of research projects. The HCC

Table 1 Cardinal features of Lynch syndrome

Family pedigree shows autosomal dominant inheritance pattern for syndrome cancers.
Proximal (right-sided) colonic cancer predilection:
• 70-85% of Lynch syndrome CRCs are proximal to the splenic flexure.
Earlier average age of CRC onset than in the general population:
• Average age of 45 years in Lynch syndrome *vs*. 69 years in the general population.
Accelerated carcinogenesis, i.e., shorter time for a tiny adenoma to develop into a carcinoma:
• Within 2-3 years in Lynch syndrome *vs*. 8-10 years in the general population.
High risk of additional CRCs:
• 25-30% of patients who have surgery for a Lynch syndrome-associated CRC will have a second primary CRC within 10 years of surgical resection if the surgery was less than a subtotal colectomy.
Increased risk for malignancy at certain extracolonic sites (6,7):
• Endometrium (40-60% lifetime risk for female mutation carriers);
• Ovary (12-15% lifetime risk for female mutation carriers);
• Stomach (higher risk in families indigenous to the Orient, reason unknown at this time);
• Small bowel;
• Hepatobiliary tract;
• Pancreas;
• Upper uro-epithelial tract (transitional cell carcinoma of the ureter and renal pelvis), especially in males with *MSH2* mutation (6);
• Brain (glioblastoma in the Turcot's syndrome variant of the Lynch syndrome);
• Multiple sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas in the Muir-Torre syndrome variant of Lynch syndrome.
Pathology of CRCs is more often poorly differentiated, with an excess of mucoid and signet-cell features, Crohn's-like reaction, and a significant excess of tumor-infiltrating lymphocytes within the tumor.
Increased survival from CRC.
The sine qua non for diagnosis is the identification of a germline mutation in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) that segregates in the family: i.e., members who carry the mutation show a much higher rate of syndrome-related cancers than those who do not carry the mutation.

CRC, colorectal cancer.

registry has been an invaluable resource for multiple national and international collaborative studies in the field of cancer genetics, inclusive of the discovery of the LS mismatch repair mutations and hereditary breast-ovarian cancer (HBOC) syndrome *BRCA* genes.

Mutations in well-characterized genes provide a basis for confirmation of syndrome involvement, personalized management of cancer patients, and predictive testing and management of at-risk relatives (8). While these may be numerically small, study of the genes involved has frequently improved our understanding of pathways involved in nonfamilial cancers (9). Within the families in which these hereditary cancers occur, there exists a tremendous opportunity to achieve early cancer detection and prevention (10-12). Family members identified as carriers of pathogenic LS mutations are provided with screening recommendations along with optional preventive surgical measures, namely risk-reducing hysterectomy and salpingo-oophorectomy in women carriers. These recommendations are provided to family members by trained genetic professionals, knowledgeable in the field of cancer genetics. This service is free of charge to all subjects who enroll in the HCC registry and wish to learn more about their cancer risk, either based on the pedigree alone or when identified through genetic testing.

The HCC registry also has an integral biorepository wherein biological samples have been stored on multiple cancer-affected and unaffected family members over the

Table 2 Hereditary colorectal cancer heterogeneity

Syndrome	Gene	CRC risk (%)	Average age of diagnosis
Sporadic cancer		4.8	69
Lynch syndrome	*MLH1/MSH2*	M: 27-74; F: 22-61	27-60
Lynch syndrome	*MSH6*	M: 22-69; F: 10-30; M/F: 12	50-63
Lynch syndrome	*PMS2*	M: 20; F: 15	47-66
FAP	*APC*	100	38-41
Attenuated FAP	*APC*	69	54-58
MUTYH-associated	*MUTYH*	43-100	48-50
Juvenile polyposis	*SMAD4/BMPR1A*	38-68	34-44
Peutz-Jeghers	*STK11*	39	42-46
Cowden syndrome	*PTEN*	9-16	44-48
Serrated polyposis	Not known	~>50	48

CRC, colorectal cancer; M, male; F, female; FAP, familial adenomatous polyposis. Reprinted by permission from Macmillan Publishers Ltd.: Syngal S, *et al*. *American Journal of Gastroenterology* 110:223-262, copyright 2015.

past 40 years. The foresight to establish cell lines on key family members has proven to be a vital strength of the biorepository in helping families learn of their cancer risk through recent discoveries and genetic testing techniques. Key, informative family members who provided a sample for genetic testing and research who subsequently passed away, had provided their family with a gift, since their sample could be analyzed and tested for genetic mutations discovered long after they had died. Collecting and storing cell lines on various family members throughout multiple generations has also led to insights on the transmission of the genetic mutations and the expressed clinical significance of pre-cancer and cancer phenotypes within each family.

The HCC registry provides a unique setting of involvement in cutting edge research by virtue of the massive collection of LS families with highly detailed data points collected on multiple family members, reaching second- and third-degree relatives and even further for certain families as targeted contacts continue to extend the family history. This unique opportunity allows for HCC researchers to conduct analyses of these families to help determine LS-related risks and associated cancers. In addition, the research conducted within these families in collaboration with cancer genetic researchers around the world allows the transmission of the research findings to the research subjects and family members.

Unfortunately, healthcare providers have difficulty keeping up with new advances in cancer genetics, and commonly are not intimately familiar with the clinical practice guidelines that explicitly include genetic testing, genetic counseling, and appropriate screening measures, with or without informative genetic testing (13). For example, although heredity in certain circumstances poses a striking etiologic factor in a subset of many forms of cancer, in certain families a hereditary diagnosis may be obscured, in part by the rarity of the syndrome, its reduced penetrance, incomplete medical records, and occasionally late age of cancer onset. There is also frequently a lack of glaring phenotypic stigmata of hereditary cancer risk. These factors may obscure a definitive diagnosis, particularly when viewed in concert with cancer's extensive phenotypic and genotypic heterogeneity. In fact, our experience with many varieties of hereditary cancer has shown similar arrays of confounders.

Clearly, it is clinically imperative to collect data on cancer-prone families, analyze the natural history of their cancers, obtain precious biospecimens when this is appropriate, and utilize cutting edge molecular tools to unravel complexities in the interest of early diagnosis and heightened cancer control. The ultimate goal is based upon an accurate clinical diagnosis, followed by genetic testing of the most pertinent germline mutation that could explain the genesis of the particular hereditary cancer syndrome as evidenced by such germline mutations as *BRCA1* and *BRCA2* in the HBOC syndrome and the mismatch repair germline mutations (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) in LS. This, of course, will be provided in accord

Table 3 The elements of informed consent for cancer genetic testing

What the test is intended to do, i.e., determine whether a mutation can be detected in a specific cancer susceptibility gene.
What can be learned from both a positive and negative test, including the health risks associated with a positive test, as well as the risks remaining after a negative test.
The possibility that no additional risk information will be obtained after testing, and the possibility of a finding of unknown significance (e.g., a polymorphism) that may require further studies.
Options for determining approximate risk without genetic testing, e.g., using empiric risk tables for differing family histories.
The risk of passing a mutation on to children.
The importance of notification of family members that they may share a hereditary risk for cancer and assistance in contracting family members and providing them access to counseling and testing.
The medical options for and limitations of surveillance and cancer prevention for individuals with a positive test, as well as the accepted recommendations for cancer screening for individuals with a negative test.
The technical accuracy of the test including sensitivity and specificity.
The risks of psychological distress and family disruption, whether or not a mutation is found.
The risk of employment and/or insurance discrimination following disclosure of genetic test results and confidentiality issues.
The risks that non-relatedness of family members will be discovered, and if and how this information will be disclosed and to whom.
The costs of testing, including the laboratory test; associated consultations with health care professionals who provide pretest education, results disclosure, and follow-up; and cancer prevention measures, which may not be covered by third party payers.

Adapted from Offit K. Clinical cancer genetics: Risk counseling and management. New York: Wiley-Liss Inc., 1998 (14).

with patients' informed consent for testing (*Table 3*). It will be absolutely essential that patients, once they receive results of the testing, receive a full explanation of the medical genetic significance of the mutation so that, if positive for the mutation, they will know its lifetime significance and pertinent penetrance, and, importantly, will receive a full description of the surveillance recommendations. It is extremely important that the genetic counselor spend as much time as necessary assuring that the patient has fully understood the implications of a deleterious germline mutation so that morbidity and mortality may be significantly reduced. The other issue pertains to the individual who is found to be negative for the family's deleterious mutation. This person must be told how common cancer is and that, while a "negative" result means that he/she will not be under the yoke of a highly significant life-long risk for syndrome cancer, nevertheless, he/she will still harbor the general population risk for these particular cancers.

Discussion

The fields of hereditary cancer and molecular genetics have advanced so rapidly that it is extremely difficult for physicians to keep up with this explosive knowledge. Clearly, the issue is "who is going to take care of all these crucial matters for patient benefit?" This is a germane question and our experience has confirmed that, in addition to certified genetic counselors, advanced practice oncology nurses who are interested in hereditary cancer can become skilled at providing this service to the patient and his/her family. This is, in fact, how our HCC has evolved, namely, an extremely well-informed oncology nurse with 20 years of experience in genetic counseling and hereditary cancer, along with availability of physician molecular genetics and pathology colleagues.

Physicians and genetic counselors rarely if ever conduct outreach activities to make contact with distant relatives in the clinical setting due to shortage of time, lack of compensation, and concerns about confidentiality and privacy. Indeed, notions of "duty to warn" are sufficiently vague, both in principle and in practice, as to deter even highly motivated clinicians (15). What inroads have been made have occurred in the setting of research studies. Such studies have shown that interventions to communicate risk information can be effectively conducted (16,17).

A key issue in LS is the lack of ascertainment of relatives of probands with germline mismatch repair (MMR)

mutations. Attention is usually given to the proband's first-degree relatives (children and siblings) in the sense that mutation-positive patients can appreciate the immediacy of the genetic risk to these individuals. Index cases can usually be counted on to provide siblings and adult children with a copy of the "family letter" that is commonly provided at the conclusion of a results disclosure genetic counseling session or to otherwise communicate the substance of the information that has been given. Multiple studies have reported that communication of genetic risk information to first-degree relatives is common; in fact, learning cancer risk information for one's relatives is often a primary motivator to pursue genetic counseling and testing (17-19).

The U.S. Department of Health and Human Services, through its Healthy People 2020 initiative (20), has deemed education of relatives to be a priority, stating that "All people who are newly diagnosed with CRC should receive counseling and educational materials about genetic testing. Family members could benefit from knowing whether the CRC in their family is a hereditary form called LS (2). Screening interventions could potentially reduce the risk of CRC among men and women with LS by 60% (21)." The efficacy of CRC surveillance has been demonstrated by a number of studies, including a 15-year trial by Järvinen *et al*. (22) which showed that colonoscopic screening of LS family members reduced the risk of CRC, prevented CRC deaths through early detection, and decreased overall morbidity and mortality. de Jong *et al*. (23) among others (16,24) found benefit in colonoscopic surveillance in LS family members. Several studies (25-27) have found positive correlation between genetic counseling and uptake of CRC screening. A previous decision analysis (28) suggests that screening of LS patients "…can yield substantial benefits at acceptable costs, presuming sufficient uptake of genetic testing by first-degree relatives of LS probands".

The benefits of genetic testing can extend beyond those tested, changing the known risk status of other family members. Watson *et al*. (29) investigated the change in the distribution of carrier risk status resulting from DNA testing among 75 HBOC syndrome and 47 LS cancer-prone families from our hereditary cancer registry. This involved 10,910 cohort members. Findings showed a change in carrier risk status in 2,906 individuals following testing of 1,408 family members. The most common type of risk change for these individuals was from at risk to noncarrier status, which involved 77% of the risk changes. In addition, 12% were changed from low risk to known carrier status. Therefore, 89% of risk status changes based on testing were from uncertainty to certainty, findings which became integral to cancer prevention recommendations and which impacted the involved family members. Furthermore, 60% of persons with a carrier risk status change were not themselves tested but, rather, their risk status changed because of a relative's test result. In order to provide a model for clinical diagnosis, germline mutation testing, and the entire process from the physician/genetic counselor, patient standpoint, we present a large LS family which we have had the privilege to diagnose, test, counsel, and manage (*Figure 1*).

Current challenges

Reaching high cancer risk individuals who might benefit from DNA testing brings up one of the biggest unmet needs in the diagnosis and management of hereditary cancer-prone families, namely the common lack of identification and education of at-risk relatives of those found to harbor deleterious germline mutations. These may include numerous individuals who are not aware of their hereditary cancer risk status or possibly even of their membership in a family prone to hereditary cancer. One of the strengths of a dedicated HCC is experience in dealing with this problem and the ability to assist mutation carriers in reaching both first-degree relatives as well as those more distantly related.

Advances in "precision oncology" or "personalized medicine" have exploded in recent years. This field deals with the matching of mutations present in a tumor with some of the most effective chemotherapy or other treatment options. Despite its promise, several barriers limit widespread clinical adoption: (I) the need to collect and properly store tissue; (II) the lack of cost-effective companion diagnostic tests; (III) limited funding for bioinformatics infrastructure; (IV) issues related to patient accrual in clinical trials targeting highly selected subsets of patients; (V) industry barriers that block rational combination regimens; and (VI) the need to better understand mechanisms of drug resistance and how to monitor patients for the emergence of resistance (30). Centers with expertise in cancer genetics are in a position to aid in overcoming these barriers.

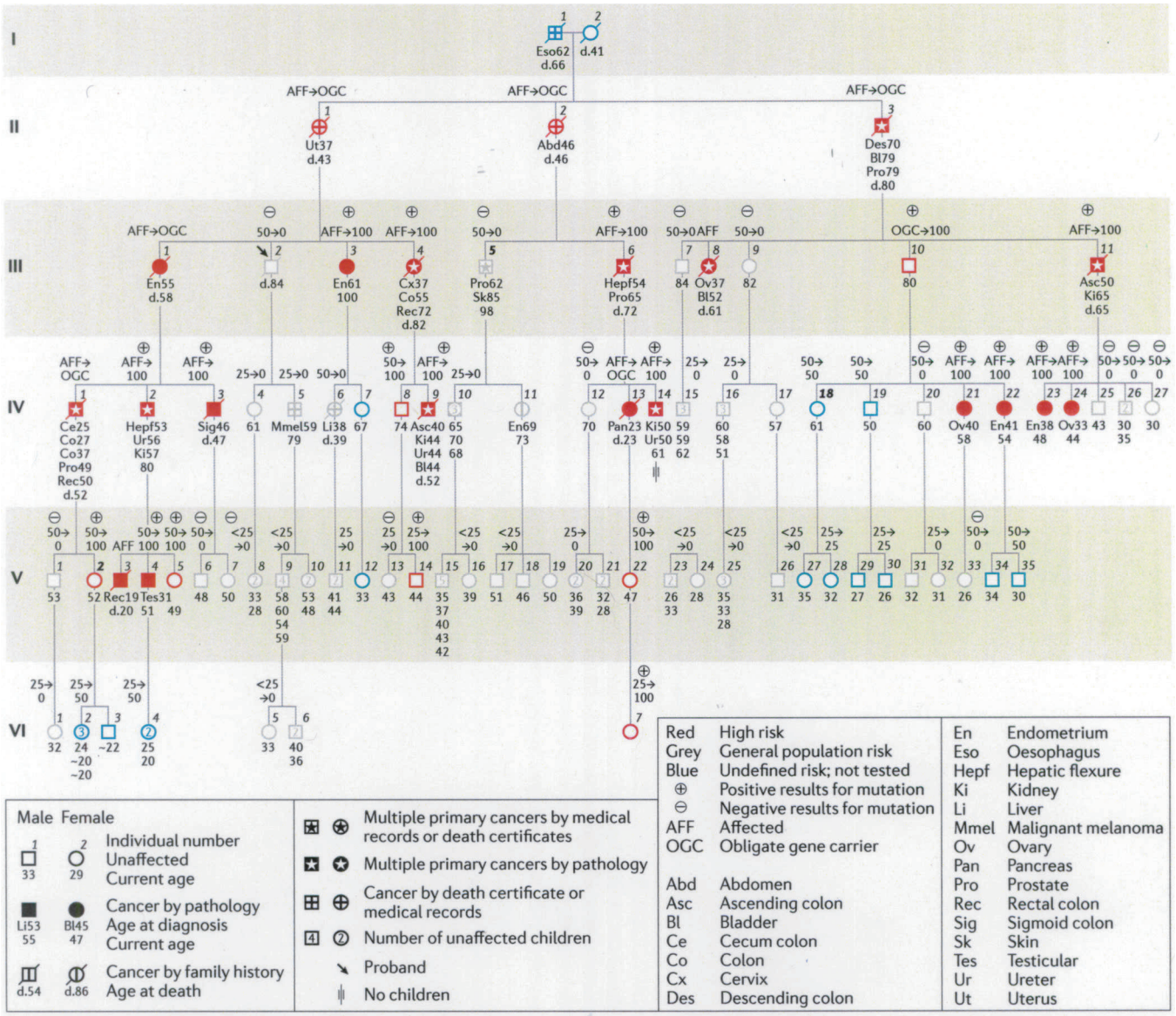

Figure 1 Pedigree of an Lynch syndrome (LS) family. This is a pedigree of an extended LS family, which depicts the importance of key indicators by molecular genetic evidence of cancer-causing mutations or the lack thereof, determining high-risk versus low-risk individuals. Pairs of numbers with arrows indicate the change in risk status that came not from a test of that individual but from test results of another family member (29). For example, <25→0 shows that the status of the family member changed from a <25% risk for carrying the mutation to a 0% risk because of the testing of another family member; cancer-affected family member (AFF)→obligate gene carrier (OGC) indicates that a AFF was determined to be an OGC. Republished with permission from Lynch *et al. Nature Reviews Cancer* 2015;15:181-194. Copyright Macmillan Publishers Limited.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Disclaimer: Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services.

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