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ORIGINAL ARTICLE

Genetic counseling and cascade genetic testing in Lynch syndrome

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Abstract Lynch syndrome is the most common cause of inherited colorectal and endometrial cancers. Individuals with Lynch syndrome have a 10–80 % lifetime risk for colorectal cancer and a 15–60 % lifetime risk for endometrial cancer. Both cancers are preventable through chemoprevention, intensive cancer surveillance, and risk-reducing surgery options. Efforts to identify as many individuals with Lynch syndrome as possible will prevent cancers and save lives. This includes the traditional cancer genetic counseling model whereby individuals with and without cancer are evaluated for a possible Lynch syndrome diagnosis based on their personal and family history of colon polyps and cancers. It also includes universal tumor screening for Lynch syndrome whereby all individuals with colorectal or endometrial cancer are screened for tumor features of Lynch syndrome at the time of diagnosis. Those with tumors suspicious for Lynch syndrome are referred for cancer genetic counseling regardless of their family history of cancer. This two approaches must be maximized to attain high patient reach. Finally, and perhaps most importantly, cascade testing among the at-risk relatives of those diagnosed with Lynch syndrome is critically important to maximize the diagnosis of individuals with Lynch syndrome. In fact, the cost-effectiveness of universal tumor screening for Lynch syndrome relies entirely on counseling and testing as many at-risk individuals as possible since young unaffected individuals stand to benefit the most from an early diagnosis of Lynch syndrome. This approach must be optimized to achieve high family reach. It will take a concerted effort from patients, clinicians and public health officials to improve current approaches to the diagnosis of Lynch syndrome and the prevention and treatment of Lynch syndrome-associated cancer but these lessons can be applied to other conditions as the ultimate example of personalized medicine.

Keywords Lynch syndrome · Genetic counseling · Cascade testing · Genetic testing

Background

Lynch syndrome is the most common cause of inherited colorectal and endometrial cancers. It affects around 1 in 35 colorectal and endometrial cancer patients [1–4] and about 1 in 370 individuals in the general population [5]. Individuals with Lynch syndrome have a 10–80 % risk for colorectal and a 15–60 % risk for endometrial cancer by age 70 [6, 7]. They are also at increased risk for gastric, ovarian, urothelial, small bowel, pancreatic and sebaceous carcinomas although the risks are not as high for these cancers. Several organizations have published surveillance guidelines for individuals with Lynch syndrome; most recommend colonoscopy every 1–2 years at age 20–30 and consideration of risk-reducing hysterectomy and bilateral salpingo-oophorectomy after childbearing [8–11]. These surveillance and prevention options have been shown to be very effective at reducing the morbidity and mortality of cancers associated with Lynch syndrome [12–16]. In addition, there is evidence that long-term use of aspirin reduces the risk for colorectal cancer and possibly other cancers among individuals with Lynch syndrome [17]. As a result, it is clear that the early identification of individuals

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with Lynch syndrome can prevent cancers and save lives through participation in cancer surveillance and prevention options.

It is perhaps surprising then, that a study in the Kaiser Permanente health system revealed that less than 5 % of colorectal cancer patients with a positive family history had any Lynch syndrome testing [18]. We obviously have a long way to go if we are to make substantive improvements in the diagnosis of Lynch syndrome. There are three main approaches to the identification of individuals with Lynch syndrome that will be explored. The first two pertain to increasing the identification of families with Lynch syndrome by increasing the number of appropriate individuals receiving genetic counseling and testing. The traditional model involves patient or physician referral of individuals suspected of having Lynch syndrome based on their personal or family history of cancer. These individuals may or may not have cancer themselves. The active approach involves universal tumor screening for Lynch syndrome among all newly diagnosed colorectal and endometrial cancer patients with follow-up genetic counseling and testing for individuals suspected of having Lynch syndrome based on the results of their tumor testing. The last approach involves increasing the number of family members who undergo genetic counseling and testing for Lynch syndrome once one member of the family is diagnosed. This is known as cascade testing since you follow the mutation through the family, testing those at 50 % risk first, followed by their children, only if they test positive. We must optimize all three approaches to begin to tackle the problem of the under-diagnosis of Lynch syndrome.

Traditional genetic counseling

The traditional genetic counseling model has been in practice for years but really took hold in the field of cancer genetics in the 1990s. This model utilizes risk assessment criteria or computer models to identify individuals who are at risk of having Lynch syndrome. These models can be applied to individuals with and without cancer. They began with the development of the Amsterdam criteria in 1990 for the identification of families likely to have Lynch syndrome for use in gene-hunting research [19]. These criteria are sometimes referred to as the "3-2-1 Rule" because the family must include at least three cases of colorectal cancer (one of whom is a first-degree relative of the other two), in at least two successive generations, with at least one individual diagnosed under age 50. The criteria were revised in 1999, to be less restrictive including some other Lynch syndrome-associated cancers and were referred to as the Amsterdam II criteria [20]. The Bethesda guidelines [21] and Revised Bethesda guidelines [22] included even less restrictive criteria in an attempt to identify colorectal and endometrial cancer patients who might benefit from tumor screening for Lynch syndrome. The result, however, may have instead complicated risk assessment for clinicians and patients since this led to four different sets of complex criteria that were difficult to apply in practice.

Newer approaches attempt to simplify this process through the use of quick patient questionnaires or on-line risk assessment tools. The Colorectal Cancer Risk Assessment Tool has been validated in a busy endoscopy practice and includes three yes or no questions [23]. If participants answer yes to any of the items, they should then be referred for cancer genetic counseling. This tool was endorsed in the U.S. Multisociety Task Force on Colorectal Cancer Guidelines for Lynch syndrome [8]. The PREMM1,2,6 risk assessment tool is available on-line (http://premm.dfci.harvard.edu/) and involves a quick series of questions about the presence of colorectal, endometrial and other Lynch syndrome-associated cancers in the patient, their first-degree relatives and their second-degree relatives [24, 25]. Individuals with a 5 % or greater likelihood of having a mutation in a Lynch syndrome gene should be referred for cancer genetic counseling. This model has been shown to outperform existing clinical criteria including the Revised Bethesda guidelines [24–26]. The major flaw in this method is that fact that clinicians are busy and may not have time to take an adequate cancer family history or to apply appropriate risk assessment tools. If they do take the history and use the model and identify an at-risk individual, they still have to make the referral to cancer genetics and the patient has to follow-through with the appointment. Cancer genetic counseling services have to be accessible within driving distance of the patient and have appointments available in a timely manner. Patients are likely lost at every step in this process and it is this process that led to only 5 % of colon cancer patients with a positive family history on chart review having had any Lynch syndrome testing in one large health system [18]. Efforts to assist in family history taking and risk assessment could help to optimize this strategy (e.g. patient-directed family history collection tools that integrate with the electronic medical record, best practice alerts in the electronic medical record for those who need referral to cancer genetics, and more cancer genetics providers so that it is easy to find a nearby clinic with a reasonable wait time).

Universal tumor screening for Lynch syndrome

The American Cancer Society predicts that there will be 134,490 new cases of colorectal cancer diagnosed in 2016 in the United States [27]. It is estimated that 4035 of these

patients have Lynch syndrome and another 12,105 of their family members also have Lynch syndrome [2, 3]. In an attempt to identify these individuals, several professional organizations have recommended universal tumor screening of all newly diagnosed colorectal cancer patients at the time of diagnosis [8, 28] and some organizations have recommended screening all newly diagnosed endometrial cancer patients [29]. Universal tumor screening consists of testing the paraffin-embedded tumor for microsatellite instability (MSI: a characteristic found in 77–89 % of tumors from individuals with Lynch syndrome) or for the presence of the four Lynch syndrome proteins (MLH1, MSH2, MSH6 and PMS2) using immunohistochemical (IHC) staining (one or more of these proteins is absent in 83 % of tumors from individuals with Lynch syndrome) [30]. Reasons for this recommendation are that patients whose tumors exhibit microsatellite instability (whether proven by MSI testing or extrapolated from abnormal IHC testing): (1) have a better prognosis [31], (2) may need treated differently [32, 33], and (3) are more likely to have Lynch syndrome [2, 3]. However, a survey performed in 2012 found that of respondents, only 73 % of comprehensive cancer centers, 36 % of College of Surgeons accredited cancer centers, and 15 % of community cancer hospitals were performing universal tumor screening of all CRC patients [34]. There are many possible barriers to the implementation of universal tumor screening for all newly diagnosed CRC patients, but a major one is that many cancer centers do not have cancer genetics professionals on staff to provide genetic counselling and follow-up genetic testing to the patients whose tumors have abnormal screening tests.

Once implemented, the next barrier occurs when trying to get patients with abnormal tumor screening to undergo genetic counseling with consideration of genetic testing. These patients are different than those seen in the traditional genetic counseling model because they did not seek out genetics due to concerns about their personal or family history, range in age from 18–89+, may have little to no knowledge about Lynch syndrome or hereditary cancers, and are dealing with their new diagnosis of cancer. It has been shown that institutions with a high level of patient follow-through with genetic counseling and testing following a screen-positive result all utilize genetic counselors to disclose the screen-positive results to the patients and genetic counselors either facilitate physician referrals to genetics or eliminated the need for referrals through an agreement with the treating surgeons and oncologists allowing them to contact the patients directly [35]. It is also important to include tests (somatic BRAF mutation testing or MLH1 promoter hypermethylation testing) to identify patients with acquired hypermethylation of the MLH1 promoter who do not need follow-up genetic counseling and testing.

To help optimize this model, it may require public policy mandating the screening of all newly diagnosed colorectal and endometrial cancer patients. Similar to the newborn screening model, the system could use centralized laboratories to conduct the tumor screening and regional genetic centers to provide the genetic counseling and testing to those with an abnormal screening test. This will enable smaller community hospitals to provide the same level of service as the larger academic centers and will ensure that patients receive the same care with regard to Lynch syndrome screening no matter where they are diagnosed.

Cascade testing

Cascade testing occurs once one member of a family has been diagnosed with Lynch syndrome. At that point, genetic counseling and testing should be offered to all of the individual's first degree relatives who are age 18 or over since they each have a 50 % chance that they have also inherited Lynch syndrome. Testing is very reliable and less expensive at this point because it is known which Lynch syndrome gene is responsible and where the exact mutation is located in that gene. Full testing of all the Lynch syndrome genes can cost $1500-4000 whereas known mutation testing for at-risk relatives once the mutation has been identified in a family costs $200–475. If an individual with Lynch syndrome has a sister who has 5 children, it is also more cost-effective to test the sister first. If she tests negative for Lynch syndrome, then her 5 children are not at-risk and do not need testing at all, saving time and money and avoiding unnecessary concern. Similarly, once it is known whether or not the Lynch syndrome was inherited from the individual's mother or father, it is clear which aunts, uncles and cousins are at-risk for Lynch syndrome (those on the side of the family with the mutation) and which are not (those on the other side of the family). Cascade testing is very important since it identifies who has Lynch syndrome and can benefit from intensive cancer surveillance and prevention options that can help prevent or lead to the early diagnosis of cancer improving morbidity and reducing mortality. It also identifies members of the family who do not have Lynch syndrome. These individuals are not at increased risk for cancer and can follow the American Cancer Society guidelines for cancer screening in the general population. This can be the difference between undergoing colonoscopy every 10 years starting at age 50 for those without the mutation in the family or undergoing colonoscopy every 1–2 years starting at age 20-30 for those with the mutation in the family.

In controlled research settings, it has been shown that six at-risk relatives can be tested for each colorectal cancer

patient identified with Lynch syndrome with three testing positive [2, 3]. Because this testing occurred in a research setting, the genetic counseling and testing were free and the counselor provided services locally in the families' homes, churches, or doctor's offices. However, outside the research setting, it appears that 3.6 relatives or fewer are tested for every individual diagnosed with Lynch syndrome [36]. Demographic factors (age < 50, female sex, parenthood, level of education, employment, participation in medical studies), psychological factors (lack of depressive symptoms) and possible family history (greater number of relatives with cancer) were positively associated with uptake of genetic testing. Another study found that individuals with Lynch syndrome share their results with first-degree relatives (parents, children and siblings) but they are significantly less likely to share their results with more distant relatives [37]. It is very important that rates of cascade testing within known Lynch syndrome families improve. In fact, this is the key factor influencing the cost-effectiveness of the universal tumor screening for Lynch syndrome approach with screening become more cost-effective as increasing numbers of relatives under genetic counseling and testing [38–40].

Efforts to improve uptake of cascade testing of at-risk relatives once a diagnosis of Lynch syndrome is made in a family will be applicable to all adult-onset genetic conditions (e.g. Hereditary Breast Ovarian Cancer syndrome, Familial Hypercholesterolemia, etc.) so the potential benefits are enormous. Researchers are beginning to explore ways to improve cascade testing through the use of secure websites for sharing results (Kintalk.org), videos that can be sent to relatives explaining the importance of genetic counseling and testing for Lynch syndrome, and direct contact of at-risk relatives by the clinician helping to take this burden off the original family member with a diagnosis of Lynch syndrome who may be dealing with their own cancer diagnosis. The results of two nationwide cascade testing programs for Familial Hypercholesterolemia have been published. The program in the Netherlands resulted in testing 25.7 relatives per proband compared to 4.5 relatives tested per proband in Norway [41]. Similar to our research Lynch syndrome cascade testing, the very successful program in the Netherlands involved direct contact of the at-risk family members by a genetic field worker who arranged to take a blood sample from the family members at their homes with treatment being coordinated by local specialist clinics. The program in Norway relied on the proband and the genetic counselor to contact the relatives and request follow-up testing coordinated by the primary care physician which required an appointment. Again, public policy may play a role if the United States was to consider some type of coordinated effort at a nationwide cascade testing program for adult-onset conditions where early detection has been shown to improve outcomes and testing has been proven to be cost-effective.

Discussion

It is clear that waiting for these patients and families to self-refer or be referred by their clinicians to cancer genetics is not sufficient on its own. There will always be a need to identify families with hereditary cancer syndromes in the traditional model but we must undergo a paradigm shift in genetic counseling to a more active approach in the identification of individuals who need a cancer genetic evaluation and testing. Similarly, relying on probands to contact their family members and refer them to local cancer genetics providers has not been a very successful approach to promoting cascade testing among at-risk relatives. An active approach to cascade testing among at-risk relatives perhaps using a nationwide system to maximize results may improve the identification of as many individuals with Lynch syndrome as possible in families with this diagnosis.

It will take a concerted effort by patients, clinicians, and others involved in public health genomics to increase the number of individuals diagnosed with Lynch syndrome. However, these efforts have the potential to prevent many cancers and save lives. In addition, any models that are successful for Lynch syndrome could be applied to other adult-onset conditions for which testing, prevention and treatment is available. Some of the solutions may be high-tech involving the electronic medical record and alerts for individuals with strong personal or family histories of cancer. Other solutions may be low-tech such as offering "house calls" to improve uptake of cascade testing among at-risk relatives. This may require new approaches to the billing and reimbursement of genetic counseling services. It will also require an open mind and consideration of alternative service delivery models (such as modeling this after the newborn screening program in the United States).

References

1. Hampel H, Frankel W, Panescu J et al (2006) Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 66(15):7810–7817
2. Hampel H, Frankel WL, Martin E et al (2008) Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 26(35):5783–5788
3. Hampel H, Frankel WL, Martin E et al (2005) Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 352(18):1851–1860
4. Hampel H, Panescu J, Lockman J et al (2007) Comment on: screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 67(19):9603

5. Hampel H, de la Chapelle A (2013) How do we approach the goal of identifying everybody with Lynch syndrome? Fam Cancer 12(2):313–317
6. Bonadona V, Bonaiti B, Olschwang S et al (2011) Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 305(22):2304–2310
7. Senter L, Clendenning M, Sotamaa K et al (2008) The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 135(2):419–428
8. Giardiello FM, Allen JI, Axilbund JE et al (2014) Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society task force on colorectal cancer. Am J Gastroenterol 109(8):1159–1179
9. NCCN (2015) National Comprehensive Cancer Network clinical practice guidelines in oncology: Colorectal Cancer Screening. V.1.2015. http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
10. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW (2015) ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 110(2):223–262 **(quiz 263)**
11. Vasen HF, Blanco I, Aktan-Collan K et al (2013) Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 62(6):812–823
12. Jarvinen HJ, Aarnio M, Mustonen H et al (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118(5):829–834
13. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP (2009) Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 27(28):4793–4797
14. Schmeler KM, Lynch HT, Chen LM et al (2006) Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 354(3):261–269
15. Engel C, Rahner N, Schulmann K et al (2010) Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol. 8(2):174–182
16. Vasen HF, Abdirahman M, Brohet R et al (2010) One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology 138(7):2300–2306
17. Burn J, Gerdes AM, Macrae F et al (2011) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 378:2081–2087
18. Cross D, Rahm A, Le A et al (2012) PS1-08: Lynch syndrome screening pattering in colorectal cancer patients in a large multi-institutional cohort. Clinical Medicine and Research 10(3):146
19. Vasen H, Mecklin J-P, Khan P, Lynch H (1991) The international collaborative group on hereditary non-polyposis colorectal cancer. Dis Colon Rectum 34:424–425
20. Vasen H, Watson P, Mecklin J-P, Lynch H (1999) New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology 116(6):1453–1456
21. Rodriguez-Bigas M, Boland C, Hamilton S et al (1997) National cancer institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidlines. J Natl Cancer Inst 89(23):1758–1762
22. Umar A, Boland CR, Terdiman JP et al (2004) Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96(4):261–268
23. Kastrinos F, Allen JI, Stockwell DH et al (2009) Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. Am J Gastroenterol 104(6):1508–1518
24. Balmana J, Stockwell DH, Steyerberg EW et al (2006) Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 296(12):1469–1478
25. Kastrinos F, Steyerberg EW, Mercado R et al (2011) The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology 140(1):73–81
26. Balaguer F, Balmana J, Castellvi-Bel S et al (2008) Validation and extension of the PREMM1,2 model in a population-based cohort of colorectal cancer patients. Gastroenterology 134(1):39–46
27. Society AC (2016) Key statistics for colorectal cancer. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-key-statistics. Accessed 2 May 2016
28. Recommendations from the EGAPP Working Group (2009) genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 11(1):35–41
29. Committee on Practice Bulletins-Gynecology; Society of Gynecologic Oncology (2014) ACOG practice bulletin No. 147: Lynch syndrome. Obstet Gynecol 124:1042–1054
30. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN (2009) EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 11(1):42–65
31. Popat S, Hubner R, Houlston RS (2005) Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 23(3):609–618
32. Des Guetz G, Schischmanoff O, Nicolas P, Perret GY, Morere JF, Uzzan B (2009) Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis. Eur J Cancer 45(10):1890–1896
33. Diaz LA Jr, Le DT (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 373(20):1979
34. Beamer LC, Grant ML, Espenschied CR et al (2012) Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. J Clin Oncol 30(10):1058–1063
35. Cragun D, DeBate RD, Vadaparampil ST, Baldwin J, Hampel H, Pal T (2014) Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. Genet Med 16(10):773–782
36. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U (2013) Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. Clin Gastroenterol Hepatol 11(9):1093–1100
37. Stoffel EM, Ford B, Mercado RC et al (2008) Sharing genetic test results in Lynch syndrome: communication with close and distant relatives. Clin Gastroenterol Hepatol 6(3):333–338
38. Grosse SD (2015) When is genomic testing cost-effective? Testing for Lynch syndrome in patients with newly-diagnosed colorectal cancer and their relatives. Healthcare 3(4):860–878
39. Grosse SD, Palomaki GE, Mvundura M, Hampel H (2015) The cost-effectiveness of routine testing for Lynch syndrome in newly diagnosed patients with colorectal cancer in the United States: corrected estimates. Genet Med 17(6):510–511
40. Mvundura M, Grosse SD, Hampel H, Palomaki GE (2010) The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genet Med 12(2):93–104
41. Hadfield SG, Humphries SE (2005) Implementation of cascade testing for the detection of familial hypercholesterolaemia. Curr Opin Lipidol 16(4):428–433