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How do we approach the goal of identifying everybody with Lynch Syndrome?

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Introduction

Lynch syndrome (LS) is the most common inherited cause of colorectal (CRC) and endometrial cancer. We here define LS as an individual with a germline deleterious mutation in one of the four mismatch repair (MMR) genes MSH2, MLH1, MSH6 and PMS2 or EPCAM [1]. Presently, most people diagnosed with LS have already had colorectal (CRC) endometrial (EC) or other LS-associated cancers; however, among all existing carriers of LS the majority has not (yet) had cancer. LS is currently seriously under-diagnosed. A recent study [2] of stages III and IV CRC patients in the Kaiser Permanente healthcare system found that family history documentation varied from site to site with 3 sites documenting family history on <70 % of cases and 4 sites documenting family history in over 85 % of cases. Despite the fact that in those with a documented family history, 61 % had a relative with cancer and 20 % of these had CRC in at least one first degree relative, <5 % of the population received any Lynch syndrome testing [2]. There are essentially three different approaches that can be taken to identify individuals with Lynch syndrome: (1) The current approach which is to educate providers about Lynch syndrome and then expect that they take a family history from their patients and refer appropriate patients for a cancer genetics evaluation; (2) screen all newly diagnosed CRC and EC patients for Lynch syndrome at the time of diagnosis; or (3) screen the general public for Lynch syndrome either at birth or in early adulthood. Since it is clear that the current approach is not sufficient alone, we discuss the latter two approaches here.

The WHO principles of screening are used to decide when a condition should be included in a population-based screening effort [3]. These criteria are as follows:

1. The condition should be an important health problem. The natural history of the condition should be understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
2. There should be a simple, safe, precise and validated test. The test should be acceptable to the population. There should be an agreed policy on the further

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diagnostic evaluation of individuals with a positive tests result and on the choices available to those individuals.

3. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. There should be agreed upon evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

4. There should be evidence from high quality randomized controlled trials that the screening program is effective in reducing mortality or morbidity. There should be evidence that the complete screening program (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public. The opportunity cost of the screening program (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole.

We will make the case that LS meets these criteria and therefore, should be considered for some sort of population-based screening approach. At this time, we believe that this screening should be targeted to individuals diagnosed with a LS-associated cancer and their at-risk relatives. However, as new testing techniques emerge and the costs decrease, it is possible that it may be a better approach to screen unaffected individuals either in the newborn setting or in early adulthood as has been suggested previously [4]. Of course, in addition to these active population-based screening approaches, we still support the traditional approach whereby healthcare providers take their patients' family histories and refer patients (both affected and unaffected) for genetic evaluation when LS is suspected.

LS is an important health problem

The true incidence of LS is not known today because systematic and comprehensive genomic sequencing of the MMR genes has not yet been done in sufficient numbers of individuals. The population incidence can be approximated by extrapolating data on incidence in cancer patients. As shown previously, this approach has led to estimates of the population incidence varying between 1:2,000 and 1:800 [5]. However, these are gross under-estimations for several main reasons. They were based mainly on just *MSH2* and *MLH1* data, systematic searches for large deletions were not done, the EPCAM deletions were not known, and the sequencing only comprised the exons and small parts of the introns. Moreover, the life-time penetrance of *MSH2* and *MLH1* mutations was overestimated (believed to be some 80 %) and the penetrance of MSH6 and PMS2 mutations was unknown. More recent systematic studies of unbiased patient cohorts suggest lower penetrance figures for colorectal cancer (around 50 % for *MLH1* and *MSH2* and 20 % for *MSH6* and *PMS2*) [6, 7]. Importantly, most figures emanate from studies of CRC patients only, ignoring probands with the other LS cancers. Individuals with LS are at increased risk for numerous cancers, notably endometrial, ovarian, gastric, urothelial, biliary, small bowel, pancreatic, and sebaceous carcinomas.

Recent population-based series in which the incidence of LS among unselected CRC patients was calculated without most of the above biases suggest that the proportion is around 2.8 % [8–14]. This means that there will be 4,017 LS patients diagnosed with CRC in the United States in 2012 (2.8 % 9 143,460 cases of CRC) [15]. To estimate the population incidence of LS, assume a lifetime risk of CRC of 5 % and an average lifetime cancer risk in LS carriers of 50 %. Then population incidences are 2.8 % of 5 % multiplied by 2. Thus in summary, the present best estimate calculated in this way is around 1:370. Of note, this number is likely to be an underestimate because; (1) it ignores probands with LS cancers other than CRC; (2) it is based on triaging by age, family history, microsatellite instability, and/or immunohistochemistry of the MMR proteins in the proband's tumor and none of these criteria have 100 % sensitivity. Some criteria are prone to error; and (3) exons and splice sites were sequenced, but not introns in most cases.

Given the above facts we conclude that the population incidence of LS is somewhere around 1:370 or perhaps even higher. At this incidence, LS is one of the most common severe Mendelian disorders. Of note, the figures quoted above apply mainly or only to Caucasian populations of European origin, and differences between European subpopulations appear to occur [13].

LS has two simple, safe, precise and validated screening tests

Microsatellite instability (MSI) testing and/or immunohistochemistry (IHC) for the four mismatch repair proteins are screening tests that can be performed on the paraffin-embedded tumor tissue from a LS-associated cancer such as colorectal cancer to identify a subset of patients that are more likely to have LS. MSI testing measures the length of repetitive areas of DNA known as microsatellites in both tumor tissue and normal adjacent tissue. If the repeats are the same length in both tissues, the tumor is considered microsatellite stable or MSI-negative and the patient is unlikely to have LS. If more than 20 % of the repeats in the tumor are a different size than they are in the normal tissue, the tumor is considered microsatellite unstable or MSI-high and the patient is more likely to have LS. IHC staining evaluates tumors for the presence or absence of the mismatch repair proteins. If any of the proteins is absent, the patient is more likely to have LS and the corresponding gene is the prime suspect for an underlying germline mutation. These tests are safe because they are performed on the tumor that was removed from the patient's body anyway as part of their cancer treatment. They are also precise [16]: MSI has a sensitivity of 89 % for detecting individuals with mutations in MLH1 and MSH2 and 77 % for detecting individuals with MSH6 mutations; IHC has a sensitivity of 83 % regardless of the underlying gene mutation. The specificity of MSI is estimated to be 90.2 % and the specificity of IHC is more variable with an estimate of 88.8 % [16]. There are practice guidelines from professional organizations detailing the appropriate follow-up testing for individuals who have an abnormal MSI or IHC result [17].

There are effective interventions for individuals diagnosed with LS

There are several evidence-based consensus guidelines [18–20] for cancer surveillance and prevention among individuals with Lynch syndrome. Several investigations have shown that

intensified clinical surveillance in known Lynch syndrome (LS) carriers (already affected or unaffected), is beneficial, leading to lower cancer morbidity and mortality [21, 22]. For example, colonoscopy every 3 years was shown to decrease the incidence of colorectal cancer among individuals with LS by 65 % and to essentially prevent colorectal cancer associated mortality among these individuals [22]. As a result, current consensus guidelines [18–20] recommend colonoscopy every 1–2 years among individuals with LS beginning at age 20–25 in *MLH1* and *MSH2* mutation carriers and at age 30 in *MSH6* and *PMS2* mutation carriers in an effort to prevent CRC development. In addition, most guidelines suggest the option of risk-reducing hysterectomy and bilateral salpingo-oophorectomy for women with LS. A research study has shown that this procedure was very effective in preventing both endometrial and ovarian cancers among women with LS [23].

The screening program is effective in reducing mortality and morbidity, is acceptable and is cost-effective

Universal screening for LS among cancer patients has been evaluated by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group of the CDC. This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors regarding the validity and utility of rapidly emerging genetic tests for clinical practice, highlights critical knowledge gaps and provides guidance on appropriate use of genetic tests in specific clinical scenarios (http://www.egappreviews.org/). The EGAPP Working Group found sufficient evidence to recommend offering screening for LS among all newly diagnosed CRC patients using either MSI or IHC to decrease the morbidity and mortality in relatives [16, 24]. Furthermore, universal screening was found to be cost-effective with an incremental cost-effectiveness ratio of <$25,000 per life year saved compared to no testing. IHC was considered more cost effective than MSI since it pinpoints which 1–2 gene(s) to test thus saving money when it comes to genetic testing. Finally, universal screening for LS among cancer patients has been implemented successfully at many institutions [25] and EGAPP reviewed data regarding psychosocial outcomes of genetic counseling and testing for LS and found that changes in distress among mutation carriers seem to be short term and there is no indication of adverse effects of genetic testing [16]. It has also been shown that 78 % of newly diagnosed CRC patients found it acceptable to have information about LS brought to their attention at the time of diagnosis [26].

Conclusions

At a minimum, we believe that all newly diagnosed CRC and EC patients should be screened for LS. These individuals have already had a LS-associated cancer which makes them more likely to have LS (1 in 35–40) compared to the general population (1 in 370). In addition, the screening tests in use presently (MSI and IHC) are performed on tumor tissue so this lends itself to screening individuals already affected by cancer. It is possible that individuals with newly diagnosed gastric and ovarian cancers (among other LS cancers) should also be screened for LS but we are lacking data about the incidence of LS in these patient populations at present.

However, it is very important to stress that the benefits of this screening program rest heavily with the unaffected, at-risk relatives of these cancer patients who can be diagnosed prior to developing cancer and attain the most benefit in terms of cancer prevention and risk reduction. This is accomplished through a process known as cascade testing. In this process once a cancer patient is diagnosed with LS, then predictive testing for the single mutation known to cause LS in the family is offered to all first-degree relatives (parents, siblings, and children) who are at 50 % risk for inheriting the mutation. Some of them will test positive for LS and then testing should be offered to their first-degree relatives (who are second degree relatives of the original cancer patient, i.e. nieces, nephews, aunts, uncles, and grandchildren). This can continue to even further removed relatives but the testing always follows the mutation through the family so no one who is not at-risk (i.e. the child of someone without the mutation) receives testing. We also believe that unaffected individuals with a strong family history of LS-associated cancers should still be referred to cancer genetics by their healthcare providers for an evaluation in the traditional genetics model. Hopefully, with the use of both the traditional model and screening of all CRC and EC patients, we can maximize the identification of all individuals with LS.

The issue of screening the entire population

The issue of screening healthy people for risk of developing disease is controversial. Nevertheless, in many countries newborn children are screened for a variety of congenital or early-onset disorders. For instance, in the state of Ohio such screening is performed for 35 conditions and almost all newborns undergo such screenings. The only accepted reason to opt out of newborn screening in Ohio is if the parents have religious objections. Of note, in some cases (e.g. phenylketonuria, PKU) those children who are not screened suffer a clearly documented health disadvantage in the form of delayed prevention leading to mental retardation. Debates over whether to screen or not to screen arise every time screening for another disease/condition is proposed. The most typical argument in favor of screening is when early diagnosis can help save lives or alleviate symptoms (such as in PKU). The typical argument against screening is when little or nothing can be accomplished to treat or prevent the condition, the classic example being Huntington's disease. We believe that LS is an example of an adult-onset condition that meets the criteria for screening and that adults who are not screened suffer a clearly documented health disadvantage (a high likelihood of a cancer diagnosis) that could be avoided through the use of colonoscopy and other cancer screening and prevention modalities.

This discussion is being written at a time when rapid improvements of the sequencing technologies and the bioinformatic methodologies occur. In LS, only five genes need to be studied and methods to enrich a sample for the regions containing the 4 MMR genes and EPCAM exist. Thus the entire genomic sequence of these genes can be determined by targeting of only some 73 kb (MSH2), 16 kb (exon 9 and downstream of EPCAM), 100 kb (MLH1) 23.8 kb (MSH6) and 35.9 kb (PMS2), or 250 kb. This can be accomplished using next-generation sequencing panels for around $2,700 (http://web.labmed.washington.edu/tests/genetics/COLOSEQ). The price is likely to come down with improved technology and increasing competition, but it is not known by how much and how soon. Already, this may affect previous cost-effectiveness analyses that were in favor of IHC since IHC won by

narrowing down the number of genes to be tested to 1–2. If all of the genes can be tested for the same cost or less than it used to cost to test 2 genes via traditional Sanger sequencing methods, then it levels the playing field for MSI in the cost-effectiveness analysis. Further, we consider it likely that this type of targeted deep sequencing alone without any prescreening using the MSI and/or IHC will become the method of choice in the future when the cost drops low enough. It may well be applied to all patients diagnosed with LS cancers, and it may also be applied to entire, unselected or selected groups of healthy individuals.

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