SHOULD WE CONSIDER INTRODUCING SYSTEMATIC SCREENING FOR LYNCH SYNDROME?

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Abstract

Lynch Syndrome is characterised by the development of colorectal, endometrial and other cancers, often at a young age. It is caused by constitutional mutations of DNA mismatch repair genes and cancers that arise in this setting are mismatch repair deficient, as demonstrated by loss of the relevant mismatch repair protein and microsatellite instability. In theory, universal screening of all index colorectal cancers for mismatch repair deficient should identify individuals who are at higher than population risk of carrying a constitutional mutation in the mismatch repair genes. A health economic evaluation in the UK found that this type of screening strategy applied to individuals under the age of 51 years was highly cost effective. In Australia, some centres routinely test all colorectal cancers for mismatch repair deficient, however there is currently no systematic national approach to screening. Given the cost effectiveness of universal screening is dependent on uptake of constitutional testing by the index case and their relatives, we suggest that research into the determinants and barriers to uptake of constitutional testing is a high priority. Further, given that the health care context can influence the assessment of cost-effectiveness, we propose that the UK economic evaluation also needs to be undertaken in an Australian context.

Lynch Syndrome (LS) is a familial cancer syndrome which predisposes to colorectal cancer (CRC), endometrial and other cancers, such as gastric and ovarian cancer. It is caused by constitutional mutations in the DNA mismatch repair (MMR) genes *MSH2, MLH1, MSH6* and *PMS2*. Rarely, some cases of LS are caused by constitutional methylation of the promoter of *MLH1* or *MSH2* rather than a constitutional sequence change.[1] Irrespective of mechanism, the normal cells of an individual with LS have proficient DNA repair despite containing a mutated allele (copy) of one of the mismatch repair genes. Once the remaining normal allele is mutated or lost, the cells accumulate a large numbers of mutations. It is unclear whether the increased mutation rate is, in itself, the driver to carcinogenesis, or whether this is a paraphenomenon and the driver is a reduction in apoptosis caused by an uncoupling of cell cycle control from recognition of DNA damage.[2,3]

The average age of onset of CRC in LS is about 40 years, but cases of teenage cancer have been described. While some individuals never develop any tumours, many patients develop more than one cancer, some many more. Previous studies overestimated the cumulative risk of cancer in individuals with LS, reporting cumulative colorectal cancer risks of 80%. Recent studies have estimated lower cancer risks and have also shown that cancer risk and type of cancer depends on which of the four genes is mutated. For instance, Bonadona et al estimated cumulative risks of CRC by age 70 years of around 40% for *MLH1* and *MSH2* mutation carriers, and 12% for *MSH6* carriers.[4] This study also showed that the risks of endometrial or ovarian cancer do not significantly increase until after the age of 40 years.

Identifying individuals with LS is important, since colonoscopic surveillance for both index cases and at-risk relatives reduces mortality from colorectal cancer. Biennial surveillance colonoscopy for LS patients is recommended because CRCs in LS appear to develop much more quickly than those in the general population.[5-7] The estimates of population prevalence of LS have steadily risen, in part because of programs for universal screening of incident cancers for the hallmarks of LS. Currently, it appears that ~1:1000 individuals have mutations in one of the four genes, giving a total population prevalence of ~1:250, thus accounting for approximately 2.8% of all CRCs.[8]

Tumour testing for LS

LS tumours are mismatch repair deficient (MMRD) and display microsatellite instability (MSI) and loss of the relevant mismatch repair (MMR) protein. The value of using MSI testing as a screening test for LS tumours is limited by the fact that 15% of sporadic CRC and some other cancers also display MSI as a consequence of somatic inactivation of the *MLH1* gene. Another limitation of MSI testing is that the panel of MSI markers has been developed for colon cancers, and the testing is less sensitive when applied to endometrial and other cancers. Finally, the standard MSI markers often do not identify MMRD tumours, which arise in the context of an inherited mutation in *MSH6* or *PMS2*.[9]

The observation that a specific somatic mutation of *BRAF*, known as V600E, is not found in LS-associated colon cancers, but is found in a majority of sporadic colon cancers with loss of MMR, has now provided the means for restricting constitutional testing to those individuals with a high likelihood of LS.[10,11]

Expression of MMR proteins in tumours can be assessed by immunohistochemistry (IHC) and it is gene specific, however it is not a functional test, so expression of an MMR protein does not necessarily equate to MMR proficiency.[12] Also, as mentioned above, the most frequent cause of loss of MMR protein staining in CRC is somatic (acquired) methylation of the *MLH1* gene promoter. Both MSI and MMR IHC testing are included in some programs such as the UK National External Quality Assurance Service program.[13,14] As with all tests, they have finite sensitivity and specificity, and there is no single test which will indicate LS with complete accuracy.

Surveillance and treatment for LS-affected individuals

Biennial colonoscopy from around the age of 25 years is the mainstay of LS surveillance and treatment.[6,7] This allows identification and removal of premalignant lesions, and downstaging of cancers. However, it is acknowledged that even in the best hands, CRC mortality in LS can only be reduced by about half. There are no proven forms of effective surveillance for any other LS-associated cancers.[6,7] For this reason, total abdominal hysterectomy and bilateral salpingooophorectomy is recommended after childbearing is completed, or from age 40 years, to reduce the risk of gynecological cancers.[6,15] Nowadays, some surgeons recommend a total colectomy rather than a hemicolectomy as the preferred option for a LS patient with CRC. The rationale for the more extensive surgery relates to the high risk of cancer in residual colon and the reports of comparable quality of life following either type of surgery.[16]

Two other approaches to cancer prophylaxis for LS are on the horizon. Firstly, in one major placebo-controlled double-blind trial, daily aspirin reduced the relative risk of CRC by 37%.[17] In this study, the frequency and magnitude of side-effects was not high, in part because of the relatively young age of the participants. Given the high dose of aspirin (600mg) used in the CAPP2 study, a further dose determination trial (CaPP3) is planned. A second approach to cancer prophylaxis is currently being tested in a phase I/IIa vaccine trial of MicOryx, a vaccine directed at the specific abnormal proteins caused by loss on MMR in tumours with MSI.[18-20]

Current identification of LS

The Amsterdam Criteria were originally developed as a research tool to find the gene/s responsible for LS, rather than a clinical diagnostic aid in identifying such families.[21] With successful identification of the MMR genes and improved understanding of LS, the Amsterdam Criteria were subsequently modified in recognition that endometrial cancer was a major LS associated tumour. However, the custom and practice became established that LS was initially diagnosed by family history, and tumour testing was an aid once a putative family had been identified. Subsequently, much time and effort has gone into models which can be used in clinical practice to predict which families have a greater chance of having a LS gene mutation, but the fact remains that diagnostic laboratories only find mutations in about 10-15% of cases referred to them.[5]

Subsequently, as LS tumour testing came into routine practice, it was realised that incident tumours could be tested without a requirement for a family history, including cases of young-onset, multiple or co-occurrence e.g. colorectal and endometrial cancer in the same individual.[22] Thus, at an international meeting in Bethesda in 1996, criteria were drawn up to aid in selection of tumours for LS testing, the so-called Bethesda Guidelines.[23] As the variety of LS tumour types became apparent, so these were revised.[24] Although the Bethesda Guidelines in their various forms do somewhat improve the specificity of LS identification, they are not sensitive. It has also been recognised that the criteria vary widely in their performance depending on the underlying gene.[9,10] Additionally, it has been found that not only do healthcare professionals rarely ask about a family history of cancer, they struggle with recognising LS and referring cases to clinical genetics.[25,26]

Furthermore, individuals who have de *novo* mutations or are adopted have little, if any hope of being identified at risk of LS in a system based on family histories.

Universal screening of tumours for LS: international overview and cost-effectiveness

In response to the realisation that ascertaining LS by means of family histories had distinct limitations, the International Society for Gastrointestinal Hereditary Tumours produced a position statement on the identification of LS in Europe, in which systematic testing of LS-associated tumours was proposed. Simultaneously, a number of countries were endeavouring to institute such programs, either nationwide (notably Denmark) or in individual regions (Australia).[5,27]

In the UK, the Peninsula Technology Assessment Group (PenTAG),[28] was contracted by the National Health Service National Institute of Health Research to undertake a health technology assessment on the diagnostic utility and cost-effectiveness of genetic testing for LS in index cases of CRC under the age of 50 years of age.[29] The PenTAG group built an economic model applicable to the National Health Service system. The model incorporated all test performance characteristics and costs, a full range of health (e.g. clinical genetics, oncology, surgery) and social care costs. Six different combinations of tumour tests (immunohistochemistry, MSI and/or BRAF) were evaluated and all were evaluated in comparison with no intervention. Also evaluated was the benefit of taking a family history and acting upon it, if it fulfilled the Amsterdam Criteria, and simply testing for constitutional mutations without tumour testing. The PenTAG model showed that all colorectal tumour testing-based strategies up to age 50 years offered the National Health Service good value for money versus no testing, with all incremental cost-effectiveness ratios below the National Institute for Health and Care Excellence threshold of <£20k(AU$36k) per quality adjusted life year (QALY) gained. The model predicts an expected average gain in longevity of 1.3-1.7 years for probands, and 1.1-1.4 years for relatives. Moreover, cost-effectiveness was positive even if only the proband was identified with LS, albeit that identifying relatives, up to a point, is more cost-effective. Interestingly, family history as a 'test' is more cost-effective than doing nothing, but not as cost-effective

as tumour testing, and simply sequencing all probands was also found to be cost-effective, although less so than tumour testing strategies. Furthermore, the model shows that it would still be cost-effective to test all tumours up to age 70, with incremental cost-effectiveness ratios <£20k(AU$36k)/QALY.

While tumour testing strategies which include MSI followed by *BRAF* testing appeared to give the best incremental net health benefit, all six tumour testing strategies are predicted to be effective and cost-effective. Thus there is little to choose between the available options and no justification to change current practices of universal screening for LS through tumour testing. A sensitivity analysis conducted as part of the modelling showed that the following factors had a substantial impact on cost-effectiveness: CRC incidence for individuals with LS; the mean number of relatives per proband (0 – 12; base = 5); the effectiveness of colonoscopy in preventing metachronous CRC; the cost of colonoscopy; and the psychological disutility associated with prophylactic total abdominal hysterectomy and bilateral salpingo-oopherectomy disutility. Thus, the model usefully predicts areas requiring careful attention and further exploration.

Implementation of LS screening

Implementation of a LS screening program should necessarily fulfill the requirements for any screening program, including that there should be: a detectable disease marker; a simple, safe, precise and validated test; and an effective treatment with evidence of early treatment leading to better outcomes than delayed treatment. Value for money is also an important consideration, specifically the opportunity cost of the screening program (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole. Moreover, assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resources.[30] In addition, there should be a plan for managing and monitoring the screening program and an agreed set of quality assurance standards, from which no doubt, the experience of other countries who have successfully implemented such programs will be germane.[13,14]

Given that universal screening for LS theoretically satisfies the requirements for adoption into routine practice, it is important to consider the possible barriers to implementation. One barrier is the behavior and circumstances of clinicians and patients. In one study of population-based universal screening for LS, over half of the individuals identified did not take up constitutional testing or refused to be informed of their results. As a consequence, one third of LS cases were missed.[31] Another barrier is the capacity of clinical genetics and thence to colonoscopic surveillance services to accept new referrals. To accommodate the additional LS patients, it may be necessary to make changes elsewhere in the system, for example changing the approach to surveillance for those at moderately increased risk of CRC.[32,33]

There are concerns that implementation of universal tumour testing amounts to genetic testing without consent. However, the situation is analogous to one where patients with polyposis are able to be diagnosed on sight and they and their relatives benefit from life-saving prophylaxis. Should those with LS be denied such a diagnosis simply because the tests they warrant are microscopic or molecular? In effect, their cancers are unanswered referral letters. We require LS families to recognise they have a family history of a complex disorder, and we require doctors to be similarly skilled, but the evidence shows that such a pathway amounts to an unfair obstruction to a diagnosis which may save lives. In any event, such a testing program does not force a diagnosis of LS on an individual – reporting pathologists merely need to say in their report: "Testing shows that this cancer may be due to an inherited syndrome. Referral of the patient to clinical genetics is strongly indicated."

Current status of universal tumour screening for LS in Australia

There is currently no consistent national approach to testing for LS in Australia. Although immunohistochemistry in tumour samples is rebatable by Medicare,[34,35] molecular MSI and BRAF mutation testing in CRC is not (although testing for BRAF mutation status is approved for other indications).[36] Genetic testing for constitutional mutations in *MLH1, MSH2, MSH6 and PMS2* is also not Medicare-reimbursed, although the State Health Departments in Victoria and Western Australia fund these tests.[37] However, two Australian LS testing experiences have been reported.[27,38,39] In an evaluation of routine screening of incident CRC in South Eastern Sydney,[27] participating cases with MMRD tumours were triaged into low- and high-likelihood LS cases based on IHC and *BRAF* mutation testing. Constitutional mutations were reported in ~7% (95%CI:3-18%). In WA, screening for LS has been in place since 2008 as part of the familial cancer program, which was established in several steps. A 2006 evaluation of the cost-effectiveness of screening CRC tumours in WA found that offering genetic testing to first-degree relatives, followed by intensive surveillance for cancer of the colorectal, endometrium, ovary, stomach and urinary tract, or prophylactic colorectal surgery, was cost-effective, incurring a net cost <$13,000 for a gain of eight CRC-free years.[40] A pilot involving retrospective testing of CRC cases <60 years diagnosed from 2000-2006 using MSI and molecular *BRAF* mutation testing was performed; high MSI tumours without *BRAF* mutation were further investigated using IHC, which led to the identification of previously unrecognised cases of LS.[41] Routine screening targeting incident CRC cases aged <60 years has been established and a recent report concluded that the program has resulted in identification of two-thirds of the expected LS cases among CRC cases aged <60 years in WA.[38]

Prior work suggests that uptake may be one of the major practical limitations of an LS screening process. In the South Eastern Sydney experience,~50% of MMRD CRC cases did not wish to proceed with further testing for LS.[27] A systematic review reported that only 52% of first-degree relatives of identified LS cases chose to receive genetic testing.[42] However, once genetic testing has been performed, surveillance uptake may be relatively high.[15,43,44] In an Australian study of confirmed LS carriers,

all had undergone colonoscopy by three years after testing and 69% of the female carriers had undergone gynaecological screening in the previous two years.[43]

Conclusion

Given the inconsistencies in current approaches to testing in Australia and the potential difficulties in achieving high uptake of testing if it were to be systematically offered, we suggest that research into the determinants and barriers to testing uptake is a high priority, as is performing a national assessment of the effectiveness and cost-effectiveness of systematic screening for LS in Australia.

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