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EDITORIAL

Australasian Gastrointestinal Pathology Society (AGPS) consensus guidelines for universal defective mismatch repair testing in colorectal carcinoma

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Summary

Lynch syndrome is the most common hereditary form of colorectal carcinoma caused by a constitutional pathogenic mutation in a DNA mismatch repair gene. Identifying Lynch syndrome is essential to initiate intensive surveillance program for the patient and affected relatives. On behalf of the Australasian Gastrointestinal Pathology Society (AGPS), we present in this manuscript consensus guidelines for Lynch syndrome screening in patients with colorectal carcinoma. The goal of this consensus document is to provide recommendations to pathologists for diagnosis of Lynch syndrome with discussion of the benefits and limitations of each test. Universal screening for defective mismatch repair is recommended, in agreement with the recent endorsement of universal testing by the National Health and Medical Research Council in Australia and the New Zealand Ministry of Health. The value of evaluating defective mismatch repair is acknowledged not only for Lynch syndrome screening but also for therapeutic decision information in patient management. AGPS advocates appropriate government funding for the molecular tests necessary for Lynch syndrome screening (*BRAF* mutation, *MLH1* methylation testing).

Key words: Lynch syndrome; colorectal cancer; mismatch repair protein; immunohistochemistry; microsatellite instability.

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INTRODUCTION

Lynch syndrome is an autosomal dominant disorder caused by constitutional pathogenic mutations in one of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2* or mutations involving adjacent genes which affect the function or expression of these genes, for example *EPCAM* (*TACSTD1*) and *MSH2*, and *LRRFIP2* and *MLH1*.[1–3] Lynch syndrome is the most common form of hereditary colorectal carcinoma (CRC), accounting for 3% of all incident cases.[4] Two to six percent of all endometrial carcinomas are caused by Lynch syndrome.[5,6] The risk of cancer for affected individuals depends on age, gender, organs and which MMR gene is altered. The cumulative incidence of CRC at age 75 years is 46% in *MLH1*-mutation carriers, 43% in *MSH2*-mutation carriers, 15% in *MSH6*-mutation carriers, and 13% in *PMS2*-mutation carriers.[7,8] Lynch syndrome individuals with a mutation in *MLH1*, *MSH2* and *MSH6* also have an increased risk of cancer of the urinary tract, pancreas, hepatobiliary tract, stomach, small intestine, ovaries, and possibly breast and prostate.

The diagnosis of Lynch syndrome is currently a multistep process which requires close cooperation across multiple specialists. Pathologists play a crucial role by screening tumours for defective MMR using either immunohistochemistry (IHC) for MMR proteins and/or microsatellite instability (MSI) testing. Patients diagnosed with a defective MMR (dMMR) tumour that is not caused by sporadic alteration in MMR genes will be offered genetic counselling and germline mutation testing. Clear communication between pathologists, clinicians and genetic counsellors is important to ensure appropriate management of patients with a suspected diagnosis of Lynch syndrome. In this consensus document, we provide a list of guidelines on behalf of the Australasian Gastrointestinal Pathology Society (AGPS) to endorse universal testing in CRC. We also highlight urge for public funding of necessary molecular tests by the government. The consensus statements have been previously presented during two AGPS annual meetings, in 2015 and 2017.

TERMINOLOGY

1. Hereditary non-polyposis colorectal cancer (HNPCC) and Lynch syndrome

HNPCC is a clinical term, initially coined to separate familial predisposition to CRC (patients fulfilling Amsterdam criteria)

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from the polyposis syndromes (familial adenomatous polyposis and hamartomatous polyposis syndromes) before MMR genes were discovered.[9] HNPCC should not be used as a synonym of Lynch syndrome, which is genetically defined by the identification of a constitutional pathogenic mutation in a gene affecting the DNA MMR function. Not all HNPCC individuals have Lynch syndrome and not all Lynch syndrome individuals have HNPCC. Another confusing issue with the term HNPCC is that colorectal polyps can occur in Lynch syndrome individuals. The term HNPCC should no longer be used.

2. Defective mismatch repair (dMMR) and microsatellite instability (MSI)

dMMR within a tumour cell results in the loss of proofreading and repairing the nucleotide sequence from insertions and deletions that normally occur during DNA replication. Highly repetitive sequences (microsatellites) are particularly susceptible to DNA replication errors, which result in differing numbers of mononucleotide and dinucleotide repeats within microsatellites, referred to as MSI. Another consequence of dMMR is the loss of expression of MMR protein(s) by IHC. MSI testing and MMR protein IHC are two different methods to evaluate tumour for dMMR; these two terms should not be used as synonyms.

3. Lynch-like syndrome

Patients with a dMMR CRC suggestive of Lynch syndrome, with no constitutional pathogenic mutation detected in MMR genes, are referred to as Lynch-like syndrome. Defective MMR suggestive of Lynch syndrome include CRCs with loss of MLH1 and PMS2 by IHC that demonstrate absence of the somatic *BRAF* V600E mutation and absence of somatic *MLH1* promoter methylation, CRC with loss of MSH2 and MSH6, isolated loss of PMS2 and isolated loss of MSH6. These patients and their first-degree relatives are usually managed clinically as if they had Lynch syndrome until further somatic or germline testing might confirm or exclude Lynch syndrome.

CONSENSUS RECOMMENDATIONS AND SUMMARY OF SUPPORTING EVIDENCE

Statement 1. All newly diagnosed colorectal carcinomas should be tested for defective MMR

Regardless of patient age, clinical presentation, family history or tumour histological features, all new CRC should be tested for dMMR using MMR protein IHC and/or MSI analysis. This approach is commonly named universal testing.

Summary of supporting evidence and discussion

Defective MMR is usually the first step in screening for Lynch syndrome. A diagnosis of Lynch syndrome is important as it may impact clinical management, including more extensive surgical resection and intensive long term surveillance. Once the diagnosis of Lynch syndrome is made in a proband, cascade testing is offered to relatives, followed by intensive surveillance for mutation carriers. This approach has been shown to reduce the incidence and mortality of Lynch syndrome-associated cancers.[10,11] Testing CRC for dMMR also provides important therapeutic-decision information. Defective MMR is associated with better overall and disease-free survival in early stage CRC.[12] In addition, dMMR provides predictive information for non-response to 5-fluorouracil-based adjuvant chemotherapy in stage II/III CRC,[13] although this is still a subject of controversy.[14] Finally, dMMR predicts the clinical benefit of immune checkpoint blockade (PD-1 and PD-L1 inhibitors) in patients with metastatic CRC who have failed conventional therapy.[15]

Until recently, revised Bethesda Guidelines have been used in many centres as criteria for dMMR testing in CRC. However, selected approaches such as the revised Bethesda Guidelines have lower sensitivity of identifying Lynch syndrome compared with universal testing.[16] This is due to using age as one of the main criteria that excludes routine screening for patients >60 years. The clinical presentation of Lynch syndrome patients is variable and depends on sex and the gene involved.[4] The prevalence of CRC is higher in males, and higher in patients with *MLH1* or *MSH2* constitutional pathogenic mutation, compared to those with *PMS2* or *MSH6* mutation. Also, the average age at diagnosis is older for patients with *PMS2* or *MSH6* mutation, compared to those with *MLH1* or *MSH2* mutation. For better sensitivity and specificity of identifying Lynch syndrome, several computational prediction models have been developed to calculate the risk of individuals having Lynch syndrome.[17,18] However, these models are difficult to implement in routine clinical practice due to frequent lack of complete clinical information for pathologists at the time of pathology reporting.

A number of international jurisdictions have recommended the testing for dMMR to screen for Lynch syndrome in all CRC patients or in patients diagnosed with CRC <70 years. This includes the Evaluation of Genomic Applications in Practice and Prevention Working Group in 2009,[19] a group of European experts in 2013,[1] the United States Multi-Society Task Force on colorectal cancer in 2014,[4] the European Society for Medical Oncology endorsed by the American Society of Clinical Oncology in 2015[20] and the American College of Gastroenterology in 2015.[21] A growing number of institutions have also started to implement universal testing for endometrial cancer,[22] with emerging evidence for cost-effectiveness of this approach.[23] In Australia, there is no national policy on screening for Lynch syndrome. However, the National Health and Medical Research Council[24] and the New Zealand Ministry of Health[25] recently recommended universal testing for dMMR in all CRCs.

Both IHC for MMR protein expression and MSI analysis can be used for dMMR testing of CRC. A recent comprehensive review in adults with CRC showed the pooled sensitivity (95% confidence interval) for finding cases of Lynch syndrome by IHC, MSI analysis and both methods were 0.91 (0.85–0.95), 0.93 (0.87–0.96) and 0.97 (0.90–0.99), respectively.[26] There is no preference for one approach over another, but because of cost, availability and ability to direct further mutation testing, MMR protein IHC is preferred by most centres.

Cost effectiveness analysis of strategies for Lynch syndrome screening has been assessed in the health care system of various countries, including the USA, the Netherlands and Australia.[27–32] Most studies reported a reasonable trade-off between cost and yield of Lynch syndrome diagnosis for screening strategies testing CRC patients <70 years. The