Clinical Oncology Society of Australia

Position Statement

HUMAN GENETICS SOCIETY OF AUSTRALASIA ... making sense of your genes

Universal tumour screening for evidence of mismatch repair deficiency in colorectal and endometrial cancer:

A national strategy to identify families with Lynch Syndrome

Position

At present, there is no national strategy to support the identification of people with Lynch Syndrome. Reliable, cost-effective and routinely applied tests are available to identify colorectal and endometrial cancers with mismatch repair deficiency (dMMR), which can help identify new families with Lynch Syndrome. We recommend the development of a national strategy of universal dMMR tumour screening in all newly diagnosed colorectal and endometrial cancers. This will allow the identification of families with Lynch Syndrome, as well as inform the clinical care of cancer patients. We recognise the need for education of clinicians and the public about Lynch Syndrome, and the provision of adequate laboratory and clinical genetics resources to enable full ascertainment of Australian Lynch Syndrome families and realise the individual and population-level health benefits of their ascertainment.

A universal colorectal and endometrial cancer dMMR screening strategy has been endorsed by a number of international groups, including the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the National Comprehensive Cancer Network (NCCN) in the United States of America, and the European Society of Medical Oncology (ESMO), as well as nationally in the Royal College of Pathologists of Australasia (RCPA) reporting guidelines. Additionally, this is supported by economic models demonstrating the cost-effectiveness of universal colorectal dMMR screening and dMMR screening of endometrial cancers in persons aged less than 70 years.[1,2,3]

What is Lynch Syndrome?

Lynch Syndrome is a multi-site cancer predisposition syndrome caused by an inherited likely pathogenic or pathogenic variant (mutation) in a DNA mismatch repair (MMR) gene: *MLH1*, *MSH2*, *MSH6*, or *PMS2*. It is the germline mechanism of tumour dMMR and is the most common form of hereditary colorectal and endometrial cancer.

Lynch Syndrome is associated with a risk of colorectal cancer to age 70 years of up to 47% for male carriers; for female carriers the risk of colorectal cancer to age 70 years is up to 37% and the risk of endometrial cancer to age 70 years is up to 30%.[4] There are effective strategies to mitigate the mortality and cancer incidence associated with Lynch syndrome. Regular colonoscopy can reduce the incidence of colorectal cancer by 62% and the mortality of the cancers that still occur by 65%.[5] Endometrial cancer can be prevented by prophylactic hysterectomy once childbearing is complete.

The population estimate of mutations in the MMR genes (1:280) and the known number of adult MMR mutation carriers (~80,000 across Australia)[6] suggest that most of the Australian families with Lynch Syndrome have not yet been identified and will therefore not be accessing the necessary cancer screening and prevention measures. Hence the current approach to Lynch Syndrome identification, using family history-based ascertainment strategies, is failing Australian Lynch Syndrome families.

Additionally, a diagnosis of Lynch Syndrome has prognostic and predictive implications that can alter the clinical care of people with cancer. In early stage colorectal cancer, the extent of colorectal resection and decisions around the role of adjuvant chemotherapy may be influenced by dMMR status.[7] The dMMR status of advanced colorectal cancers also influences treatment decisions, with evidence supporting a progression free survival benefit of immune checkpoint inhibition therapy.[8] Similarly, in early endometrial cancers, dMMR may influence decisions around the addition of chemotherapy to adjuvant radiotherapy[9] and in advanced disease dMMR predicts response to immune checkpoint inhibition therapy.[10]

What tests are available to detect Lynch Syndrome?

Identification of families with Lynch Syndrome starts with a tumour test looking for evidence of dMMR. Individuals whose tumours are found to have dMMR, in the absence of evidence of a somatic cause (see below), should proceed to germline genetic testing for Lynch syndrome.

Tumour screening tests:

- Screening may be performed by immunohistochemical testing of MMR protein expression with interpretation by an experienced Pathologist and consideration of quality control related to testing volume and antibody choice.
- Microsatellite instability (MSI) testing may also be used to screen for dMMR.
- Tumour mutation burden (TMB) testing from emerging comprehensive cancer genomic tests can be used to screen for dMMR.
- *MLH1* promoter methylation (colorectal and endometrial cancer) and/or *BRAF* V600E immunohistochemistry or genetic testing (colorectal cancer only) can help to refine the selection of people for germline MMR gene testing by identifying somatic causes of dMMR.
- Tumour screening is a phenotypic test; it is not diagnostic of Lynch Syndrome.

Germline genetic testing:

Germline genetic testing is the diagnostic test for Lynch Syndrome and requires specialist input and informed consent. Identifying a germline pathogenic or likely pathogenic variant (mutation) in a MMR gene confirms the diagnosis and allows other family members to access germline genetic testing. This facilitates cancer risk stratification and the implementation of risk management strategies. The first step in this process is tumour screening, as outlined above, to identify the appropriate population for germline testing.

What is the current status of tumour-based MMR deficiency screening in Australia?

Access to tumour-based dMMR screening is neither adequate nor equitable in Australia. Variability based on jurisdiction exists. A 2018 survey of Australian laboratories demonstrated that the majority have a MMR immunohistochemical based Lynch Syndrome tumour screening program. However, only half used a universal approach for colorectal tumours. Many respondents indicated they have a screening program in place for endometrial tumours, but nearly half reported this was clinician initiated only.[11] Extending universal screening to all endometrial cancers could increase the number of Lynch Syndrome cases diagnosed by 50%.[12]

There is expertise to undertake tumour dMMR tumour testing in most regions of Australia but for this to be expanded to support a universal dMMR tumour screening strategy resources to scale up capacity will be required. For example, the funding of some tumour testing, eg IHC tests, is available through current pathology Medicare Benefits Scheme (MBS) item numbers. However, there is no support for secondary tumour testing, including *MLH1* promoter methylation testing or screening via microsatellite instability testing (MSI).

Key Summary Points

- Mismatch repair screening should be universally performed on all colorectal and endometrial cancers
- Mismatch repair immunohistochemistry is a screening test; identification of an abnormality mandates further investigation for a somatic and/or germline cause
- Identification of mismatch repair deficiency in a tumour:
    - Influences treatment-related decision for the patient with cancer
    - Allows the identification of families with Lynch Syndrome
- Current ascertainment methods for families with Lynch Syndrome in Australia are poor
- Risk management strategies in Lynch Syndrome are cost effective and reduce cancer incidence and mortality

About COSA

The Clinical Oncology Society of Australia (COSA) is Australia's peak multidisciplinary society for health professionals working in cancer research, treatment, rehabilitation and palliative care with over 1000 members. COSA is recognised as an activist organisation whose views are valued in all aspects of cancer care. We are allied with and provide high-level clinical advice to Cancer Council Australia.

About HGSA

The Human Genetics Society of Australasia (HGSA) was formed by clinicians and scientists in 1977 to provide a forum for the various disciplines collected under the title of Human Genetics including clinical genetics, cytogenetics, genetic counselling, molecular genetics, biochemical genetics, genetics in education and cancer genetics. HGSA is recognised as the peak professional body providing education and training (accreditation) to human genetics professionals.

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