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: a national strategy to identify people with Lynch Syndrome

Position

We recommend the development of a national strategy of universal mismatch repair deficiency tumour screening of all newly-diagnosed colorectal and endometrial cancers to identify families with Lynch Syndrome. Lynch Syndrome is the most common form of hereditary colorectal and endometrial cancer and there are effective strategies to mitigate the mortality and cancer incidence associated with the syndrome.

At present, there is no national strategy to support the identification of people with Lynch Syndrome. Simple tests are available to identify colorectal and endometrial cancers with mismatch repair deficiency, which can help identify new families with Lynch Syndrome.

We recognise that education of clinicians and the public about Lynch Syndrome and provision of adequate laboratory resources and genetics services will be required to enable full ascertainment of Australian families with Lynch Syndrome and realise the individual population-level health benefits of their ascertainment.

What is Lynch Syndrome?

Lynch Syndrome is a multi-site cancer predisposition syndrome due to DNA mismatch repair deficiency caused by inherited mutations in the four DNA mismatch repair (MMR) genes, MLH1, MSH2, MSH6 and PMS2.

The population estimates of mutations in the MMR genes (1:500) and the known number of adult MMR mutation carriers (~3500 across Australia)[1] suggest that most of the Australian families with Lynch Syndrome have not yet been identified and will not be having the necessary cancer screening or accessing effective cancer prevention. Hence the current approach to find families with Lynch Syndrome using family history-based ascertainment strategies is failing Australian families with Lynch Syndrome.

Lynch Syndrome is associated with a risk of colorectal cancer to age 70 years of 47% (36%-60%) for male carriers and 37% (27%-50%) for female carriers and of endometrial cancer of 30% (18%-45%).[2] Regular colonoscopy can reduce the incidence of colorectal cancer by 62% and the mortality of those cancers that still occur by 65%.[3] Endometrial cancer can be prevented by prophylactic hysterectomy once childbearing is complete.

A diagnosis of Lynch Syndrome can also alter the clinical care of people newly diagnosed with colorectal cancer (CRC) by influencing the extent of colorectal resection and the decision around the role of adjuvant chemotherapy for people with Stage II CRCs

demonstrating evidence of MMR deficiency.[4] The MMR deficiency status (somatic or germline) of CRCs may become even more important in future treatment decisions if the programmed cell death ligand (PD-L1) inhibitors live up to their initial promise in the treatment of a range of tumours displaying mismatch repair deficiency[5].

What tests are available to detect Lynch Syndrome?

Identification of families with Lynch Syndrome starts with a tumour test looking for evidence of mismatch deficiency. People whose tumours are found to be mismatch repair deficient, and with no evidence of a somatic mutation, proceed to a germline genetic test looking for a germline mismatch repair mutation.

Tumour testing:

- The tumour test is an immunohistochemical test looking at the MMR protein expression.
- A secondary tumour test, MLH1 promoter methylation (colorectal and endometrial cancer) or a BRAF V600E mutation test (colorectal cancer only) is important to refine the select of people for germline MMR gene testing.
- Tumour testing is not a genetic test but is a phenotypic test that can indicate which people MAY have an inherited predisposition to cancer.

Germline testing:

- Requires genetic counselling and informed consent.
- Finding a germline MMR mutation means other family members are able to have a genetic test to determine their own cancer risk.

A population-based colorectal and endometrial cancer MMR-deficiency screening strategy has been endorsed by a number of guideline groups supported by economic models of cost-effectiveness. Some examples:

- NICE has recently issued its guidance that ALL CRCs in the UK should be tested for Lynch syndrome: "Offer testing to ALL people with colorectal cancer, when first diagnosed, using immunohistochemistry for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair, and to guide further sequential testing for Lynch syndrome"[6]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) has performed a thorough clinical and cost-effectiveness evaluation of MMR deficiency testing for patients with CRC[7] and recommends universal MMR deficiency tumour testing for patients with CRC.[8]

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

Access to tumour-based MMR deficiency screening is not equitable in Australia; it is available in some jurisdictions (Western Australia for colorectal cancer only), partly available in some (some health authorities in NSW; for people diagnosed with colorectal cancer <50years in VIC) and not available at all in most regions of Australia.

A recent Australian survey of all laboratories to determine their current practice and capacity around tumour MMR deficient screening has shown that the majority of the

respondents reported having a routine Lynch Syndrome tumour screening program and nearly half of them used a universal approach for colorectal tumours. Many respondents indicated they have a screening program in place for endometrial tumours, but nearly half of the time this was clinician initiated.[9]

Therefore there is expertise to undertake tumour MMR deficiency colorectal tumour testing in most regions of Australia but for this to be expanded to be able to support a universal MMR tumour screening strategy more resources will be needed to scale up capacity.

Funding of tumour testing, eg IHC tests, is available through current pathology item numbers, but there is no item number to support methylation testing.

What is the current status of germline MMR genetic testing in Australia?

Germline genetic testing is predominantly provided through the publically-funded familial cancer clinics and genetics services in Australia together with a small number of private genetic clinics.

Genetics clinics have experienced a rapid increase in demand for services over the last few years and most have a wait list of some months for new patients.

Funding for genetic testing is predominantly through block funding provided by State governments to the public genetics clinics or by self-pay through private genetics clinics; there is no private health care reimbursement for germline genetic tests. This funding mechanism may change in the future if MSAC supports the issuing of an item number for germline genetic testing.

References

1. The Inherited Cancer Connect Partnership (ICCon) funded by the Cancer Council NSW
2. Møller P, Seppälä T, Bernstein I, Holinski-Feder E, et al. [Mallorca Group (http://mallorca-group.eu)] Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2017 Mar;66(3):464-472.
3. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, De La Chapelle A, Mecklin JP: Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000, 118(5): 829-834
4. Sargent, D.J., et al., Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer. Journal of Clinical Oncology, 2010. 28(20): p. 3219-3226.
5. Le, D.T., et al., *PD-1* Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine, 2015. 372(26): p. 2509-2520.
6. NICE guidelines: Molecular testing strategies for Lynch syndrome in people with colorectal cancer. https://www.nice.org.uk/guidance/DG27
7. Mismatch Repair Deficiency Testing for Patients with Colorectal Cancer: A Clinical and Cost-Effectiveness Evaluation. Ottawa: CADTH; 2015 Sep. (CADTH optimal use report

vol.5, no.3a). https://www.cadth.ca/sites/default/files/pdf/OP0522_d-MMR_Testing_for_CRC_Protocol.pdf

8. DNA mismatch repair deficiency tumour testing for patients with colorectal cancer: recommendations. Ottawa: CADTH; 2016 Aug. (CADTH optimal use report; vol.5, no.3d). https://www.cadth.ca/sites/default/files/pdf/OP0522_dMMR_Report_Recommendations.pdf

9. Lyon Mascarenhas, Gillian Mitchell, Susan Shanley, Alex Boussioutas, Amanda Spurdle, Finlay Macrae, Nicholas Pachter, Daniel Buchanan, Robyn Ward, Stephen Fox, Elaine Duxbury, Rebecca Driessen. Current mismatch repair deficiency tumour testing practices and capabilities: A Survey of Australian pathology providers. Submitted for review to the Asia-Pacific Journal of Oncology.

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.