Molecular Testing of Colorectal Cancer in New Zealand

Minimum standards for molecular testing of newly diagnosed colorectal cancers

Background

Lynch syndrome is the most common cause of inherited colorectal cancer, affecting approximately 3 percent of newly diagnosed cases of colorectal cancer. Yet it is under-recognised in clinical practice. People with Lynch syndrome are also at increased risk of other types of cancer, including endometrial, ovarian and urological cancers. The usual causes of the syndrome are germline mutations in one of four mismatch repair (MMR) genes: MLH1, MSH2, PMS2 and MSH6. MMR genes repair errors that occur during cell division. When these genes are mutated, mutations accumulate and the chance of malignancy increases.

It is possible to test tumours for MMR status by immunohistochemistry or by microsatellite instability (MSI) to work out if the cancer occurred because of Lynch syndrome. Knowing whether Lynch syndrome is the cause is important as it has implications not only for managing the initial tumour but also for subsequent screening of the individual affected and their family members. In addition, an increasing amount of evidence indicates that MMR status may predict how all patients with colorectal cancer, not just those with Lynch syndrome, respond to chemotherapy.

Currently in New Zealand, testing for Lynch syndrome is recommended in those considered to be at high risk of having this condition. This includes people younger than 50 years at diagnosis or with synchronous or metachronous tumours or who have a strong family history of cancer. However, we know that almost a third of colorectal cancer associated with Lynch syndrome occurs in patients who are over 60 years of age (Hartman et al 2013). Current testing will miss these cases. Recent years have seen a growing trend towards universal testing internationally. Both the United Kingdom's National Institute for Health and Care Excellence (NICE) and the American Society of Gastroenterologists have released guidelines recommending universal testing of all new diagnosed colorectal cancers for possible Lynch syndrome (NICE 2017; Syngal et al 2015).

Although MMR-deficient tumours may indicate a possibility of Lynch syndrome, they can also occur in sporadic cancers. In sporadic cancers, loss of MLH1 protein expression may be due to MLH1 promoter abnormalities. *BRAF* V600E mutation or MLH1 promoter hypermethylation testing can detect these cancers, indicating they are not due to Lynch syndrome and that the patient does not require further genetic testing.

Furthermore, molecular testing is also useful in colorectal cancer for both prognostic and predictive reasons, helping inform likely outcomes from both funded and unfunded chemotherapeutic agents. Good evidence indicates that the benefit of 5-FU adjuvant chemotherapy is limited to MMR-proficient (normal MMR) stage II colorectal cancers (Jover et al 2009; Sargent et al 2008). Other evidence shows that *BRAF* V600E mutation is an independent prognostic factor for poor outcome in microsatellite stable colorectal cancer (Ogino et al 2012). For this reason, some – including the American Society for Clinical Pathology and the American Society of Clinical Oncology (Sepulveda et al 2017) – have recently recommended universal *BRAF* V600E mutational analysis. This information can be helpful in making decisions about chemotherapy as it allows more accurate prognostic stratification.

BRAF V600E mutation may also predict whether a patient is likely to respond to anti-epidermal growth factor receptor (EGFR) therapy (De Roock et al 2010).

Good evidence suggests that RAS mutations also predict a negative response to EGFR-targeted monoclonal antibody therapy (De Roock et al 2010) and therefore are essential before considering this therapy. However, we note that these treatments are not currently available in the public sector in New Zealand.

Consultation

Consultation on this document was undertaken in September 2017 with the bowel cancer sector.

Recommendations

1 Test all newly diagnosed cases of colorectal cancer for mismatch repair deficiency preferably on initial biopsy

- Immunohistochemistry for MMR proteins or MSI testing are appropriate methodologies.
- If performing immunohistochemistry, then use a four-panel test for MLH1, PMS2, MSH2 and MSH6.
- If MSH2, MSH6 or PMS2 are abnormal (deficient), then the patient will need genetic testing. For this testing, refer them to the New Zealand Familial Gastrointestinal Cancer Service.
- If MLH1 is abnormal (deficient), then you must perform further testing to differentiate a sporadic cancer from a cancer associated with Lynch syndrome . See recommendation 2.
- If performing MSI testing, then you will need to conduct further testing for a positive result, in line with recommendation 2.
- All laboratories performing these tests should have accreditation from International Accreditation New Zealand (IANZ) and be enrolled in an external quality assurance programme.

2 Undertake *BRAF* V600E mutation analysis or analysis for MLH1 promoter methylation in all newly diagnosed colorectal cancers showing MLH1 protein loss or microsatellite instability

- If the tumour demonstrates MLH1 protein loss or MSI, then perform BRAF V600E mutational analysis.
- Perform testing using a validated assay. Various molecular methods such as PCR, sequencing and mass spectrometry are available for detecting BRAF V600E mutations.
- If the BRAF V600E mutational analysis is negative, then perform MLH1 promoter hypermethylation testing.
- If the promoter hypermethylation testing is negative, then refer the patient to the New Zealand Familial Gastrointestinal Cancer Service.

3 Conduct *BRAF* V600E mutation analysis in all newly diagnosed stage IV colorectal cancers

- MMR-proficient stage IV tumours with *BRAF* V600E mutation have a significantly poorer prognosis, which can be significant information when making decisions about chemotherapy.
- It can be predictive if considering EGFR-targeted monoclonal antibody therapy.

4 Conduct extended RAS mutation testing before considering treatment with EGFR-targeted monoclonal antibodies

- If mutation is present, it is predictive of poor response.

- Because these treatments are not available in the public system, these recommendations do not propose universal testing.

- Molecular technology is developing rapidly so these recommendations should be reviewed in two to three years.

References

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Further reading

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