Detecting Lynch Syndrome in a BowelScreen Population

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Introduction

Lynch Syndrome(LS) is the most common cause of hereditary colorectal cancer (CRC), accounting for 2-4% of all CRC's[1]. LS is an autosomal dominant condition characterised by pathogenic mutations in MLH1, PMS2, MSH2, MSH6 and EPCAM genes, which are involved in the mismatch repair(MMR) pathway.

International guidelines recommend universal testing for Lynch Syndrome in all cases of newly diagnosed CRC[2]. Tumors can be tested with microsatellite instability(MSI) testing or immunohistochemistry(IHC) for MMR proteins.

For tumors with MLH1 deficiency by IHC further testing for BRAF V600 mutation and hypermethylation of MLH1 promotor region can determine if the tumor is likely to be sporadic. If neither are detected or if the tumor is deficient in MSH2 or MSH6 germline testing is the next most appropriate step.

Aim

- To identify the number of CRCs, diagnosed through BowelScreen, tested for Lynch Syndrome and to examine the outcomes of testing at two BowelScreen sites.

Methods

CRCs diagnosed through BowelScreen at two screening sites between 2015 and 2020 were identified. Histopathology reports were utilised to determine if tumors were tested for LS with IHC and the outcomes of testing.

For those found to have MMR deficiency histopathology reports and clinical notes were used to determine if any further investigation took place and the outcomes of these investigations.

Figure 1. Percentage CRC tested for Lynch Syndrome 2015 - 2020

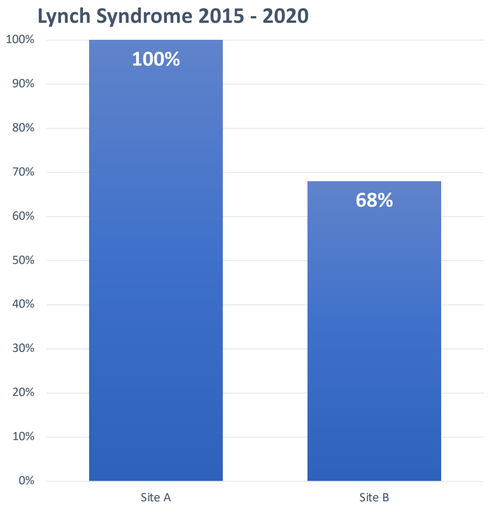
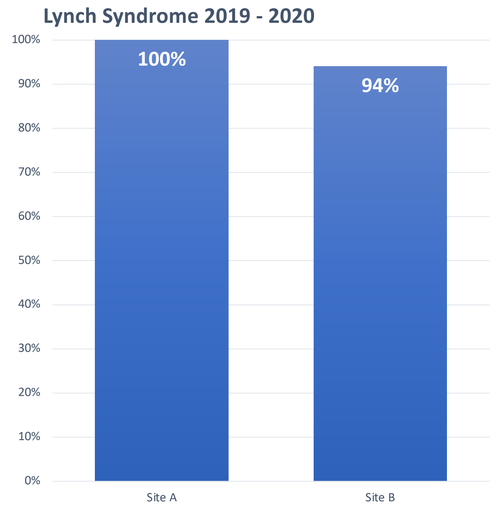


Figure 2. Percentage CRC tested for Lynch Syndrome 2019 - 2020



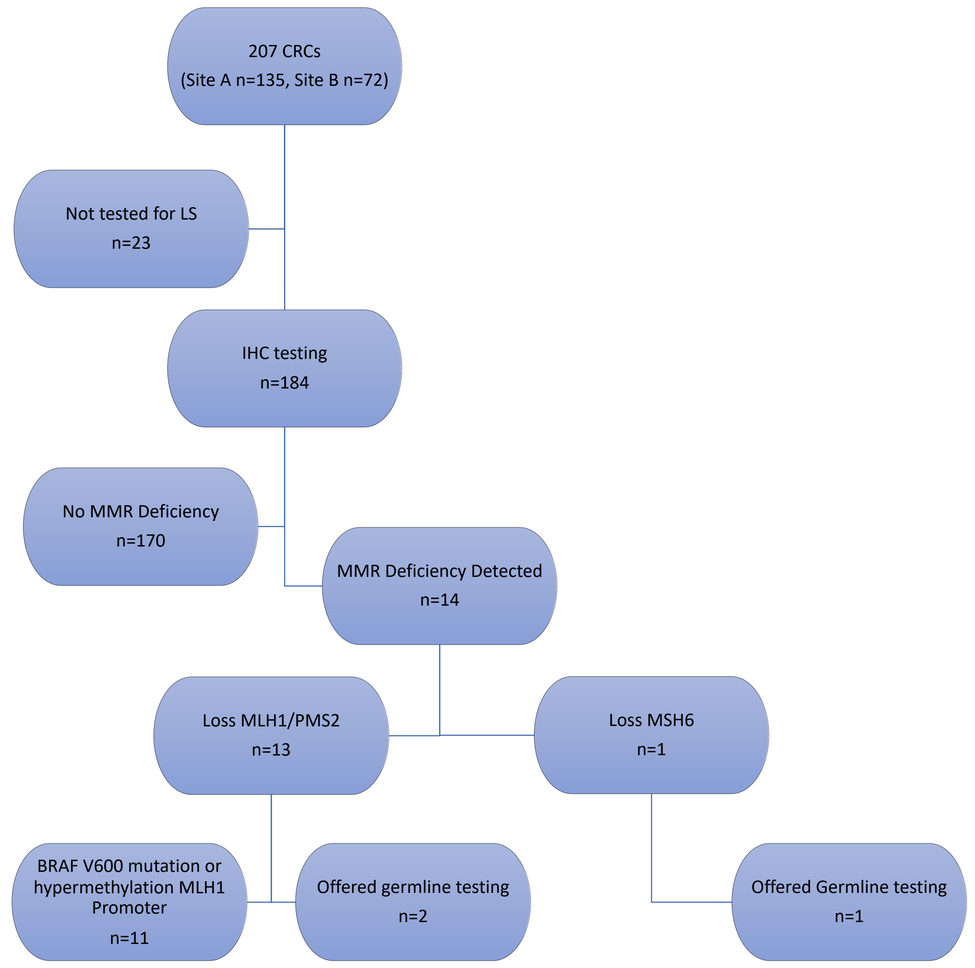
Results

207 CRCs were identified between 2015 and 2020. At site A 100% of CRC's underwent LS testing with IHC compared to 68% of cases in site B. However, in 2019 and 2020 94% of CRCs at site B were tested.

6.7% of CRCs detected through BowelScreen had a deficiency in MMR proteins. Loss of MLH1/PMS2 accounted for 93% of abnormalities. Of these 84% were determined to be sporadic based on either detection of a BRAF V600 mutation(46%) or hypermethylation of the MLH1 promoter region(38%). 1 patient was found to have loss of MSH6

A total of 3 patients were offered germline testing. 2 patients proceeded with testing and 1 declined testing. No germline mutations were detected.

Figure 3. Lynch Syndrome testing and outcomes 2015 - 2020



Discussion

Our study has shown that from 2019 onwards almost all CRCs diagnosed through BowelScreen at the two screening sites were tested for LS with IHC, in keeping with current guidance on universal screening for Lynch Syndrome.

Although only a small proportion of CRCs detected through BowelScreen had a deficiency in MMR proteins it is important that resources and infrastructure are in place to follow up and manage these patients appropriately.

References:

1. Lynch H, Lynch P, Lanspa S, Snyder C, Lynch J, Boland C. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clinical Genetics. 2009;76(1):1-18.

2. National Institute for Health and Care Excellence. Molecular Testing Strategies for Lynch Syndrome in people with Colorectal Cancer. London: NICE Guidance DG 27; 2017.