

Recommendations for Future Research

1) How can interventions including colonic surveillance be risk stratified utilising somatic tumour molecular data or constitutive genomic risk scores?

The stratification of risk in those with a family history of CRC is increasingly being defined through molecular assessment of constitutive mutations and somatic genomic variation in tumours. With the advent of universal MMR testing in standard clinical practice the frequency and intensity of surveillance may be appropriately targeted at those who are truly at high-risk. In order to refine this model further prospective studies incorporating this molecular data and the outcomes of surveillance are required, ideally with randomisation to different strategies.

2) What is the detection rate of pathogenic germline variants in isolated EOCRC cases at different ages of diagnosis?

The diagnostic yield of germline testing may be predicted by age, family history, and patient-related information, however there is limited data of the yield genetic testing in populations defined by age of diagnosis.

3) What is the effect of aspirin and other chemoprophylactic agents in patients at hereditary risk of CRC?

The effect of aspirin in the prevention of cancer in LS patients in the subject of a RCT, however the role of aspirin in the prevention of CRC in other high-risk populations is unclear. Other emerging chemopreventative agents may have significant benefits patients as an alternative to largely procedural preventative modalities.

4) What is the impact of high-quality colonoscopy in CRC prevention in high-risk populations?

There is existing evidence for “experts” being able to complete previously incomplete colonoscopy but better-quality studies are required – stratifying for lesion, operators, comorbidity or other patient factors, such as GA/Propofol etc. for repeat with expert

endoscopists to be of additional value. A related question on the optimal/maximal length of time elapsed between the initial and the repeat to prevent an adverse outcome depending on the expertise and quality of prior colonoscopy. It may be possible to standardise operators (as in BCSP,BSW) with minimal KPIs/Quality and compare this with a non-screening colonoscopist cohort – with randomisation and/or stratification for centre/operator and advanced endoscopic imaging technologies.

5) What methods of surveillance are appropriate, which incorporate the risks and benefits of competing interventions?

Currently colonoscopy is the gold standard mode of surveillance for those at high-risk of CRC. However there exists an array of less invasive methods which may potentially be highly valuable in these populations, including stool testing with FIT, liquid biopsies and advanced imaging techniques which may complement or replace colonoscopy, or be of value in the surveillance of neoplasia in other organs, for example extracolonic malignancy in LS.

6) What is the optimal surveillance interval for those with Lynch Syndrome?

The benefit of surveillance in patients with Lynch Syndrome may predominantly be in either the prevention of CRC, or early diagnosis of CRC, or as a combination of these outcomes. There exist different molecular mechanisms for carcinogenesis, and varying penetrances of the phenotype in this population which require elucidation, and surveillance may be tailored in future accordingly.

7) Is there utility in offering genetic testing to unaffected individuals at high familial risk?

As we progress with molecular characterisation of risk in those with a personal or family history of CRC, we gradually change clinical practice defined by clinical parameters alone, e.g. family history. However the best balance between population screening, identification of variants of uncertain significance, and genetic diagnosis has not yet been defined. ‘Agnostic’ genetic diagnosis is increasingly accessible to patients, and to a wider range of clinicians. The

application of this in higher risk individuals (for example those with a family history of CRC) may facilitate risk-stratified preventative strategies.

8) Should patients with a FH of fewer than 10 adenomas undergo surveillance?

Although a family history of colorectal polyps (in the absence of a classical polyposis phenotype) may be associated with increased CRC risk in relatives, the value of endoscopic surveillance in the mitigation of this risk has not been demonstrated.

What is the detection rate of pathogenic germline variants in isolated EOCRC cases at different ages of diagnosis?

9) How might genotype be used to personalise surgical decision making in those at hereditary CRC risk?

The relationship between genotype and phenotype may help predict desmoid formation in patients with APC mutation, and similarly underlying MMR gene mutation may impact on decision making in colorectal resection of LS patients with CRC. The precise application of genomic information in surgical management may be enhanced by rapid pre-operative genetic diagnosis in patients with CRC and previously undiagnosed hereditary CRC syndromes. It also has the potential to assist decision making in regard to the timing, risks and benefits of surgery in the prophylactic setting.

10) What is the diagnostic yield of germline testing and colonoscopic surveillance in people with rare predisposition syndromes (and their relatives)?

As we improve identification of patients with germline mutations in genes which predispose to multiple polyps, via gene discovery and increased availability of genetic testing, there is recognition of the heterogeneous nature of multiple polyp syndromes, and the requirement to develop gene and phenotype specific interventions.

Implementation and cost issues

The expansion of national screening in the United Kingdom since the previous version of this guideline, national screening has significantly expanded as has our ability to risk-stratify using molecular data. Thus we can safely reassure many patients that frequent colonoscopy may not be necessary, and others who are truly at high-risk of CRC may benefit from more intensive intervention. Somatic testing in Lynch-like syndrome is an example of a precision molecular approach which will likely result in significant clinical resource and cost-savings by recategorizing risk in 60-70% of patients previously considered to be at high-risk.

The implementation of MMR testing for new cases of CRC has opened up clinical pathways from diagnosis of cancer to diagnosis of LS. The NICE DG27 guideline recommended local 'genomics champions' be established within each local CRC MDT to ensure delivery of universal testing for LS[1]. In this guideline we attempt to address some of the infrastructure required to deliver this and other advances in molecular assessment of patient at hereditary CRC risk.

Optimal care as defined in this guideline requires development of local and regional networks of clinicians managing hereditary risk in primary, secondary and tertiary care. In secondary care many institutions operate family history clinics which facilitate patient-centred quality improvement[2], however this should be prioritised to reduce regional variability in provision[3]. Improved access to genomic testing is being facilitated nationally by mainstreaming projects, for example the 100k genomes project led by Genomics England[4]. However in order for clinicians to develop relevant experience of this testing, a structured support network is required linked to tertiary care and the genomic laboratory hubs.

- 1 Molecular testing strategies for Lynch syndrome in people with colorectal cancer (NICE Diagnostics Guidance DG27)
. 2017.<https://www.nice.org.uk/guidance/dg27>
- 2 Adams LK, Qiu S, Hunt AK, *et al.* A dedicated high-quality service for the management of patients with an inherited risk of colorectal cancer. *Color Dis* 2019;;codi.14622. doi:10.1111/codi.14622
- 3 Monahan KJ, Alsina D, Bach S, *et al.* Urgent improvements needed to diagnose and manage Lynch syndrome. 2017;**356**. doi:10.1136/bmj.j1388
- 4 Turnbull C, Scott RH, Thomas E, *et al.* The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ* 2018;**361**:k1687. doi:10.1136/bmj.k1687

