NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG27: Molecular testing strategies for Lynch syndrome in people with colorectal cancer

This guidance was issued in February 2017.

The review date for this guidance is August 2022.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Accelerated update of the guidance - an accelerated update of the Diagnostics Guidance will be planned into NICE's work programme.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

Although the testing strategies recommended in DG27 are in use in the NHS, paired somatic/germline testing for Lynch syndrome using next generation sequencing is becoming available (see section 6.1) and may provide clinical and cost benefits over current practice. It is therefore proposed that this guidance is updated to take account of these new developments.

An accelerated review is proposed as the care pathway has not changed significantly, and much of the modelling work should remain relevant. Therefore, the review should be able to be done in a shorter time than a standard update.

3. Original objective of guidance

To assess the clinical and cost effectiveness of molecular testing strategies for Lynch syndrome in people with colorectal cancer

Current guidance

Adoption recommendations

1.1. 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 (see 1.2 and 1.3). Do not wait for the results before starting treatment.

1.2. If using immunohistochemistry, follow the steps in Table 1.

Table 1: Steps in the immunohistochemistry testing strategy

Step 1	Do an immunohistochemistry 4-panel test for MLH1, MSH2, MSH6 and PMS2	
Step 2	If the MLH1 immunohistochemistry result is abnormal, use sequential BRAF V600E and MLH1 promoter hypermethylation testing to differentiate sporadic and Lynch syndrome-associated colorectal cancers. First do a BRAF V600E test. If the MSH2, MSH6 or PMS2 immunohistochemistry results are abnormal, confirm Lynch syndrome by genetic testing of germline DNA.	If the MSH2, MSH6 or PMS2 immunohistochemistry results are abnormal, confirm Lynch syndrome by genetic testing of germline DNA.
Step 3	If the BRAF V600E test is negative, do an MLH1 promoter hypermethylation test.	
Step 4	If the MLH1 promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.	

1.3. If using microsatellite instability testing, follow the steps in Table 2.

Table 2: Steps in the microsatellite instability testing strategy

Step 1	Do a microsatellite instability test.
Step 2	If the microsatellite instability test result is positive, use sequential BRAF V600E and MLH1 promoter hypermethylation testing to differentiate sporadic and Lynch syndrome-associated colorectal cancers. First do a BRAF V600E test.
Step 3	If the BRAF V600E test is negative, do an MLH1 promoter hypermethylation test.
Step 4	If the MLH1 promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.

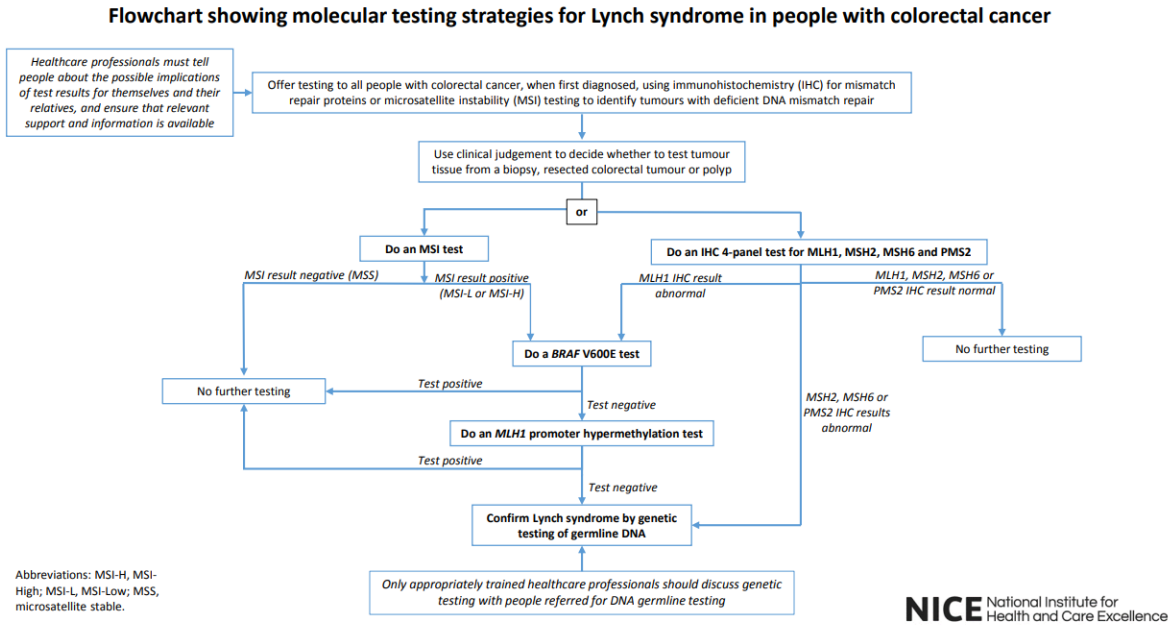
1.4. Healthcare professionals should ensure that people are informed of the possible implications of test results for both themselves and their relatives, and ensure that relevant support and information is available. Discussion of

genetic testing should be done by a healthcare professional with appropriate training.

1.5. Laboratories doing microsatellite instability testing or immunohistochemistry for mismatch repair proteins should take part in a recognised external quality assurance programme.

The recommendations from Tables 1 and 2 are summarised in Figure 1 (NICE DG27 tools and resources).

Figure 1: Flowchart showing molecular testing strategies for Lynch syndrome in people with colorectal cancer



Research recommendations

5.19 The committee discussed the value of developing research recommendations for tumour testing for Lynch syndrome. It considered that further research was unlikely to change its recommendations on molecular testing strategies for Lynch syndrome in people diagnosed with colorectal cancer.

5.20 The committee heard that good communication between colorectal cancer multidisciplinary teams and genetics or pathology laboratories is important for implementing tumour-based testing for Lynch syndrome to ensure that testing and reporting of results is coordinated. The committee noted that similar systems are embedded in breast cancer care pathways, in which reflex testing for human epidermal growth factor receptor 2 (HER2) and BRCA are done as part of the first assessment. The committee therefore wished to encourage centres adopting Lynch syndrome testing strategies to audit and publish their clinical and diagnostic outcomes to ensure that assessment of Lynch syndrome is timely and appropriate.

5.21 The committee heard from the clinical experts that centres already offering tumour-based testing for Lynch syndrome often carry out both MSI and IHC testing on samples. The committee encouraged these centres to publish their previously generated comparative results.

4. Implications for other guidance producing programmes

No overlaps were identified during internal consultation.

5. New evidence

The search strategy from the original diagnostics assessment report was re-run on Ovid MEDLINE, Embase, Web of Science, Cochrane and Health Management Information Consortium databases. References from January 2016 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

Clinical experts advised that the recommended molecular testing strategies for Lynch syndrome in people with colorectal cancer have not changed since the guidance was published in 2017, although there is now an NHS England genomic medicine service with a commissioned test directory which could help to deliver the recommendations from DG27.

In addition to the recommended molecular testing strategies, next generation sequencing (NGS) for mismatch repair (MMR) genes is available in NHS genomic laboratory hubs and some specialist centres. NGS can be applied to either somatic or germline MMR gene testing, and provides more clinical information in fewer steps. Using NGS approaches may also address some of the limitations of germline MMR gene testing, such as the detection of the Lynch-like syndrome cases which make up a substantial portion of MMR deficient cases (see section 6.2). Clinical experts advised that NGS may currently be used after the Lynch syndrome testing pathway, either because of Lynch-like syndrome or to inform choice of therapy.

Paired tumour/germline testing is an approach in which both somatic and germline testing are done simultaneously (using NGS) as a first step in the pathway. This could provide an 'all-in-one' approach which would be able to provide information about genetic diagnoses (like Lynch syndrome) as well as inform individualised

treatment and prognosis. Paired testing is currently only available in specialised centres in the UK, although clinical experts suggested that it is routine practice in the USA. Clinical experts predicted that availability of paired testing using NGS will increase over the next 5 years.

6.2 Clinical practice

Under the current DG27 recommendations, a sequential BRAF V600E and MLH1 promoter hypermethylation test is recommended after abnormal IHC or MSI testing. Experts highlighted that these tests give the same information (whether or not the tumour is sporadic), and therefore that it may be inefficient to follow the guidance and test for both. This is especially relevant as the results of the BRAF test are available much faster than the MLH1 promoter hypermethylation results (which can take up to 2 months). The EAC note that a comparison of the 2 tests was done as part of the initial DG27 appraisal.

The advent of targeted therapies for colorectal cancer such as pembrolizumab has made identification of MMR deficient tumours more important. There may be differences in treatment response between sporadic MSI tumours and Lynch syndrome tumours, therefore increasing the clinical value of the information gained by testing for Lynch syndrome. An evaluation of the DG27 guidance pathway in a population of 5.2 million found that the results of Lynch syndrome screening were used to inform treatment pathways (West 2021).

Overall, no changes to the diagnostic and care pathway for people diagnosed with colorectal cancer were identified regarding molecular testing strategies for diagnosing Lynch syndrome, although clinical experts advised that NGS and paired testing would soon replace current practice.

Lynch-like syndrome

Lynch-like syndrome describes a subgroup of patients with colorectal cancer or other Lynch syndrome-related tumours that manifest with MMR deficiency (MSI and/or loss of MMR protein expression) that is neither explained by somatic MLH1 promoter hypermethylation, BRAF pathogenic variant or a detectable pathogenic constitutional variant in an MMR gene. Such patients cannot readily be assigned to either the sporadic or inherited MMR deficiency categories. Clinical experts advised that this occurs in approximately 1 out of 3 people with colorectal cancer, and according to the British Society of Gastroenterology guidelines for the management of hereditary colorectal cancer, an estimated 59% of deficient MMR colorectal cancer cases are unexplained and categorised as Lynch-like syndrome (Monahan et al. 2020). Lynch-like syndrome was not discussed in DG27 and clinical experts advised that further testing for Lynch-like syndrome may be a necessary addition to any future pathway. Clinical experts noted that an NGS approach to testing for Lynch syndrome could also address Lynch-like syndrome.

6.3 New studies

Due to the large number of records identified from the searches, the EAC consulted clinical experts to identify 4 main areas of interest to focus the review:

- IHC versus MSI testing
- BRAF V600E followed by MLH1 hypermethylation testing
- Lynch-like syndrome
- Paired testing (somatic and germline testing)

The EAC identified 51 relevant full-text records, of which 28 were full publications and 23 were abstracts. One systematic review was considered to have relevance to all 4 areas.

Eikenboom 2022 is a large systematic review and meta-analysis of IHC followed by MMR germline analysis for Lynch syndrome in 58,580 colorectal carcinomas across 56 studies from around the world. In studies that completed all diagnostic stages, unexplained MMR deficiency constituted just 0.61% of cases. The review noted that in the future, whole tumour sequencing will also likely contribute to finding previously missed germline or somatic variants. The authors recommended further research be conducted to accurately characterise the small and heterogenous group of people with unexplained MMR deficiency.

The EAC also highlighted 1 prospective longitudinal cohort study which was designed to evaluate the pathway recommended in DG27. In West 2021, 2,791 people in the Yorkshire and Humber region over 50 years old with newly diagnosed colorectal cancer were followed through the screening pathway for Lynch syndrome. The authors concluded that the DG27 pathway was deliverable at scale. MMR deficient tumours were identified in 15% of cases. In the final analysis, 2.9% of people had an indication for germline testing.

IHC versus MSI testing

The EAC identified 11 new studies relating to MSI versus IHC testing, consisting of 9 retrospective cohort studies and 2 prospective studies. Generally, concordance between the methods was found, although the degree of concordance varied between studies. Choice of method may depend on local practice and availability, but IHC was noted to be a cheaper option in 3 publications (Chen 2018; Signoroni 2019; Tantoglu 2018). Two studies recommended using both techniques to provide the most reliable data (Bai 2020; Mathews 2019).

BRAF V600E and MLH1 Promoter Hypermethylation testing

The EAC identified 5 new studies relating to BRAF V600E and MLH1 testing.

Three of the 5 studies were from China, and several publications noted that genetic differences in Chinese populations compared to Western populations may have an effect on screening efficacy. Dong 2020, Wang 2021, and Xiao 2020 were retrospective cohort studies of people with colorectal cancer comparing BRAF V600E testing to MLH1 promoter hypermethylation testing. The studies found that BRAF mutation testing alone is less effective in Chinese populations than MLH1 testing alone or a hybrid approach (using both methods), and generally combined methods were recommended.

Adar 2017 was a prospective cohort study of 1011 colorectal cancer tumours in the USA, characterising the correlation between BRAF and MLH1 testing. Overall concordance was 81%, but a hybrid approach was recommended to reduce unnecessary genetic counselling and improve screening yield.

Lynch-like syndrome

The EAC briefly reviewed evidence on the diagnosis and management of people with Lynch-like syndrome. Six studies were identified that related to Lynch-like syndrome.

Golubicki 2021 was a small case series of 15 patients in Argentina and Spain focusing on people less than 40 years old with colorectal cancer. Germline and tumour sequencing was performed to characterise the somatic variation of Lynch-like syndrome. The study identified intrinsic biological differences between Lynch-like syndrome with and without somatic alterations that could help target treatment.

Guillerm 2020 was a small case series of 16 patients with Lynch-like syndrome in France looking at the molecular mechanisms of underlying Lynch-like syndrome using NGS. Authors proposed an algorithm for research purposes for assessing people with Lynch-like syndrome and their relatives.

Lefol 2021 was a case series of 113 colorectal cancer tumours from people suspected of having Lynch-like syndrome in France. Somatic MMR alterations (mainly MLH1 and MSH2) were found in 86% of cases, including “double hits” in 64%.

Xicola 2020 was a combined prospective and retrospective case series of 654 colorectal cancer tumours from people in the USA. Both tumour and germline mutation analysis were done). Authors summarised that Lynch-like syndrome seems to be a heterogenous phenotype with a significant number of cases harbouring mutations in genes that maintain genome integrity.

Xu 2020 was a case series of 81 colorectal cancer tumours from people in China using a multigene panel test. In the Lynch-like syndrome group, a total of 52 variants were detected in 44 (54%) people. The proportion of early-onset patients was significantly higher among the Lynch syndrome probands than among the Lynch-like

syndrome probands. The proportion of primary colorectal cancer developed in the rectum was higher in the Lynch-like syndrome group than in the Lynch syndrome group. Authors concluded that Lynch-like syndrome should be classified as a mixed entity containing cases of Lynch syndrome, other hereditary cancer syndromes and sporadic colorectal cancer.

Yao 2021 was a retrospective cohort study of 1,294 colorectal cancer tumours from people in China, using MMR IHC and NGS to develop a stratification algorithm for differentiating Lynch syndrome and Lynch syndrome mimics. MMR IHC was performed on all tumours which were then sorted by cause (MMR deficient versus MMR proficient). Diagnoses were Lynch syndrome (8 cases), suspected Lynch syndrome (13 cases), Lynch-like syndrome (6 cases), familial colorectal cancer type X (3 cases), and sporadic colorectal cancer (4 cases).

Paired tumour/germline testing

The EAC found 5 studies relating to paired testing, all from the USA.

Three studies highlighted the potential benefits of paired testing. Barrus 2022 was a retrospective chart review of 6,556 people that highlighted how tumour testing did not always lead to germline testing for those who may have Lynch syndrome (76% of people with tumour testing suggestive of Lynch syndrome were not referred for germline testing. Of 10 people who then elected to have germline testing, 3 had Lynch syndrome which would have been missed). Conversely, the case series reported in Dixon 2021 investigated the clinical utility of tumour sequencing in the diagnosis and management of suspected Lynch syndrome. They reported that almost half of the cases identified by tumour sequencing could not be explained by germline variants, and suggested that this supports integrating tumour sequencing into Lynch syndrome screening programmes. Pearlman 2021 was a prospective screening study comparing MSI with IHC, but also included multigene panel testing for 1,462 participants. The authors concluded that tumour testing with MSI or IHC alone was insufficient, and would have missed 39% of people with pathogenic germline variants detected using the multigene panel.

Gray 2018 and Salvador 2019 were retrospective studies examining the use of paired testing approaches. In Gray 2018, a custom NGS panel 'TumorNext-Lynch-MMR' was used to do paired testing on 58 samples. The panel was found to have high concordance with other NGS panels (sensitivity: 96%, specificity 100%). Authors concluded that the assay could differentiate between somatic and germline mutations, classify variants and resolve discordant cases. Salvador 2019 was a case series of 375 people with colorectal cancer and 327 people with endometrial cancer having paired testing of genes associated with Lynch syndrome. Paired testing identified a cause of MMR deficient tumours in 76% and 61% of people without and with prior Lynch syndrome germline testing, which authors stated supported

inclusion of both tumour and germline sequencing in the Lynch syndrome testing algorithm.

6.4 NICE's research commissioning activities

No reports were commissioned for DG27.

7. Summary of new evidence and implications for review

The new evidence identified largely supports the efficacy and clinical utility of the pathway currently described in DG27. No new data was found to support the use of either IHC or MSI over the other. Studies investigating BRAF V600E and MLH1 testing supported a hybrid approach using both methods. Validation of the clinical pathway recommended in DG27 found that it was deliverable at scale.

However, the current pathway does not provide guidance on how to identify people with Lynch-like syndrome, who make up a significant proportion of people with MMR deficient tumours. Additionally, the advent of NGS and paired somatic/germline testing may allow more comprehensive genetic testing in fewer steps, which could provide clinical and cost benefits. Clinical experts gave the opinion that these new testing strategies are likely to be adopted within NHS current practice within the next 5 years. Therefore, an update of DG27 could account for the changing clinical landscape and address Lynch-like syndrome.

8. Implementation

NGS is currently only available in genomic laboratory hubs and certain specialist centres. Clinical experts advised that it will become more widely available over the next 5 years.

9. Equality issues

In DG27 the following equality issues were noted:

- Women with Lynch syndrome have an increased incidence of gynaecological cancers.
- Older people have an increased risk of colorectal cancer and other Lynch syndrome associated cancers. Microsatellite instability is more common in colorectal cancer tumours in older people.

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	Yes
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	No
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Suspected cancer: recognition and referral (2021) NICE guideline NG12

Colorectal cancer (2020) NICE guideline NG151

Colorectal cancer (2022) Quality Standard QS20

Testing strategies for Lynch syndrome in people with endometrial cancer (2020) Diagnostics guidance DG42

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (2017) Technology appraisal TA439

Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer (2021) Technology appraisal TA668

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (2021) Technology appraisal TA709

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (2021) Technology appraisal TA716

In progress

Nintedanib for previously treated metastatic colorectal cancer [ID1030]. Technology appraisal. Publication date to be confirmed.

Nivolumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]. Technology appraisal. Publication date to be confirmed.

Quantitative faecal immunochemical tests to guide colorectal cancer pathway referral for people with a change in bowel habit or abdominal pain. Diagnostics guidance GID-DG10036. Publication date to be confirmed.

Regorafenib for previously treated metastatic colorectal cancer [ID4002]. NICE technology appraisal guidance. Awaiting development

Suspended/terminated

Atezolizumab for treating metastatic colorectal cancer after 2 therapies [1298]. Technology appraisal. Publication date to be confirmed.

Colorectal cancer (metastatic) - MABp1 (after previous treatment) [ID917]. Technology appraisal. Publication date to be confirmed.

Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency [ID1071]. NICE technology appraisal guidance. Publication date to be confirmed.

Registered and unpublished trials

No relevant ongoing trials were identified.

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