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Heart of England FT	General	General	Role of IMRT in treated nodal recurrence	Thank you for your comment. We have included methods for treating metastases as a key issue in the scope. The guideline committee will have the opportunity to select relevant treatments for nodal recurrence for the evidence review.
Heart of England FT	General	General	Pelvic clearance and sacretomy for locally advanced & recurrent rectal cancer	Thank you for your comment. We agree this is an important issue. We have added a question to the scope on the effectiveness of exenterative surgery for locally advanced or recurrent rectal cancer.
Medtronic UK	General	General	This may be more appropriate to consider in a related NG12 guideline entitled ' Suspected cancer_ recognition and referral (2015)	Thank you for your comment. It is unclear what aspect of the scope you are specifically referring to. However, consideration has been given to which aspects of the scope would be better addressed within NG12.
Royal College of General Practitioners	General	General	The guideline update does not appear to have any comment re the faecal blood testing (not normally available to primary care) and its role in diagnosis. A recent systematic review suggest detection rates using this method appear to depend on location of cancer in the colon Hirai, H.W., Tsoi, K.K.F., Chan, J.Y.C., Wong, S.H., Ching, J.Y.L., Wong, M.C.S., Wu, J.C.Y., Chan, F. K. L., Sung, J. J. Y. and Ng, S.	Thank you for your comment. Faecal occult blood testing for suspected colorectal cancer is covered in NICE guideline NG12 and for this reason was not included in the scope of this guideline.

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			C. (2016), Systematic review with meta-analysis: faecal occult blood tests show lower colorectal cancer detection rates in the proximal colon in colonoscopy-verified diagnostic studies. Aliment Pharmacol Ther, 43: 755–764. doi:10.1111/apt.13556	
British Society of Gastroenterology	General	General	Again as discussed at Stakeholders meeting, gastroenterologist ought to be a full rather than co-opted member of the Committee – they are involved in diagnosis, management (stenting) and managing consequences of treatment.	Thank you for your comment. We agree that the gastroenterologist should be a full member of the committee and have amended our constituency to include this as a full member role.
Biocompatibles UK Ltd	General / intervention	General	More consideration should be given to loco regional treatments for metastatic disease to liver (SIRT, TACE) and lung metastases (Cryoablation)	Thank you for your comment. Loco-regional treatments for liver and lung metastases are covered by the key issue "methods for treating metastases".
Biocompatibles UK Ltd	General / practice	General	Disease profiling should occur at the point of diagnosis and should encompass: molecular profiling, location of primary (right versus left), genotyping etc. Cost saving achieved through personalisation of intervention based on outcome of profiling. Treatment personalisation may lead to enhanced outcome for patients.	Thank you for your comment. We anticipate this issue will be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.
Biocompatibles UK Ltd	General / practice	General	A treatment plan should be configured at the point of diagnosis which stretches beyond first-line.	Thank you for your comment. This issue should be covered by key question 2.1: the use of molecular

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			Disease profiling will enable physicians to produce better treatment plans improving outcomes by reducing the time between progression of disease and initiation of treatment.	biomarkers to guide chemotherapy choice.
Biocompatibles UK Ltd	General / practice	General	With the evolving treatment landscape, MDT review of disease progression cases should take place after progression of 1st line in mCRC Patients may derive benefit from locoregional intervention of lung metastases and locoregional therapies of breakthrough liver disease. Guidelines should make reference that after progression of disease clinical studies in the setting should be considered and make specific reference to EPOCH. Involvement of the MDT will enable better recruitment of patients into studies.	Thank you for your comment. Although this is an interesting area this was not identified as a priority for inclusion during our initial searches of the published evidence or at the stakeholder workshop. We anticipate that locoregional interventions for lung or liver metastases would be covered by the key issue "methods for treating metastases".
Bristol-Myers Squibb Pharmaceuticals Limited	1	26	Reference should be added specifically to DG27 recently issued by NICE.	Thank you for your comment. Reference to DG27 is made in the related NICE guidance section.
Roche Diagnostics Ltd	2	10 - 14	We would like to request that the committee include all patients with a history of colorectal cancer, microsatellite instability (MSI) or mismatch repair (MMR) for pathologic staging in the Diagnosis section of the guideline.	Thank you for your comment. We anticipate this issue will be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.

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Medtronic UK	2	10 - 13	Consider the role of capsule colonoscopy for incomplete or refused colonoscopy as a diagnostic intervention; especially in view of the "2WW pathway' and service delivery challenges in meeting this pathway's targeted timeline	Thank you for your comment. This topic was not prioritised for inclusion because capsule colonoscopy is not commonly used in clinical practice and we think there would be insufficient evidence on which to base useful recommendations.
Bristol-Myers Squibb Pharmaceuticals Limited	2	8	Emerging evidence suggests that biomarkers are important for their prognostic (i.e. BRAF) and predictive (i.e. dMMR/MSI status) impact.[1-3].	Thank you for your comment. We anticipate this issue should be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.
Bristol-Myers Squibb Pharmaceuticals Limited	2	10	Reference to DG27 should be added in that NICE recommends molecular testing to identify potential Lynch syndrome in patients presenting with a new diagnosis of colorectal cancer. The tests recommended by NICE include the widely available IHC and PC methods (see DG27). Although Lynch syndrome is an inherited condition and DG27 was developed primarily to identify these patients in order for them to receive appropriate risk-reducing interventions, it will also identify sporadic dMMR/MSI cases and in turn, determine appropriate adjuvant or systemic therapy in this niche group of patients.	Thank you for your comment. This section is a brief overview of the management of colorectal management and not meant to cover the fine detail. Reference to DG27 is made in the related NICE guidance section later in the document.
Roche Diagnostics Ltd	3	29 - 30	We would like the committee to consider that there is initial data which correlates well with published values and suggests that EGFR ligands are predictive of therapy response[1].	Thank you for your comment. This issue should be covered by key question 2.1: the use of molecular

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			Reference: D J Jonker, et al. Epiregulin gene expression as a biomarker of benefit from cetuximab in the treatment of advanced colorectal cancer. British journal of Cancer 2014, 110, 648–655 | doi: 10.1038/bjc.2013.753	biomarkers to guide chemotherapy choice.
Bristol-Myers Squibb Pharmaceuticals Limited	3	2	As above; Reference to DG27 should be added that NICE recommends molecular testing for Lynch syndrome in patients presenting with an initial diagnosis of colorectal cancer. There is an advantage in performing upfront/reflex testing in line with DG27 guideline in order to identify both germline (Lynch) and sporadic dMMR/MSI patients. Further, emerging evidence suggests that patients with dMMR/MSI-H mCRC benefit less from first-line chemotherapy and have a shorter overall survival than patients with pMMR CRC in the metastatic setting.[4-9]. Due to advancements in biomarker research and a more comprehensive understanding of the tumour microenvironment, immuno-oncology therapies such as checkpoint inhibitors are in the process of filing with the European regulatory agencies, and have been granted regulatory approval in the USA[10-11]. These new treatment options could provide an alternative for patients who are poor responders to the current standard of care treatment available on the NHS. Ongoing drug development is in progress in the lymphocyte-activation gene 3 (LAG3) and Indoleamine 2,3-	Thank you for your comment. Reference to DG27 is made in the related NICE guidance section. We believe there is insufficient evidence to make recommendations about the listed immuno-oncology therapies at this stage and this issue was not prioritised for inclusion. In addition these treatments will almost certainly be covered by technology appraisals once they receive marketing authorisation.

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			dioxygenase (IDO) checkpoint pathways and agents targeting these pathways may become available in the future[12-13].	
Royal College of Pathologists (UK)	4	21 - 22	Small cell carcinoma is a form of neuroendocrine carcinoma, so these would be best combined as "People with pure small cell carcinoma, *or other pure neuroendocrine carcinomas,* of the colon and rectum." Inclusion of the word "pure" is important as mixed adenoneuroendocrine carcinomas (MANECs) typically behave like adenocarcinomas and should be included.	Thank you for your comment. The suggested change has been made.
Bristol-Myers Squibb Pharmaceuticals Limited	4	7	There are other groups of high risk syndromes that need to be considered in addition to Lynch Syndrome: - MUTHYH-associated polyposis - Peutz-Jeghers syndrome (PJS) - Juvenile polyposis syndrome (JPS) - Serrated polyposis syndrome (SPS)	Thank you for your comment. The surveillance review did not identify evidence for treatments in these other high risk syndromes – however trial evidence exists for chemoprevention in Lynch syndrome which should enable evidence based recommendations.
British Society of Gastroenterology	4	13	As discussed at Stakeholders meeting, it seems odd to include just patients with Lynch syndrome and not other hereditary syndromes (FAP, MYH etc). This is especially the case as only chemoprevention is discussed and not further management and international Guidelines are about to be published.	Thank you for your comment. The surveillance review did not identify evidence for treatments in these other high risk syndromes – however trial evidence exists for chemoprevention in Lynch syndrome which should enable

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				evidence based recommendations.
Bristol-Myers Squibb Pharmaceuticals Limited	4	15	Please add: adults diagnosed with CRC who receive molecular testing for Lynch syndrome and their results indicate that they have sporadic dMMR/MSI (with or without BRAF mutation). As noted above, drug development is ongoing and dMMR/MSI-H mCRC specific treatments have been granted regulatory approval in the US[10-11]. Please note NICE are currently appraising nivolumab for dMMR/MSI-H mCRC [ID1136], therefore the guidance update should explicitly include the above group.	Thank you for your comment. We believe there is insufficient evidence to make recommendations in a clinical guideline about the listed immuno-oncology therapies at this stage - and this topic would be more appropriate for the NICE technology appraisal process. We are aware of the mentioned NICE technology appraisal and we will review it when published.
Bristol-Myers Squibb Pharmaceuticals Limited	4	19	Paediatric population with Lynch syndrome and constitutional mismatch repair deficiency syndrome should be within scope. This is especially important for families who have been identified as having Lynch syndrome via the DG27 pathway. Their children may be predisposed to having the condition. Education and communication for the paediatric patients with the hereditary condition is important for improving compliance and outcomes in this group[14].	Thank you for your comment. Whilst this is an important issue the guideline excludes the management of children aged 18 or under due to the different way in which services are organised and delivered for children and young people with cancer. We have changed scope to make it clear that all children under 18 are excluded.

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Heart of England FT	5	General	Management of patients with peritoneal disease either primary or recurrent and role of HIPEC and cyto reductive surgery	Thank you for your comment. This issue is most relevant to those with appendicial tumours and this group is excluded from the scope. This is the potential to address this issue under key question 4.3 if the guideline committee agree it is a priority.
Bristol-Myers Squibb Pharmaceuticals Limited	5	18 - 20	- Reference should be added in DG27 and testing for dMMR/MSI-H status and Lynch syndrome. - Advancement of biomarker research and understanding of the tumour micro-environment has led to the exploration and approval of immuno-oncology treatments in specific cohorts of patients, e.g. dMMR/MSI-H mCRC patients[10-11]. Therefore, the treatment of metastatic colorectal cancer according to biomarker status should be included in the final scope. - Testing for dMMR/MSI in patients who have metastatic colorectal cancer will help clinician decision making for suitability for adjuvant therapy.	Thank you for your comment. Reference to DG27 is made in the related NICE guidance section. This issue should be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.
Newcastle University	5 (& P7 table Pt 1)	9 - 11	**This response by Professor Sir John Burn is submitted on behalf of the following:**	Thank you for this information. We will consider this evidence alongside the results of our

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			Professor Sir John Burn, MD FRCP FRCPE FRCOG FRCPCH FMedSci Professor of Clinical Genetics Institute of Genetic Medicine, Newcastle University International Centre for Life, Newcastle upon Tyne, NE1 3BZ T: +441912418734 E: john.burn@newcastle.ac.uk Professor Peter Sasieni, MA PhD Professor of Biostatistics & Cancer Epidemiology Deputy Director of Barts Clinical Trials Unit Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine Charterhouse Square, EC1M 6BQ, London E: p.sasieni@qmul.ac.uk Professor Jack Cuzick, PhD, FRS CBE John Snow Professor of Epidemiology Director, Wolfson Institute of Preventive Medicine Head, Centre for Cancer Prevention Charterhouse Square, EC1M 6BQ, London E: j.cuzick@qmul.ac.uk Professor D Timothy Bishop Ph.D. FMedSci Director, Leeds Institute of Cancer and Pathology School of Medicine, University of Leeds	literature searches for inclusion in the guideline.

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			Cancer Genetics Building, St James's University Hospital, Beckett St, Leeds, LS9 7TF E: tim.bishop@cancer.org.uk Professor Karen Brown Department of Cancer Studies, University of Leicester Leicester, LE2 7LX *Chair of the UK Therapeutic Cancer Prevention Network* *Member of NCRI Screening, Prevention and Early Diagnosis Advisory Group and the Screening and Prevention Sub-group of the NCRI Colorectal Cancer Clinical Studies Group* E: kb20@leicester.ac.uk Professor Mark Hull Section of Molecular Gastroenterology Leeds Institute of Biomedical & Clinical Sciences St James's University Hospital Leeds, LS9 7TF *NCRI Colorectal Cancer Clinical Studies Group Chair* *NIHR CRN: Gastroenterology National Lead* E: M.A.Hull@leeds.ac.uk Farhat Din MBChB MD FRCS Senior Lecturer & CSO Senior Fellow Honorary Consultant Surgeon Academic Coloproctology, Western General Hospital	

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			Crewe Rd S, Edinburgh, EH4 2XU E: Farhat.Din@ed.ac.uk Professor Ann C Williams *BSc PhD* Professor of Experimental Oncology Colorectal Tumour Biology Group, University of Bristol University Walk, Bristol, BS8 1TD E: Ann.C.Williams@bristol.ac.uk Dr Mangesh Thorat, MBBS, MS(Surgery), DNB (Surgery), MNAMS, PhD Deputy Director (Clinical) - Barts Clinical Trials Unit Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine Barts & The London School of Medicine and Dentistry Queen Mary University of London Charterhouse Square, London EC1M 6BQ E: m.thorat@qmul.ac.uk *Page 5 Lines 9-11* *Prevention of colorectal cancer* *-Role of aspirin in the prevention of colorectal cancer in carriers of Lynch syndrome (hereditary nonpolyposis colorectal cancer)* *Page 7 Table Point 1*	

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			NEW Role of aspirin in the prevention of colorectal cancer in carriers of Lynch syndrome (hereditary nonpolyposis colorectal cancer) Review evidence: new area in the guideline **Our recommendation is that adults with a pathogenic mismatch repair gene defect predisposing to Lynch syndrome should be advised that there is convincing evidence that daily aspirin reduces the risk of colorectal and other cancers associated with this condition. The risk of colorectal cancer in Lynch syndrome is around 2% per annum from the age of 25 years. Regular aspirin reduces this risk by about half. The benefits take around three to five years to become evident. There is ongoing research to establish the optimal dose and duration. For those not involved in this research, a pragmatic recommendation is to commence daily 75mg enteric coated aspirin in consultation with their general practitioner.** **It is recommended that H pylori testing be undertaken at commencement with appropriate eradication treatment if needed as this chronic and common infection is associated with a low grade gastric inflammation which increases the risk of gastric irritation by aspirin and is associated with an increased risk of gastric cancer in Lynch syndrome. Approximately 0.1% of aspirin users suffer a gastric bleed each year. This is more common with higher doses and in the people**	

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			over 65 years of age. The benefits of aspirin continue to be apparent for several years after discontinuation. To minimise the risk of adverse events, aspirin use should be decreased or stopped after the age of 70. **Very rarely, people suffer a bleed from vessel inside the skull. The risk of a stroke due to this cause is increased if people are taking any dose of aspirin. It is estimated that the extra risk is around 1 in 14,000 per annum in individuals aged 50 to 70, and much lower in those younger than 50 years of age. This risk may be associated with hypertension. People on aspirin should have their blood pressure checked regularly and receive treatment to reduce this into the normal range if necessary. The benefits of aspirin in reducing the more common thrombotic strokes and in preventing myocardial infarction more than offset the adverse effects in the over 50's** **Some people are sensitive to aspirin or are receiving other treatments which may interact such as anticoagulants. There is evidence to support the view that other anti-inflammatory drugs such as ibuprofen will also reduce cancer risk. If aspirin causes indigestion or abdominal discomfort, a proton pump inhibitor such as omeprazole can be prescribed. This is not thought to reduce the protective effects of aspirin.**	

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			There is extensive ongoing research into the possible mechanisms of the therapeutic cancer prevention with aspirin. The long lead time is thought to be the result of enhanced destruction, either by the immune system, apoptosis or both, of stem cells in the colonic crypts that carry mutations which make future neoplastic change more likely. There is widespread professional agreement that regular aspirin prevents colorectal cancer. [1] The risk of colorectal cancer in people with a pathogenic mismatch repair gene defect, a form of CRC predisposition known as Lynch syndrome (LS), is around 2% per annum from the age of 25. The CAPP2 trial began recruiting in 1998 and extended to 43 centres in 16 countries. One thousand and nine LS patients were randomized to either 600 mg daily aspirin or placebo and 30 g of a resistant starch, Novelose, for 2–4 years with a planned follow-up to 10 years. Analysis of adenomas and cancers at the end of the intervention stage revealed no significant reduction in adenomas and a non-significant excess of major bleeding events (7 versus 5) offset by a reduction in probable occlusive events. [2] A subsequent report analysed cancers across the cohort when the first recruits reached the planned 10-year follow-up mark giving a mean follow-up of 55.7 months for the group as a whole. Patients randomized to aspirin had risk reduction of up to 60% compared to placebo with a beneficial effect being seen for all cancer related to	

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			the genetic predisposition such as endometrial and upper gastrointestinal cancers. [3] The last of the CAPP2 recruits began treatment in 2006. The final analysis covering 10 years follow-up for the whole study population is being prepared for publication. Of the 861 Lynch syndrome patients who agreed to be randomised to the aspirin limb of the factorial designed trial, 427 received 600mg aspirin daily while 434 received placebo. With a small number of exceptions, the population remained blind to the dose they received. Most did not receive aspirin after the end of the intervention period. A total of 130 LS cancers have now occurred in this study group, 109 of which occurred during the 10 year follow up window. Of the latter group, 47 were in the aspirin group and 62 in the placebo group.	
Newcastle University	5 (& P7 table Pt 1)	9 - 11	The 2011 CAPP2 report coincided with the culmination of major studies by Rothwell and colleagues. Extended follow-up of over 25 000 people who had participated in the early cardiovascular trials showed a significant risk reduction in CRC and other cancers commencing around 5 years after the initial recruitment compared to the placebo groups. [4] These authors did not detect a clear difference between different doses of aspirin used in the different trials. The effect on CRCs appeared to be most evident in cancers of the ascending colon, an area of particular risk in Lynch syndrome.	Thank you for this information. We will consider this evidence alongside the results of our literature searches for inclusion in the guideline.

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			The US-based Women's Health Study is the only other large scale RCT of aspirin as a cancer preventive agent. The NIH funded team allocated 39 876 healthy women to alternate day 100mg aspirin or vitamin E versus controls with a 10-year follow-up. At publication in 2005 there was no evidence of a reduced cancer risk. Following the subsequent publications described, the authors returned to the study population and discovered an 18% reduction in colorectal cancer (CRC) among the women who had taken the active aspirin (p=0.024). [5] The beneficial effect was confined to the colorectum. A recent observational study from the Colon Cancer Family Register adds weight to the case for a protective effect for the more familiar very low dose aspirin regime. This very large-scale NIH funded observational study contains over 1800 people known to have Lynch syndrome [6]; based on their self-reported use of NSAIDs, there was a major protective effect of aspirin and ibuprofen. In each case the Hazard Ratio was 0.25 for CRC in those who reported use for over 5 years. A secondary analysis of CAPP2 data has shown that the risk of cancer is 2 to 3 times higher in overweight and obese patients with LS. This effect is less abrogated in those who were randomised to receive aspirin. [7]	
Newcastle University	5	9 - 11		Thank you for this information. We will consider this evidence

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	(& P7 table Pt 1)		The CaPP3 trial, which began recruiting in 2014, is a randomized trial in patients with proven molecular genetic predisposition to Lynch syndrome where they are being randomized to either 100, 300 or 600mg/day enteric coated aspirin for 2 years and compare CRC incidence and bleeding rates during the 5–10-year follow-up period (www.capp3.org). To date over 1100 LS patients have been randomised, the majority in the UK where all 26 genetic centres are open to recruitment. The target of 2000 recruits is expected to be reached in late 2018 and the five year follow up data on cancer incidence in the three groups will be reported in 2023. Since aspirin is an anti-platelet agent, bleeding risk is its most important side effect. There is a relative increase in risk of haemorrhagic strokes by 32–36% and extracranial (mostly gastrointestinal) bleeds by 30–70% from baseline with low or standard dose aspirin treatment. It is possible that the ~ one in 14 000 extra risk of intracerebral bleeding is in part related to unrecognized hypertension; aspirin does not cause such haemorrhage. Rather, it exacerbates the clinical impact of a burst vessel. In the Hypertension Optimal Treatment trial, which examined different approaches to the management of high blood pressure, the 18 790 participants were also randomized to 75 mg/day aspirin or placebo. There was no difference in the risk of haemorrhagic stroke or fatal complications but a clear excess of gastric bleeds in the aspirin group. [8]	alongside the results of our literature searches for inclusion in the guideline.

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			There is a sharp increase in gastrointestinal bleeding risk beyond the age of 70 years. There is clear evidence that Helicobacter pylori infection exacerbates the risk of gastric bleeds in aspirin users [9] in addition to being a factor in gastric cancer predisposition in LS. All people considering long-term aspirin prophylaxis should be investigated for occult infection. Cuzick and colleagues have examined the overall risk–benefit ratio for aspirin [1,10] and conclude that the benefits of regular aspirin outweigh the adverse events in all people over the age of 50 provided aspirin is discontinued in old age. The much higher risk of colorectal and other cancers in Lynch syndrome make the case for routine use of aspirin as a therapeutic preventive agent much stronger.	
Newcastle University	5 (& P7 table Pt 1)	9 - 11	**References** 1. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2015; **26**(1): 47-57. 2. Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *The New England journal of medicine* 2008; **359**(24): 2567-78. 3. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an	Thank you for this information. We will consider this evidence alongside the results of our literature searches for inclusion in the guideline.

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			analysis from the CAPP2 randomised controlled trial. *Lancet* 2011; **378**(9809): 2081-7. 4. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *The Lancet Oncology* 2012; **13**(5): 518-27. 5. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Annals of internal medicine* 2013; **159**(2): 77-85. 6. D AO, SG D, R C, et al. Aspirin, Ibuprofen, and the Risk of Colorectal Cancer in Lynch Syndrome. *Journal of the National Cancer Institute* 2015; **107**(9). 7. Movahedi M, Bishop DT, Macrae F, et al. Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study. *J Clin Oncol* 2015; **33**(31): 3591-7. 8. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**(9118): 1755-62. 9. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002; **16**(4): 779-86.	

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			10. Thorat MA, Cuzick J. Prophylactic use of aspirin: systematic review of harms and approaches to mitigation in the general population. *Eur J Epidemiol* 2015; **30**(1): 5-18.	
Newcastle University	5 (& P7 table Pt 1)	9-11		Thank you for the information which was provided to us confidentially. We will consider this evidence alongside the results of our literature searches for inclusion in the guideline.
Royal College of General Practitioners	5	10	The use of aspirin in any guideline needs to take into account cvd risk and benefit, interactions of doac, and co -prescribing of gastro protection and the long term problems this may cause as well as risks of intra cranial and other bleeding.	Thank you for your comment. Evidence about the harms and benefits of each intervention will inform the guideline committee's recommendations.
Royal College of Pathologists (UK)	5	12	This is a broad but important area, and clearly will overlap with some of the related technology appraisals e.g. most recently "Cetuximab and panitumumab for previously untreated metastatic colorectal 16 cancer (2017) NICE technology appraisal guidance TA439". A very important, more specific question to address under "Use of molecular biomarkers to guide chemotherapy choice" relates to tumour mismatch repair status. This has been a longstanding and contentious issue and appraisal of evidence to inform the role of tumour mismatch repair status in directing post-surgical therapy (mainly for colonic adenocarcinomas) would be very beneficial,	Thank you for your comment. This issue should be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.

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			especially given recent NICE guidance recommending mismatch repair testing in all new diagnoses of colorectal adenocarcinoma (Molecular testing strategies for Lynch syndrome in people with colorectal 12 cancer (2017) NICE guideline DG27).	
Royal College of General Practitioners	5	12	Molecular biomarkers should also be considered as part of the diagnostic and monitoring processes. Carter JV, Galbraith NJ, Yang D, Burton JF, Walker SP, Galandiuk S. Blood-based microRNAs as biomarkers for the diagnosis of colorectal cancer: a systematic review and meta-analysis. Br J Cancer. 2017 Mar 14;116(6):762–74.	Thank you for your comment. Molecular markers for diagnosis is was not prioritised for inclusion within the scope during our initial searches of the literature and our stakeholder workshop. This area may be more relevant for the Referral for Suspected Cancer guideline (NG12). Monitoring is potentially covered by key question 5.1 the optimal methods and frequencies of follow-up.
Bristol-Myers Squibb Pharmaceuticals Limited	5	13	In addition to currently recognised biomarkers, dMMR/MSI status should be added due to accumulating evidence of its importance in disease prognosis and as a predictive factor for response to IO therapies. Prognosis and treatment choices should also be explored for patients diagnoses as sporadic dMMR/MSI whilst offered screening for Lynch syndrome. In essence, the management of colorectal cancer will become increasingly molecularly stratified in line with the emerging evidence	Thank you for your comment. We anticipate this issue will be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.

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			base for consensus molecular subtyping and associated response to therapy[15-16]. This has already been seen in dMMR/MSI-H CRC where patients may not gain a survival benefit with adjuvant therapy in early stage disease [17-22].	
Bristol-Myers Squibb Pharmaceuticals Limited	5	15	Testing for dMMR/MSI in patients who have localised/early stage colorectal cancer will assist clinician decision making for suitability for adjuvant therapy.	Thank you for your comment. This issue should be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.
Royal College of General Practitioners	5	21	Has the NICE committtee considered the use of CT colonography for surveillance of people with colorectal cancer? Porté F, Uppara M, Malietzis G, Faiz O, Halligan S, Athanasiou T, et al. CT colonography for surveillance of patients with colorectal cancer: Systematic review and meta-analysis of diagnostic efficacy. European Radiology. 2017 Jan 1;27(1):51–60.	Thank you for your comment. We anticipate this will be addressed in key question 5.1 the optimal methods and frequencies of follow-upas one of the methods of follow-up.
Roche Diagnostics Ltd	6	7	Please also consider adding first degree relatives (children and parents) of Lynch Syndrome patients to the groups that will be covered by this guideline.	Thank you for your comment. The scope was limited to those with established Lynch syndrome because the evidence for prophylactic treatment comes from that group. Testing strategies for first degree relatives of people with Lynch syndrome

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				may be better covered by the NICE diagnostics guidance program. .
Bowel Cancer UK	7	General	We are very pleased to see the management of post treatment sequelae featured in the 'Proposed outline for the guideline'. The side-effects caused by the intense, and often prolonged, treatments colorectal cancer patients undergo can significantly impact their quality of life and often require separate and additional interventions to address. The personal and often distressing nature of side effects can be traumatic for patients and their families. However, emphasis should be placed not only on the management of sequelae; but also their prevention. For example, acute radiation-induced diarrhoea is a common side-effect of colorectal cancer treatment that impinges on a patient's recovery and quality of life.[i] Research indicates that patients that undergo probiotic therapy alongside radiation therapy experience significantly reduced incidences of radiation induced side effects.[ii] We would strongly encourage NICE to include prevention of sequelae within the scope of the guideline. NICE must also consider surgical methods that reduce the severity and number of post-treatment side effects. For example, patients with rectal cancer that receive Anterior Perineal Plan E for Ultra-low Anterior Resection of the Rectum, or the APPEAR technique, are able to have their sphincter preserved, allowing for significant reduction in surgical-related side effects.[iii]	Thank you for your comment. The key questions list two examples of post treatment sequelae – however the guideline committee will have an opportunity to prioritise others if they are seen as more important.

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			We would highly recommend that underneath ***ongoing care and support***, NICE should include – **prevention of sequelae across the treatment pathway**, as doing so would ensure action is taken to prevent patients from experiencing conditions like radiation induced diarrhoea before they occur.	
British Society of Gastroenterology	8	Table	I note the proposal to exclude diagnostic and staging investigations from the Guideline as there is 'no longer variation in practice'. I think that is not correct and evidence looking at MRI liver vs CT liver as well as role of PET ought to be assessed.	Thank you for your comment. We did not prioritise this area on the basis of the surveillance evidence review and discussions at the stakeholder workshop.
Medtronic UK	8	Table _Diagnosis section	With reference to the rationale behind removal on the basis that there is no longer variation in relation to diagnosis, nevertheless there are considered service delivery challenges with the diagnostic pathway and associated timelines especially for patients who refuse or experience an incomplete colonscopy	Thank you for your comment. This issue is not specific to colorectal cancer and was not identified as a priority during our initial searches of the literature and stakeholder workshop.
Norgine	8	3	There is a proposal to removal sections 1.1.1.1 – 1.1.1.5 of the NICE guideline on Colorectal cancer: diagnosis and management (CG131) which deal with diagnosis due to lack of variation in practice in the diagnostic investigations available. Rather than removing the section, we suggest that it should be revised to include capsule endoscopy as well as review the place of barium enema. In a statement released by the BSG on the 13th of Jan 2017 on publication of the 2nd Atlas of variation in NHS Diagnostic Services in England, the President commented that's "*procedures such as*	Thank you for your comment. We did not prioritise this area on the basis of the surveillance evidence review and discussions at the stakeholder workshop.

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			barium enema, that have no place in modern gastroenterology", but they are still being performed in the NHS.	
Norgine	8	3	In addition consideration should be made, within sections 1.1.1.1 – 1.1.1.5 of CG131, about the impact of equipment, bowel preparation, availability of trained endoscopists and continued training on the outcomes of diagnostic procedures such as colonoscopy. There is wide variation in outcomes of colonoscopy, evidenced by the wide variation in polyp and adenoma detection rates across the UK and we suggest that there should be some advice on which centres should receive requests for investigations based on quality outcomes. Sub-optimal colonoscopy (including sub-optimal bowel preparation) impacts not just patient outcomes but also service provision.	Thank you for your comment. This issue is not specific to colorectal cancer and was not identified as a priority during our initial searches of the literature and stakeholder workshop.
Norgine	8	3	There is unwarranted variation in the number of colonoscopies and flexible sigmoidoscopies performed, with values ranging from 76.5 per 10,000 population to 248.8 per 10,000 population, during 2014/2015 (2nd Atlas of variation in NHS Diagnostic Services in England). Potential reasons for this variation could be lack of referral guidelines for colonoscopy, flexible sigmoidoscopy and CT colonography, which we suggest should be included in section 1.1.1.1 – 1.1.1.5 of CG131	Thank you for your comment. This issue is not specific to colorectal cancer and was not identified as a priority during our initial searches of the literature and stakeholder workshop.
Norgine	8	11	There is a proposal to removal the section related to diagnosis within the NICE guideline on Improving outcomes in colorectal cancer (CSG5) due to lack of variation in practice in diagnosis. Rather than removing the section, we suggest that it should be revised to include	Thank you for your comment. We did not prioritise this area on the basis of the surveillance evidence review and discussions at the stakeholder workshop.

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			capsule endoscopy as well as review the place of barium enema (see comment 1 above),.	
Bristol-Myers Squibb Pharmaceuticals Limited	9	1 - 3	Although population screening is not covered by this guidance, its importance is crucial for maximization of population health benefits and equal access to health and therefore the final scope and updated guideline should refer to relevant guidelines from other NICE programmes to facilitate their implementation.	Thank you for your comment, however the issue of population screening is outside the remit of this guideline.
Bowel Cancer UK	11	24 - 25	Bowel Cancer UK strongly believes that based on currently available evidence, Aspirin is an effective chemopreventative therapy, and must be included within the scope of the guideline. As a cost effective preventive intervention, a recommendation to use low dose aspirin in Lynch syndrome is without parallel. There is consistent evidence over a 30 year period in favour of the use of aspirin in reducing the risk of colorectal cancer. These span observational studies, case control data, adenoma prevention trials, reviews of the late outcomes in cardiovascular aspirin trials, and the CAPP2 trial, which involved a double blind evaluation of aspirin in Lynch syndrome across 43 centres in 16 countries. These have indicated that aspirin prevents the over-formation of platelets, which in turn prevents tumours from using said platelets to mask cancerous cells from immune surveillance.[iv] Studies have also pointed to the potential impact Aspirin has on the proliferation of cancer cells, in that it is thought to promote programmed cell death, which would prevent the formation and growth of abnormal cells.[v]	Thank you for your comment, this issue should be covered by key question 1.1 - Is aspirin effective in the prevention of colorectal cancer in carriers of Lynch syndrome.

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			The international CAPP2 trial provides the strongest evidence for the use of aspirin as a preventative therapy for people with Lynch syndrome. The trial showed a substantial reduction, of up to 59%, in colorectal cancer incidence in people who took Aspirin, compared with those who did not.[vi, vii] Beyond the substantial evidence supporting the use of Aspirin as a preventative therapy, there are significant national and international bodies that advocate its use in a chemopreventative setting. For example, the Mallorca Group European guidelines endorsed the use of Aspirin in the management of people with Lynch syndrome, concluding that 'regular aspirin significantly reduces the incidence of cancer in LS [Lynch syndrome]'.[viii] The American Gastroenterological Association similarly recommends the use of aspirin as a preventative therapy.[ix] More importantly, the National Institute for Health Research (NIHR) recognised the health economic benefits of aspirin use are clear given that, in Lynch syndrome, the cancer prevention properties of aspirin are equivalent to routine colonoscopy and associated with a similar risk of adverse events. Routine colonoscopy and aspirin are complimentary in this condition.[x] Based on the above evidence, we urge that aspirin be included in the guidance as an effective chemopreventative therapy that has, and	

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			continues to prove its ability to prevent, and reduce incidences of colorectal cancer in people with Lynch syndrome.	
Bristol-Myers Squibb Pharmaceuticals Limited	11	26	DG27 is able to detect sporadic dMMR/MSI-H patients, however, the draft scope does not explicitly state them as a group of interest.	Thank you for your comment. The way the key question is worded allows guideline committee can look at the evidence for this sub-group if they agree it is a priority.
Royal College of Pathologists (UK)	12	1	Some early colon cancers are not polypoid, but may still be amenable to local excision alone. This question may be better phrased as "Which people with early colon cancer can be treated with local excision alone?	Thank you for your comment. We have made the suggested change.
The Royal Liverpool and Broadgreen University Hospitals NHS Trust	12	7 - 9	The proposition for this guideline is defining that optimal non-operative strategy for patients who 'obtain a complete clinical response'. This is in fact a very arbitrary definition as good datas now exists to show that the majority of patients with a complete **pathological** response DO NOT have a complete clinical response. As such many studies assessing watch and wait also treat a 'good response' (not necessarily the purist definition of complete response where there is absolutely nothing to see or feel in any modality). Many studies also deem shallow mucosal ulcers as a complete response for example…which by Habr Gama definitions are features on incomplete response. Also, the timepoint and manner in which response is assessed is critical to making decisions about who may be or may not be suitable for attempted watch and wait….Also, findings can be swayed by how definite a patient is that they do not	Thank you for your comment. We agree that terminology and definitions in this area are not fully established and can be arbitrary. We have amended the wording of the question to 'Which patients having neoadjuvant chemotherapy or chemoradiotherapy for rectal cancer do not need surgery?'. The guideline committee will consider the details of issue, including the definition of the

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			want surgery. Also, it is documented that complete response can evolve over longer timepoints that the standard 6-8 week restaging timepoint conventionally used pre operatively.	population when developing the review protocol.
The Royal Liverpool and Broadgreen University Hospitals NHS Trust	12	7 - 9	With reference to the above, the infrastructure for watch and wait is in our institutions opinion, a critical component of the technique. We have published on this and have the UKs (and actually international) largest experience of this technique. What is critical is making fully sure that there is a dedicated and educated surveillance team following patients. This should include high quality endoscopy facilities and ideally the same endoscopists (or as we do in our institution - ideally have dual experienced endoscopists doing the cases together). This means that subtleties and digital exam findings can be made less subjective. As an example, many institutions that we are aware of simply add these patients to flexible sigmoidoscopy list and they are done by e.g trainees/locums/nurse practitioners who are not in any way trained in assessing response. It is also very important that patients are well counselled about this approach and understand about watch and wait and that their tumour may come back. This ideally means longer clinic slots and dedicated specialist nurse input. In addition, we are establishing an electronic follow up protocol to ensure that patients are tracked and flagging those who have missed tests at certain timepoints.	Thank you for this information. The committee will consider evidence for the clinical effectiveness of watch and wait but will also have regard to cost effectiveness when making recommendations. The resources required to deliver the watch and wait approach effectively will form part of this consideration.
The Royal Liverpool and Broadgreen University	12	7 - 9	There needs to be standardisation regarding who is suitable for watch and wait. By this I mean that I have personal experience of patients who want to attempt it because they are told that they would otherwise need an APR when in fact they could be candidates for a	Thank you for this information. We anticipate that the selection of suitable candidates for watch and

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Hospitals NHS Trust			low colorectal/coloanal anastomosis. We have set up what we believe to be the UKs first dedicated watch and wait MDT where we review all of the imaging and patient details and we sometimes seen this phenomenon. Ideally regional centres of excellence for rectal cancer should be established and clinicians experienced in all of the available options should discuss them with patients to ensure that they make an informed choice.	wait will be covered in the guideline.
The Royal Liverpool and Broadgreen University Hospitals NHS Trust	12	7 - 9	Ideally all patients being treated for rectal cancer should have formal quality of life/symptom scoring assessment on an ongoing basis. This is because now there are often several ways to treat the same cancer and in order for patients to choose what is right for them they need to know the expected outcomes. Mortality data is one thing, but details essential for survivorship such as continence/bladder dysfunction, sexual dysfunction, pain and body image scores etc , stoma free survival are crucial and yet are currently not resourced and so difficult to collect in NHS systems. A statistical model published by our group actually shows that watch and wait is less expensive than radical surgery and can improve short term mortality too. By understanding more about watch and wait and organ preservation then the NHS may actually save money in the long run by resourcing data collection on alternatives to radical surgery.	Thank you for this information. The guideline committee will consider evidence for the long term harms and benefits of watch and wait strategies when making recommendations.
The Royal Liverpool and Broadgreen University	12	7 - 9	This proposition suggests that only patients that are being considered for surgery should be given '**Preoperative** chemoradiotherapy'. There is good data to show that earlier stage tumours respond better to chemoradiation and so the new guidelines should reflect a patients autonomy to choice. By only offering	Thank you for your comment. The guideline committee will have the chance to decide whether patient subgroups need to be considered separately in this question -

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Hospitals NHS Trust			patients who are candidates for standard pre operative chemoradiotherapy based on current NICE guidance, you select out only the most advanced disease and hence the tumours least likely to achieve a complete response. This is especially pertinent in patients who are too unfit for…or refuse an operation who ideally should be offered definitively chemoradiation with curative intent.	accepting that the majority will be those considered for surgery. However, taking into consideration your comment, we have amended the wording of the question to 'Which patients having neoadjuvant chemotherapy or chemoradiotherapy for rectal cancer do not need surgery?'.
The Royal Liverpool and Broadgreen University Hospitals NHS Trust	12	7 - 9	This proposition suggests that only patients that are being considered for surgery should be given '**Preoperative** chemoradiotherapy'. There is good data to show that earlier stage tumours respond better to chemoradiation and so the new guidelines should reflect a patients autonomy to choice. By only offering patients who are candidates for standard pre operative chemoradiotherapy based on current NICE guidance, you select out only the most advanced disease and hence the tumours least likely to achieve a complete response. This is especially pertinent in patients who are too unfit for…or refuse an operation who ideally should be offered definitively chemoradiation with curative intent.	Thank you for your comment. The guideline committee will have the chance to decide whether patient subgroups need to be considered separately in this question - accepting that the majority will be those considered for surgery.
Bowel Cancer UK	12	12 – 13	The current consensus regarding the duration of adjuvant chemotherapy for colorectal cancer is generally six months.[xi] However, the Short-Course Oncology Treatment (SCOT) trial has highlighted that three months' worth of adjuvant chemotherapy – capecitabine and oxaliplatin – can be no less effective than six months' worth in some patients.[xii] As a reduction in chemotherapy	Thank you for your comment. This issue should be addressed by key question 3.7 - what is the optimal duration of adjuvant chemotherapy for colorectal cancer.

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			cycles results in fewer side-effects for patients, and decreased cost, it would be highly beneficial to both patients and care providers if chemotherapy cycles were reduced.[xiii] We strongly recommend that NICE consider duration of adjuvant chemotherapy treatment within the scope of the guideline in light of this research.	
Bristol-Myers Squibb Pharmaceuticals Limited	12	17	DG27 is able to detect sporadic dMMR/MSI patients. A question should be added around the prognosis of disease in that subgroup and what are the most effective treatment combinations for a group of patients which is considered to have very poor outcomes once with metastatic disease4-9.	Thank you for your comment. This issue should be covered by key question 2.1: the use of molecular biomarkers to guide chemotherapy choice.
SIRTEX	12	22	SIRT using SIR Spheres Y90 Resin microspheres should be considered as a local regional therapy	Thank you for your comment. The guideline committee have the opportunity to consider this treatment in key question 4.3 for liver metastases, if they deem it relevant.
Bristol-Myers Squibb Pharmaceuticals Limited	13	12 - 17	Evidence based recommendations should also take into account patient health related quality of life which can be affected due to adverse events. Please supplement list with relevant adverse events as an outcome of the CG update and specifically mention health related quality of life as a main outcome for the CG update.	Thank you for your comment. The treatment related morbidity outcome includes adverse events. More relevant adverse event outcomes will be agreed for each clinical question during the development of the guideline.

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