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Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer

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ABSTRACT

Objective Colorectal cancer (CRC) leads to significant morbidity/mortality worldwide. Defining critical research gaps (RG), their prioritisation and resolution, could improve patient outcomes.

Design RG analysis was conducted by a multidisciplinary panel of patients, clinicians and researchers (n=71). Eight working groups (WG) were constituted: discovery science; risk; prevention; early diagnosis and screening; pathology; curative treatment; stage IV disease; and living with and beyond CRC. A series of discussions led to development of draft papers by each WG, which were evaluated by a 20-strong patient panel. A final list of RGs and research recommendations (RR) was endorsed by all participants.

Results Fifteen critical RGs are summarised below: *RG1*: Lack of realistic models that recapitulate tumour/tumour micro/macroenvironment; *RG2*: Insufficient evidence on precise contributions of genetic/environmental/lifestyle factors to CRC risk; *RG3*: Pressing need for prevention trials; *RG4*: Lack of integration of different prevention approaches; *RG5*: Lack of optimal strategies for CRC screening; *RG6*: Lack of effective triage systems for invasive investigations; *RG7*: Imprecise pathological assessment of CRC; *RG8*: Lack of qualified personnel in genomics, data sciences and digital pathology; *RG9*: Inadequate assessment/communication of risk, benefit and uncertainty of treatment choices; *RG10*: Need for novel technologies/interventions to improve curative outcomes; *RG11*: Lack of approaches that recognise molecular interplay between metastasising tumours and their microenvironment; *RG12*: Lack of reliable biomarkers to guide stage IV treatment; *RG13*: Need to increase understanding of health related quality of life (HRQOL) and promote residual symptom resolution; *RG14*: Lack of coordination of CRC research/funding; *RG15*: Lack of effective communication between relevant stakeholders.

Conclusion Prioritising research activity and funding could have a significant impact on reducing CRC disease burden over the next 5 years.

INTRODUCTION

The global burden of colorectal cancer (CRC) is rising, with 2.2 million predicted new cases (and 1.1 million deaths) by 2030.¹ In the UK, >41 000 new cases were diagnosed in 2014, and ~16 000 people died of the disease.² Estimates of the global economic burden of CRC approach \$100 billion;³ in the USA, medical expenditure alone is predicted to rise to >\$20 billion by 2020.⁴ In the UK, total economic costs of CRC exceeded £1.6 billion in 2009.⁵

In 2014, the US National Cancer Institute (NCI) spent \$223 million for CRC research, placing it fourth behind breast cancer (\$530 million), lung cancer (\$254 million) and leukaemia (\$237 million).⁶ Cancer Research UK (CRUK) figures indicated that its annual expense specifically on CRC research in 2016–2017 was £35 million, second behind lung cancer research (£43 million) and ahead of breast cancer research (£33 million).⁷ Recognising the need to identify current and emerging CRC research gaps (RG) to inform research policy and prioritisation, the UK charity Bowel Cancer UK (BCUK), aided by the UK National Cancer Research Institute (NCRI) Colorectal Cancer Clinical Studies Group and The Association of Coloproctology of Great Britain and Ireland (ACPGBI), drew together health professionals, scientists and those affected by CRC to identify those research priorities which, if addressed, would make the greatest impact on lessening global CRC burden.

METHODOLOGY

During 2015–2016, BCUK recruited an all-encompassing panel of 71 CRC healthcare professionals (HCP), scientists and individuals affected by CRC to participate in the *BCUK Critical Research Gaps in Colorectal Cancer Initiative*. The process is outlined in [figure 1](#) and reflects previous approaches to identifying RGs in other diseases.⁸ A detailed description of the process/methodology is provided in online supplementary appendix 1.

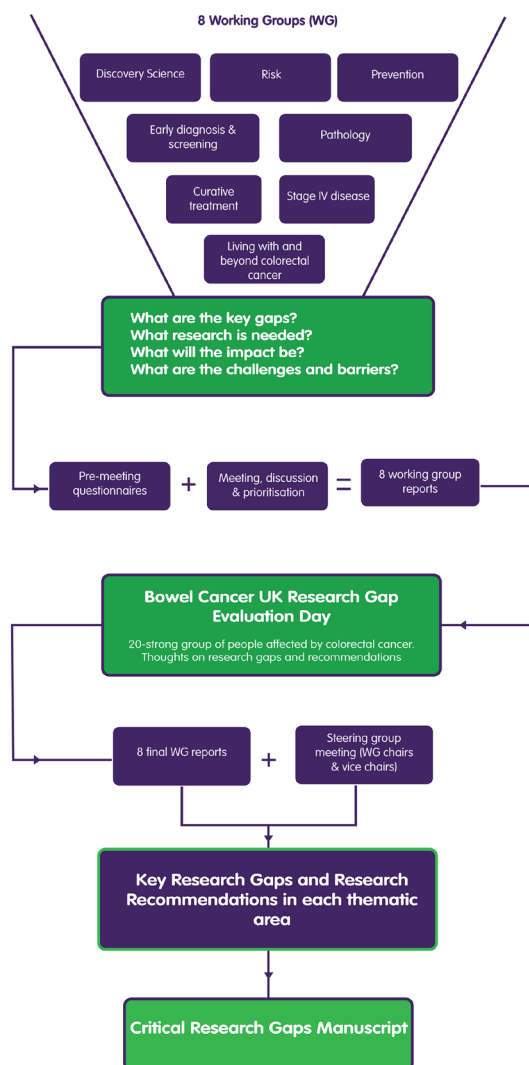


Figure 1 Bowel Cancer UK Critical Research Gaps in Colorectal Cancer Initiative process.

RESULTS

Fifteen critical RGs were identified through the process indicated in figure 1 and described in detail in online supplementary appendix 1. These RGs are summarised in table 1, and the evidence base for the RGs, together with accompanying research recommendations (RR), is detailed below in relevant thematic areas.

EVIDENCE BASE FOR RESEARCH GAPSS AND RECOMMENDATIONS

Discovery science

Current status

Interrogating colorectal biology has revealed important clues to key events driving CRC growth, including aberrant Wnt signalling and specific defects in DNA mismatch repair (MMR).^{9–13} Gene expression profiling efforts are identifying specific CRC molecular subtypes, although their clinical relevance requires further elucidation.^{13–18}

Many key areas require further in-depth study. While intracancer molecular diversity has been highlighted,^{16–18} we are only starting to understand the greater complexity associated with CRC evolution and metastasis.¹⁹ Transforming growth factor-beta/bone morphogenic protein signalling appears

important for CRC growth and metastasis,²⁰ but there is scant knowledge of the key proteins involved. Other pathways, for example, Hippo, and STING, are intriguing players in CRC biology, but are currently of uncertain relevance.^{21,22} The tumour micro/macroenvironment, including the microbiome, is largely unexplored. Crucially, the dearth of reliable CRC model systems is compromising both relevant fundamental research and development of novel therapies.

Research Gap (RG1): A need for realistic in silico, in vitro and in vivo models that more precisely recapitulate the tumour and its micro/macroenvironment, to enable comprehensive dissection of the relevant mechanisms governing the transition from normal colorectum to the different malignant stages of the disease.

Model systems for CRC research

While cell line models have informed our overall understanding of CRC biology, the recognition that they may not represent a specific tumour within its particular genetic context and micro-environment milieu has prompted researchers to develop more realistic models that recapitulate different premalignant/malignant stages of CRC. Genetically engineered mouse models,²³ for example, the *Apc*^{Min/+} mouse,²⁴ have allowed interrogation of particular disease biology, while the advent of patient-derived xenografts has underpinned development of animal models representing different stages of human CRC.²⁵ Organoids have allowed the 3D structure/microenvironment of the CRC tumour to be recreated and manipulated.²⁶ However, as our molecular knowledge of CRC expands,^{13–17} we require models that map to distinct disease subtypes, and others that address issues such as CRC evolution, intratumoural heterogeneity and treatment resistance.

Research Recommendation 1.1 (RR1.1): Develop and share appropriate model systems that mimic different premalignant/malignant stages of colorectal cancer (CRC), to ensure discovery research questions are addressed in the relevant genetic/clinical context.

Investigating CRC signalling pathways and their tractability

Given that pathogenic adenomatous polyposis coli (APC) mutations are rare outside CRC, performing a comprehensive, cell type-specific molecular analysis of the normal and APC-mutant colorectal crypt would improve understanding of the critical pathways/processes underpinning malignant colorectal epithelium development. A concerted Wnt pathway investigation programme in normal cells, benign tumours, and primary and metastatic CRC (mCRC) tissue is warranted. Challenges include development of appropriate quantitative readouts of signalling pathways, and novel model systems, perhaps including large animal models with greater resemblance to humans. Precise elucidation of specific malignant cellular processes could underpin identification of novel targets, both for prevention and treatment.

RR1.2: Comprehensively interrogate the normal and APC-mutant colorectal crypt to reveal differences that may be exploitable for CRC prevention/control.

The CRC micro/macroenvironment

We need to consider the role of non-neoplastic cells, particularly stromal cells/fibroblasts and immune infiltrates as important arbiters of CRC processes and treatment responses, to better understand the tumour microenvironment and how it is controlled by the cancer itself.^{16–18} Organoid models, or appropriate animal

Table 1 Critical RGs in colorectal cancer

Research area	Critical RGs
Discovery science	RG1: A need for realistic <i>in silico</i> , <i>in vitro</i> and <i>in vivo</i> models that more precisely recapitulate the tumour and its micro/macroenvironment, to enable comprehensive dissection of the relevant mechanisms governing the transition from normal colorectum to the different malignant stages of the disease.
Risk	RG2: Insufficient evidence on the precise contributions of genetic, environmental and lifestyle factors, and in particular how they interact together, to influence the risk of developing CRC.
Prevention	RG3: A need for intervention trials of preventive strategies addressing 'dose', timing, target group and acceptability, as well as mechanism of action. RG4: Lack of interdisciplinary collaboration is undermining evaluation of real-life preventative interventions in CRC.
Early diagnosis and screening	RG5: Lack of an optimal strategy for screening for CRC. RG6: Lack of an effective triage system for symptomatic patients that can determine who will benefit most from invasive investigation.
Pathology: diagnosis – prognosis – prediction	RG7: Imprecise pathological assessment of CRC is an unmet challenge. RG8: Lack of qualified personnel to apply state-of-the-art knowledge in genomics, big data science and digital pathology.
Curative treatment	RG9: Inadequate assessment and communication of risk, benefit and uncertainty of treatment choices where cure is possible. RG10: A need for novel technologies/interventions that have the potential to improve curative outcomes.
Stage IV disease	RG11: Lack of approaches that take cognisance of the molecular interplay between the metastasising tumour and its microenvironment and help guide evolution of innovative treatments that deliver improved health outcomes for the stage IV patient. RG12: Lack of reliable prognostic and predictive biomarkers to help guide stage IV patient pathways.
Living with and beyond CRC	RG13: The need to increase understanding of health-related quality of life (HRQL) issues and resolve residual symptoms as part of a research effort to enhance survivorship for those living with and beyond CRC.
Overarching RGs that need to be addressed	RG14: Lack of coordination of CRC research and its funding, leading to fragmented efforts to elucidate the biology of the disease and translate this knowledge into new preventative agents, screening tools, diagnostics and therapeutics. RG15: Lack of effective communication strategies between healthcare professionals, patients with CRC/survivors, those at elevated risk of developing CRC, and the general public and varying levels of awareness of key risk factors, prevention options and benefits/risks associated with different treatment options.

CRC, colorectal cancer; RG, research gap.

models encompassing both neoplastic clones and realistic micro-environments are paramount. Development of *in silico* systems biology platforms that capitalise on these rich data sources will allow modelling and deciphering of the complex interplay between CRC tumour cells and their microenvironment.

Macroenvironmental effects from gut microbes have been implicated in CRC development in experimental animal models, but their relevance in humans is less clear. Recent evidence published in this journal suggests that altered mucosal microbiota are present throughout the colorectum,²⁷ that they have a role in regulating the host immune-inflammatory response, and may have prognostic relevance for patients with CRC. A deeper understanding of the gut microbiome in CRC will also facilitate its therapeutic manipulation for improved outcomes in both preventative and treatment settings.

RR1.3: Better understand the molecular/cellular interplay between the CRC tumour and its microenvironment.

RR1.4: Determine the role of the gut microbiome and how it can be exploited to improve CRC disease outcomes.

Risk

Current status

Identifying individuals at increased risk of CRC allows introduction of appropriate screening/surveillance approaches, leading to earlier cancer diagnosis and underpinning improved survival. However, there is currently an incomplete picture of the absolute risk attributable to inherited, environmental or lifestyle factors for CRC. Understanding global risk will underpin stratified interventions tailored to individual patients for disease modification and precision medicine interventions.²⁸

Known Mendelian conditions account for a relatively small proportion of inherited risk, with the remainder thought to be due to lower penetrance risk factors, including common/rare genetic variants.²⁹ Approximately 40 common, low penetrance CRC risk alleles have been identified.²⁹ Estimations from

whole-exome sequencing (WES) studies suggest that higher penetrance rare variants may additionally account for 16% of hereditary risk.³⁰ However, much of the 'missing heritability' remains unidentified. Additionally, the interaction between the microbiome, epigenetics and heritable risk factors remains poorly characterised.³¹

A better understanding of environmental/lifestyle risk factors is also required. While associations with diet,^{32–34} comorbidities including diabetes³⁵ and aspirin/non-steroidal anti-inflammatory drug use,³⁶ have been identified, the interplay between these risk factors is complex. A greater understanding would permit targeted public health approaches to increase risk factor awareness in the general population, leading to reduced CRC incidence.³⁷

RG2: Insufficient evidence on the precise contributions of genetic, environmental and lifestyle factors, and in particular how they interact together to influence the risk of developing CRC.

Genetic risk factors for CRC

There is incomplete elucidation of CRC heritable risk factors, especially of polygenic risk (ie, where the contribution of multiple genes must be enumerated/quantified). Collaborative initiatives such as GECCO (Genetics and Epidemiology of Colorectal Cancer Consortium)³⁸ and GAME-ON (Genetic Associations and Mechanisms in Oncology Consortium)³⁹ have significantly contributed to identification of risk-susceptibility loci.^{40–42} However, additional gene discovery initiatives are required, with increased concentration on evaluation of genetic risk in a broader diversity of populations/ethnic groups.^{43–44} International data sharing collaboratives will be required, particularly to evaluate significance of rare genetic variants. Developing a gene panel for common CRC risk variants, mirroring a similar recently applied approach in breast cancer,⁴⁵ may allow more precise delineation of CRC risk.

RR2.1: Conduct comprehensive genetic susceptibility studies, supported by enabling data sharing platforms, in appropriately diverse human populations to maximise identification of genetic risks factors that have general applicability, or are relevant to specific ethnic populations.

Environmental/lifestyle contributions to CRC risk

There are significant environmental/lifestyle contributors to enhanced CRC risk. Increasingly, we require precise data-analytic tools to evaluate, assign and quantify gene-gene,⁴⁶ gene-environment and gene-lifestyle risk.^{47,48} Recent studies have linked high-quality diets (assessed by diet quality indices) with low CRC risk in a multiethnic cohort,⁴⁹ while a genome-wide diet-gene interaction analysis indicated a novel association between processed meat consumption, a particular genetic variant and increased CRC risk.⁴⁸ Studies have also investigated interactions between gene variants, smoking/alcohol consumption and risk of developing CRC.⁵⁰ Ensuring the robustness of data-analytic methodologies and applying them to high-quality large data sets will help confirm current hypotheses, and identify novel nature-nurture interactions for further modelling and testing in diverse populations and cohorts, to determine the universality of their ability to predict increased/reduced risk.

RR2.2: Develop robust data analytical tools that define and quantify the precise interplay between genetic and environmental/lifestyle factors to attributable CRC risk.

Population-based assessment of CRC risk

International collaboration is continually cataloguing potential independent lifestyle risk indicators in population studies.³⁴ However, we need prospective high-quality pan-population studies of CRC risk factors, with complete ascertainment, accurate longitudinal clinical and pathological data, and supporting blood/tissue samples. Collection of high-quality treatment response and toxicity data should also be mandated to help identify risk factors for relapse or treatment-related side effects. A national registry approach to managing risk may be the best way to identify an unbiased population set of high-risk patients. This should be linked to clinical networks, including national approaches to surveillance and screening, enabling development of enhanced prevention and surveillance programmes for high-risk patients,⁵¹ and reallocation of valuable resources for those at low risk.⁵²

RR2.3: Design and implement prospective high-quality pan-population studies of risk factors for CRC, with robust clinical/pathological data, supporting blood and tissue samples, to inform a population-based assessment of risk.

Prevention

Current status

Despite widespread awareness that efforts to avoid CRC development are critical,⁵³ prevention research is under-represented in the CRC research portfolio. The UK NCRI funding in 2015 for all cancers was £498 million, but only 3% was spent on prevention.⁵⁴ The gap in CRC prevention research is particularly notable in high-risk populations, such as patients with Lynch syndrome.⁵⁵ The preventability estimate (World Cancer Research Fund) indicates that ~45% of CRCs are accounted for by lifestyle factors (dietary factors, obesity, lack of physical activity and alcohol consumption⁵⁶). Dietary factors (low dietary fibre intake, high red/processed meat intake) are considered the

main lifestyle area of concern.⁵⁶ An evolving understanding of the gut microbiome and diet-microbial interactions has highlighted the potential for modulation of the diet-microbiome-metabolome axis for cancer prevention.⁵⁷

The global impact of obesity on cancer is significant, contributing to ~10% of the overall cancer burden in North America, Europe and the Middle East.⁵⁸ This is reflected in a significant association between increasing body mass index (BMI) and CRC development.⁵⁹ The International Agency for Research on Cancer recently convened a working group (WG) to assess body fatness and cancer risk. For CRC, their findings confirmed the association between increased BMI and CRC risk and indicated that a significant body of preclinical data supported a preventative effect of caloric restriction;⁶⁰ this should be actively pursued. Increased physical activity also has an important role in CRC prevention strategies.⁶¹

There is compelling evidence that chemopreventive interventions such as aspirin^{55,62,63} in high-risk patients can be effective, prompting the US Preventive Services Task Force to recommend its use in primary CRC prevention.⁶⁴ However, complications, including GI bleeding, need to be considered, although the harm-versus-benefit ratio is frequently exaggerated.⁶⁵ Additionally, a recent study has indicated a lack of awareness of aspirin's chemopreventive effects by >50% of primary care physicians surveyed,⁶⁶ particularly for high-risk populations (eg, Lynch syndrome carriers), highlighting the need for appropriate education/guidance strategies. Many intervention trials (of diet, physical activity or chemoprevention) occur in the postdiagnosis setting—we need to ensure more CRC preventive trials which target specific high-risk populations with robust endpoints are conducted prior to CRC onset.

RG3: A need for intervention trials of preventive strategies addressing 'dose', timing, target group and acceptability, as well as mechanism of action.

RG4: Lack of interdisciplinary collaboration is undermining evaluation of real-life preventative interventions in CRC.

Integrating dietary, lifestyle and chemopreventive interventions

There is an increasing need to reflect how interventions can be delivered in 'real life' (eg, combining screening, lifestyle interventions and chemoprevention), going beyond traditional discipline boundaries when designing efficacy and, particularly, effectiveness studies. New research models and transdisciplinary paradigms must be established in CRC prevention, perhaps in an approach analogous to NCI's Transdisciplinary Research on Energetics and Cancer Initiative,⁶⁷ which brought together expertise in behaviour, biostatistics, computer science, discovery science, endocrinology, engineering, epidemiology, genetics, health economics, medicine, nutrition and physical activity. We need multidisciplinary approaches to help define optimal ways to implement lifestyle change programmes. Another example is the microbiome,⁶⁸ where our increased understanding of gut microbiota⁶⁹ and their manipulation is highlighting how diet/nutrient/physical activity-based interventional approaches can help prime the microbiome as a preventative agent.

RR3.1: Encourage transdisciplinary, multimodal approaches to CRC prevention, through cross-community collaboration.

The need for long-term studies

There is a dearth of studies which enable observational (and other) evidence to be tested robustly in long-term studies. Challenges include recruitment (due to incorrect perceptions about

disease prevention, particularly lifestyle interventions, and lack of HCP support), protocol implementation and adherence, and lack of appropriate endpoints. We need longer term analysis of robust interventions demonstrating feasibility and acceptability with promising indicative outcomes,⁷⁰ which can then be tested in full-scale trials of relevant duration, with clinically relevant outcomes in at-risk patients.

RR3.2: Ensure future delivery of high-quality robust long-term studies that identify the appropriate level of intervention including dose, duration, timing, feasibility and acceptability as well as clinically relevant outcome(s).

Ensuring coordination of intervention trials and research into barriers to uptake

Intervention trials and research into barriers to uptake of research findings and clinical impact must occur concurrently. We also need to break down current regulatory and funding hurdles to timely and cost-effective prevention research, particularly for interventions employing off-licence drugs, undesignated drugs (eg, food supplements), or requiring human resource, for example, a counsellor/dietitian/trained volunteer/physical activity trainer. Stronger public involvement in evaluating optimal ways to promote more effective diet and lifestyle interventions, including the need to optimise teachable moments⁷¹ should be encouraged.

RR4.1: Coordinate interventional trial activity to ensure maximum impact of precise and effective prevention strategies across the population.

Defining mechanism of action of selected interventions

A better understanding of mechanism(s) of action of prevention interventions is needed in order to define the most effective intervention, its timing and 'dose', as well as identifying individuals most likely to benefit. Intervention trials and observational cohorts could usefully include blood/tissue biobanks as key enablers of mechanistic research. Specific research calls for multimodal intervention studies should be developed with emphasis on effectiveness (including non-cancer secondary endpoints) and health economic outcomes.

RR4.2: Promote studies that help elucidate mechanism of action of prevention interventions.

RR4.3: Develop precise individual risk stratification approaches to ensure prevention interventions are employed most effectively.

Early diagnosis and screening

Current status

Although colonoscopy is widely employed for screening asymptomatic individuals in the USA, most countries have adopted a single biennial faecal immunochemical test (FIT) for blood in the stool for programmatic screening.⁷² As a population screening tool, colonoscopy is expensive, associated with low uptake and is potentially hazardous. FIT is easy to deliver and affordable in cost-limited or colonoscopy-limited settings, by simply adjusting the FIT sensitivity thresholds. High sensitivity from low FIT thresholds decreases specificity and test precision, leading to higher false-positive rates, increased patient anxiety and pressure on colonoscopy services.^{73 74}

Population screening using a single flexible sigmoidoscopy (FS) has proven efficacy with reduced CRC incidence and mortality.⁷⁵ FS at age 55 has been adopted by the English Bowel Screening Programme prior to guaiac-based Faecal Occult Blood

Test at age 60. Limited FS resource and poor pathology yield in the age group chosen for the English programme may challenge the prospective clinical benefits observed in randomised clinical trials (RCT).

Early diagnosis by prompt recognition and reporting of symptoms by the public has been advocated, but to date has only succeeded in increasing rates of referral for investigation (usually colonoscopy), with no impact on rates of diagnosis of early disease.^{76 77} These initiatives have created increased pressure on diagnostic services; the need for effective triage of symptomatic patients is urgent. There is interest in the use of 'low threshold FIT' as an aid to decision-making.⁷⁸ The National Institute for Health and Care Excellence has recently issued guidance recommending highly sensitive FIT testing in patients with low-risk colorectal symptoms.⁷⁹

Colonoscopy in population screening is being examined worldwide, but mortality data will not be available for 10–15 years.⁸⁰ CT colonography is another screening modality, but pilot RCTs have yet to provide mortality data.^{81 82} Aside from expediting adoption of FS at an appropriate age(s), future developments in population screening include refining use of FIT by cost analysis of different thresholds, introduction of risk-adjusted screening with conventional or machine learning techniques and development of new markers.

RG5: Lack of an optimal strategy for screening for CRC.

RG6: Lack of an effective triage system for symptomatic patients that can determine who will benefit most from invasive investigation.

Risk adjustment

The threshold of faecal haemoglobin concentration that triggers a colonoscopy can be adjusted to increase sensitivity.^{73 74} While modelling studies have assessed the cost-effectiveness of changes to the FIT threshold, RCTs would supplement these studies.

RR5.1: Embed research RCTs in FIT-based screening programmes to explore the optimal FIT threshold and/or the role of flexible sigmoidoscopy, incorporating risk adjustment algorithms.

Another approach to FIT-based risk assessment is to incorporate age, gender^{83 84} and participant's screening history (eg, adherence to biennial screening, previous FS or colonoscopy, and so on, and other risk markers such as primary care blood results,⁸⁵ BMI or smoking status). An alternative or additional approach is to vary the screening interval, depending on FIT concentration or concentration trends or more comprehensive risk scores which incorporate age, gender and specific symptoms.

New technologies

Several technologies including analysis of DNA from faecal samples⁸⁶ and use of peripheral blood biomarkers such as methylated Septin 9⁸⁷ have not yet proven to be as clinically sensitive as FIT in population screening. Current developments include the detection of volatile metabolites in breath,⁸⁸ use of liquid biopsies,⁸⁹ the potential role of changes in the microbiome⁹⁰ and colon capsule endoscopy.⁹¹ These emerging technologies could be combined with morpho-molecular parameters if not for screening, then for risk stratification in early-stage disease and predicting disease recurrence.^{92 93}

RR6.1: Establish accurate risk-based assessment of symptomatic patients, incorporating FIT and promising novel technologies.

RR6.2: Develop and trial sensitive and specific tests that could be employed in both screening and symptomatic services.

Pathology: diagnosis–prognosis–prediction**Current status**

The present gold standard to assign patients with CRC to prognostic groups is the TNM (tumour, node, metastases) classification.^{94 95} This anatomic staging approach frequently clusters patients with biologically different diseases and allows only approximate estimates of survival outcomes. Increasing the accuracy and reproducibility of morphological prognostic factors is therefore a major challenge for pathologists.^{96–98}

Ongoing research promotes incorporation of an increasing number of molecular biomarkers into the CRC specimen reporting.⁹⁹ Well-established elements include immunohistochemistry testing of MMR protein expression, analysis of microsatellite instability and *MLH1* promoter hypermethylation. Clinical next-generation sequencing can underpin the fast, reliable, broadly applicable and cost-effective detection of mutations for prognostication and prediction of response to targeted agents.^{100–102} Understanding the patient's genetic context is also important for prognosis, treatment response and toxicity.^{103 104} Clinical success of immune-checkpoint inhibitor therapy in hypermutated CRC is driving the search for novel biomarkers to help stratify immunotherapy-based approaches.¹⁰⁵ Advances in gene expression profiling^{106–108} have culminated in a consensus molecular subtype classification,¹³ but its clinical value is currently unclear.

Overall, there is a critical need to revitalise CRC biomarker research, which has previously been limited by inconsistent methodologies and lack of reproducibility. Digital pathology, translational bioinformatics and machine learning must become critical components of modern pathology,¹⁰⁹ integrating rapidly expanding clinical and laboratory data sets to underpin algorithm development for risk prediction/disease stratification. This creates a presently unmet demand for large numbers of highly qualified personnel in the pathology sector.

RG7: Imprecise pathological assessment of CRC is an unmet challenge.

Risk stratification in early-stage disease

RGs are evident in the morphology-based risk stratification of colorectal precursor lesions and in clinical surveillance of patients with IBD. Although pathologists are mostly effective at diagnosing high-grade lesions, morphological categories are broad and interobserver reproducibility is limited.¹¹⁰ Translation of discovery research findings on the molecular pathogenesis of IBD-associated neoplasia will help improve utility and cost-effectiveness of screening approaches at the population level.

In stage I disease, most patients are cured by endoscopic polyp removal. However, up to 20% of cases may have occult nodal micrometastasis at time of resection.^{111 112} Stratification through assessment of additional histomorphological risk factors is heterogeneously reported and prone to variable reproducibility.^{98 99 113} Methodological standardisation and integration of biological data is needed to improve risk prediction in early-stage disease.

RR7.1: Precisely define the morpho-molecular taxonomy of precursor lesions and early-stage disease to help inform risk stratification in CRC.

Predicting disease recurrence and treatment response

Better approaches to predict recurrence, therapy response and toxicity are required to guide personalised treatment of patients with CRC. Reliable identification of high-risk stage II patients is

a presently unmet challenge.^{114–117} Most patients with stage III disease will receive standard chemotherapy or radiotherapy.¹¹⁸ However, up to 70% will not relapse following potentially curative resection, derive no benefit from chemotherapy and suffer toxic side effects.¹¹⁹ In stage IV disease, there is a need for accurate stratification for surgical treatment and early detection of evolving drug resistance. Further integration of genomic,¹⁰² immune¹²⁰ and transcriptomic approaches^{13–17 106–108} into pathologic tumour staging is a critical enabler for personalised treatment of patients with CRC.

RR7.2: Develop new standardised molecularly informed multiparameter algorithms to permit improved prediction of disease recurrence and therapy response.

Developing robust molecular signatures for precision pathology analysis

Molecular taxonomy studies have highlighted the important contribution of the stroma to CRC, and its association with poor prognosis disease.^{16 17} However, intratumoural heterogeneity, due to variations in stromal content,^{15–18} can compromise clinical application of molecular profiling. The recent discovery of a CRC intrinsic signature¹⁴ may have more robust prognostic/predictive relevance,¹⁵ and should be considered for inclusion in molecular pathology workflows. A key enabling technology is the improved analysis of formalin-fixed paraffin-embedded tissues (and alternative non-formalin-based fixatives), given the logistical challenges with use of fresh-frozen tissue.

RR7.3: Use our evolving understanding of the CRC tumour and its microenvironment to underpin standardised approaches for pathology specimen analysis.

Growing the talent pool and skilling the pathology workforce

Genomic medicine is given limited space in medical curricula and pathology training. Know-how in digital image analysis, bioinformatics and machine learning is currently lacking, compromising development and application of next-generation diagnostic tools. Pathologists are thus at risk of losing their methodological competence to lead, evaluate and guide biomarker testing in personalised medicine and biomedical research.

RG8: Lack of qualified personnel to apply state-of-the-art knowledge in genomics, big data science and digital pathology.

The UK government's life sciences strategy lists molecular diagnostics, digital pathology and artificial intelligence as key strategic areas for further development.¹²¹ Structured educational programmes in genomics/bioinformatics should be offered to complement existing training. Exemplary efforts to promote genomic pathology education have been made (eg, Health Education England's Medical Genomics Programme (UK)¹²²; Training Residents in Genomics Working Group (USA)).¹²³ A network approach in conjunction with national/international pathological societies is warranted to advance learning for the present and future workforce. Funded programmes should be established to encourage collaboration of histopathologists with molecular geneticists, bioinformaticians and physical scientists to establish optimal methodologies of data accumulation/integration, thus retooling and empowering the emerging molecular pathology generation.

RR8.1: Embed interdisciplinary education/training within undergraduate/postgraduate and continuing professional education curricula to ensure recruitment, retention and upskilling of

qualified personnel to deliver modern pathology to the CRC community.

Curative treatment

Current status

Recent technological advances have improved the quality of curative therapies: the advent, evaluation and widespread adoption of laparoscopic colorectal surgery, for example, have improved short-term recovery at no expense to survival.^{124 125} However, there are significant regional variations in the delivery of certain innovations because of a lack of definitive research studies.¹²⁶

Cure is becoming increasingly feasible, but effective patient-centred care requires consideration of broader treatment effects. Patients with advanced disease may have access to novel therapies with only limited survival benefits but which cause major morbidity. Similarly, patients with very 'curable' disease may want to explore treatment options with reduced chance of cure but minimal impact on health-related quality of life (HRQOL).¹²⁷ Current research continues to investigate treatments that minimise toxicity (SCOT and IDEA trials)^{128 129} or amplify survival for patients undergoing established treatments (eg, ADD-ASPIRIN, CHALLENGE and FOxTROT trials).^{130–132}

RG9: Inadequate assessment and communication of risk, benefit and uncertainty of treatment choices where cure is possible.

RG10: A need for novel technologies/interventions that have the potential to improve curative outcomes.

Informing shared decision-making

Great advances have been made in understanding, implementing and optimising patient-centred care;¹³³ however, further work is needed to address the specific issues in new and evolving CRC therapies. Appropriate research, answering key questions that inform shared decision-making, must be conducted.

It is now accepted, for example, that definitive radiotherapy and organ preservation may be a viable alternative to major resectional surgery.^{134 135} Communicating the balance between patient experience and maximising survival in rectal cancer is extremely relevant. A non-surgical approach may lead to better HRQOL but with a reduced chance of cure, while a major surgery has greater immediate risks, but may have a higher chance of cure.

RR9.1: Develop an appropriate evidence base to inform shared decision-making for potentially curative therapies for patients.

Establishing optimum peritherapeutic interventions

Critical to shared decision-making is anaesthetic risk assessment¹³⁶ but currently there remain limitations in tools that give us a valid risk assessment for more frail patients and/or those with significant comorbidities.¹³⁷ Mitigating risk or optimally reducing its impact is a vital component in improving outcomes. We need to improve pre/post/perioperative management to enhance patient experience (both short term and long term) and survival after 'curative therapies'.

RR10.1: Establish optimum peritherapeutic interventions to improve curative outcomes.

Optimising health-preserving benefit in metastatic/recurrent disease

We have continued to push the boundaries of curative interventions in CRC.¹³⁸ Selecting an individual for potentially more aggressive approaches when the disease has spread beyond the confines of the bowel has become commonplace, but each time we extend these boundaries, further evaluation to fill our

knowledge gap is required. Specifically, questions arise such as: 'How should we select patients for novel curative therapeutic interventions for oligometastatic disease?', 'What is the role of ablative technologies for cure in metastatic disease?' and 'What is the evidence for highly aggressive surgical intervention for recurrent/locally advanced disease?'

RR10.2: Optimise curative approaches for metastatic or recurrent disease that balance patients' expectations with treatment efficacy and health-preserving benefit.

Biomarkers for optimal treatment selection

Broad technological advances have been made in CRC therapy including surgery, radiotherapy and molecular-based treatment.^{139–141} These advances may impact upon existing therapeutic options, for example, by optimising the use of chemotherapies in the adjuvant setting to avoid excessive toxicities, or by underpinning newer biomarker-driven treatment selection. This aims to move beyond the standard of care to a more individualised approach.

RR10.3: Develop biomarkers that define the optimal curative therapeutic strategy for an individual or group, preventing overtreatment and improving treatment selection.

New methodologies

Methods to ensure optimal evaluation of new surgical and radiotherapy-related devices and procedures^{142 143} are needed to demonstrate appropriately robust clinical and cost-effective outcomes. Such methods have been promoted by the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) collaboration,¹⁴⁴ but further methodological development is needed, particularly in early phase studies. This will promote consistency in standard therapeutic pathway development, ensuring that the best therapies are more widely used, based on compelling evidence at an earlier stage. It is critically important to define the interventions to be tested, but equally important are methodologies for their evaluation, providing the evidence base to encourage their integration into clinical practice to enhance curative outcomes.

RR10.4: Develop research methodologies to optimally evaluate new curative approaches.

Stage IV disease

Current status

Around 20% of patients presenting with CRC have metastatic disease (mCRC) at time of diagnosis.¹⁴⁵ A further 20%–25% will develop mCRC during follow-up after initial curative intent treatment of their primary tumour. Recently, there has been an expansion in the range of modalities available for treating stage IV CRC. More aggressive approaches to resection of mCRC (particularly major liver resection), combined with ablative technologies and loco-regional treatments, are allowing potentially curative options to be offered to more patients. For chemotherapy, the single agent (5-fluorouracil) available 20 years ago has multiplied into 13 available drugs in 2016.¹⁴⁶ Despite these incremental advances in patient treatment, disease cure remains unattainable for many.

Genomic technologies have given valuable insights into CRC heterogeneity, leading to identification of distinctive molecular subtypes.^{13–15} Knowledge of the associated clinical ramifications of these subtypes should help optimise treatment strategies. Recent advances in immunotherapy have resulted

in significant clinical benefit in non-small cell lung cancer and melanoma.^{147–149} We need to translate these successes into new treatment approaches in CRC, beyond the benefit already seen with immune-checkpoint inhibition in the ~5% of patients with metastatic disease whose tumours have deficient DNA MMR.¹⁵⁰

RG11: Lack of approaches that take cognisance of the molecular interplay between the metastasising tumour and its microenvironment and help guide evolution of innovative treatments that deliver improved health outcomes for the stage IV patient.

Multimodality treatment in stage IV disease

There have been major developments in surgical resection of both primary and metastatic diseases, with advanced techniques permitting radical resection.¹⁵¹ However, fundamental questions remain unanswered such as whether primary tumour resection in the presence of synchronous inoperable metastatic disease affects the natural history of the disease. It is now possible to perform radical peritonectomies and major pelvic exenterations for primary and recurrent disease,^{152 153} but significant variations in practice from preoperative imaging through to clinical intervention remain. Understanding which patients to select for which procedure is challenging, and outcome data, including increasingly relevant long-term patient-reported outcome measures (PROMs) are not robust.

Minimally invasive surgical techniques are being evaluated in mCRC management,¹⁵⁴ and in the UK a trial is open comparing resection and percutaneous ablation in operable liver metastases.¹⁵⁵ Disappointingly, the initial promise observed in trials investigating radioembolisation in patients with inoperable liver metastases has not translated into improved overall survival.¹⁴³ Currently, only patients with low-burden, circumscribed metastases are potentially curable. Consensus guidelines on the sequence, setting (eg, supraregional centres for certain aspects of care) and timing of multimodality treatment, including systemic therapy to downsize inoperable disease, would translate into more patients being cured, including those with multisite metastatic disease. Even in non-curable disease, the role of multimodality therapy combining downstaging systemic therapies, resection and ablation of the majority of multiorgan mCRC, may allow prolonged survival with good HRQOL and freedom from symptoms. This concept of 'optimal debulking', based on clinical practice in ovarian cancer, is now being investigated in CRC, in clinical trials such as ORCHESTRA,¹⁵⁶ and should be explored more widely.

RR11.1: Develop evidence-based approaches utilising multimodality treatment for patients with stage IV CRC to maximise the utility of cutting-edge technologies to improve outcomes.

RG12: Lack of reliable prognostic and predictive biomarkers to help guide stage IV patient pathways.

Stratification of patients

The lack of widely accepted prognostic and predictive biomarkers results in limited consensus to guide stage IV patient pathways. For example, how should we adopt WES/whole-genome sequencing into our standard of care and how do we interpret and transmit large-scale multiomics data for clinical decision-making? Transcriptomic analysis is starting to yield clinically relevant results which can help inform molecular stratification of patients with CRC to improve outcomes. Trials such as FOCUS-4, a multistage multiarm approach in CRC, may provide the appropriate model going forward.¹⁵⁷ An important consideration is the increasing age of the population, as more frail

patients with complex medical needs are diagnosed. Accurately recognising and understanding which aspects of patient frailty are reversible (and potentially be amenable to prehabilitation) remains challenging.

RR12.1: Establish robust prognostic and predictive biomarkers to stratify patients to ensure every patient receives 'bespoke' treatment, relevant to their particular disease course.

Understanding the microenvironment to help develop innovative treatments

Colon carcinogenesis occurs within an inflammatory microenvironment where gut bacteria provide constant immune stimulation. Therefore, many immunosuppressive processes have been developed in colonic epithelium to prevent these bacteria-induced inflammatory triggers.¹⁵⁸ Interplay between the gut microbiome, inflammation and carcinogenesis is complex but is critical to understand to improve CRC treatment.

CRC stem cells play a significant role in intratumoural heterogeneity.¹⁵⁹ As a dynamic population of cells, they respond to genetic and epigenetic factors along with microenvironmental signals to influence key processes such as metastatic potential and chemotherapy resistance. CRC cells can thus continuously adapt to their environment, highlighting the difficulty of developing suitable models to target cancer stem cells by directed therapies.

To date, despite significant efforts, immune-mediated approaches in CRC have had limited success. High gene mutational load¹⁶⁰ and the presence of DNA MMR deficiency and DNA polymerase E proofreading mutations^{150 161} correlate with improved outcomes to immune-checkpoint inhibitors. Immunoscore is a scoring system based on quantifying the number of cytotoxic and memory T cells infiltrating the core and leading edge of the tumour.^{97 162} Using this approach may allow identification of a prognostic biomarker of responsiveness to immune-checkpoint inhibitors. Significant work is ongoing to understand how the role of the microenvironment (including the gut microbiome) influences immune-evading mechanisms or immune-editing in CRC,¹⁶³ and this should help unlock the potential of immunotherapy in this disease.

RR12.2: Employ our evolving understanding of the role of the tumour microenvironment in CRC to develop innovative therapies that modulate the microenvironment for clinical benefit.

Living with and beyond CRC

Current status

Congruent with prioritisation of research to promote effective prevention, enable earlier more precise diagnosis and deliver optimal treatments to enhance CRC outcomes, there is a need for more research-informed approaches to improve HRQOL and enhance survivorship for the expanding population now living with and beyond CRC. Instruments such as the EORTC QLQ-CR29 questionnaire are invaluable in assessing HRQOL in CRC,¹⁶⁴ while the recently introduced ESMO Magnitude of Clinical Benefit Scale¹⁶⁵ includes HRQOL in its evaluation of benefit/value of new treatments. Despite this progress, there are still substantial gaps in our knowledge about optimising HRQOL; thus further research is required to inform appropriate intervention(s) and promote a responsive HRQOL agenda for the CRC survivor over the coming decade.

RG13: The need to increase understanding of health-related quality of life (HRQOL) issues and promote their resolution as part of

a research effort to enhance survivorship for those living with and beyond CRC.

Health-related quality of life

A recent systematic review indicated that >75% of reported studies addressing HRQOL in CRC were of inadequate methodological/reporting quality.¹⁶⁶ Additionally, many HRQOL studies are retrospective; introduction of preplanned analyses would significantly enhance data quality,¹⁶⁷ and identify those patients who might benefit from early discontinuation of induction therapy or continuation/de-escalation of active maintenance treatment. Immune-checkpoint targeting is an exciting new therapeutic modality, with unparalleled efficacy in MMR-deficient CRC,^{105 160 161} but knowledge of both short-term and long-term HRQOL issues and PROMs are limited. More precise research is also required to improve understanding of the psychological consequences (eg, emotional reactions, survivorship guilt, lack of reintegration into normal life) and social challenges (eg, employment, self-esteem, discrimination) for those living with and beyond CRC. Development of evidence-based models that elucidate relevant predictors of HRQOL¹⁶⁸ would help pinpoint individuals at risk and provide potential solutions to help resolve the clinical/psychosocial sequelae of CRC and their treatment.

RR13.1: Precisely characterise the landscape of HRQOL sequelae in patients living with and beyond CRC, including those in receipt of novel treatment approaches (eg, immunotherapy).

Symptom management

A high proportion of patients have troublesome, embarrassing and potentially disabling symptoms after surgery/radiotherapy for CRC. Many patients experience a permanent change in bowel habit after anterior rectal resection (AR),¹⁶⁹ with major negative impacts on daily living.^{170 171} A meta-analysis of >3300 AR patients has found a 35% incidence of faecal incontinence (FI).¹⁷² Following pelvic radiotherapy, GI symptoms are the most common chronic side effect, with 50% of patients reporting significant effects on HRQOL.¹⁷³ Chronic FI frequently occurs after radiotherapy for rectal cancer.¹⁷³

Published systematic reviews have found remarkably few intervention studies and no RCTs in patients with anterior resection syndrome.^{174–176} Hyperbaric oxygen has frequently been used to treat patients following pelvic radiotherapy, but a recent RCT demonstrated no benefit, highlighting the urgent need for new approaches.¹⁷⁷ After radiotherapy, it is possible to improve symptoms with relatively low-cost interventions,^{178 179} but studies of lifestyle interventions, self-management and choice of optimal support services are lacking.

We need to better understand which aspects of treatment cause symptoms and define their underlying mechanism, in order to test measures to prevent/ameliorate symptom development and treat symptoms when they are troublesome.

RR13.2: Elucidate the causes of symptoms following CRC treatment and develop viable solutions for their prevention and/or management.

Lifestyle interventions

Emerging evidence suggests that lifestyle interventions promoting increased physical activity,¹⁸⁰ healthy eating¹⁸¹ and weight control can have significant benefits, but research on their impact following CRC treatment or during recurrence is limited.^{182 183} More longitudinal studies are required to underpin

the evidence base for introduction of such interventions and to identify appropriate tools to measure their proposed benefits.¹⁸⁴

RR13.3: Evaluate the evidence base and impact of lifestyle interventions, including increased physical activity and better nutrition in CRC.

Survivorship

Survivorship care planning must involve meaningful two-way dialogue. However, surveys reveal that only a minority of HCPs regularly discuss survivorship issues or provide survivorship care plans to those living beyond CRC.^{185 186} It is imperative to implement research-informed National Cancer Survivorship Plans.^{187–189} Research to develop appropriate CRC survivorship care guidelines¹⁹⁰ can underpin creation of relevant tools to nurture open and effective interactions between HCPs and CRC survivors, empowering a shared decision-making culture.

RR13.4: Develop research to support survivorship care planning and promote shared decision-making for people living with and beyond CRC.

Overarching RGs that need to be addressed

In addition to the thematic RGs outlined above, there are also several cross-cutting RGs raised by a number of the WGs.

RG14: Lack of coordination of CRC research and its funding, leading to fragmented efforts to elucidate the biology of the disease and translate this knowledge into new preventative agents, screening tools, diagnostics and therapeutics.

The need for a national cancer research forum

Congruent with the multidisciplinary team approach delivering optimal care to patients with CRC is the need to bring together the diverse expertise increasingly required to answer the complex research challenges outlined in this paper. Linking biologists, physical scientists and mathematicians can fuel development of testable chemoprevention models. Integrating epidemiological, bioinformatic, pathological and clinical expertise can underpin rational biomarker-informed clinical trial design. Capturing all of this expertise under the umbrella of a national CRC research conference in the UK, for example, would provide the impetus for a coordinated interdisciplinary approach to successfully address the critical challenges in CRC research.

RR14.1: Establish an annual national multidisciplinary CRC research conference that draws together the entire CRC community in a coordinated research effort.

The need for data sharing

A recurrent theme from a number of the WGs was the need to provide mechanisms and tools that enable sharing of the ever-expanding data outputs generated through CRC research. Sharing of genomic, clinical, epidemiological and lifestyle data can be challenging, but international collaborative efforts such as the Global Alliance for Genomics and Health¹⁹¹ provide a blueprint for effective but responsible data sharing in cancer that addresses the technical, ethical, legal and security barriers.^{192 193} Development of bespoke data-analytic platforms,¹⁹⁴ tailored to the requirements of the CRC community, could maximise the value of the rich sources of data being generated and yield significant benefits for CRC researchers, patients and society.

RR14.2: Develop bespoke data-analytic platforms that maximise the value of CRC genomic, clinical, epidemiological and lifestyle data.

Prioritising funding for CRC research

As well as prioritising research activity, the BCUK's *Critical Research Gaps in Colorectal Cancer Initiative* provides an excellent opportunity for research funders (eg, research councils, cancer charities, non-governmental organisations) to concentrate their funding in particular areas of focus where there is a defined research need, and/or investigate the potential for collaborative research grant calls between complimentary research funding organisations. An example of this approach is the Medical Research Council-CRUK jointly funded Stratified Medicine in Colorectal Cancer consortium,^{157 195} which brings together diverse stakeholders in a research collaborative to develop predictive and prognostic markers that drive precision medicine approaches in CRC.

RR14.3: Prioritise research resource allocation to recognise research gaps and encourage collaborative research grant calls between complimentary research funding organisations.

RG15: *Lack of effective communication strategies between health-care professionals, patients with CRC/survivors, those at elevated risk of developing CRC, and the general public and varying levels of awareness of key risk factors, prevention options and benefits/risks associated with different treatment options.*

Closing the communication gap

There are distinct challenges around CRC health literacy and communication between HCPs and patients with CRC/survivors, those at elevated risk of developing CRC and the general public. Patients are becoming increasingly empowered to make their own personalised health decisions; this should be encouraged and nurtured. However, awareness of personal CRC risk/risk factors,^{196 197} appropriate prevention options¹⁹⁸ and benefits/risks associated with treatments¹⁹⁹ is variable. Patient-adapted educational materials and shared decision-making tools^{200 201} must be made available, empowering individual choice while facilitating formal assessment of 'what is or was the right choice' for that individual.

RR15.1: Development of patient and person-adapted educational materials and shared decision-making tools in order to empower individual choice.

Research into the most appropriate communication strategies for explaining risk and benefit in different settings (eg, cancer risk modification, surgery, adjuvant therapy) is crucial. Recent work on knowledge of, and attitudes to, CRC chemoprevention has highlighted that a majority of primary care physicians were unaware of the chemopreventive properties of aspirin.²⁰² There is a need for better communication with patients about treatment-related symptoms, emphasising that it is legitimate to seek help (and not simply accept treatment-related complications as the price of a successful cure) and investigate both professionally led and self-help interventions.

From a patient communication perspective, PROMs play a key role in identifying specific needs, while also providing important information on outcomes.²⁰³ However, there are major variations in how PROMs are measured and employed.²⁰⁴ Studies should identify which PROMs best reflect the views/experiences of individuals living with and beyond CRC, and how they may signpost early indicators of disease recurrence.

Evidence is also required as to whether long-term access to a CRC nurse or other relevant HCP improves communication

and shared decision-making, empowering survivors as active participants in their own care.²⁰⁵ A better understanding of why patients with CRC do or do not participate in RCTs would help facilitate recruitment and allow development of RCT protocols more relevant/acceptable to patients.²⁰⁶ A recent multinational survey indicated a high awareness of patients with breast, lung or CRC regarding the potential of precision medicine to deliver personalised care,²⁰⁷ but highlighted important regional variations and the patient's need for additional information.

RR15.2: Embedding strategies that ensure appropriate communication of risk and benefit and best capture patient-reported outcome measures (PROM) in order to ensure optimal outcomes for patients, their families and carers, and those at risk of developing CRC.

Research addressing these diverse communications issues can help ensure that patients with CRC/survivors and those at risk of developing CRC receive optimal information and participate in their health-preserving decisions as equals.

CONCLUSIONS

In this position paper, we present the informed considerations of a wide-ranging multidisciplinary group of experts from UK-based research institutions, complemented by significant input from those affected by CRC. We articulate their collective viewpoint in a series of critical RGs and RRs (see online supplementary table 1), which if appropriately implemented would significantly impact on the prevention, early diagnosis, treatment and improved quality of life for people living with and beyond CRC. Prioritisation of CRC research activity, supported by effective policy decisions and appropriate resource allocations, will help us tackle this life-threatening, debilitating disease that kills ~800 000 of our citizens globally each year.

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