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Review

Improving outcomes in colorectal cancer: Where do we go from here?

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Abstract Colorectal cancer (CRC) places a considerable burden on individuals and society in Europe, being the second most common cause of cancer-related death in the region. While earlier diagnosis and advances in treatment have considerably improved survival in recent years, further progress is needed. One of the greatest challenges associated with the treatment of CRC is the fact that current therapies for advanced disease are not curative, necessitating treatment for many years and placing a significant healthcare burden on society. To reduce the burden of CRC, care delivery must be more efficient and cost-effective. In particular, development of adequate screening programmes is needed, along with chemo-preventative strategies and newer, more active therapies. Further challenges include the lack of optimal selection of patients for adjuvant therapy, identification of the most appropriate target populations for current treatments and the optimum sequence for new molecular targeted agents. This article outlines current developments and unmet needs in CRC, and provides a detailed vision for improvements in the management of the disease. Implementation of some of these strategies will go some way to improving outcomes for patients with CRC.

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1. Introduction

Cancer places a considerable burden on society, being responsible for 29% of male and 23% of female deaths in Europe in 2008, and 7.6 million deaths globally.[1] Against this backdrop, the American Society of Clinical Oncology (ASCO) has developed a blueprint for action in an effort to accelerate progress in oncology.[2] The blueprint calls for a new approach to therapeutic development, employing molecularly-driven clinical trials leading to a more cost-effective process. While many of the proposals outlined in ASCO's vision are applicable to Europe, the region faces a number of unique challenges requiring a Europe-focussed approach. This article, focussing on unmet needs in colorectal cancer (CRC), forms the first in a series of reviews outlining current requirements in oncology and proposing future directions in a 'European call to action' across the healthcare community.

2. The healthcare burden and the challenges of CRC

CRC has a considerable impact on patients and healthcare systems in developed countries, and is the second most common cause of cancer-related death in Europe.[3,4] Around 25% of patients present with metastatic disease that significantly impacts on prognosis.[5] For those with localised CRC (Tumour, Nodes, Metastasis [TNM] stages I and II) the 5-year survival rate is as high as 93%, declining to 60%, 42% and 25% for patients with TNM stages IIIA, IIIB and IIIC, respectively. However, most patients with metastatic CRC (mCRC; stage IV) are not curable, with the 5-year survival rate falling to less than 10%.[6,7]

While early diagnosis of CRC in recent years combined with advances in treatment has considerably improved survival,[4] management of the disease remains challenging and further progress is needed. One problem associated with treatment is the heterogeneity of the CRC population.[8] In addition, as current therapies for advanced CRC are not curative, patients require treatment for many years, placing a significant healthcare burden on society. For this reason, development of adequate screening programmes is needed, along with chemo-preventative strategies and newer, more active therapies. Additional challenges include the lack of optimal selection of patients for adjuvant therapy, identification of the most appropriate target populations for current treatments and the optimum sequence for new molecular targeted agents.

3. Identifying new pathways in CRC through improved understanding of pathogenesis

An understanding of the genetics of inherited CRCs is important in order to identify at-risk individuals and improve diagnostic and therapeutic approaches. Familial predisposition is responsible for approximately one-quarter of CRCs, though hereditary syndromes with a known genetic defect are responsible for <5% of patients with CRC (Table 1).[8–14]

Three key pathways of genetic instability have been identified in CRC: chromosomal instability, microsatellite instability and CpG island methylator phenotype (CIMP), the methylator pathway.[14] These pathways are responsible for both sporadic and inherited cases, the most prevalent of which is Lynch syndrome, accounting for 2–4% of CRCs.[8] Other common syndromes include familial adenomatous polyposis (FAP) and serrated polyposis, a recently identified disease affecting 1 in 3000 individuals undergoing CRC screening.[15] While screening and surveillance strategies are now available for most inherited CRC syndromes, treatments for primary or secondary chemoprevention are lacking and new agents are needed, particularly for early-onset syndromes such as FAP and Lynch syndrome.

The identification of relevant molecular targets for cancer initiation and/or progression is an important focus for the development of targeted therapies in CRC and significant advances have been made recently as a result of projects such as the National Cancer Institute's Cancer Genome Atlas Network.[16] Patients whose tumours depend on particular targets can then be selected to avoid or minimise primary resistance to therapy. Mutations in the adenomatous polyposis coli (*APC*) and *KRAS* genes are thought to be among the earliest events in colorectal tumorigenesis.[17] *APC* mutation occurs through aberrant activation of the Wnt/β-catenin signalling pathway, with mutations within this pathway being responsible for around 90% of sporadic colon cancers.[18] *APC* is also the gene responsible for FAP and is a key target for intracellular signalling. A further important molecular target is epidermal growth factor receptor (EGFR), since around 10% of CRC tumours and 20–30% of *KRAS* wild-type tumours are dependent on the EGFR pathway.[19] EGFR activates multiple signalling pathways, including RAS/RAF/MEK/ERK and PTEN/PI3K/Akt (Fig. 1).[20,21] RAS/RAF/MEK/ERK is the main pathway upregulated when EGFR is activated,[21] though upregulated genes differ between tumour types, underlining the need for gene profiling for all CRC tumours.

4. Improving survival through advancements in CRC prevention and diagnosis

Effective screening to detect precursor lesions and early CRC is critical to reduce the burden of the disease on the healthcare system. Identification of adenomas before the development of carcinoma not only improves survival but also reduces cancer incidence. Indeed, the utility of this strategy has been accepted by the European Commission, which encourages the implementation of screening programmes throughout Europe.[22,23]

Table 1
Sporadic and syndromic forms of CRC and associated genetic mutations.[8–14]

Form of CRC	Lifetime CRC risk	Pathway	Genetic alterations identified to date
Syndromic			
Familial adenomatous polyposis	95% (at 50 years of age)	Suppressor	*APC* mutations
Lynch syndrome	50–80%	Mutator	MMR mutations: *hMSH2*, *hMLH1*, *hMSH6* and *hPMS2*
Serrated polyposis	~35%	Methylator	*BRAF*, *KRAS*, CIMP-H, *MLH1* methylation, *MGMT* methylation
Sporadic			
Chromosomal instability	N/A	Suppressor	*APC* mutations/aberrant Wnt/β-catenin signalling
Microsatellite instability	N/A	Mutator	*MLH1* gene promoter hypermethylation, *BRAF V600E* mutation
CpG island methylator phenotype	N/A	Methylator	CIMP-H

APC, adenomatous polyposis coli; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; MMR, mismatch repair; N/A, not applicable.

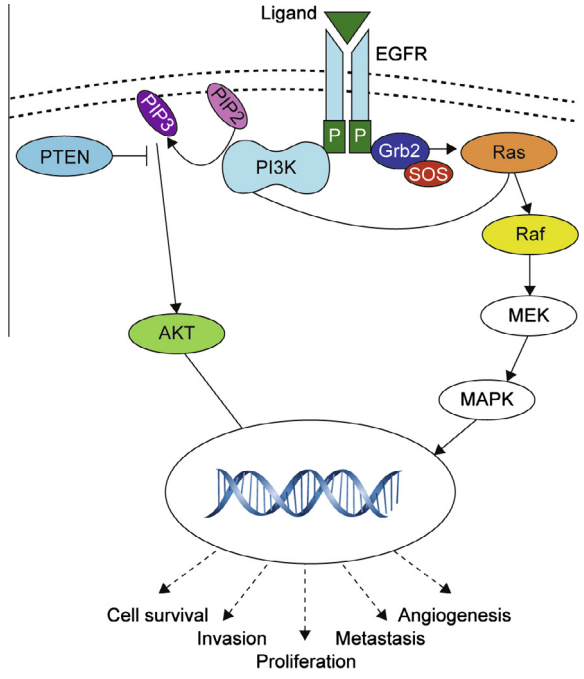

Fig. 1. Epidermal growth factor receptor (EGFR) signalling pathway. Reproduced from Krasinskas (2011).[20] Ligand binding induces dimerisation and activates the EGFR, and subsequent autophosphorylation of tyrosine residues activates downstream signalling. Ras/Raf/MEK/MAPK is one axis of the EGFR signalling cascade. Activation of this pathway, via growth factor receptor-bound protein 2 adapter protein (Grb2) and son of sevenless (SOS), leads to activation of Ras GTPases and Raf (ARAF, BRAF and CRAF) and MEK (MEK1 and MEK2) kinases, followed by activation of transcription factors in the cell nucleus that control cell growth, differentiation and survival. PI3K/AKT is the other axis of EGFR signalling that is important in colorectal carcinogenesis. Activation of this pathway via PI3K results in conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which promotes AKT activation. Activated AKT then activates various targets that also result in cell growth, differentiation and survival, paralleling the Ras/Raf/MEK/MAPK pathway. These two axes are closely related and some overlap exists. Phosphatase with tensin homology (PTEN) is a phosphatase that converts PIP3 back to PI2, negatively regulating the PI3K/AKT pathway.

Screening for CRC in high-risk groups (hereditary or familial predisposition) is performed by colonoscopy. While this strategy has been proven to reduce the incidence of new CRCs in countries offering colonoscopy every 10 years for those >50 years of age (e.g. Germany),[24] the technique may not reduce mortality in those with right-side tumours.[25] However, the guaiac-based faecal occult blood test (gFOBT) or most often the faecal immunochemical test (FIT) are usually implemented in organised screening programmes targeting average-risk populations due to better compliance and higher participation versus colonoscopy.[26] Identification of early-stage disease as a result of large-scale screening has the potential to increase the population of patients with stage I/II CRC considerably, underlining further the need for the development of chemoprevention agents.

Besides adenomatous polyps, it is now clear that precursor colon epithelial polyps are heterogeneous and also include serrated polyps, sessile serrated adenomas, traditional serrated adenomas and mixed polyps.[27] The risk of developing CRC may also differ depending on polyp type. While the optimum screening method, frequency and follow-up for serrated polyps have not been determined, the results of recent studies suggest that the number detected is correlated with the risk of developing CRC.[15] To prevent malignant progression, adequate detection and endoscopic removal of all polyps seems advisable, with surgical resection being considered if this is not feasible.

Daily aspirin is a further potential preventative strategy for patients with Lynch syndrome due to their overexpression of cyclooxygenase II (COX-2). While prophylactic aspirin has been shown to reduce the incidence of cancer substantially in Lynch syndrome carriers,[28] the precise dose to be used has yet to be defined. Demonstration of the benefit of chemopreventive strategies and agents is challenging and will require very large studies.

5. Current treatment options and unmet needs in CRC

Treatment for CRC is dependent on a number of factors, including the disease stage (Table 2),[29] tumour

Table 2
American Joint Committee on Cancer (AJCC) staging system for colorectal cancer.[29].

AJCC stage	TNM stage	Definition
I	T1; N0; M0	T1: tumour invades submucosa
I	T2; N0; M0	T2: tumour invades muscularis propria
IIa	T3; N0; M0	T3: tumour invades through muscularis propria into subserosa or non-peritonealised pericolic tissues
IIb	T4; N0; M0	T4: tumour directly invades other organs or structures and/or perforates visceral peritoneum
IIIa	T1 or T2; N1; M0	T1/2; N1: metastases to 1–3 regional lymph nodes
IIIb	T3 or T4; N1; M0	T3/4: N1: metastases to 1–3 regional lymph nodes
IIIc	Any T; N2; M0	N2: metastases to $\geqslant$4 regional lymph nodes
IV	Any T; Any N; M1	M1: distant metastases

T, tumour; N, node; M, metastases.

biology, patient considerations, drug efficacy, toxicity, availability and cost. For patients with stage I/II CRC, the primary treatment is surgery, with adjuvant therapy also used in patients with high-risk stage II disease. For stage III colon cancer, a chemotherapy doublet including a fluoropyrimidine and oxaliplatin has clearly improved survival, while neoadjuvant (chemo)radiotherapy improves the outcome of locally advanced rectal cancer.[30] With the development of a multimodal strategy along with improved surgical and pathological care, the local recurrence rate in rectal cancer is now <10%. However, many patients still develop distant metastases, despite an adjuvant treatment, underlying the need to identify better treatment options to reduce the occurrence of metastatic disease.

For patients with metastatic disease, <0.5% are cured by chemotherapy alone; therefore, surgery is the only curative treatment option. One of the challenges is to bring more patients with metastatic disease towards resection with curative intent, though combination chemotherapy with a doublet of cytotoxic agents plus a biological targeted agent has the potential to convert unresectable to resectable metastases.[30]

While the availability of novel biologicals used in combination with chemotherapy over the past decade has had a positive impact on survival in CRC,[31] their optimal integration into the management of mCRC remains difficult. In particular, identifying the subgroups of patients and molecular profiles that respond to different targeted agents is challenging. Despite active research,[32] validated predictive biomarkers for angiogenesis inhibitors are not yet available and, although interesting data are available for cetuximab and panitumumab,[33,34] *KRAS* mutation status remains the only validated biomarker used to predict therapeutic efficacy for anti-EGFR antibodies. Recently, it has been shown that cancer cells are subject to evolutionary selection pressure, and patients whose tumours were initially *KRAS* wild type can develop different *KRAS* mutations.[35–37] This may explain the acquired resistance to EGFR blockade that occurs in most patients with *KRAS* wild-type tumours within months of initiating therapy. Collection of multiple biopsies will help to identify novel biomarkers and inform on how tumours evolve over time and in response to treatment. However, the development of less invasive methods of monitoring tumour evolution may be required to improve patient acceptability. Advances in mutation analysis on liquid biopsies (plasma or blood samples) may be important in this regard.[38] Every effort must be made to find predictive markers for new biological targeted agents in development in order to improve affordability for patients with CRC (and other cancers), since they place a considerable economic burden on health-care budgets. Defining the best strategy and sequence of biological targeted agents is another clinical challenge. However, there are accumulating data suggesting that the progression continuation of angiogenesis inhibitors improves the outcome of patients with mCRC.[39] Some patients may also benefit from early integration of anti-EGFR antibodies, especially if conversion from unresectable to resectable disease can be considered.

There is a need for the development of newer, more active agents in CRC for metastatic disease, adjuvant treatment and chemoprevention. The unravelling of the taxonomy of CRC will certainly contribute to the discovery of new active agents in these different situations. Additionally, the search for molecular markers in parallel with the development of novel agents and molecular tests will contribute to the identification of new predictive markers for these agents.

New agents or innovative combinations of new agents interfering with different targets within signal transduction pathways are also needed (see Table 3). Intriguingly, the BRAF inhibitor vemurafenib failed to demonstrate relevant activity in BRAF mutant CRC,[40] while this drug has considerable activity in patients with melanoma harbouring the same mutation.[41] Preclinical studies, however, suggest that dual blockade of BRAF and EGFR may be required in this population.[42] The clinical activity of novel selective MEK1/2 inhibitors when used as single agents has also not been robust.[43,44] However, these agents may be effective in patients with *KRAS* mutations, a population resistant to EGFR inhibition, through inhibition of the key MEK downstream target kinase, ERK.[45] Blockade of the MET pathway may, therefore, be an important means of delaying or reverting EGFR resistance.[46] Other possible future areas for drug development include inhibition of the hepatocyte growth factor pathway, microRNA (miRNA) profiling and colon cancer stem cells.[47]

Table 3
New cellular targets in colorectal cancer and novel agents in development.

Molecular target	Agents in development	Company	Development phase
RAF inhibition	Vemurafenib (PLX4032)	Roche	I
	Dabrafenib (GSK2118436)	GlaxoSmithKline	I
	LGX818	Novartis	I
MEK inhibition	Pimasertib (MSC1936369B)	Merck	I
	Selumetinib (AZD6244)	AstraZeneca	I/II
	AS703026	Merck	I
	GSK1120212	GlaxoSmithKline	I/II
	ARRY-162 (MEK162)	Array Biopharma/Novartis	I/II
MET inhibition	ARQ197	ArQule/Daiichi Sankyo	III
	PHA-665752	Pfizer	Preclinical
Beta-catenin pathway	Various inhibitors	Avalon/Novartis	Preclinical/I
VEGF inhibition	Tivozanib	Astellas	II

VEGF, vascular endothelial growth factor.

More effective adjuvant therapies for CRC are also required as the results of trials with agents active in stage IV CRC have been disappointing in the adjuvant setting (e.g. irinotecan, bevacizumab and cetuximab).[48,49] Additionally, the role of adjuvant chemotherapy in patients with stage II disease has been difficult to define, with 15–20% of individuals relapsing despite such treatment.[50] Identifying those who will benefit from adjuvant treatment in this heterogeneous group of patients is a major challenge, and selection of the appropriate population for clinical development is also difficult.

6. Importance of clinical and molecular biomarkers in therapeutic development

The use of clinical and molecular biomarkers holds great potential for individualising treatment for patients with CRC. Incorporating biomarkers into clinical trials will allow the selection of smaller, enriched populations, improving the chance of treatment success. It is becoming clear that CRCs will be divided into 5–6 different subtypes, based on distinct molecular characteristics. It can be predicted that description of this molecular taxonomy of CRC will have profound clinical implications. Some of these markers are already well established in clinical practice. In particular, testing for *KRAS* mutation is now recommended in clinical guidelines to determine eligibility for EGFR monoclonal antibody therapy.[51,52] Other biomarkers under investigation as possible positive or negative predictors of EGFR-targeted therapy include BRAF, N-RAS and PIK3CA (downstream effectors of EGFR signalling). While the presence of these mutations is associated with a low response rate to cetuximab, determining their predictive and prognostic value is challenging as alterations in these effectors can be inter-related.[53]

Expression of EGFR ligands such as amphiregulin, epiregulin, transforming growth factor-α, epidermal growth factor, EGFR, PTEN and Fc-receptor polymorphisms may also have value in predicting cetuximab activity. In *KRAS* wild-type patients there was a significant association between the expression of both amphiregulin and epiregulin, and response to cetuximab, both alone and in combination with irinotecan.[54,55] In addition, it has been suggested that the combination of *PTEN* expression and *KRAS* mutation status may be a better predictive marker of response to cetuximab than *KRAS* status alone.[56] Nevertheless, the use of amphiregulin, epiregulin and PTEN proteins as predictive markers may be limited by the difficulty in establishing cut-off and threshold levels for interpretation. Polymorphisms of Fc receptors (FcγRIIa and FcγRIIIa) have been associated with better outcomes in patients treated with rituximab for follicular lymphoma and trastuzumab for metastatic breast cancer.[57] These findings may also translate to CRC, since such alterations were associated with better rates of progression-free survival (PFS) and overall survival (OS) in patients with mCRC receiving second-line cetuximab combination therapy.[58] Additionally, xenograft studies suggest a correlation between *HER2* amplification and resistance to cetuximab, with combined inhibition of HER2 and EGFR inducing long-lasting tumour regression.[59]

Despite the plethora of potential markers for response to EGFR inhibitors there are currently no validated biomarkers for angiogenesis inhibitors. Of the biomarkers investigated to date (plasma vascular endothelial growth factor [VEGF], single nucleotide polymorphisms [SNP], TSP-2, *KRAS*, *BRAF* and *TP53* mutation status), none have been shown to be predictive for bevacizumab activity,[60–62] although *BRAF* mutation status may be prognostic for OS.[63]

Functional imaging, such as positron emission tomography and functional magnetic resonance imaging (MRI), is used increasingly in the assessment of CRC. Such techniques not only aid diagnosis and tumour

characterisation, but can also be used to help establish patient prognosis and evaluate very early responses to therapy.[64] For example, dynamic contrast-enhanced MRI can be used to predict the biological response to angiogenesis inhibitors.[65] Nevertheless, the predictive power of imaging will require comprehensive validation in clinical trials before incorporation into clinical practice.

7. Development of new models for clinical trials in CRC

In order to improve efficacy and cost-effectiveness and reduce toxicity, there is a need to standardise studies with new agents through smarter, faster clinical trials involving a niche population and smaller sample sizes (Table 4). Appropriate patient selection is crucial to avoid ineffective studies, and one aim of new CRC trials should be to 'personalise medicine', selecting specific populations and using biomarkers to identify the individuals most likely to respond, thereby optimising outcomes. This strategy also spares those unlikely to benefit from unnecessary toxicity, as well as reducing cost.[66] A multidisciplinary approach is required for this strategy along with rapid molecular screening. Multiple tumour biopsies and plasma samples (for circulating free DNA and miRNA determination) should also be collected from all patients for assessment of known biomarkers and identification of novel biomarkers. One innovation that will help in this regard is the creation of platforms such as the European Organisation for Research and Treatment of Cancer (EORTC) screening network, which allows patients to be screened for a number of targets so that the most appropriate trial and drug can be selected. This database will improve trial opportunities for patients with CRC, provide key information on management in Europe and enable trials in small populations to be conducted. It will also prepare investigators for breakthroughs in knowledge on the taxonomy of CRC.

To improve efficiency and increase the chance of success further, biomarkers should be included early in the clinical development process (Phase I or II) or co-developed alongside new agents. While gene signatures may be used to define biomarkers, profiling is difficult to correlate with clinical practice and prospective validation is needed. Acceptance of biomarkers by regulatory authorities may also be an issue; therefore, clinicians must help to educate decision-makers about their value, shifting focus from validation towards identification of clinically relevant end-points. Nevertheless, it is likely that regulatory agencies will be more receptive to trials that robustly select subpopulations of patients who are likely to gain substantial benefit from a specific treatment.

One of the challenges facing the development of new clinical trials in CRC is the need to define the most appropriate end-points. Trials have traditionally employed OS as the primary end-point, though use of shorter-term end-point(s), if sufficiently validated, could significantly hasten the translation of advances into clinical practice.[67] PFS has been suggested as a surrogate end-point, though most patients are not treated until disease progression or unacceptable toxicity occurs and its use is controversial and unproven.[68–70] Possible alternative end-points under investigation include skin toxicity and hypertension, which may be future surrogate end-points of efficacy for EGFR and angiogenesis inhibitors, respectively.[71] Imaging can also be used to evaluate early responses to angiogenesis inhibitors and

Table 4
Problems associated with the design of clinical trials in CRC and strategies for improvement.

Issues in clinical trial design	Improvement strategy
Many trials of new treatments for CRC have been costly and ineffective	• Use of niche populations and smaller sample sizes • Development of biomarkers to identify patients likely to respond • Inclusion of biomarkers early in the drug development process
Selecting populations most likely to respond is problematic	• Use of rapid molecular screening • Collection of tumour biopsies and plasma samples from all patients
Existing biomarkers must be validated before use in clinical trials	• Clinical trial design for biomarker validation is driven by scientific, clinical, statistical and ethical considerations • Prospective RCTs are the 'gold standard' approach and include: o Targeted or enrichment designs o Unselected or all-comers designs o Hybrid designs • Retrospective analysis can be done to speed translation to clinical practice, though use of RCTs is essential
Regulatory authorities have not been receptive to inclusion of biomarkers in clinical trials	• Clinicians must help to educate regulatory agencies • Focus should be shifted from validation to clinically relevant end-points
The most appropriate end-points have not been defined	• Development and prospective validation of alternative or surrogate end-points

CRC, colorectal cancer; RCT, randomised controlled trial.

EGFR antibodies.[72] It should be noted, however, that prospective validation of alternative end-points is required before their use in clinical trials.

8. New approaches to the medical management of CRC

Multidisciplinary collaboration will be key to the future management of CRC, combining surgery, radiotherapy, radiology, endoscopy, oncology, basic and translational research and genetics. The harnessing of information technology should also be maximised in order to share and disseminate clinical, genomic and translational data, and collect details for as many specimens as possible. While oncology is already a major focus for most European governments, future CRC care delivery must become more efficient and cost-effective. This may require prioritisation of investment by health authorities into different areas of oncology, such as prevention, screening, early diagnosis, multidisciplinary treatment, quality of care and treatments for advanced disease. Nevertheless, collaboration with industry is likely to be required for initiatives to be cost-effective.

Further measures aimed at improving the quality of care are likely to involve a more patient-focussed approach to the diagnosis and treatment of CRC, as well as optimisation of long-term follow-up for cure patients. Additional areas for improvement include adherence to local treatment guidelines, coordination of hospital services and patient access to clinical trials.

One area that has seen an explosion in research in recent years is gene profiling. This technology now allows the possibility of rapid mass screening for large numbers of genes at one time. Testing for *KRAS* mutation status is already commonplace in many European countries, and the next step is to generate gene signatures in order to identify high-risk subsets of patients. This is just starting to be used in some regions, though at present gene signatures have mainly a prognostic value and still lack a predictive benefit. Reimbursement remains an issue for gene profiling in some countries, and health authorities may need to be convinced of its value as its use is not recommended presently in any guidelines.

A number of innovations for drug delivery and surgery have become available for patients with CRC in

Table 5
Issues in the management of patients with CRC and proposals for addressing them.

Management issue	Proposal for addressing
>20% of patients present with metastatic (stage IV) disease at the time of diagnosis	• Improvement of screening strategies for earlier diagnosis • Rapid access to early diagnosis facilities in patients with high-risk symptoms
CRC places a high burden on society	• Development of chemopreventive strategies, early diagnosis and more active therapies • Primary prevention (diet and physical exercise)
Identifying subpopulations of patients appropriate for targeted therapies is problematic	• Undertaking gene profiling in all patients
CRCs are heterogeneous and upregulated genes differ between tumour types	• Undertaking gene profiling in all patients
Most patients develop resistance to EGFR inhibitors after a few months of therapy	• Treatment strategies aimed at combined HER2/EGFR inhibition • Blockade of the MET pathway
Colon cancer precursor polyps are heterogeneous, complicating screening guidance	• Detection and removal of all polyps • Surgical resection if removal is not feasible
CRC tumours evolve over time	• Collection of multiple biopsies from all patients to monitor tumour evolution over time and in response to treatment
To reduce the burden of CRC on society, care delivery must be more efficient and cost-effective	• Prioritisation of investment by health authorities into different areas of oncology • More efficient patient journey through the levels of care • Collaboration with industry to reduce costs
CRC treatment is not curative and requires long-term treatment	• Patient-focussed approach to diagnosis, treatment and follow-up • Adherence to guidelines • Coordination of hospital services, including palliative care • Improved access to clinical trials

CRC, colorectal cancer; EGFR, epidermal growth factor receptor.

recent years. These include hepatic intra-arterial and intraperitoneal chemotherapy, which allow delivery of higher-dose concentrations of drugs at the tumour site while limiting systemic exposure and associated toxicity.[73] Additionally, significant global investment has been made in targeted drug delivery using nanotechnology, since it has the potential to improve quality of life and outcomes, and reduce toxicity. The technology is already being used for early diagnosis and pre-treatment, and to deliver guided chemoprevention and chemotherapy drugs, controlling the pattern of drug release and targeting the killing of specific tumour cells by local heat ablation activated by fluorescence. Despite its great potential, however, there may be issues with the uptake of nanotechnology in some European countries due to the justification of the initial cost and stringent regulations for radiolabelled treatment (e.g. in France).

9. Summary

This article has identified a number of key areas concerning the management of patients with CRC that require a 'call to action' in Europe and details a vision for improvement (Table 5). While a number of improvements have been made in the management of patients with CRC in recent years, challenges still remain. Incorporation of the approaches described here will go some way to improving the quality of life and survival for those with this common malignancy.

Conflict of interest statement

Eric Van Cutsem has received research funding from Amgen, Merck Serono, Novartis, Pfizer, Roche and Sanofi. Fortunato Ciardiello has provided consultancy and participated in advisory boards for Roche, Merck Serono and Bayer. Josep Tabernero has provided consultancy for Amgen, Boehringer, Bristol-Myers Squibb, Genentech, Imclone, Lilly, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche, Sanofi and Astellas, and has received honoraria for presentations for Amgen, Merck KGaA, Novartis, Roche and Sanofi. All other authors report no conflict of interest.

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