RAS Biomarker Testing:
Improving Patient Outcomes in Metastatic Colorectal Cancer

White Paper

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Get tested
UNLOCK YOUR TREATMENT OPTIONS
International Colorectal Cancer Association

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Call-To-Action

To improve outcomes for patients newly diagnosed with metastatic colorectal cancer (mCRC), by routinely performing RAS biomarker testing prior to first-line treatment decision making as part of a personalised cancer care plan.

Executive Summary

Globally, colorectal cancer (CRC) is the second most common cancer in women and the third most common cancer in men.[1] However, a quarter of these patients only receive a diagnosis once the cancer has spread to other parts of their body (or 'metastasised'),[2] known as mCRC, which significantly impacts their prognosis. Before the cancer has spread beyond the lymph nodes, the 5-year survival rate is 70 to 89%, however, for metastatic disease, the 5-year survival rates plummet to just 12%.[3]

This document outlines the burden imposed by treatment options and, in collaboration with global experts and support from industry partners, aims to improve awareness of the important benefits that knowing the RAS tumour status can offer in selecting the right treatment for each patient. This document is targeted to challenge the European Parliament to drive awareness and stimulate a policy debate, to ensure that RAS biomarker tests are uniformly conducted at the point of mCRC diagnosis.

An increased understanding of the biology of cancer has underpinned the ability to select or stratify patients based on their genetic makeup, and use this information to tailor therapy to the individual patient. This **personalised** or **precision cancer medicine** approach has the potential to significantly improve outcomes for patients.[4] Its emerging importance can be judged by the fact that "Precision Medicine in Cancer Care" was the overarching theme of the 2014 European Society of Medical Oncology Annual Congress, one of the most influential cancer conferences in Europe.

In mCRC, this enhanced biological understanding has pinpointed mutations or genetic changes in a gene called RAS as key indicators or predictors of treatment response. A specific test – a RAS biomarker test – at the point of diagnosis has been found to help predict which treatment an individual mCRC patient might best respond to, which could ultimately improve patient survival rates.[1,4] Utilising a RAS biomarker testing approach not only ensures optimal therapy for responding patients, but also ensures that non-responding patients are not exposed to any of the side effects of a particular treatment approach. Health economic analysis has also highlighted how national testing programmes can lead to significant cost savings.[5] Employing RAS testing in a uniform fashion can improve patient outcomes, reduce side effects and increase cost effectiveness, thus benefiting both patients and society.

Support is required from the European Commission to ensure that RAS biomarker tests are uniformly conducted at the point of diagnosis throughout Europe, and to underpin the introduction of personalised cancer care plans on the basis of these test results. Therefore, **we are specifically calling on the European Commission to:**

1. Defend Equity and Quality in Healthcare

Promote patient-centred quality healthcare that builds on the values of universal and timely access to innovative molecular testing and treatment options, including RAS biomarker testing technology and targeted personalised medicines which have been shown to improve patient outcomes.[3,5]

2. Promote the Harmonisation of Medical Standards

Deliver the best options for patients, by adopting international best practice and ensuring harmonisation with clinical and national guidelines.

3. National Cancer Plans

Assist EU member states in developing national cancer plans that facilitate the delivery of biomarker testing, as an essential and standard part of clinical practice.

4. Encourage Collaboration

Between patients, academia, healthcare professionals (HPCs) and regulatory agencies, to embrace the uptake of the new technologies that integrate RAS biomarker testing into current clinical practice.

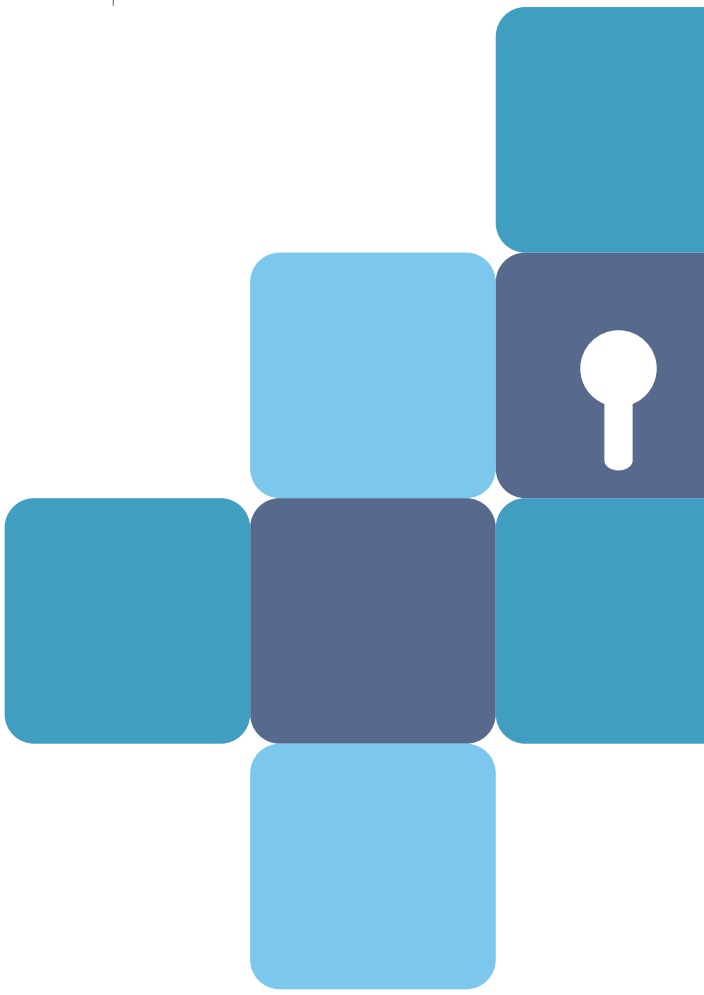
5. Develop Adequate Infrastructure

Provide sustainable funding at the EU and country levels, to support adequate health infrastructure for the use of precision medicine in clinical practice.

- Provide diagnostic and treatment facilities at the national level
- Invest in the progression of pathologist and physician expertise – i.e. appropriate education and training on RAS biomarker testing

6. Facilitate Pricing and Reimbursement

Encourage pricing and reimbursement processes at the national level to embrace the value proposition of precision medicine and targeted therapies as an integral part of a personalised cancer care plan.



CRC: A Complex and Difficult-to-Manage Disease

CRC is cancer of the colon or rectum, and it can affect both men and women. The majority of CRC tumours develop from small growths on the wall of the colon or rectum. In mCRC, the original tumour will have spread to other areas of the body, after being carried through the wall of the bowel or through the blood system; mCRC has a tendency to spread particularly to the liver and the lungs.

An estimated 694,000 deaths from CRC occur worldwide every year, accounting for 8.5% of all cancer deaths and making it the third most common cause of death from cancer globally.[1,6] At a European level, CRC is the second most common form of cancer death with over 212,000 (2012 figures).[7] More than 25% of patients are diagnosed when the cancer has already metastasised to other parts of the body, making the cancer more complex and difficult to treat,[2] thus explaining at least in part its high mortality rate in Europe.

CRC incidence has gradually decreased because of increased awareness, early detection, physical activity and novel treatments and regimens; likewise, mortality rates have also steadily declined.[6–8] However, mCRC remains a significant health challenge, due to a variety of factors. Firstly, the general public are not well informed about the impact their diet can have in increasing the risk of developing CRC. Diets rich in processed foods, red meat and alcohol are known risk factors that contribute to the development of CRC.[9,10] Secondly, people who are overweight or obese are at an increased risk of developing CRC. People with a body mass index (BMI) greater than 30 have a 33% higher risk of developing CRC than those with a healthy BMI.[11] Thirdly, people are generally unaware of the early disease symptoms, so typically they do not seek medical advice until their cancer is at an advanced stage.

While there have been improvements, the survival rates for patients with mCRC are still worryingly low; a mere 12% will survive a further 5 years following diagnosis.[8] The median overall survival rate for patients with mCRC is only about 2 years (when compared to similar individuals who do not have cancer).[2] If patients receive treatment at a stage before their disease has spread, the proportion attaining 5-year survival increases to 90%.[7,8]

CRC remains the 2nd most common type of CANCER in Europe

While RAS testing does not replace the need for lifestyle changes or other preventative measures, employing results of RAS biomarker testing to inform mCRC treatment decision making has been shown to help improve patient outcomes and overall survival.[12–15] The adoption of a personalised cancer care plan approach is therefore a key factor in resolving the unnecessarily poor outcomes and reduced chances of cancer patient survival that we experience in mCRC, across the globe.

There is a real need in mCRC to promote quality healthcare through universal and timely access to innovative testing and treatment options – including RAS biomarker testing and precision medicine, which improve patient outcomes.

In order to drive change for mCRC patients in Europe and increase awareness and understanding of the importance of RAS biomarker testing, the **International Colorectal Cancer Association's*** *Get Tested* campaign – which is supported by EuropaColon, the European Cancer Patient Coalition, the Global Colon Cancer Association, the European Alliance for Personalised Medicine plus other national level organisations – calls on the European Parliament to raise awareness and embed the practice of RAS biomarker testing in mCRC in European health systems.

Treatment Approaches

Although overall survival in a subset of mCRC patients has increased significantly to a total of over 30 months[4] – largely driven by improvements in treatment and standards of care – CRC remains the second most common type of cancer in Europe, with deaths from CRC exceeded only by those from lung cancer.[7]

Optimal treatment for CRC depends on several factors, including the stage and location of the cancer, the tumour biology (including RAS biomarker status) and considerations around the patients themselves. Therefore, it is imperative that every patient has a personalised cancer care plan that is based on a robust assessment of their individual case.

Following a diagnosis of mCRC, and dependent on the factors outlined above, a patient is likely to receive one, or more, of the following treatments:

- surgery
- chemotherapy
- radiotherapy
- precision medicine.

The selection of the appropriate treatment/ treatment combinations, and even the sequence of any multiple treatments, can dictate the eventual long-term outcomes for the patient. In particular, both the percentage of patients who respond to treatment and the chance of increased long-term survival is largely determined by the choice of first-line treatment.[4]

Improvements in mCRC Care: RAS Biomarker Testing and Personalised Cancer Care Plans

'Predictive' biomarkers help to determine how an individual patient's tumour will respond to a particular type of therapeutic intervention. Predictive biomarkers are particularly relevant for precision medicine, where their use can stratify patients for a targeted therapy approach. The development of predictive biomarkers in cancer care now makes it feasible to select the most appropriate treatment for the right patient at the right stage of their care – an approach termed a 'personalised care plan'. In mCRC, a key predictive biomarker is the RAS biomarker, which can be used to differentiate between patients who have a 'wild-type' tumour and those who have a 'mutant' tumour (approximately half of patients belong in each category). As the two tumour types respond differently to certain cancer treatments, doctors can use RAS biomarker status to effectively determine which precision medicine is appropriate for which patient.

In 2012, the rationale for this biomarker-led treatment approach was reinforced when the European Society for Medical Oncology (ESMO) released new guidelines recommending that all patients with mCRC have a RAS test before any first-line treatment is prescribed.[15] **These guidelines were an important milestone, as they helped to harmonise the clinical advice and medical standards in various national guidelines, on the basis of applying international best practice to deliver the best options for patients.** RAS biomarker testing at the time of diagnosis enables medical teams to select the most appropriate first-line treatment for individual patients, and so helps improve their long-term outcomes.

RAS biomarker testing usually involves taking a small sample of the tumour during surgery (a surgical biopsy) typically at the time of diagnosis – and in some instances a repeat biopsy is required. However, in the future it will be possible to employ a simplified and rapid sampling method, termed 'liquid biopsy testing', or blood-based biomarker testing, in which only a blood sample from a patient is needed for RAS analysis rather than a biopsy or surgical tissue sample. This would potentially remove the need for an invasive surgical procedure to obtain samples from patients to test for RAS mutation status, but more importantly provide timely specimens representing the most up-to-date RAS status of the patient, allowing for optimal therapy decisions.

EU member states may need support in developing their national cancer care plans to incorporate biomarker testing as an essential and standard part of best clinical practice. The academic community, regulatory agencies, clinicians and patients will also need to collaborate to ensure the uptake of the latest technologies that will enable routine RAS biomarker testing in clinical practice.

Given the increasing financial pressures on the delivery of healthcare in Europe, it is important that improved outcomes are achieved in a cost-effective manner. A number of health economic assessments have highlighted how RAS testing not only unlocks increased therapeutic value, but also achieves improved outcomes in a cost-effective or cost-saving manner.[5,16]

Changing Clinical Outcomes

The accumulating results from clinical research and clinical trials in mCRC – such as the PRIME, PEAK, OPUS, CRYSTAL and FIRE-3 studies – have demonstrated the value of biomarker testing in helping to determine the appropriate treatment choice for an individual patient.[4,12–15] These studies found that there are clinically significant improvements in overall survival in mCRC patients whose tumour status is categorised as RAS wild-type, when treated with appropriate, targeted, precision medicine approaches, in comparison with other treatment options.[4,12–15] These studies also demonstrate that RAS tumour status should be used as a criterion for selecting precision medicine. It is important to note, however, that some treatments are not recommended for patients with 'RAS-mutant' status.

Nevertheless, despite this evidence – especially the studies highlighting the significant benefits for mCRC patients of predictive biomarker tests – the adoption of the biomarker testing and personalised cancer care plans in clinical practice across Europe is not consistent in all countries.

EU funding support for an adequate health infrastructure, along with provision of medical expertise, would help to remedy this situation. Sustainable funding at EU and country level is needed to ensure there is widespread use of personalised cancer care plans in clinical practice.

Empowering Patients to Demand Biomarker Tests

Personalised cancer care plans in CRC require a combined effort from HPCs, patient advocacy organisations and patients to be successful. It is essential that patients are well informed about the benefits of precision medicine. Educated and empowered patients are more aware of the clinical improvements that can be achieved through the use of tools such as RAS tests. They therefore need to have good access to information, and be empowered to participate fully in discussions about the management of their disease.

A recent multinational survey, entitled *'Awareness and Understanding of Stratified/Personalised Medicine in Patients Treated for Cancer'* gave a good insight into patients' perspectives of biomarker testing across three cancers.[17] The survey confirmed that patients want to know about all treatment options available to them and to be integrally involved in their treatment decisions. The great majority also recognised that their tumour can be tested to help the doctor decide on the treatment option for their individual cancer. In the case of mCRC, 66% of patients stated they were prepared to wait for additional tests to be completed – even if it delayed the start of their treatment – to ensure they received an optimal personalised care plan. Also, more than two-thirds of patients were willing to have a repeat tumour biopsy procedure if necessary, in order to benefit from biomarker-led personalised care. This survey makes it abundantly clear that patients are interested in biomarker testing, react positively to this treatment approach and are willing to undergo additional procedures or tests to increase their chance of improved outcomes.[17]

An interesting finding of the survey was that although the majority of all cancer patients felt they were fully informed about their treatment, around a third assumed that no tests existed for determining which cancer treatment might work better for their specific cancer type. Moreover, in a similar survey conducted with HCPs, 78% of oncologists thought

their patients need more information to help them understand that there are different types of cancer, and also how cancers progress. There is clearly a need for patients to have access to additional sources of information that will allow them to fully understand their treatment options and thereby better engage in decision making.[17–19]

Promoting health literacy on this topic – including patient awareness, education and understanding of personalised cancer care – is crucial. Additionally, precision medicine literacy needs to be improved for HCPs, to ensure that the most appropriate personalised cancer care plans are put in place for individual patients.

A sustained effort is needed to establish patient-centric care, based on good communication between multidisciplinary medical teams and the patients themselves. This will enable RAS biomarker testing to become an established part of personalised cancer care plans, and ultimately help improve patient outcomes in the future.

As with all health issues, it is vital that patient outcomes are the highest priority, but it must be acknowledged that health economic pressures are a challenge for many countries. Pricing and reimbursement processes at national level should therefore reflect the value proposition of precision medicines as an integral part of a personalised cancer care plan.

Conclusion: Driving Optimal Outcomes in mCRC – What Can Be Done?

Patient outcomes in mCRC have significant room for further improvement. Uniform care across the European member states must become the norm.

This can only occur if the European Parliament drives awareness and stimulates a policy debate, and if the European Commission takes steps to ensure that RAS biomarker tests are uniformly conducted at the point of diagnosis. Without support and implementation of our Call-To-Action, we will continue to see inconsistent outcomes in mCRC.

The *Get Tested* Campaign

We invite you, therefore, to join us in our mission to unlock treatment options for patients via the *Get Tested* campaign.

The *Get Tested* campaign aims to improve outcomes for mCRC patients through the use of biomarker testing as part of a personalised cancer care plan, by:

- raising awareness and understanding of the importance of biomarker testing amongst newly diagnosed mCRC patients, their families and carers
- establishing a Call-To-Action that encourages all newly diagnosed mCRC patients to discuss biomarker testing with their HCPs at diagnosis, and/or prior to the selection of treatment as part of their personalised cancer care plan
- partnering and networking with existing groups and initiatives in mCRC

To support our Call-To-Action and learn more about the *Get Tested* campaign, please visit: www.GetTestedCampaign.com

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*The ICCA is currently undergoing registration in Brussels as an International Non-Profit Making Association (INPMA).

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