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Review

# Towards personalized medicine of colorectal cancer

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ABSTRACT

Efforts in colorectal cancer (CRC) research aim to improve early detection and treatment for metastatic stages which could translate into better prognosis of this disease. One of the major challenges that hinder these efforts is the heterogeneous nature of CRC and involvement of diverse molecular pathways. New large-scale 'omics' technologies are making it possible to generate, analyze and interpret biological data from molecular determinants of CRC. The developments of sophisticated computational analyses would allow information from different omics platforms to be integrated, thus providing new insights into the biology of CRC. Together, these technological advances and an improved mechanistic understanding might allow CRC to be clinically managed at the level of the individual patient. This review provides an account of the current challenges in CRC management and an insight into how new technologies could allow the development of personalized medicine for CRC.

## 1. Introduction

The global healthcare burden of colorectal cancer (CRC) is enormous. In 2016, United States will have 70,820 estimated new cases and 26,020 estimated deaths due to CRC (Siegel et al., 2016). CRC is ranked among the highest incidence cancers across the world in both men and women. 1.6 million cases of CRC and 0.8 million deaths due to CRC were reported in 2015. (Global Burden of Disease Cancer C., 2016). However, large proportion of CRC cases are preventable and early detection is associated with good prognosis and better survival (Anon, 2017). A major challenge in the treatment of CRC is the heterogeneous nature of this disease. Intertumor and intratumor heterogeneity of cancer is being acknowledged as a major problem in devising accurate therapies (Ogino et al., 2012). Evidence is mounting in favor of the unique identity of a human being in health or diseased state. Colorectal cancer poses a formidable challenge in the form of molecular heterogeneity with involvement of several molecular pathways and molecular changes unique to an individual's tumor (Linnekamp et al., 2015). Two main pathways often described in reference to colorectal cancer are chromosomal instability (CIN) and microsatellite instability (MSI) pathway accounting for 85% and 15% of total CRC cases respectively. Though these molecular pathways have been used to classify CRC patients and guide treatment regimens, there is a need to better customize treatment strategies keeping in view the heterogeneity of CRC found in every patient (Lugli, 2015; Sinicrope et al., 2016). In this scenario, the best option is to customize treatment strategies tailored to the need of an individual patient. This is known as Personalized Medicine.

Personalized medicine could be defined as customized form of treatment for an individual based on information available for its

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unique biological attributes. In its true sense, personalized medicine would mean customized prevention, therapy and management of a disease for a patient. The benefits of personalized medicine are twofold. On one hand, personalized medicine provides more accurate and precise way to prevent and cure a disease, while, on the other hand, it avoids unnecessary interventions. The concept of personalized medicine has been empirically practiced for some time, but evidence to support and drive this notion has only recently been available. We have yet to develop tools powerful enough to perfectly achieve this aim. What has been achieved is better classification of patients in more specific groups and the identification of biomarkers like KRAS proto-oncogene, GTPase (KRAS gene) (Zocche et al., 2015). The identification and validation of these [sub] groups is continuously being challenged by new data. Several types of omics e.g. genomics, transcriptomics etc., has made it feasible to record the molecular changes in CRC at an unprecedented scale. Though technological advancements have made it possible to generate the data needed for a dynamic model of customized therapy for individual patients, many challenges exist when it comes to analyzing the data. Moreover, the implementation of these analyses in the form of clinically relevant procedures and interventions has yet to be assessed. In CRC, any preventive intervention has to be carefully weighed against its benefits for every individual patient. For metastatic stage patients, intervention has to be affordable, both economically and physically, with lower cost and fewer toxic adverse effects.

In this review, we present the concept of personalized medicine in context to CRC. The current status of treating CRC based on available molecular evidence is insufficient to capture the molecular heterogeneity and thus necessitates a paradigm shift. Several omics technologies have been discussed that promise to provide data which would help in developing personalized medicine for CRC. The concept of personalized medicine as applied to CRC followed by the challenges that it would face are discussed. Probable solution to these challenges is provided to help design the future course of personalized medicine in CRC.

## 2. Current management of CRC

### 2.1. Molecular model for development of CRC and its clinical applications

Most of the sporadic CRC cases are explained using CIN model. This model for the development of CRC suggests a predictable progression with sequential accumulation of mutations in specific genes like APC, WNT etc. The model provides signs that can be used for risk assessment, early detection, prognosis and treatment of the disease (Fearon and Vogelstein, 1990; Kinzler and Vogelstein, 1996; Huang et al., 1996; Polyak et al., 1996; Morin et al., 1996). Several molecules have been known to be associated with different stages of colorectal cancer with some of them known to play a causal role (Fig. 1). Whether this molecular model of CRC development is clinically relevant and whether its predictable nature provides any benefit to the patients is still unknown. According to this model, the sequential accumulation of mutations that eventually leads to CRC provides a window of opportunity to prevent CRC before these mutations reach a threshold level. Prevention and screening strategies have been shown to be most successful in decreasing the trends of incidence and mortality due to CRC. The average age of onset of CRC is 50 years, and, with good surveillance, the prognosis is good (Lynch and de la Chapelle, 2003). However, no well-defined procedures are currently in place for early diagnosis or screening at the population level, with the exception of a few successful programs recently reported. Germany has reported an increase in preventable cases from < 100 in 2005 to 6500 in 2015 (Brenner et al., 2015). The USA and New Zealand have also reported a modest decline in incidence mainly due to preventive strategies (Haggar and Boushey, 2009). Colonoscopy is the most commonly used procedure for early detection, but it is an invasive procedure and the results are inconsistent depending on how it is performed. There are limitations to colonoscopy that make alternative screening procedures necessary (Young and Womeldorph, 2013). Current practice of prevention and therapy of CRC is based on models that presume the population to be homogenous, but the cancer community is increasingly recognizing that a 'one size fits all' model has not been successful.

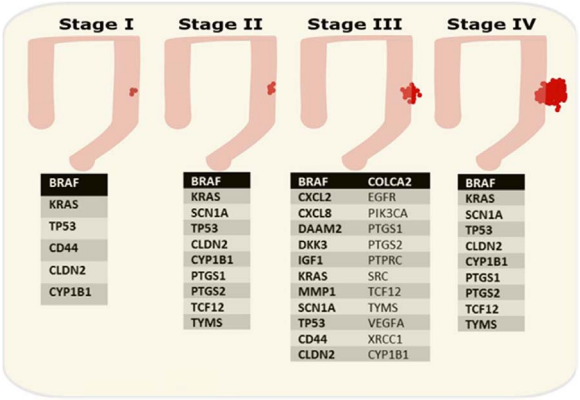


**Fig. 1.** Genes involved in different stages of colorectal cancer. These genes were found through bioprofiler tool of Ingenuity pathway analysis. A different stage of CRC shows involvement of genes that can be causal or correlation.

### 2.2. CRC therapies

Besides surgery, systemic chemotherapy has been the mainstay of CRC treatment. 5-Fluorouracil [5-FU]-based regimens are the standard of care in adjuvant settings for stage III which is characterized by the spread of cancer cells to nearby lymph nodes but not to other body parts (Gustavsson et al., 2015). 5-FU has also been combined with other cytotoxic agents such as leucovorin, oxaliplatin and irinotecan with conflicting reports of therapeutic gain. Systemic chemotherapy is complemented by targeted therapies. Newer targeted therapies are focused against specific molecules that are associated with CRC. Epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab, and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, have been used in combination with 5-FU (Gustavsson et al., 2015; Iwamoto et al., 2015; Bazarbashi et al., 2015; Heinemann et al., 2014; Stintzing, 2014; Sebio et al., 2014; Stremitzer et al., 2014). In CRC therapy regimens, gene expression levels of VEGF and EGFR provide the basis for selecting drug combinations. Despite this, for anti-VEGF-based regimens, predictors of therapy efficacy remain largely elusive, and CRC tumors exhibit many mechanisms of resistance to anti-EGFR therapies (Linnekamp et al., 2015). Many of these combinations have been selected for clinical use in CRC on the basis of their success in clinical trials (Laurie et al., 1989; Moertel et al., 1990, 1995; Modulation, 1992; Wolmark et al., 1993; Haller et al., 2005; Wolmark et al., 1999). However, even the best drug combinations in these clinical trials cannot be replicated in most of the affected subjects in a population. Only a subset of the patient population gets a response from these targeted therapies. MSI tumors were shown to respond better with 5-FU based therapies. However, with accumulating evidence the use of MSI as a predictive and prognostic marker for determining the use of 5-FU-based chemotherapy is very contentious (Klingbiel et al., 2015; Saridaki et al., 2014). A recent report suggests that MSI status has no effect on the outcome of 5-FU-based chemotherapy (Webber et al., 2015). Biomarker driven clinical decision is making its way into the tumor boards (Pritchard CC, Grady WM. Colorectal cancer molecular biology moves into clinical practice. Gut. 2011;60(1):116-29.). EGFR, KRAS, PTEN, AREG, EREG, VEGF and TP53 are established biomarkers to monitor response to 5-FU based therapies (Maughan TS, Meade AM, Adams RA, Richman SD, Butler R, Fisher D, et al. A feasibility study testing four hypotheses with phase II outcomes in advanced colorectal cancer (MRC FOCUS3): a model for randomised controlled trials in the