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*MINIREVIEWS*

# Consensus molecular subtypes of colorectal cancer in clinical practice: A translational approach

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## Abstract

The identification of several genetic mutations in colorectal cancer (CRC) has allowed a better comprehension of the prognosis and response to different antineoplastic treatments. Recently, through a systematic process, consensus molecular subtypes (CMS) have been described to characterize genetic and molecular mutations in CRC patients. Through CMS, CRC patients can be categorized into four molecular subtypes of CRC by wide transcriptional genome analysis. CMS1 has microsatellite instability and mutations in CIMP and BRAF pathways. CMS2, distinguished by mutations in specific pathways linked to cellular metabolism, also has a better prognosis. CMS3 has a KRAS mutation as a hallmark. CMS4 presents mutations in fibrogenesis pathways and mesenchymal-epithelial transition, associated with a worse prognosis. CMS classification can be a meaningful step in providing possible answers to important issues in CRC, such as the use of adjuvant chemotherapy in stage II, personalized first-line chemotherapy for metastasic CRC, and possible new target treatments that address specific pathways in each molecular subtype. Understanding CMS is a crucial step in personalized medicine, although prospective clinical trials selecting patients by CMS are required to pass proof-of-concept before becoming a routine clinical tool in oncology routine care.

**Key Words:** Colorectal neoplasms; Precision medicine; Microsatellite instability; Next-generation sequencing



**Core Tip:** Colorectal cancer has a variable response to different treatments that could be

**quality classification**
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0



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explained by genetic and molecular heterogeneity in the neoplasm. Recently, a novel classification according to consensus molecular subtype has been proposed to explain this neoplasm heterogeneity. From a clinical oncology perspective, this classification opens opportunities to resolve some current clinical questions in the treatment of colorectal cancer.

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## INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death by cancer worldwide[1]. Despite important advances in early diagnosis and management, 25% of patients debut in metastatic stages and 50% localized stages, later presenting disseminated disease[2]. Currently, CRC management is based on tumor-node-metastasis (TNM) system staging, and in recent years, on several genetic mutations such as microsatellite instability (MSI), KRAS/NRAS, and BRAF. These mutations have a role in selecting better candidates for certain systemic therapies[3,4]. Improvements in classic systemic therapies for CRC have allowed more effective and tolerable chemotherapy regimens, mainly based on fluoropyrimidines with oxaliplatin and/or irinotecan. Proposing novel target therapies is also possible for selected patients[5,6].

A new paradigm has resulted from the problem of heterogeneity of CRC[7], which explains the significant impact of variable responses to classic systemic therapies. Thus, some patients present satisfactory and sustained responses. In contrast, other patients with CRC present low response rates to standard therapies, with rapidly progressive disease and high mortality. It has been argued that one way to approach this paradigm is through the characterization and creation of a framework based on genetic and molecular characteristics to explain the heterogeneity of colon cancer. Recently, a major initiative has emerged to describe CRC heterogeneity. The consensus molecular subtypes (CMS) provide a systematic way to classify CRC into four molecular subtypes according to their molecular and genetic profile[8].

Characterizing molecular subtypes in the CRC could optimize the management of these patients. Through knowledge of the biology of the disease, we could better predict the response to therapeutic alternatives to select the most appropriate therapy for each patient[9,10]. This approach is a crucial step in the development of personalized therapies in this disease. In this context, the current review aims to present a translational approach for routine oncology clinical practice regarding the implications of CMS classification with a focus on prognosis and promising novel antineoplastic agents in different stages of CRC.

## CHARACTERISTICS OF EACH CMS

In recent years, different models have been proposed based on genetic, molecular, epigenetic, and phenotypic profiles to explain the heterogeneity of CRC[11-15], obtaining different molecular classifications with different clinical outcomes. A major collaborative effort to integrate all CRC classifications into a single model was identified by experts from the CRC Subtyping Consortium through the analysis of six independent classification studies, obtaining a CRC classification of four CMS[8]. This presents an integrated framework to capture the heterogeneity of CRC at the gene expression and molecular level through transcriptome-wide analysis[9]. The methodology of the consensus assessed redundant pathways and upregulation of signaling pathways that are independent of DNA mutations to provide a characterization of the molecular status[16].

CRC classification based on genome-wide transcriptional profiles has seen important research developments during the last decade; no single genetic defect can be unequivocally assigned to a specific molecular profile. CMS classifications have certain

hallmarks characterizing each subtype[9,17,18]. In brief, each CMS is characterized as follows.

CMS1 (immune) is characterized by MSI, with high mutations of CIMP and BRAF and a low prevalence of SNCA. It is associated with lymphocyte infiltration and immune activation, in addition to hypermethylation and decreased signaling through the WNT pathway[19].

CMS2 (canonical) has epithelial characteristics. It is characterized by high chromosomal instability, high somatic copy number alterations (SCNA) counts, and WNT and MYC mutations, causing high activity of these intracellular signaling pathways [18,19]. It also features increased expression of EGFR, its ligands AREG and EREG, and TP53, APC, and RAS mutation[20]. These can be distinguished from other CRC subtypes by marked upregulation of the downstream targets of WNT and MYC and increased expression of EGFR oncogenes, ERBB2 (also known as HER2), insulin-like growth factor 2, insulin receptor substrate 2, hepatocyte nuclear factor transcription factor 4, and cyclins[19].

CMS3 (metabolic) has a distinctive global genomic and epigenomic profile with mixed characteristics, metabolic reprogramming, and dysregulated pathways, with increased activity in glutaminolysis and lipidogenesis[20], enriched with KRAS-activating mutations. It presents a moderate or low mixed state of MSI and intermediate CIMP, and moderate activation of WNT and MYC, with PIK3CA mutation and IGBP3 overexpression, without BRAF mutations[19].

CMS4 (mesenchymal) has positive gene regulation and overexpression of proteins involved in stromal infiltration, mesenchymal activation, extracellular matrix remodeling, neoangiogenesis, prominent TGF-β activation, and complement pathways. These are characteristic of mesenchymal epithelial transition, overexpressing EMT genes, evidence of prominent EMT gene TGF-β activation, and high SCNA counts. Six immune genes (PROK1, THBS1, FGF11, CRP, S100A14, and CCL19) have been identified as the key factors of CMS4 and can potentially be applied for risk assessment of CRC patients[19,21]. The main hallmarks of CMS are briefly described in Figure 1.

## IDENTIFYING THE PATIENT MOLECULAR SUBTYPE

Classification by CMS in real clinical settings, outside clinical trials, is challenging. In recent years, certain genetic hallmarks have been routinely determined. For example, MSI mutations are involved in advanced stages of CRC and are highly predictive of CMS1. MSI can be detected by polymerase chain reaction based on a panel of different microsatellite loci or applying immunohistochemistry (IHC) with antibodies against mismatch repair (MMR) proteins[22]. For the other subtypes, heterogeneous groups of genetic and molecular conditions are commonly found in pathogenic mutations in CRC, such as KRAS, BRAF, and APC[9,22]. For these mutations, in clinical settings, a commercial genetic panel that includes genes contained in CMS are the NanoString nCounter®, Almac Xcel microarray assay, and Affymetrix GeneChip® Human Transcriptome Array 2.0 (HTA).

Several research groups have aimed to obtain a practical and robust CMS classifier that works on formalin-fixed, paraffin-embedded primary CRC tissues, based on gene expression or IHC[23]. Categorizing patients relies fundamentally on mutational, transcriptomic, and proteomic data analysis[24]. A novel CMS classifier based on a filtered set of cancer cell-intrinsic, subtype-enriched gene expression markers, referred to as CMS caller[25], provides robust classification of CMS groups in datasets generated on different gene expression platforms and biological sample types, readily available for its purpose. A 40-gene ColoType signature has recently been developed, which uses genome-wide assays, frozen tissue-specific RNA sequences, or FFPE. The results correlate highly with those reported by the other two systems, in addition to allowing accurate and reproducible CMS subtype analysis for clinical applications[26].

Routinely practicing CMS classification for patients with CRC is challenging due to the difficult applicability and costs of this method[27]. However, an IHC approach has been proposed, which could represent a reasonable option for the molecular classification of CRC through morphological phenotype and a simpler way to guide case management[23,28]. Several IHC protocols have been proposed, such as a phenotypic subtyping method based on immune infiltrate, stromal invasion, and proliferation rate [27]. Another protocol proposed to correlate specifically with CMS is the IHC detection of MSI with antibodies against MSH1-2 MMR proteins, allocating samples with high-level MSI to CMS1, then classifying the remaining subtypes through staining for four

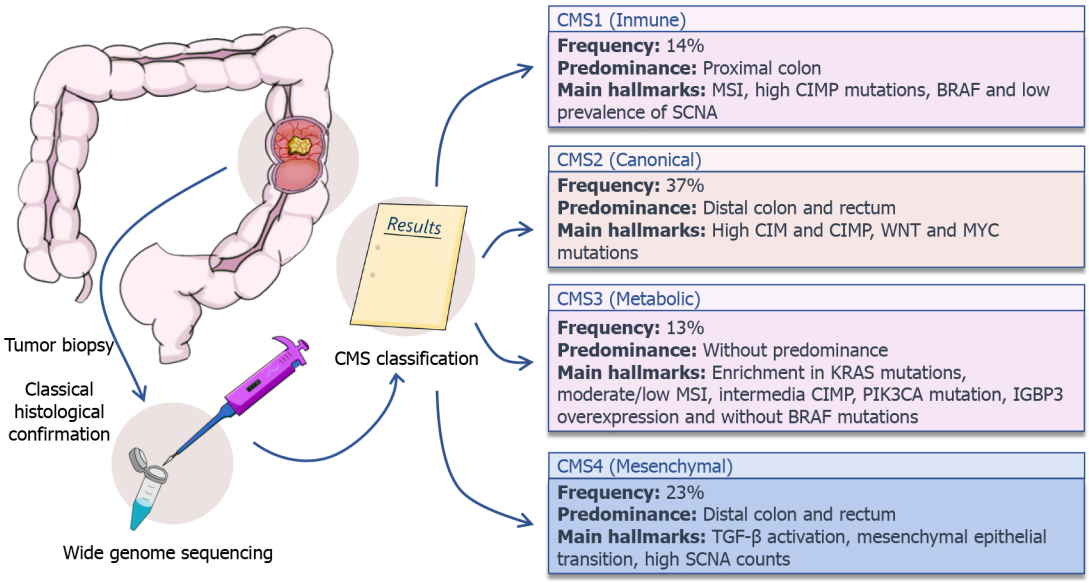


**Figure 1 Main characteristics of consensus molecular subtypes in colorectal cancers.** After the patient undergoes a biopsy, the diagnosis of colorectal cancer is made and subsequent stratification by tumor-node-metastasis is performed. Samples can be obtained to allow wide genome sequencing analysis with the objective of characterization into one of four consensus molecular subtypes. CMS: Consensus molecular subtypes; SCNA: Somatic copy number alterations.

gene product proteins (CDX2, FRD6, HTR2B, and ZEBI), allowing differentiation between CMS2/3 with CMS4[22]. This method, complemented with an IHC-based classifier, has demonstrated 87% concordance with transcriptome-based classification [23], indicating that IHC can be used to categorize CRC molecular subtypes, although not with 100% concordance. However, it has the disadvantage of being unable to distinguish between CMS2 and 3 because both subtypes share similar epithelial features. Recently, an improvement to this protocol has been proposed, adding IHQ for β-catenin to differentiate between CMS2 and 3, with 71.4% concordance compared to an RNA-sequencing-based classifier. This is based on CMS2 activating WNT pathway-regulated β-catenin expression[29].

However, the translation of CMS by genome-wide transcriptional profiles into clinical practice is subject to several obstacles[16], such as the complexity, difficulties of translation to routine pathology, and costs of this method of classification[24,27]. Until genomic profiling becomes more widespread in clinical practice, the molecular subtypes of CRC can be assessed by IHC but with less accuracy compared to the transcriptome gold standard[23]. Nevertheless, CMS is expected to be able to be used in routine clinical practice by overcoming these obstacles and becoming widely available in the near future for the classification of CRC through genome-wide transcriptional profiles.

## CMS AND PROGNOSIS

Traditionally, the prognosis and treatment selection of patients with CRC has been based on the clinical pathological classification of TNM[30]. However, morphologically similar tumors can have different genetic expression and molecular profiles[9] with the capacity to determine different prognoses[31]. Currently, the main international clinical guidelines recommend determining certain biomarkers in specific clinical contexts, such as dMMR/MSI, BRAF, and RAS in metastatic CRC (mCRC) to select the optimal chemotherapy treatment[3,4]. In particular, the CMS classification was designed to categorize CRC heterogeneity in a transcriptional profile, although each subgroup has also been reported to have a different prognosis. In an analysis of 4151 patients with CRC[8], the overall survival (OS) in CMS4 was worse compared to CMS1–3, and a better OS was found in patients with CMS2. Notably, the OS calculation included patients in all TNM stages. In addition, CMS1 patients have a worse survival rate after relapse, and CMS2 patients have a longer survival after relapse.

Despite the important contribution of CMS classification to understanding the oncogenesis of CRC, whether this classification can better predict the prognosis of CRC patients is still uncertain[32]. In particular, in patients with stage II CRC, contro-

versies exist about the clinical benefits of chemotherapy[33]. Stage II patients are selected for chemotherapy if they have a pathological or clinical risk factor such as T4 status, suboptimal lymph node resection, perineural and perivascular invasion, or colon perforation[4]. In this context, it has been proposed that better markers such as CMS could provide a better selection of patients to undergo chemotherapy. Studies that shown that in stages II–III, patients with CMS 4 have a worse prognosis[34]. One study hypothesized that this is a consequence of resistance to fluorouracil–leucovorin regimens commonly used in these stages[35]. Likewise, in low-risk stage II CRC patients who did not undergo adjuvant chemotherapy, CMS4 had significantly worse outcomes in relapse-free survival (RFS) compared to other CMS groups[36]. Using IHQ CMS classification, Li *et al*[37] described a worse OS and disease-free survival in CMS4 and a better OS with adjuvant chemotherapy for stage II CRC in CMS2-3. Furthermore, it has been suggested that certain gene mutations in each CMS can modify outcomes. For instance, BRAF mutations were associated with metastasis in patients with MSS and CM1(OS 22% in BRAF mutated *vs* 81% in wild-type BRAF, $P$ = 0.001). In CMS2-3 patients, mutated KRAS had worse outcomes (OS 59% in KRAS mutated *vs* 75% in wild-type KRAS)[38]. Moreover, patients with MSI and CMS1 have a better OS and RFS compared to CMS2-4. Contrary to previous results, Purcell *et al* [39] reported that stage II patients with CMS3 had a worse prognosis in OS than patients in CMS1-2, although an imbalance between CMS groups, with few CMS4 patients, could explain this result. Besides the possibility for CMS to determine CRC subtypes with worse prognosis for proposing personalized treatments, CMS still needs more studies to define the differences in the prognosis of patients through the different TNM stages of CRC.

In recent years, a special interest has emerged in defining molecular characteristics in patients with mCRC to select the best chemotherapy regimen[40]. In particular, the applicability of CMS has been studied most in this subgroup of patients. An analysis of the CALGB/SWOG 80405[16] trial determined the CMS of 664 patients using a genetic panel (NanoString). It found a positive relationship between OS and progression-free survival (PFS) and each CMS, determining a mean survival (months) of 15 for CMS1, 40.3 for CMS2, 24.3 for CMS3, and 31.4 for CM4, independent of assigned first-line chemotherapy treatment. In a sub-analysis of the AGITG MAX trial, 237 patients with mCRC were classified by CMS using an Almac Xcel microarray assay. A statistically significant association was found between CMS and OS, but not with PFS, independent of assigned first-line chemotherapy treatment. Similar OS were reported: CMS2 had the larger OS (median 24.2 mo), CMS1 had the worst (8.8 mo), and CMS3 (17.6 mo) and CMS4 (21.4 mo) had intermediate OS[41]. Similarly, the FIRE-3 trial[20] that included 438 patients categorized by CMS using the Almac Xcel microarray showed a correlation with OS and PFS independent of assigned treatment, with a worse mean OS in CMS1 (15.9 mo) and better OS in CM2 (29.0 mo). Whilst CM3 (18.6 mo) and CMS4 (24.8 mo) had a medium OS. Similar results were also reported by a retrospective analysis finding a worse OS in CMS1 and a better OS in CMS2[42]. Finally, a retrospective analysis of the TRIBE2 trial found better PFS and OS outcomes in CMS2 and CMS4 compared to CMS1 and CMS3[43]. A summary of the main prognoses in published reports of CMS is shown in Table 1. Questions remain in the prognosis of each CMS, especially when analyzing the results at each stage measured by TNM. However, encouraging results have been seen when predicting the subtypes of patients with worse prognoses in mCRC and stage II, opening possibilities to propose personalized treatments based on the molecular landscape of the CRC of each patient.

## IMPORTANCE OF CONSIDERING CMS FOR FUTURE CLINICAL TRIALS

Considering the significant recent advances in the molecular and genetic profile of CRC through CMS classification, this knowledge must be projected using a proof-of-concept approach, applying it in clinical trials[17]. Patient selection by CMS characterization could be a crucial step in cancer staging and personalized treatment guided by biomarker selection. However, CMS interpretation in the context of clinical trials has some factors that need to be considered when interpreting the results, such as the sample collection site (colon *vs*. rectum), the trial inclusion and exclusion criteria, the first-line chemotherapy scheme used, specific mutations that alone produce different outcomes, and the method used to predict the CMS[44]. Despite these limitations, the identification of CMS in future clinical trials is projected to allow better precision in selecting specific treatments for each patient, especially in the use of immunotherapy

**Table 1 Outcomes in four consensus molecular subtype profiles**

| Ref. | *n* | Outcomes | CMS1, mean (95%CI) | CMS2, mean (95%CI) | CMS3, mean (95%CI) | CMS4, mean (95%CI) |
|---|---|---|---|---|---|---|
| **Stages I-IV** | | | | | | |
| Purcell *et al*[39], 2019 | 257 | 5-yr OS (%) | 63.7 (51.1-79.4) | 64.4 (56.6-73.4) | 52.8 (37.1-75.1) | 42.8 (23.8-76.8) |
| | | 5-yr PFS (%) | 61.2 (48.8-76.8) | 59.8 (51.8-68.9) | 52.7 (47.5-74.0) | 38.8 (21.0-71.9) |
| Guinney *et al*[8], 2015 | 2129 | 5-yr OS (%) | 74 (70-75) | 77 (74-80) | 75 (70-80) | 62 (58-66) |
| | | 5-yr DFS (%) | 75 (70-80) | 73 (70-77) | 73 (68-80) | 60 (55-65) |
| **Stage II** | | | | | | |
| Shinto *et al*[36], 2020 | 232 | 5-yr DFS (%) | 100 | 85.5 | 92.3 | 73 |
| **Stage IV** | | | | | | |
| Borelli *et al*[43], 2021 | 426 | OS (mo) | 13.7 (6.1-27.9) | 27.0 (23.9-30.1) | 18.3 (16.1-24.0) | 26.2 (21.4-29.9) |
| | | PFS (mo) | 5.4 (3.8-9.9) | 12.9 (11.0-14.3) | 8.3 (7.4-10.1) | 10.7 (9.8-13.1) |
| Stintzing *et al*[20], 2019 | 438 | OS (mo) | 15.9 (11.0-20.8) | 29.0 (26.7-31.4) | 18.6 (15.4-21.7) | 24.8 (22.6-27.1) |
| | | PFS (mo) | 8.2 (6.7-9.6) | 11.7 (10.8-12.6) | 8.5 (6.8-10.3) | 9.6 (8.6-10.6) |
| Lenz *et al*[16], 2019 | 581 | OS (mo) | 15.0 (11.7-22.4) | 40.3 (36.1-43.1) | 24.3 (16.4-29.0) | 31.4 (26.3-36.9) |
| | | PFS (mo) | 7.1 (5.7-8.6) | 13.4 (12.8-15.4) | 8.7 (7.2-9.8) | 11.0 (9.7-12.0) |
| Mooi *et al*[41], 2018 | 237 | OS (mo) | 8.8 (6.5-16.0) | 24.2 (19.1-27.4) | 17.6 (11.3-24.6) | 21.4 (15.8-23.1) |
| | | PFS (mo) | No statistical differences in this cohort | | | |
| Okita *et al*[42], 2018 | 193 | OS (mo) | 21.4 (13.3-35.5) | 48.1 (34.8-65.6) | 38.7 (30.6-45.6) | 44.0 (33.0-50.5) |

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

for mCRC[10,45]. In the case of immunotherapy, ongoing trials (NCT03436563) are testing M7824 treatment, an anti-PD-L1/TGF-β Trap fusion protein. This treatment has demonstrated an anti-tumor response by TGF-βand PD-L1 immunosuppressive pathways with successful results in murine CRC models[46,47]. It has been proposed as a possible treatment for CMS4 because it activates the TGF-pathway[9,48]. In addition, CMS identification could allow selecting a personalized first-line chemotherapy regimen in mCRC. For instance, a possible hypothesis has recently been proposed after analysis through CMS classification in two important clinical trials, FIRE-3[20] and CALGB/SWOG 80405[16], which both compared the response to first-line chemotherapy in addition to cetuximab or bevacizumab. The authors theorized that the combination of irinotecan and cetuximab in all CMS classification, when patients have received oxaliplatin, has a synergic effect in CMS2 and CMS3, but in CMS1 and CMS4 it has an antagonistic effect due to the poor efficacy of oxaliplatin in a fibroblast-rich microenvironment[49]. Recently, different retrospective studies of clinical trials have shown associations between CMS and the prognosis of different chemotherapy regimens[43,50]. However, these results must be confirmed using clinical trials with prospective designs that include different CMS patients.

## CONCLUSION

The CMS provides an interesting opportunity to explore the heterogeneity of CRC. CMS classification can approximate research in frequently unsolved daily clinical practice problems. For instance, in patients with stage II colon cancer, where the benefit of chemotherapy is still unclear, CMS classification could determine which patients would benefit from adjuvant chemotherapy. Likewise, CMS will allow defining the best first-line chemotherapy regimen in mCRC. Understanding the genetic profile of tumors could allow developing new interventions to target treatments that address specific pathways to each molecular subtype. Therefore, CMS comprehension is a crucial step towards personalized medicine, though any interesting perspective must be proven through prospective clinical trials selecting patients by CMS.

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