The Pharmacogenomics Journal (2020) 20:136–158
https://doi.org/10.1038/s41397-019-0102-4

CONSENSUS STATEMENT

Pharmacogenomics, biomarker network, and allele frequencies in colorectal cancer

Andrés López-Cortés[1,2,3] · César Paz-y-Miño[1] · Santiago Guerrero[1,4] · Gabriela Jaramillo-Koupermann[5] · Ángela León Cáceres[6] · Dámaris P. Intriago-Baldeón[7,8] · Jennyfer M. García-Cárdenas[1] · Patricia Guevara-Ramírez[1] · Isaac Armendáriz-Castillo[1] · Paola E. Leone[1] · Luis Abel Quiñones[3,9] · Juan Pablo Cayún[3,9] · Néstor W. Soria[10]

Received: 9 October 2018 / Revised: 9 September 2019 / Accepted: 2 October 2019 / Published online: 15 October 2019
© Springer Nature Limited 2019

Abstract

Colorectal cancer is one of the leading causes of cancer death worldwide. Over the last decades, several studies have shown that tumor-related genomic alterations predict tumor prognosis, drug response, and toxicity. These observations have led to the development of several therapies based on individual genomic profiles. As part of these approaches, pharmacogenomics analyses genomic alterations which may predict an efficient therapeutic response. Studying these mutations as biomarkers for predicting drug response is of a great interest to improve precision medicine. We conduct a comprehensive review of the main pharmacogenomics biomarkers and genomic alterations affecting enzyme activity, transporter capacity, channels, and receptors; and therefore the new advances in CRC precision medicine to select the best therapeutic strategy in populations worldwide, with a focus on Latin America.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide [1]. In the last decade, numerous exciting advances have been made to treat patients even with metastatic CRC (mCRC) [2]. However, patient-tailored therapies are still needed to overcome this disease. The advance of precision medicine requires the accurate identification of mutations driving each patient's tumor [3]. In this regard, genetic mutations may have a great impact on disease prognosis and therapy response. Germline mutations are heritable alterations found in individuals while somatic mutations appear after an oncogenic

Supplementary information The online version of this article (https://doi.org/10.1038/s41397-019-0102-4) contains supplementary material, which is available to authorized users.

✉ Andrés López-Cortés
aalc84@gmail.com

✉ César Paz-y-Miño
cesar.pazymino@ute.edu.ec

[1] Centro de Investigación Genética y Genómica, Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE, 170527 Quito, Ecuador

[2] RNASA-IMEDIR, Computer Science Faculty, University of Coruna, 15071 Coruna, Spain

[3] Red Latinoamericana de Implementación y Validación de Guías Clínicas Farmacogenómicas (RELIVAF-CYTED), Santiago, Chile

[4] Gene Regulation, Stem Cells and Cancer Programme, Centre for Genomics Regulation (CRG), The Barcelona Institute for Science and Technology (BIST), Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain

[5] Laboratorio de Biología Molecular, Subproceso de Anatomía Patológica, Hospital de Especialidades Eugenio Espejo, 170403 Quito, Ecuador

[6] Global Health Institute, Faculty of Medicine, Heidelberg University, 69120 Heidelberg, Germany

[7] Division of Molecular Genome Analysis, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany

[8] Faculty of Biosciences, Heidelberg University, 69120 Heidelberg, Germany

[9] Laboratory of Chemical Carcinogenesis and Pharmacogenetics, Department of Basic-Clinical Oncology, Faculty of Medicine, University of Chile, 70111 Santiago, Chile

[10] Cátedra de Biotecnología, Facultad de Ciencias Químicas, Universidad Católica de Córdoba, Unidad Asociada al CONICET, 5000 Córdoba, Argentina

insult within the tumoral tissue [4]. As part of CRC pharmacogenomics, precision medicine allows tailoring drug development based on the human multi-omics profile [5–7]. Thus, personalized therapy not only maximizes the drug therapeutic effects but also reduces the possibility of experiencing adverse drug reactions [8]. In this review, we focus primarily on the current status of pharmacogenomics in CRC, its biomarkers and allele frequencies worldwide, with a focus on Latin American populations in order to improve precision medicine.

CRC oncogenomics

CRC was one of the first solid tumors to be molecularly characterized, in whose pathogenesis several signaling pathways intervene [9]. Vogelstein et al. [10] described the model of progressive step-wise accumulation of epigenetic events of CRC. This model provides information about the role of driver mutations whose objective is to give a selective advantage for tumor progression [11]. In addition, the accumulation of pathogenic mutations in the transforming growth factor-β (TGFβ), WNT-β-catenin, PI3K, EGFR, and downstream MAPK pathways induces CRC [12–15].

In contrast, the development of CRC also occurs when RNA-binding proteins cause alterations of the post-transcriptional regulation [16], and when defects in telomere stability, chromosomal segregation, and mutations in *TP53* gene cause chromosomal instability (CIN) [15]. The 15% of early-stage colorectal tumors present mismatch repair-deficient (MMRd) system, triggering hypermutation and microsatellite instability (MSI) [13]. According to Dienstmann et al., the epigenetic profile of tumors with CIN presents mutations in *APC*, *KRAS*, *TP53*, *SMAD4*, and *PIK3CA*, promoting the formation of the nonhypermutated consensus molecular subtypes (CMSs): CMS2, CMS3, and CMS4 [17]. Whereas tumors with MSI harbor mutations in the *MSH6*, *RNF43*, *ATM*, *TGFBR2*, *BRAF,* and *PTEN* genes of the hypermutated molecular subtype CMS1 [17].

A consensus of molecular subtypes

Gene expression-based subtyping is widely accepted as a relevant source of disease stratification [18]. Nevertheless, the translational utility is hampered by divergent results that are probably related to differences in algorithms applied to sample preparation methods, gene expression platforms, and racial/ethnic disparities [19, 20]. Inspection of the published gene expression-based CRC classification revealed an absence of a clear methodological 'gold standard' [15, 21–24]. To facilitate clinical translation, the CRC subtyping consortium was formed to assess the core subtype patterns among existing gene expression-based CRC subtyping algorithms [19, 25].

In spite of heterogeneities, subtype concordance analysis readily yielded four CMSs [19], being CMS1 the immune subtype, CMS2 the canonical subtype, CMS3 the metabolic subtype and CMS4 the mesenchymal subtype (Fig. 1) [19, 26]. Upon evaluation of this classification system, Calon et al. discovered that their prediction power arises from genes expressed by stromal cells that associate robustly with disease relapse [27]. Mesenchymal stromal cells (MSC) may represent a pivotal part of stroma in CRC, but little is known about the specific interaction of MSC in CRC [28].

Recognizing that transcriptomics represents the level of high-throughput molecular data which is most intimately linked to tumor phenotype and clinical behavior, it is important to characterize the CRC genomics alterations. Tumor genomes contain thousands of mutations. However, only a few of them drive tumorigenesis by affecting driver genes, which upon alteration, confers selective growth advantage to tumor cells [29–35]. Since the identification of the first somatic mutation in human bladder carcinoma cell line (HRAS G12V) [36, 37], the Pan-Cancer Atlas from The Cancer Genome Atlas have undertaken omics analyses identifying 20 CRC driver genes (*ACVR2A*, *AMER1*, *APC*, *ARID1A*, *BRAF*, *CTNNB1*, *FBXW7*, *GNAS*, *KRAS*, *NRAS*, *PCBP1*, *PIK3CA*, *PTEN*, *SMAD4*, *SMAD2*, *SOX9*, *TCF7L2*, *TGIF1*, *TP53*, and *ZFP36L2*) that are included in the Catalog of Somatic Mutations in Cancer (COSMIC), the Cancer Gene Census (CGS), and the Cancer Genome Interpreter (CGI) [38–41]. The CGI identifies 71 biomarkers among biallelic markers, copy number alterations, somatic mutations, fusion genes, and amplifications [41]. Likewise, the CGI annotates CRC tumor variants which constitutes state-of-art biomarkers of drug response as shown in Supplementary Table 1.

Drugs, biomarkers, and allele frequencies

According to the National Comprehensive Cancer Network (NCCN) guidelines v1.2018 and the European Society for Medical Oncology (ESMO) guidelines [42–44], the two main drug categories in CRC treatment are cytotoxic and biological therapies. Cytotoxic agents are platinum derivatives (oxaliplatin), antimetabolites (5-fluorouracil and capecitabine), and antitopoisomerases (irinotecan). Biological therapy includes drugs against the epidermal growth factor receptor (EGFR) (cetuximab, panitumumab) and antiangiogenics (bevacizumab, ziv-aflibercept, ramucirumab). In addition, the recommendation includes PD-1 and PD-L1 inhibitors (nivolumumab, pembrolizumab) as new immunological molecules for MSI or MMRd [44] (Table 1 and Fig. 2).

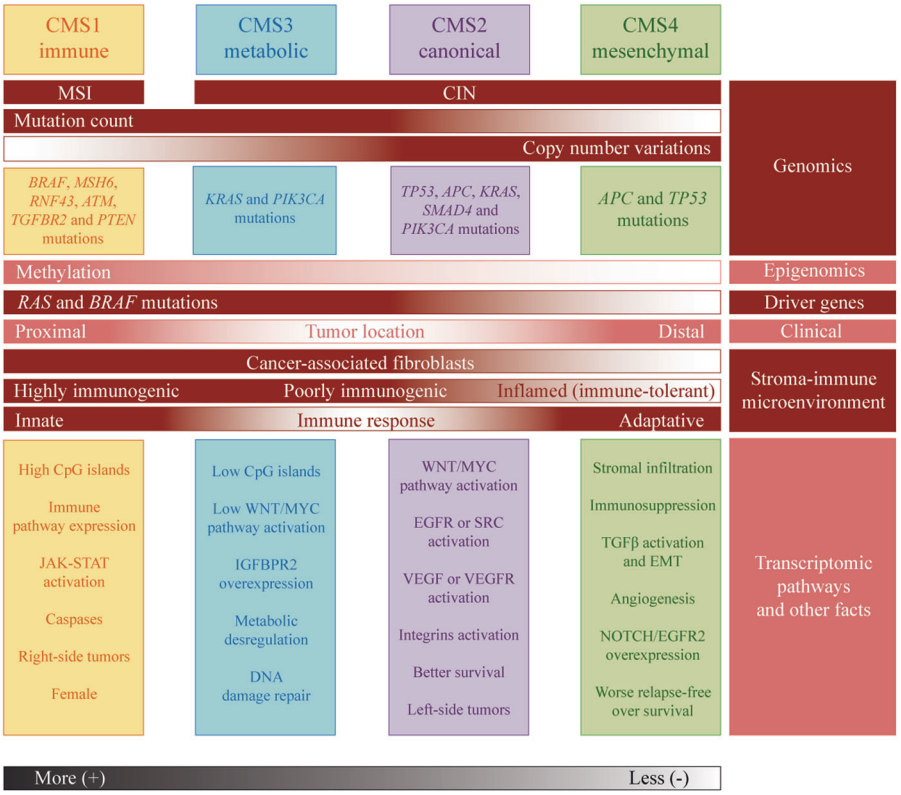

Fig. 1 Integrating multi-omics features in CRC subtypes. Microsatellite instability (MSI) is linked to hypermutation, hypermethylation, highly immunogenic response, and locations in the proximal colon (consensus molecular subtype 1 (CMS1)). Tumors with chromosomal instability (CIN) are linked to copy number variations, poorly immunogenic or inflamed, non-hypermutated subtypes, stromal infiltration, and locations in left colon or rectum (CMS2, CMS3, and CMS4)

Table 1 Category of drugs applied in CRC treatments

Category	Agents	Drugs
Cytotoxic agents	Platinum derivatives	Oxaliplatin
	Antimetabolites	5-FU/leucovorin, capecitabine
	Antitopoisomerase	Irinotecan
	Nucleoside analog[a]	Trifluridine, tripiracil
Monoclonal antibodies	Antiangiogenic[b]	Bevacizumab, ziv-aflivercept, ramucirumab
	Anti EGFR[b]	Cetuximab, panitumumab
	Anti BRAF V600E[b]	Vemurafenib
	Anti PD-L1, PD-1[b]	Nivolumab, pembrolizumab
Tyrosine kinase inhibitors[a]	Poli anti kinase inhibitors	Regorafenib, sorafenib

5-FU 5-fluorouracil, *EGFR* epidermal growth factor receptor, *BRAF* B-Raf protooncogene, *PD-1* programmed cell death protein 1, *PD-L1* programmed cell death ligand 1

[a]For patients who have progressed through all available regimens

[b]For advanced or metastatic disease only

Platinum derivatives

These compounds form covalent bonds with guanine and adenine in the DNA. The most important drugs in this group are cisplatin, carboplatin, and oxaliplatin (Fig. 2). Drugs containing platinum salts exert their cytotoxic effect by means of DNA adduct formation, leading to inhibition of DNA replication and apoptosis [45]. The major path of adduct elimination is the nucleotide excision repair (NER). During NER, damaged DNA and unwound DNA helices are identified by the action of several factors, including xeroderma pigmentosum protein (XPD, XPC, and XPA) [46]. Cleavages of the damaged DNA strand are performed by nucleases *XPG* (3′) and *ERCC1* (5′), and adducts are removed [47].

The glutathione S-transferases (GSTs) are involved in the inactivation of platinum compounds, thus preventing cellular DNA damage and increasing the treatment efficacy [48]. Single nucleotide polymorphisms (SNPs) in *GSTP1*, *GSTT1,* and *GSTM1* can alter GST activity [49]. The

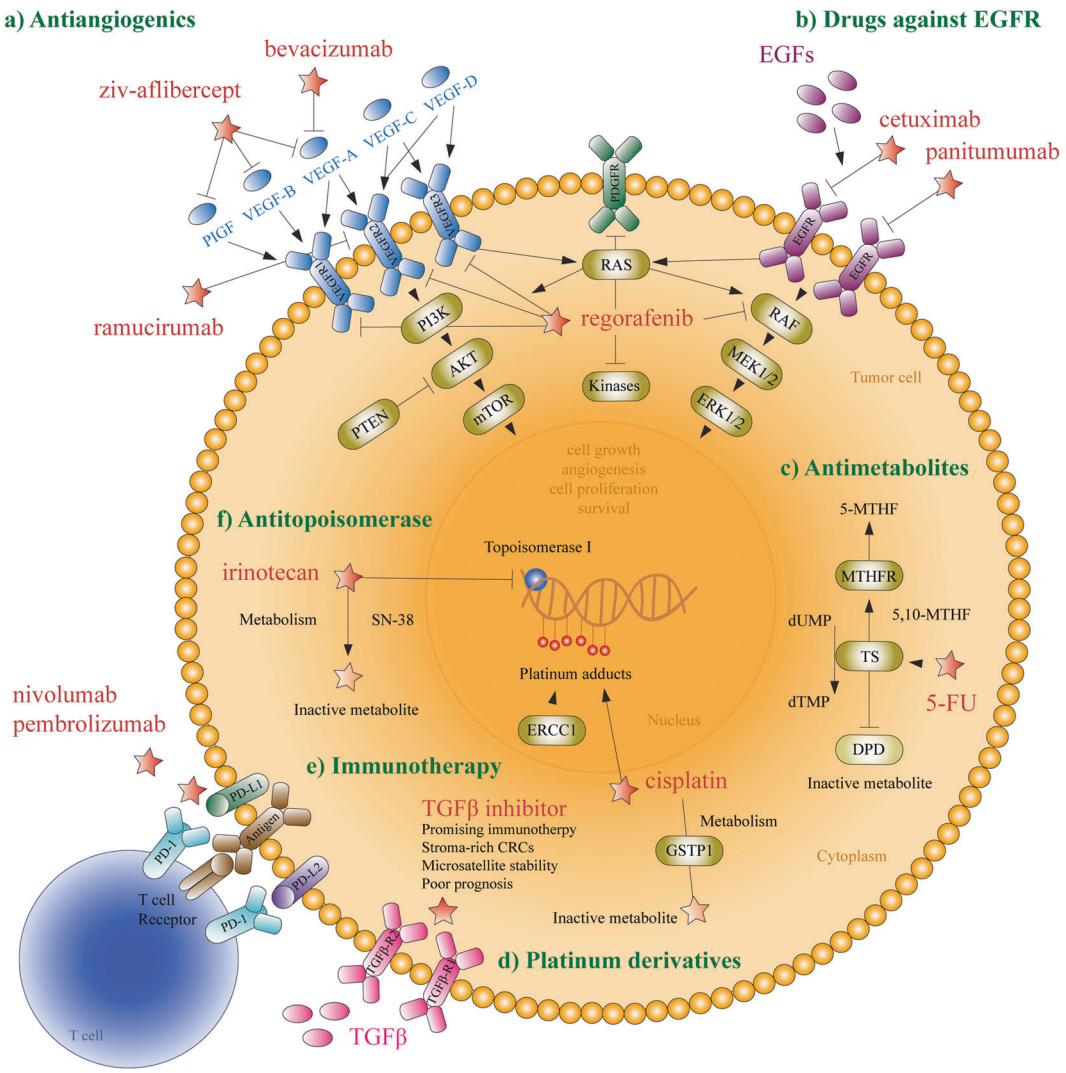

Fig. 2 Overview of different drugs used in the CRC treatments: **a** antiangiogenics, **b** drugs against EGFR, **c** antimetabolites, **d** platinum derivatives, **e** immune checkpoint inhibitors (anti PD-1, anti PD-L1, and TGFβ inhibitor), and **f** antitopoisomerase

decrease in enzyme activity has been linked to reduced detoxification capacity, leading to increased efficacy of platinum compounds. *GSTP1* (Ile105Val) has been associated with reduced enzyme activity [50], a deletion in *GSTT1* leads to the absence of enzyme activity and a deletion in *GSTM1* is linked with decreased survival rate [51, 52].

The excision repair cross-complementation protein (ERCC) is involved in nucleotide repair system [53]. Polymorphisms in genes encoding these repair proteins may contribute to inter-individual differences to platinum toxicity. The association between toxicity and *ERCC1* rs11615 has been studied in CRC [54]. The mutant T allele has been related to grade 1 neuropathy in oxaliplatin-treated patients, even though no association with a higher degree of neuropathy was observed. Moreover, *ERCC2* (XPD) is involved in the oxaliplatin pathway. rs13181 has been related with treatment effectiveness [55]. Meanwhile, *ERCC4* rs1799801, *ERCC5* rs2016073, and rs751402 are associated with platinum response [56].

The X-ray repair cross-complementing protein (XRCC1) and its variant *XRCC1* rs25487 are involved in the repair of broken DNA strands which can be induced by platinum compounds; such repair is carried out by an excision repair system [57]. It has been suggested that a deterioration in the efficiency of DNA repair caused by Gln's allele leads to greater efficacy of oxaliplatin. Conversely, the presence of *XRCC3* rs1799794 has been associated with an increased risk of neutropenia [58]. Biomarkers focused on oxaliplatin are listed in Table 2 [49, 55–57, 59–62].

Pharmacogenomics identifies mutations, which may predict an efficient therapeutic response; however, genetic alterations significantly varies depending on different race/ethnic origins worldwide [63]. The allele frequencies of

Table 2 Biomarkers focused on oxaliplatin

Gene	Polymorphism	Clinical relevance	Function	Type of inheritance	Reference
GSTP1	rs1695 (A313G)	Neurotoxicity, neutropenia	Enzyme	Germinal	[57, 59]
GSTM1	Del	Poor survival, neutropenia	Enzyme	Germinal	[59]
ERCC1	rs11615 (T354C)	Neuropathy / Survival	Repair protein	Germinal	[57]
ERCC2	rs13181 (A2251C/T)	Effectiveness / Survival	Repair protein	Germinal	[49, 55]
ERCC4	rs1799801 (T2505C)	Response	Repair protein	Germinal	[60]
ERCC5	rs2016073 (A-763G); rs751402 (A + 25G)	Response	Repair protein	Germinal	[56]
XRCC1	rs25487 (G1196A)	Response	Repair protein	Somatic	[57, 61]
XRCC3	rs1799794 (A316G)	Neutropenia	Repair protein	Germinal	[62]

GSTP1 glutathione S-transferase pi 1, *GSTM1* glutathione S-transferase mu 1, *ERCC1* excision repair 1, *ERCC2* excision repair 2, *ERCC4* excision repair 4, *ERCC5* excision repair 5, *XRCC1* X-ray repair cross complementing 1, *XRCC3* X-ray repair cross complementing 3, *del* deletion, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

platinum derivative variants rs1695, rs11615, rs13181, rs1799801, rs2016073, rs2234671, rs25487, and rs1799794, according to the 1000 Genomes Project (phase 3) are shown in Table 3 [64].

Antimetabolites

These drugs inhibit enzymes related to purine and pyrimidine synthesis, resulting in cell depletion and alteration of nucleic acid synthesis. Among these, there are pyrimidine analogs such as 5-fluorouracil (5-FU) and oral pro-drugs such as gemcitabine, capecitabine and tegafur (Fig. 2) [65].

Fluoropyrimidines (5-FU, capecitabine and tegafur) are antimetabolite drugs used in CRC treatment. 5-FU is a fluoropyrimidine derivative with two major mechanisms of action that explain its cytotoxic effect [66]. The main active metabolite of 5-FU (5-FdUMP) prevents DNA synthesis by forming a complex with thymidylate synthase (TS) stabilized by 5,10-methylenetetrahydrofolate (5,10-MTHF), thus inhibiting the conversion of monophosphate 2′-deoxyuridine-5′ (dUMP) to deoxythymidine-2′-5′-monophosphate (dTMP), an essential precursor for DNA synthesis. In addition, the incorporation of 5-FU to nucleotides in DNA and RNA strands leads to an alteration in the processing of nucleic acids [66]. Gemcitabine is a structural analog of deoxycytidine, which is metabolized by nucleoside kinase to nucleoside diphosphate and triphosphate [67].

TYMS protein is a homodimeric methyltransferase enzyme that catalyzes the synthesis reaction of thymidylate. This reaction is a critical step in the formation of deoxythymidine 5′-triphosphate (dTTP), an indispensable metabolite in DNA synthesis. The *TYMS* gene contains a tandem of a polymorphic 28-base-pair sequence repeated in the promoter (TSER) 5′ untranslated region (5′-UTR) [67].

Inactivation of 5-FU depends on dihydropyrimidine dehydrogenase (DPYD) activity [68]. The deficient activity of *DPYD* leads to prolonged 5-FU plasma half-life, causing a severe hematological toxicity [69]. *DPYD* deficiency is present in ~3% of all cancer patients, but it represents approximately 50% of patients manifesting severe toxicity. So far, ~30 polymorphisms in *DYPD* have been identified; however, a mutation of G>A at the splicing site in exon 14 (IVS14 + 1G>A) leads to the formation of a truncated protein without residual activity [70, 71]. The incidence of this allele is rare, with a heterozygote population frequency of 0.9–1.8%. Nevertheless, it is estimated to be responsible for approximately 25% of all cases of 5-FU unexpected toxicity [66].

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-MTHF to 5-MTHF. The most common polymorphisms of *MTHFR* are C677T and A1298C. These polymorphisms lead to decreased enzyme activity, which induces a more effective stabilization of the FdUMP-TS ternary complex, potentiating 5-FU toxicity [72, 73].

ATP-Binding Cassette Sub-Family B1 (*ABCB1*) is a member of the ABC transporter superfamily and its protein is known as P-glycoprotein [74]. *ABCB1* overexpression in tumors has been associated with resistance to chemotherapeutic drugs. *ABCB1* is a highly polymorphic gene that significantly differs among ethnic groups. Some of the most studied SNPs are rs1128503, rs2032592, and rs1045642 [75].

Cytidine deaminase (CDA) is involved in capecitabine metabolism in the liver to form 5-fluorodeoxyuridine, which in turn becomes 5-FU by the action of thymidine phosphorylase (TP) [67]. The decreased activity of CDA leads to the accumulation of potentially toxic metabolites. The variation in expression of CDA has been linked to polymorphisms in the promoter region of *CDA* and affects the

Table 3 Allele frequencies for clinically relevant genetic variants *GSTP1* rs1695, *ERCC1* rs11615, *ERCC2* rs13181, *ERCC4* rs1799801, *ERCC5* rs2016073, *CXCR1* rs2234671, *XRCC1* rs25487, and *XRCC3* rs1799794 in populations worldwide

Gene	Polymorphism	Human populations		
		Latin American	Caucasian	Asian
GSTP1	rs1695 (A313G)	Colombia: 0.36 (G)[a]; Mexico: 0.56 (G); Peru: 0.67 (G); Puerto Rico: 0.37 (G)	Spain: 0.36 (G); British: 0.32 (G); Finland: 0.28 (G); Italy: 0.29 (G)	Han Chinese: 0.18 (G); Bangladesh: 0.22 (G); Japan: 0.10 (G); Vietnam: 0.20 (G)
ERCC1	rs11615 (T354C)	Colombia: 0.52 (G); Mexico: 0.74 (G); Peru: 0.75 (G); Puerto Rico: 0.50 (G)	Spain: 0.37 (G); British: 0.32 (G); Finland: 0.37 (G); Italy: 0.46 (G)	Han Chinese: 0.75 (G); Bangladesh: 0.65 (G); Japan: 0.71 (G); Vietnam: 0.73 (G)
ERCC2	rs13181 (A2251C/T)	Colombia: 0.24 (G); Mexico: 0.19 (G); Peru: 0.17 (G); Puerto Rico: 0.24 (G)	Spain: 0.31 (G); British: 0.30 (G); Finland: 0.40 (G); Italy: 0.45 (G)	Han Chinese: 0.11 (G); Bangladesh: 0.35 (G); Japan: 0.07 (G); Vietnam: 0.08 (G)
ERCC4	rs1799801 (T2505C)	Colombia: 0.22 (G); Mexico: 0.19 (G); Peru: 0.24 (G); Puerto Rico: 0.19 (G)	Spain: 0.38 (G); British: 0.28 (G); Finland: 0.25 (G); Italy: 0.29 (G)	Han Chinese: 0.21 (G); Bangladesh: 0.24 (G); Japan: 0.33 (G); Vietnam: 0.37 (G)
ERCC5	rs2016073 (A-763G)	Colombia: 0.73 (A); Mexico: 0.61 (A); Peru: 0.48 (A); Puerto Rico: 0.78 (A)	Spain: 0.87 (A); British: 0.80 (A); Finland: 0.82 (A); Italy: 0.77 (A)	Han Chinese: 0.65 (A); Bangladesh: 0.66 (A); Japan: 0.73 (A); Vietnam: 0.63 (A)
CXCR1	rs2234671 (G2607C)	Colombia: 0.08 (G); Mexico: 0.14 (G); Peru: 0.31 (G); Puerto Rico: 0.08 (G)	Spain: 0.01 (G); British: 0.08 (G); Finland: 0.04 (G); Italy: 0.03 (G)	Han Chinese: 0.10 (G); Bangladesh: 0.18 (G); Japan: 0.08 (G); Vietnam: 0.06 (G)
XRCC1	rs25487 (G1196A)	Colombia: 0.63 (C); Mexico: 0.73 (C); Peru: 0.69 (C); Puerto Rico: 0.71 (C)	Spain: 0.58 (C); British: 0.66 (C); Finland: 0.67 (C); Italy: 0.63 (C)	Han Chinese: 0.75 (C); Bangladesh: 0.66 (C); Japan: 0.72 (C); Vietnam: 0.77 (C)
XRCC3	rs1799794 (A316G)	Colombia: 0.19 (C); Mexico: 0.16 (C); Peru: 0.25 (C); Puerto Rico: 0.16 (C)	Spain: 0.28 (C); British: 0.19 (C); Finland: 0.23 (C); Italy: 0.19 (C)	Han Chinese: 0.52 (C); Bangladesh: 0.42 (C); Japan: 0.42 (C); Vietnam: 0.39 (C)

GSTP1 glutathione S-transferase pi 1, *ERCC1* excision repair 1, *ERCC2* excision repair 2, *ERCC4* excision repair 4, *ERCC5* excision repair 5, *XRCC1* X-ray repair cross complementing 1, *XRCC3* X-ray repair cross complementing 3, *CXCR1* C-X-C motif chemokine receptor 1, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

[a]Frequency of minor allele

metabolism of gemcitabine and capecitabine [74]. rs602950 and rs532545 have been associated with increased expression of CDA in vitro in capecitabine-treated patients [74].

TP is involved in 5-FU metabolism, where 5-FU is converted to 5-fluoro-2′-deoxyuridine (FUDR-5) [76]. rs11479 generates an amino acid change of serine to leucine that leads to a lower treatment response. Enolase superfamily member 1 (*ENOSF1*) gene encodes an antisense RNA against *TYMS*. *ENOSF1* regulates mRNA and protein expression of *TYMS*. Hence, *TYMS* variants with lower or higher activity affect its function [70, 71]. Lastly, biomarkers focused on capecitabine, 5-FU and gemcitabine drugs are listed in Table 4 [70, 71, 74–80].

The allele frequencies of rs3918290, rs1801133, rs1128503, rs2072671, rs9344, rs9344, and rs2612091 polymorphisms in populations worldwide are shown in Table 5 [64].

Agents interacting with topoisomerases

Topoisomerases play a key role in the cell replication, transcription, and DNA repair. It modifies the tertiary DNA structure without altering the nucleotide sequence. In humans, three types of topoisomerases (I, II, and III) have been identified. Within this group, camptothecin derivatives such as irinotecan are included [81] (Fig. 2).

Irinotecan is a potent inhibitor of topoisomerase I [82]. It promotes an oxidation bioreaction mediated by *CYP3A* to form *APC*, a cytotoxic substance. Alternatively, irinotecan is converted by hepatic carboxylesterase to SN-38. This compound is conjugated further by several UDP glucuronyl to reach the inactive metabolite SN-38G [83]. To enable excretion, SN-38 and irinotecan are actively transported out of the cell by ATP-dependent efflux pump (*ABCB1*). After biliary excretion, SN-38G can become active SN-38 by

Table 4 Biomarkers focused on capecitabine, 5-FU and gemcitabine drugs

Gene	Polymorphism	Clinical relevance	Function	Type of inheritance	Reference
TYMS	rs45445694 (*2R/*3R)	Neutropenia	Enzyme	Germinal	[70, 77]
DPYD	rs3918290 (G1905 + 1A);	Toxicity	Enzyme	Germinal	[70, 71, 78]
	rs67376798 (A2846T);	Toxicity			
	rs1801158 (G1601A);	Toxicity			
	rs55886062 (T1679G);	Toxicity			
	rs1801159 (A1627G);	Neutropenia			
	rs12132152 (G97057448A);	Diarrhea			
	rs12022243 (C97397224T)	Diarrhea			
MTHFR	rs1801131 (A1298T);	Toxicity	Enzyme	Germinal	[77, 79]
	rs1801133 (C677T)	Toxicity			
ABCB1	rs1128503 (C1236T);	Neutropenia	Transporter	Germinal	[74, 75]
	rs1045642 (C3435T)	Diarrhea			
CDA	rs2072671 (A79C);	Toxicity	Enzyme	Germinal	[74]
	rs602950 (A-92G);	Diarrhea			
	rs532545 (C-451T)	Diarrhea			
CCND1	rs9344 (G870A)	Prognosis	Cyclin	Germinal	[80]
TP	rs11479 (C1412T)	Response	Enzyme	Germinal	[76]
ENOSF1	rs2612091 (805-227G>A)	Diarrhea	Enzyme	Germinal	[71, 74]

ABCB1 ATP-binding cassette subfamily B member 1, *CCND1* cyclin D1, *CDA* cytidine deaminase, *DPYD* dihydropyrimidine dehydrogenase, *ENOSF1* enolase superfamily member 1, *MTHFR* methylenetetrahydrofolate reductase, *TP* thymidine phosphorylase, *TYMS* thymidylate synthetase, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

bacterial beta-glucuronidase, which can lead to gastrointestinal toxicity.

It has been revealed that reduced glucuronidation of SN-38 significantly increases irinotecan gastrointestinal toxicity. The main UDP-glucuronosyltransferase (UGT) involved in conjugating SN-38 is *UGT1A1*. At least 25 *UGT1A1* polymorphisms have been described, from which the most common in the promoter region consists of seven TA-repetitions (−53 [TA] 6 > 7, *UGT1A1**28) instead of six [84, 85]. The highest number of TA repeats is associated with a reduction of *UGT1A1* expression, leading to reduced glucuronidation. *UGT1A1**28 has proven to be a significant predictor of severe toxicity following administration of irinotecan [86, 87].

ABC transporters, including *ABCC1*, *ABCC2*, *ABCB1*, and *ABCG2* regulate output of hepatic and biliary CPT-11 metabolites [88]. SNPs in *ABCB1* and *ABCC2* have been recently associated with modulation of CPT-11 and SN-38 exposure [82]. Moreover, other SNPs in *ABCC5* and *ABCG2* genes have been correlated with both hematological and nonhematological toxicities [89].

The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) is an important prptein expressed in the basolateral membrane of hepatocytes, which mediates the availability of active irinotecan metabolite [90]. rs4149056 has been associated with an increased SN-38 concentration in patients with mCRC. Meanwhile, other polymorphisms are linked to faster response rate and higher PFS [83]. Finally, biomarkers focused on irinotecan drug are shown in Table 6 [52, 59, 62, 74, 75, 84, 85, 87, 89–95].

The allele frequencies of genes that interact with topoisomerases rs2244613, rs1045642, rs2074087, rs262604, rs1051266, and rs2306283 in populations worldwide are shown in Table 7 [64].

Antiangiogenics

Vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis and inhibition mediated by bevacizumab which reduces tumor volume [96, 97]. Bevacizumab is a recombinant humanized monoclonal IgG antibody directed against all isoforms of *VEGFA*. Hypoxia is a potent stimulus for *VEGF* expression and one of the control elements in this mechanism is the hypoxia-inducible factor 1A (*HIF-1a*) [98]. This factor binds to a 28-bp promoter in the 5′ upstream region of *VEGF*, thereby/hence-stimulating transcription. In addition, other regulatory elements for *VEGF* expression are found in the 3′-UTR as shown in Table 8 [98–101].

Table 5 Allele frequencies for clinically relevant genetic variants *DPYD* rs3918290, *MTHFR* rs1801133, *ABCB1* rs1128503, *CDA* rs2072671, *CCND1* rs9344, *TP* rs9344, and *ENOSF1* rs2612091 in populations worldwide

Gene	Polymorphism	Human populations		
		Latin American	Caucasian	Asian
DPYD	rs3918290 (1905+1G>A)	Colombia: 0.00 (T)[a]; Mexico: 0.00 (T); Peru: 0.01 (T); Puerto Rico: 0.00 (T)	Spain: 0.00 (T); British: 0.00 (T); Finland: 0.02 (T); Italy: 0.00 (T)	Han Chinese: 0.00 (T); Bangladesh: 0.00 (T); Japan: 0.00 (T); Vietnam: 0.00 (T)
MTHFR	rs1801133 (C677T)	Colombia: 0.54 (A); Mexico: 0.47 (A); Peru: 0.44 (A); Puerto Rico: 0.45 (A)	Spain: 0.44 (A); British: 0.32 (A); Finland: 0.27 (A); Italy: 0.47 (A)	Han Chinese: 0.47 (A); Bangladesh: 0.12 (A); Japan: 0.38 (A); Vietnam: 0.19 (A)
ABCB1	rs1128503 (C1236T)	Colombia: 0.57 (G); Mexico: 0.53 (G); Peru: 0.67 (G); Puerto Rico: 0.60 (G)	Spain: 0.62 (G); British: 0.58 (G); Finland: 0.57 (G); Italy: 0.58 (G)	Han Chinese: 0.30 (G); Bangladesh: 0.37 (G); Japan: 0.40 (G); Vietnam: 0.42 (G)
CDA	rs2072671 (A79C)	Colombia: 0.27 (C); Mexico: 0.32 (C); Peru: 0.36 (C); Puerto Rico: 0.28 (C)	Spain: 0.34 (C); British: 0.33 (C); Finland: 0.19 (C); Italy: 0.37 (C)	Han Chinese: 0.12 (C); Bangladesh: 0.17 (C); Japan: 0.21 (C); Vietnam: 0.10 (C)
CCND1	rs9344 (G870A)	Colombia: 0.33 (A); Mexico: 0.33 (A); Peru: 0.30 (A); Puerto Rico: 0.42 (A)	Spain: 0.55 (A); British: 0.47 (A); Finland: 0.42 (A); Italy: 0.51 (A)	Han Chinese: 0.56 (A); Bangladesh: 0.58 (A); Japan: 0.47 (A); Vietnam: 0.63 (A)
TP	rs11479 (C1412T)	Colombia: 0.11 (A); Mexico: 0.25 (A); Peru: 0.24 (A); Puerto Rico: 0.12 (A)	Spain: 0.06 (A); British: 0.05 (A); Finland: 0.08 (A); Italy: 0.07 (A)	Han Chinese: 0.24 (A); Bangladesh: 0.16 (A); Japan: 0.25 (A); Vietnam: 0.32 (A)
ENOSF1	rs2612091 (805-227G>A)	Colombia: 0.61 (T); Mexico: 0.59 (T); Peru: 0.69 (T); Puerto Rico: 0.61 (T)	Spain: 0.54 (T); British: 0.53 (T); Finland: 0.57 (T); Italy: 0.56 (T)	Han Chinese: 0.70 (T); Bangladesh: 0.55 (T); Japan: 0.69 (T); Vietnam: 0.70 (T)

ABCB1 ATP binding cassette subfamily B member 1, *CCND1* cyclin D1, *CDA* cytidine deaminase, *DPYD* dihydropyrimidine dehydrogenase, *ENOSF1* enolase superfamily member 1, *MTHFR* methylenetetrahydrofolate reductase, *TP* thymidine phosphorylase, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

[a]Frequency of minor allele

Variations in the *VEGF* receptor 1 (rs9582036) and 2 (rs12505758) are associated with tyrosine kinase (TKI) domain. High expression levels of these receptors contribute to a less favorable outcome when treated with bevacizumab, linked with PFS and overall survival (OS) [96, 100, 102].

Various studies from mCRC have investigated the predictive impact of some SNPs present in *VEGFA*, which are involved in bevacizumab response. Loupakis et al. conducted a retrospective analysis which found that rs833061 was associated with PFS and OS [100]. Meanwhile, Sibertin-Blanc et al. [103] showed that T-carriers of the C237T SNP had shorter time-to-treatment failure as well as shorter PFS and OS.

Annexin A11 (*ANXA11*) has been associated with a spectrum of regulatory functions in calcium signaling, cell division, and apoptosis [104]. *ANXA11* rs1049550 leads to an amino acid change (R230C) of the first conserved domain of annexin, which is responsible for Ca^{+2} dependent intracellular traffic. Response to bevacizumab revealed that patients carrying rs1049550 were more sensitive to chemotherapy than those having at least one C allele [101].

CXC chemokine receptors (*CXCR1* and *CXCR2*) are integral membrane proteins which specifically bind and respond to CXC chemokine family cytokines [99]. They represent a family of seven receptors linked to G-protein which plays an important role in angiogenesis. *CXCR1* rs2234671 and *CXCR2* rs2230054 are linked with overall response rates (ORR) [105].

Finally, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved new molecules that improve the therapeutic effectiveness, OS, and PFS. In particular, research efforts have been focused on novel agents targeting tumor angiogenic activity, cell growth, and migration in mCRC. The use of molecules targeting VEGF pathways (ziv-aflibercept, regorafenib and ramucirumab) have been integrated into clinical practice [96] (Fig. 2).

The allele frequencies of variants that interact with antiangiogenic agents rs9582036, rs12505758, rs3025039,

Table 6 Biomarkers focused on irinotecan drug

Gene	Polymorphism	Clinical relevance	Function	Type of inheritance	Reference
CYP3A5	rs776746 (*3C)	Response	Enzyme	Germinal	[52]
UGT1A1	rs8175347 (*28); rs4148323 (*6)	Neutropenia and Diarrhea Neutropenia	Enzyme	Germinal	[84, 85, 87]
UGT1A7	rs17868324 (*3)	Neutropenia	Enzyme	Germinal	[85, 87]
UGT1A9	rs3832043 (*22)	Neutropenia	Enzyme	Germinal	[85, 87, 91]
ABCB1	rs1128503 (C1236T); rs1045642 (C3435T); rs2032582 (G2677T/A)	Asthenia Diarrhea Global Survival	Transporter	Germinal	[74, 75]
ABCC1	rs2074087 (C2461-30G)	Neutropenia	Transporter	Germinal	[59, 62]
ABCC2	rs3740066 (T3972C)	Neutropenia	Transporter	Germinal	[92, 94, 95]
ABCG2	rs262604 (−20 + 805A>G); rs2231142 (C421A); rs7699188 (C61414T)	Myelosuppression Neutropenia Toxicity	Transporter	Germinal	[89]
SLC19A1	rs1051266 (A80G)	PFS	Transporter	Germinal	[90]
SLCO1B1	rs2306283 (A388G)	PFS	Transporter	Germinal	[90]

ABCB1 ATP binding cassette subfamily B member 1, *ABCC1* ATP binding cassette subfamily C member 1, *ABCC2* ATP binding cassette subfamily C member 2, *ABCG2* ATP binding cassette subfamily G member 2, PFS progression-free survival, *CYP3A5* cytochrome P450 family 3 subfamily A member 5, *UGT1A1*, UDP-glucuronosyltransferase family 1 member A1, *UGT1A7* UDP glucuronosyltransferase family 1 member A7, *UGT1A9* UDP glucuronosyltransferase family 1 member A9, *SLC19A1* solute carrier family 19 member 1, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *G* guanine, *A* adenine, *C* cytosine, *T* thymine, * repetitions

rs1049550, and rs2230054 in populations worldwide are shown in Table 9 [64].

Agents against EGFR

Cetuximab and panitumumab are monoclonal antibodies (mAb) that block the action of EGF and may be employed in mCRC treatment [9, 98]. These drugs exert their action by binding to the extracellular domain of EGFR, with a greater affinity compared with the wild-type EGF, thereby blocking phosphorylation induced by EGFR ligands. Some variants are shown in Table 10 [69, 70, 80, 107–113–114].

The EGF/EGFR pathway plays an important role in cancer pathogenesis. EGF and EGFR are commonly over-expressed in CRC and they appear to be associated with poor prognosis and increased metastatic risk [115]. EGFR is a transmembrane glycoprotein which is involved in cell proliferation, migration, and survival. *EGFR* R497K attenuates TKI activation [116], and *EGF* G61A increases its production when individuals have GG or GA genotypes [111]. The EGF/EGFR pathway is a predictive marker for cetuximab treatment in patients with locally advanced CRC [117].

KRAS oncogene is a member of the human RAS family, which produces a self-inactivating guanosine triphosphate (GTP), binding signal transducer located on the inner surface of the cell membrane [118]. *KRAS* mutations may compromise the intrinsic GTPase activity, resulting in constitutively active KRAS protein that affects various signaling pathways [118]. The 45% of CRC cases have *KRAS* mutations and it has been shown that these mutations are predictive biomarkers of poor outcome in mCRC treated with cetuximab [119]. The anti-EGFR mAb therapy significantly improves both PFS and OS tumors without mutations in *RAS*. Therefore, mutations in *KRAS* predict resistance to mAb directed to *EGFR* with cetuximab and panitumumab [106]. *NRAS* codifies an isoform of RAS protein, involved primarily in the regulation of cell division [114]. Mutations in exon 2, 3, and 4 of *NRAS*, in addition to those in exon 2 of *KRAS*, must be detected before administration of a monoclonal anti-EGFR [106]. According to the NCCN, *KRAS* and *NRAS* are the only one predictive biomarkers approved in mCRC. Cetuximab and panitumumab are applied on patients with nonmutated *RAS* whereas bevacizumab is applied on patients with mutated *RAS* [11].

Regarding Fc receptor range, modulating the immune response could be a further important mechanism to cetuximab sensitivity. The immune mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC) through Fc receptors (Fc gamma R) made by immune cells, plays a main role in the effect of IgG1 antitumor antibodies [120, 121]. The most common polymorphisms in *FCGR2A* and *FCGR3A* are rs1801274 and rs396991, respectively [122, 123].

Table 7 Allele frequencies for clinically relevant germline polymorphisms *CES1* rs2244613, *ABCB1* rs1045642, *ABCC1* rs2074087, *ABCG2* rs262604, *SCL19A1* rs1051266 and *SLCO1B1* rs2306283 in populations worldwide

Gene	Polymorphism	Human populations		
		Latin American	Caucasian	Asian
CES1	rs2244613 (C1168-33A)	Colombia: 0.80 (T)[a]; Mexico: 0.70 (T); Peru: 0.64 (T); Puerto Rico: 0.75 (T)	Spain: 0.80 (T); British: 0.84 (T); Finland: 0.84 (T); Italy: 0.87 (T)	Han Chinese: 0.38 (T); Bangladesh: 0.60 (T); Japan: 0.37 (T); Vietnam: 0.43 (T)
ABCB1	rs1045642 (C3435T)	Colombia: 0.56 (G); Mexico: 0.52 (G); Peru: 0.62 (G); Puerto Rico: 0.57 (G)	Spain: 0.54 (G); British: 0.47 (G); Finland: 0.42 (G); Italy: 0.53 (G)	Han Chinese: 0.62 (G); Bangladesh: 0.39 (G); Japan: 0.52 (G) Vietnam: 0.60 (G)
ABCC1	rs2074087 (C2461-30G)	Colombia: 0.79 (G); Mexico: 0.77 (G); Peru: 0.77 (G); Puerto Rico: 0.78 (G)	Spain: 0.85 (G); British: 0.88 (G); Finland: 0.84 (G); Italy: 0.79 (G)	Han Chinese: 0.78 (G); Bangladesh: 0.57 (G); Japan: 0.78 (G); Vietnam: 0.88 (G)
ABCC2	rs3740066 (T3972C)	Colombia: 0.36 (T); Mexico: 0.42 (T); Peru: 0.24 (T); Puerto Rico: 0.36 (T)	Spain: 0.39 (T); British: 0.38 (T); Finland: 0.37 (T); Italy: 0.37 (T)	Han Chinese: 0.25 (T); Bangladesh: 0.33 (T); Japan: 0.23 (T); Vietnam: 0.27 (T)
ABCG2	rs262604 (−20 + 805A>G)	Colombia: 1.00 (C); Mexico: 1.00 (C); Peru: 1.00 (C); Puerto Rico: 1.00 (C)	Spain: 1.00 (C); British: 1.00 (C); Finland: 1.00 (C); Italy: 1.00 (C)	Han Chinese: 1.00 (C); Bangladesh: 1.00 (C); Japan: 1.00 (C); Vietnam: 1.00 (C)
SLC19A1	rs1051266 (A80G)	Colombia: 0.51 (G); Mexico: 0.65 (G); Peru: 0.63 (G); Puerto Rico: 0.57 (G)	Spain: 0.49 (G); British: 0.60 (G); Finland: 0.55 (G); Italy: 0.55 (G)	Han Chinese: 0.52 (G); Bangladesh: 0.62 (G); Japan: 0.46 (G); Vietnam: 0.46 (G)
SLCO1B1	rs2306283 (A388G)	Colombia: 0.48 (G); Mexico: 0.38 (G); Peru: 0.47 (G); Puerto Rico: 0.53 (G)	Spain: 0.42 (G); British: 0.36 (G); Finland: 0.44 (G); Italy: 0.39 (G)	Han Chinese: 0.78 (G); Bangladesh: 0.56 (G); Japan: 0.66 (G); Vietnam: 0.78 (G)

CES1 carboxylesterase 1, *ABCB1* ATP binding cassette subfamily B member 1, *ABCC1* ATP binding cassette subfamily C member 1, *ABCC2* ATP binding cassette subfamily C member 2, *ABCG2* ATP binding cassette subfamily G member 2, *SLC19A1* solute carrier family 19 member 1,*SLCO1B1* solute carrier organic anion transporter family member 1B1, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

[a]Frequency of minor allele

It is known that cetuximab is a standard-of-care treatment for *RAS* wild-type mCRC but not for those harboring *KRAS* mutations since MAPK pathway is constitutively activated. Nevertheless, cetuximab also exerts its effect by its immunomodulatory activity despite the presence of *RAS* mutations [124]. According to Borrero-Palacios *et al*., cetuximab has the potential therapeutic in *KRAS* mutated mCRC carrying nonfunctional receptor *KIR2DS4* and *FCGR2A* H131R polymorphism since these patients significantly prolonged their OS. Moreover, these results explain the variable efficacy of cetuximab in mCRC patients with *KRAS* mutations and confirm the role of ADCC-mediated toxicity to tumor cells by cetuximab [124].

The phosphatidylinositol 3-kinase (PI3K/AKT) pathway is involved in cancer pathogenesis, being imperative the design of therapeutic inhibitors [125]. *PIK3CA* gene encodes the p110 catalytic subunit of PI3K alpha. *PIK3CA* mutations (associated with *KRAS* mutation and MSI) stimulate AKT pathway and promote cell growth in CRC [125]. *PIK3CA* mutations in exon 9 and 20 affects the helical and kinase domains of the protein, promoting a lack of effectiveness in drug treatments [112].

BRAF protein is part of the RAS/MAPK signaling pathway, which regulates cell growth, proliferation, migration, and apoptosis [126]. *BRAF* is a driver gene whose mutations are inversely associated with treatment response and are mutually exclusive with *RAS* mutations

Table 8 Biomarkers focused on antiangiogenics and bevacizumab drug

Gene	Polymorphism	Clinical relevance	Function	Type of inheritance	Reference
VEGFR1	rs9582036 (C-834A)	OS	Receptor	Germinal	[100]
VEGFR2	rs12505758 (2266 + 1166A>G)	PFS	Receptor	Germinal	[98, 100]
VEGFA	rs3025039 (C*237T)	PFS	Growth factor	Germinal	[100]
	rs13207351 (G-152A)	PFS		Germinal	
ANXA11	rs1049550 (C688T)	ORR	Calcium-dependent phospholipid-binding proteins	Germinal	[101]
CXCR1	rs2234671 (G827C)	Response	Receptor	Germinal	[99]
CXCR2	rs2230054 (C786T)	ORR	Receptor	Germinal	[99]

ANXA11 annexin A11, *CXCR1* C-X-C motif chemokine receptor 1, *CXCR2* C-X-C motif chemokine receptor 2, *VEGFA*, vascular endothelial growth factor A, *VEGFR1* vascular endothelial growth factor receptor 1, *VEGFR2* vascular endothelial growth factor receptor 2, *G* guanine, *A* adenine, *C* cytosine, *T* thymine, *OS* overall survival, *PFS* patient-free survival, *ORR* overall response rates

Table 9 Allele frequencies for clinically relevant germline polymorphisms *VEGFR1* rs9582036, *VEGFR2* rs12505758, *VEGFA* rs3025039, *ANXA11* rs1049550 and *CXCR2* rs2230054 in populations worldwide

Gene	Polymorphism	Human populations		
		Latin American	Caucasian	Asian
VEGFR1	rs9582036 (C-834A)	Colombia: 0.73 (A) [a]; Mexico: 0.84 (A); Peru: 0.94 (A); Puerto Rico: 0.64 (A)	Spain: 0.69 (A); British: 0.70 (A); Finland: 0.78 (A); Italy: 0.75 (A)	Han Chinese: 0.83 (A); Bangladesh: 0.84 (A); Japan: 0.85 (A); Vietnam: 0.79 (A)
VEGFR2	rs12505758 (2266 + 1166A>G)	Colombia: 0.13 (C); Mexico: 0.17 (C); Peru: 0.31 (C); Puerto Rico: 0.09 (C)	Spain: 0.12 (C); British: 0.07 (C); Finland: 0.10 (C); Italy: 0.12 (C)	Han Chinese: 0.19 (C); Bangladesh: 0.34 (C); Japan: 0.27 (C); Vietnam: 0.15 (C)
VEGFA	rs3025039 (C*237T)	Colombia: 0.13 (T); Mexico: 0.30 (T); Peru: 0.34 (T); Puerto Rico: 0.18 (T)	Spain: 0.13 (T); British: 0.07 (T); Finland: 0.14 (T); Italy: 0.12 (T)	Han Chinese: 0.18 (T); Bangladesh: 0.12 (T); Japan: 0.16 (T); Vietnam: 0.16 (T)
ANXA11	rs1049550 (C688T)	Colombia: 0.45 (A); Mexico: 0.39 (A); Peru: 0.64 (A); Puerto Rico: 0.38 (A)	Spain: 0.47 (A); British: 0.44 (A); Finland: 0.54 (A); Italy: 0.41 (A)	Han Chinese: 0.63 (A); Bangladesh: 0.35 (A); Japan: 0.65 (A); Vietnam: 0.59 (A)
CXCR2	rs2230054 (C786T)	Colombia: 0.45 (T); Mexico: 0.45 (T); Peru: 0.57 (T); Puerto Rico: 0.54 (T)	Spain: 0.51 (T); British: 0.47 (T); Finland: 0.42 (T); Italy: 0.50 (T)	Han Chinese: 0.36 (T); Bangladesh: 0.49 (T); Japan: 0.28 (T); Vietnam: 0.39 (T)

ANXA11 annexin A11; *CXCR2*, C-X-C motif chemokine receptor 2, *VEGFA* vascular endothelial growth factor A, *VEGFR1* vascular endothelial growth factor receptor 1, *VEGFR2* vascular endothelial growth factor receptor 2, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

[a]Frequency of minor allele

[114, 127]. Hence, *BRAF* V600E mutation correlates with worse prognosis [128]. Vemurafenib is a third-line therapeutic option in advanced mCRC with *BRAF* mutations [129]. Furthermore, it has been proposed that patients with *KRAS* and *BRAF* mutations could be eligible for mAb treatment against *EGFR*. Finally, *BRAF* must not present any mutation for a favorable treatment response when panitumumab or cetuximab are applied [113].

COX is the limiting enzyme in the conversion of arachidonic acid into prostaglandins. COX2, encoded by prostaglandin endoperoxide synthase 2 (*PTGS2*), is involved in metastasis and chemotherapy resistance [130].

Table 10 Biomarkers focused on gefitinib, erlotinib, imatinib, vemurafenib, cetuximab, and panitumumab drugs

Gene	Polymorphism	Clinical relevance	Function	Type of inheritance	Reference
EGFR	rs2227983 (G1562A);	Better prognosis	Receptor	Somatic	[108–110]
	rs712830 (C-191A);	Toxicity		Germinal	
	rs1050171 (G2226A);	PFS		Somatic	
	CA-repeat in intron 1	PFS		Germinal	
	rs1057519860 (S492R, A1474C)	Response		Somatic	
	S464L	Treatment resistance		Somatic	
		Treatment resistance		Somatic	
	G465R	Treatment resistance		Somatic	
	I491M			Somatic	
	rs377567759 (R451C, C1351T)	Treatment resistance		Somatic	
	K467T	Treatment resistance			
EGF	rs4444903 (G61A)	Response	Growth factor	Germinal	[111]
FCGR2A	rs1801274 (A535G)	Survival	Receptor	Germinal	[69]
FCGR3A	rs396991 (A818C)	Survival	Receptor	Germinal	[108]
PIK3CA	Exon 9 and 20 (Mutations) consider alternative therapy for cetuximab and panitumumab	Treatment resistance	Oncogene	Somatic	[112]
BRAF	V600E: if the mutation is present considering alternative therapy for cetuximab and panitumumab	Treatment resistance	Protein kinase	Somatic	[113, 114]
KRAS	Exon 2 (codons 12 and 13) and exon 4 (codon 61). If the mutation is present, not use cetuximab or panitumumab	Treatment resistance	Protooncogene	Somatic	[106, 107]
NRAS	Exon 2 (codons 12 and 13), exon 3 (59 and 61), and exon 4 (117 and 146)	Treatment resistance	Protooncogene	Somatic	[106, 107]
COX2	rs20417 (G765C)	PFS	Enzyme	Germinal	[70]

EGF epidermal growth factor, *EGFR*, epidermal growth factor receptor, *FCGR2A* Fc fragment of IgG receptor IIa, *FCGR3A* Fc fragment of IgG receptor IIIa, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *KRAS* KRAS protooncogene, GTPase, *NRAS* neuroblastoma RAS viral oncogene homolog, *COX2* cytochrome c oxidase subunit II, *PFS* progression-free survival, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

Table 11 Allele frequencies for clinically relevant genetic variants *EGFR* rs2227983, *EGF* rs4444903, *FGGR2A* rs1801274, *FCGR3A* rs396991 and *COX2* rs20417 in populations worldwide

Gene	Polymorphism	Human populations		
		Latin American	Caucasian	Asian
EGFR	rs2227983 (G1562A)	Colombia: 0.35 (A)[a]; Mexico: 0.31 (A); Peru: 0.36 (A); Puerto Rico: 0.30 (A)	Spain: 0.25 (A); British: 0.24 (A); Finland: 0.38 (A); Italy: 0.25 (A)	Han Chinese: 0.46 (A); Bangladesh: 0.34 (A); Japan: 0.62 (A); Vietnam: 0.53 (A)
EGF	rs4444903 (G61A)	Colombia: 0.51 (G); Mexico: 0.62 (G); Peru: 0.70 (G); Puerto Rico: 0.52 (G)	Spain: 0.39 (G); British: 0.41 (G); Finland: 0.37 (G); Italy: 0.38 (G)	Han Chinese: 0.70 (G); Bangladesh: 0.64 (G); Japan: 0.71 (G); Vietnam: 0.70 (G)
FCGR2A	rs1801274 (A535G)	Colombia: 0.39 (G); Mexico: 0.51 (G); Peru: 0.47 (G); Puerto Rico: 0.45 (G)	Spain: 0.53 (G); British: 0.61 (G); Finland: 0.54 (G); Italy: 0.41 (G)	Han Chinese: 0.34 (G); Bangladesh: 0.36 (G); Japan: 0.19 (G); Vietnam: 0.28 (G)
FCGR3A	rs396991 (A818C)	Colombia: 0.00 (C); Mexico: 0.00 (C); Peru: 0.00 (C); Puerto Rico: 0.00 (C)	Spain: 0.00 (C); British: 0.00 (C); Finland: 0.00 (C); Italy: 0.00 (C)	Han Chinese: 0.00 (C); Bangladesh: 0.00 (C); Japan: 0.00 (C); Vietnam: 0.01 (C)
COX2	rs20417 (G-765C)	Colombia: 0.22 (G); Mexico: 0.21 (G); Peru: 0.21 (G); Puerto Rico: 0.21 (G)	Spain: 0.15 (G); British: 0.14 (G); Finland: 0.11 (G); Italy: 0.19 (G)	Han Chinese: 0.05 (G); Bangladesh: 0.17 (G); Japan: 0.04 (G); Vietnam: 0.02 (G)

EGF epidermal growth factor, *EGFR* epidermal growth factor receptor, *FCGR2A* Fc fragment of IgG receptor IIa, *FCGR3A* Fc fragment of IgG receptor IIIa, *COX2* cytochrome c oxidase subunit II, *G* guanine, *A* adenine, *C* cytosine, *T* thymine

[a]Frequency of minor allele

High levels of COX2 are linked with shorter OS in CRC. The C allele of *COX2* G765C polymorphism has been associated with a significantly lower promoter activity [110, 131].

The allele frequencies of rs2227983, rs4444903, rs1801274, rs396991, and rs20417 genetic variants in populations worldwide are shown in Table 11 [64].

CRC immunogenomics

Recent advances in cancer immunology have highlighted the immunogenic nature of CRC and provided insights regarding the complex tumor-immune system interactions that drive immune evasion in CRC [132–134]. One of the mechanisms that mediates tumor-associated immune escape is the activation of inhibitory co-receptors or immune checkpoints on the T lymphocyte surface by tumor cells through the expression of immunosuppressive molecules [132, 133, 135].

Programmed cell death protein 1 (PD-1, CD279) is an inhibitory co-receptor expressed by exhausted tumor-infiltrating lymphocytes (TILs) present within the tumor microenvironment [135–137]. PD-1 engages with programmed-death ligands 1 (PD-L1, BT-H1, CD274) and 2 (PD-L2, B7-DC, CD273) which are expressed by CRC cells [138–141]. PD-1/PD-L1 interaction inhibits $CD8^+$ T-cell activation, cytokine production, proliferation, and cytotoxicity which suppresses the host immune response and allows CRC cells to proliferate and metastasize [135–137].

Immune checkpoint inhibition has revolutionized cancer immunotherapy since it has proven to be very successful for treatment of melanoma and nonsmall cell lung cancer [143–144]. It has been shown that PD-1 blockade is a highly efficient therapeutic strategy against MSI-high and MMRd CRC tumors since these tumors display dense lymphocyte infiltrates due to their increased expression of immunogenic neo-antigens [145–147]. Moreover, these tumors exhibit higher PD-1 expression on TILs and PD-L1 expression than microsatellite stable tumors [147, 148]. Subsequently, the FDA approved pembrolizumab and nivolumab, two anti PD-1 antibodies, for treatment of metastatic MSI-high or MMRd solid tumors.

According to Tauriello et al., inhibition of the PD-1 and PD-L1 immune checkpoints provoked a limited response in quadruple-mutant mice [149]. By contrast, his results strongly suggest that inhibition of TGFβ signaling could be promising as immunotherapy for patients with microsatellite stability and stroma-rich CRCs, enduring cytotoxic T-cell response against tumor cells that prevent metastasis [149–151]. The clinical implications of CRC immunogenomics continue to expand, and it will likely serve as a guide for next-generation immunotherapy strategies for improving outcomes for this disease (Fig. 2).

Table 12 Pathogenic germline variants in CRC according to the pan-cancer atlas and allele frequencies according to the exome aggregation consortium

Gene	Polymorphism	Alleles	Consequence	Variation type	Overall classification	Frequency[a]
APC	rs752519066 (L69*)	T>A	Stop gained	SNV	Likely pathogenic	*A* = 0.00001
ATM	rs587782652 (V2716A)	T>C	Missense	SNV	Pathogenic	*C* = 0.00004
ATR	rs777982083 (E409*)	C>T	Missense	SNV	Likely pathogenic	*T* = 0.00002
	rs755272769 (C142553741T)	C>T	Splice acceptor	SNV	Likely pathogenic	*T* = 0.00001
	rs781260235 (L2093X)	delAG	Frameshift	Deletion	Likely pathogenic	delAG = 0.00001
BARD1	rs587780021 (Q564*)	G>A	Stop gained	SNV	Pathogenic	*A* = 0.00005
BLM	rs200389141 (Q548*)	C>T	Stop gained	SNV	Pathogenic	*T* = 0.00018
BRCA1	rs80357669 (S819X)	delG	Frameshift	Deletion	Pathogenic	delG = 0.00002
BRCA2	rs80359550 (S1982X)	delT	Frameshift	Deletion	Pathogenic	delT = 0.00027
	rs80359013 (W2626C)	G>A, G>C	Missense	SNV	Pathogenic	*C* = 0.00002
BRIP1	rs137852986 (R798*)	G>A	Stop gained	SNV	Pathogenic	*A* = 0.00015
CHEK2	rs137853011 (S571F)	G>A	Missense	SNV	Pathogenic	*A* = 0.00031
COL7A1	rs753819164 (R226*)	G>A	Stop gained	SNV	Likely pathogenic	*A* = 0.00001
FANCI	rs121918164 (R1285*)	C>T	Stop gained	SNV	Pathogenic	*T* = 0.00005
GJB2	rs766975999 (S222*)	G>T	Stop gained	SNV	Likely pathogenic	*T* = 0.00002
MLH1	rs63751615 (R226*)	C>T	Stop gained	SNV	Pathogenic	*T* = 0.00001
	rs780956158 (I691IX)	dupT	Frameshift	Insertion	Likely pathogenic	dupT = 0.00001
MSH2	rs63749932 (R680*)	C>G, C>T	Stop gained	SNV	Pathogenic	*G* = 0.0000
	rs760228651 (L407LX)	dupC	Frameshift	Insertion	Likely pathogenic	dupC = 0.00001
MSH6	rs587781691 (R248X)	delC	Frameshift	Deletion	Pathogenic	delC = 0.00001
	rs771764652 (SK536–537X)	delAGTA	Frameshift	Deletion	Likely pathogenic	delAGTA = 0.00001
PALB2	rs515726124 (R170X)	–	Frameshift	Deletion	Pathogenic	–
	rs756660214 (L253LX)	–	Frameshift	Insertion	Pathogenic	–
POT1	rs750470470 (−357 to358X)	dupA	Frameshift	Insertion	Likely pathogenic	dupA = 0.00006
RAD51D	rs775045445 (W36*)	C>T	Stop gained	SNV	Likely pathogenic	*T* = 0.00006
RECQL4	rs386833845 (C525X)	delA	Frameshift	Insertion	Pathogenic	delA = 0.00026
RET	rs78347871 (R912P)	G>A, G>C, G>T	Missense	SNV	Pathogenic	*T* = 0.0000
RHBDF2	rs777871789 (W574*)	C>T	Stop gained	SNV	Likely pathogenic	*T* = 0.00001
SDHA	rs766667009 (G251104T)	G>T	Splice donor	SNV	Pathogenic	*T* = 0.00001

SNV single nucleotide variant, * stop gained, *dup* duplication, *del* deletion, *APC* APC WNT signaling pathway regulator, *ATM* ATM serine/threonine kinase, *ATR* ATR serine/threonine kinase, *BARD1* BRCA1 associated RING domain 1, *BLM* bloom syndrome RecQ like helicase, *BRCA1* BRCA1 DNA repair associated, *BRCA2*, BRCA2 DNA repair associated, *BRIP1* BRCA1 interacting protein C-terminal helicase 1, *CHEK2* checkpoint kinase 2, *COL7A1* collagen type VII alpha 1 chain, *FANCI* Fanconi anemia complementation group I, *GJB2* gap junction protein beta 2, *MLH1* mutL homolog 1, *MSH2* mutS homolog 2, *MSH6* mutS homolog 6, *PALB2* partner and localizer of BRCA2, *POT1* protection of telomeres 1, *RAD51D* RAD51 paralog D, *RECQL4* RecQ like helicase 4, *RET* ret proto-oncogene, *RHBDF2* rhomboid 5 homolog 2, *SDHA* succinate dehydrogenase complex flavoprotein subunit A

[a]Frequency of minor allele

The Pan-Cancer Atlas: germline pathogenic variants

The Pan-Cancer Atlas provides a panoramic view of the oncogenic processes that contribute to human cancer. It reveals how genetic variants collaborate in cancer progression and explores the influence of mutations on cell signaling and immune cell composition, providing insight to prioritize the development of new immunotherapies [152].

According to Huang et al., the Pan-Cancer Atlas analyzed 564 CRC samples and found several pathogenic germline variants in the *APC*, *ATM*, *ATR*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *COL7A1*, *FANCI*, *GJB2*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *POT1*, *RAD51D*, *RECQL4*, *RET*, *RHBDF2*, and *SDHA* genes [153]. In addition, Table 12 shows the allele frequencies of those 29 pathogenic germline variants according to The Exome Aggregation Consortium (ExAC) [154].

Clinical trials for metastatic CRC

Figure 3 shows the current status of clinical trials for mCRC according to the Open Targets Platform [155]. There are 79

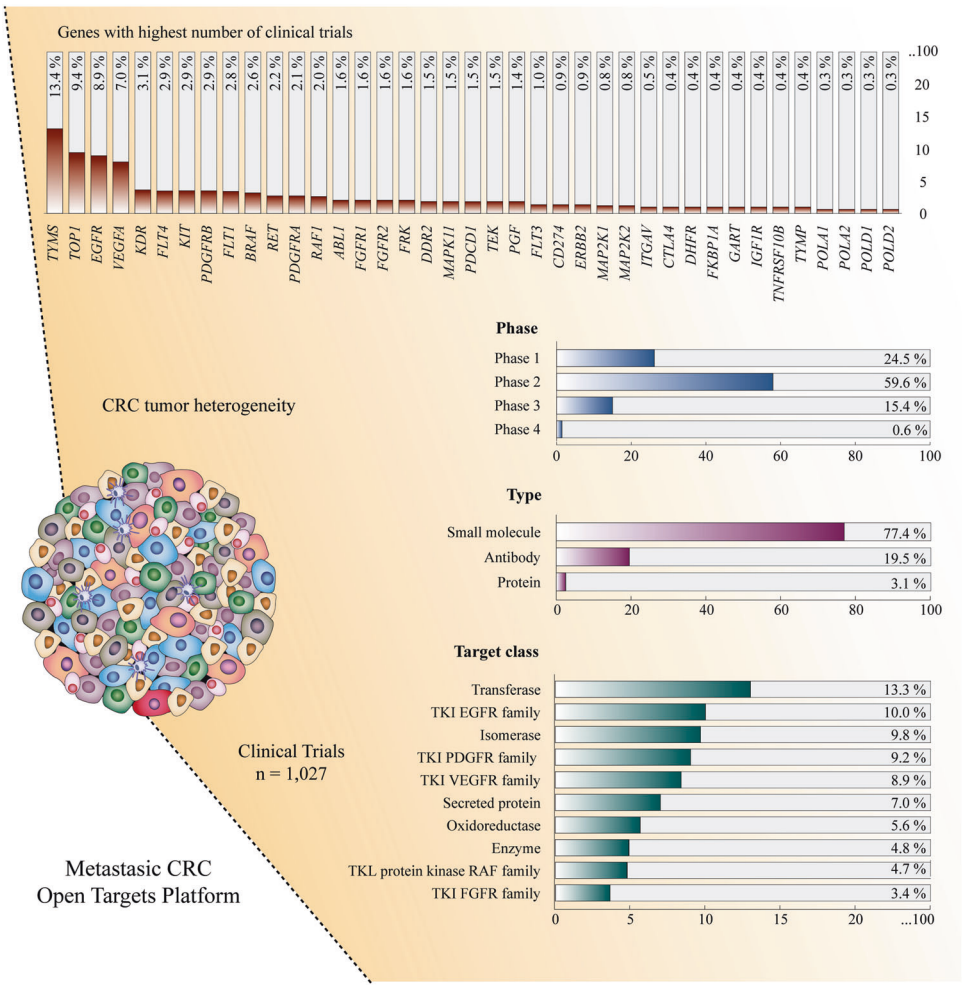

Fig. 3 Clinical trials for metastasic colorectal cancer. **a** genes with highest number of clinical trials, **b** phases, **c** type, and **d** target class. TKI tyrosine protein kinase inhibitors

drugs that are being analyzed in 1027 clinical trials in 160 genes. The top 10 genes with the highest number of clinical trials in process or completed were *TYMS*, *TOP1*, *EGFR1*, *VEGFA*, *KDR*, *FLT4*, *KIT*, *PDGFRB*, *FLT1*, and *BRAF*. The greatest number of clinical trials was in phase 2 (60%). Small molecules were the most analyzed type of drug (77%), followed by antibodies (20%) and proteins (3%). Lastly, the target classes with the greatest number of clinical trials were transferases (13%), followed by TKIs of EGFR family (10%) and isomerases (10%). However, all TKIs made up the 41% of target classes [155] (Supplementary Table 2).

Biomarker network in CRC

Figure 4 shows the proposed biomarker network in CRC. The protein–protein interaction (PPi) network with a highest confidence cutoff of 0.9 was created using String Database [156]. This network is made up of known and predicted interactions of driver genes [157], nodes with pathogenic germline and somatic mutations according to the Pan-Cancer Atlas [39, 153] and the CGI [41], respectively, and druggable enzymes according to the Pharmacogenomics Knowledge Base (PharmGKB) [158, 159].

The enrichment analysis of gene ontology terms related to biological processes and metabolic pathways were carried in the 87 genes of CRC biomarker network (Fig. 4). The top biological processes with significant false discovery rate (FDR) < 0.01 were DNA synthesis involved in DNA repair, strand displacement and response to drug. Meanwhile, the top metabolic pathways with FDR < 0.01 were colorectal, endometrial, and pancreatic cancer types [160].

Pharmacogenomics in clinical practice

In addition to the NCCN and ESMO guidelines [42–44], the Canadian Pharmacogenomics Network for Drug Safety, the Royal Dutch Association for the Advancement of Pharmacy, and the Clinical Pharmacogenetics Implementation Consortium have published precise guidelines for the application of pharmacogenomics in clinical practice [161–163]. All this information is published in the PharmGKB, which is a comprehensive resource that curates knowledge

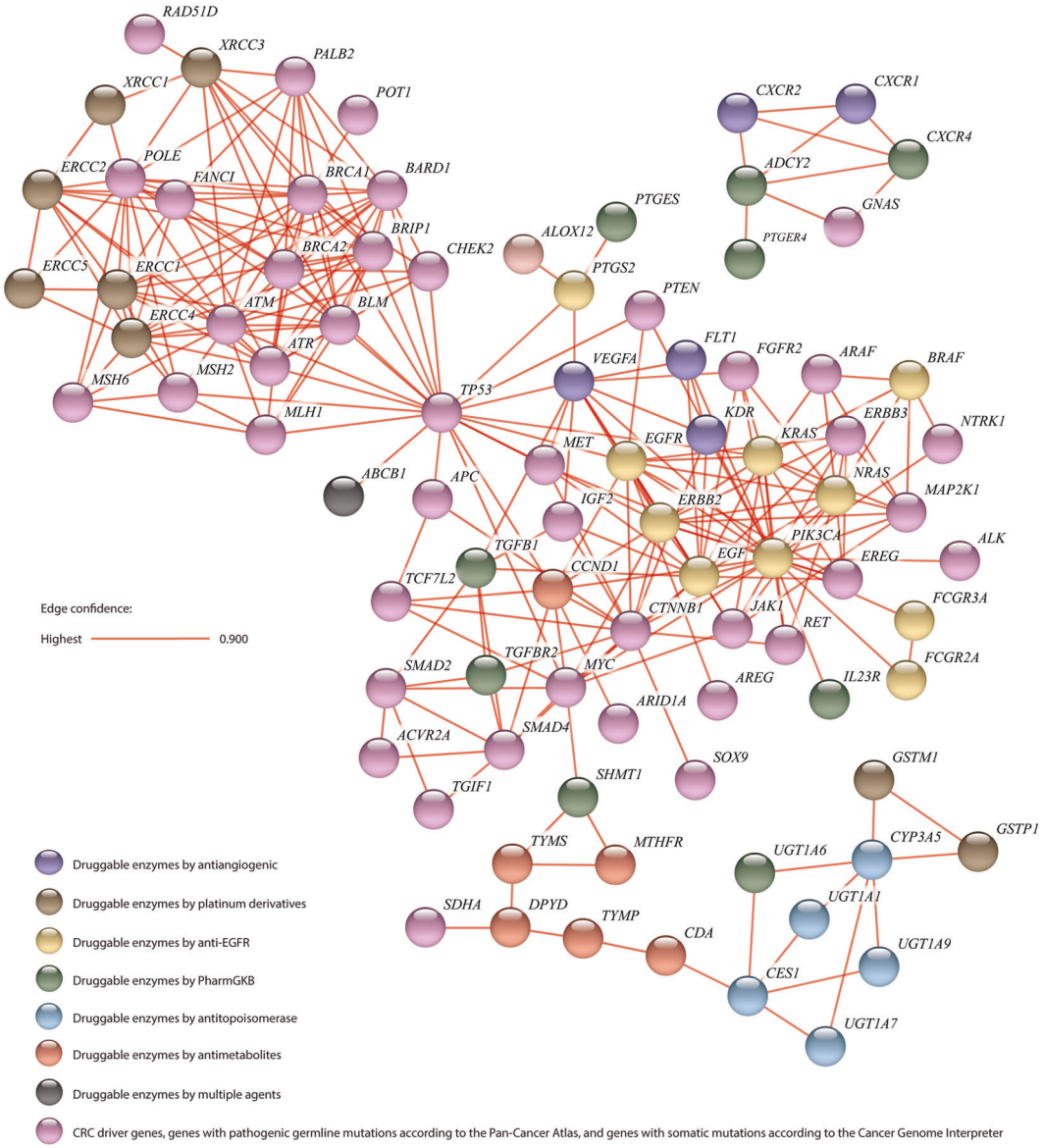

Fig. 4 Biomarker network in CRC made up of driver genes, genes with pathogenic germline mutations, genes with somatic mutations, and druggable enzymes by antitopoisomerase, antimetabolite, platinum derivative, and antiangiogenic drugs. The PPi network with a highest confidence cutoff of 0.9 was created using String Database

about the impact of 80 clinical annotations on drug response [158] (Supplementary Table 3).

Additionally to the 1000 Genomes Project (Phase 3) [64], we included 33 studies that have published the allele frequencies of mutations in several druggable enzymes in 34 different ethnic populations from Latin America (Supplementary Tables 4–11). Human populations from this geographic region have multi-hybrid genetic composition, being relevant its inclusion in cancer pharmacogenomics [164, 165]. Figure 5 is an innovative way to visualize and correlate the minor allele frequencies of 43 genes related to the different categories of drugs applied in CRC treatments in 8674 samples from 9 Latin American countries ($p < 0.001$). This information will make it easier for public health decision-makers to take decisions regarding CRC treatments. The inclusion of political support can guide the clinical practice in order to decrease the gap of inequalities among the populations that cannot access to private services, especially cancer treatments, which are extremely expensive. For instance, the minor allele (G) of GSTP1 rs1695 can alter GST activity reducing detoxification capacity and leading to increased efficacy of platinum compounds [49, 50]. Thus, the Latin American countries whom best reduce the detoxification capacity and increase the efficacy of platinum compounds are Venezuela, Mexico and Peru due to their populations have a G allele frequency ≥ 0.50.

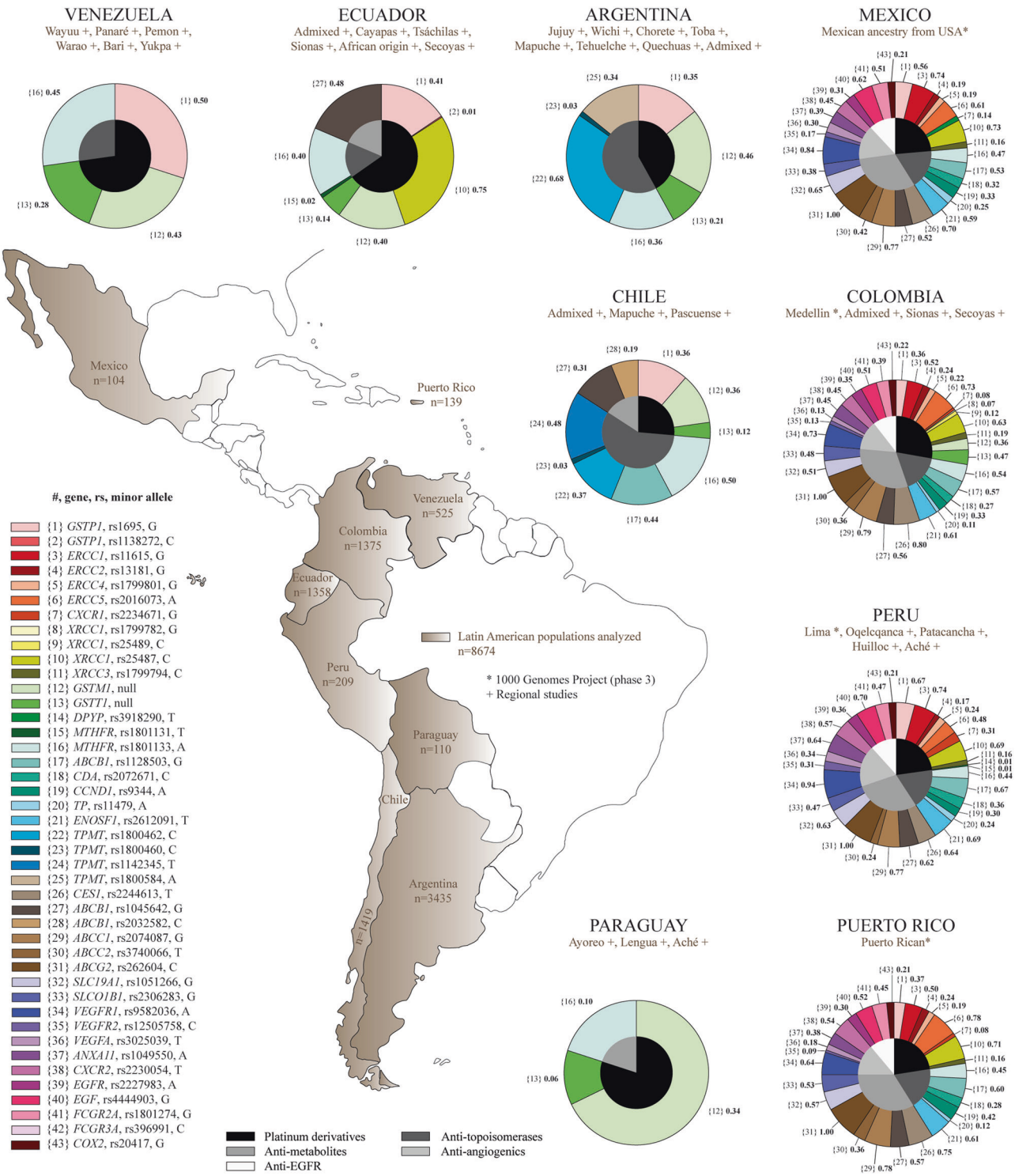

Fig. 5 Minor allele frequencies of druggable enzymes studied in 8674 samples from Latin American populations, and its relation with the category of drugs applied in CRC treatments

On the other hand, it is imperative to unify efforts between private companies and governments to increase investment in pharmacogenomics fomenting precision medicine in CRC treatments. The most relevant barriers to implement pharmacogenomics testing in Latin America are the need for clear guidelines for the use of pharmacogenomics, the insufficient awareness of pharmacogenomics among clinicians, the absence of a regulatory institution that

facilitates the use of pharmacogenomics tests, and the importance of including the public health scenario that ensures the benefits of precision medicine to the most vulnerable people [166]. By overcoming the previously mentioned barriers, pharmacogenomics will make it possible to improve the efficiency on the use of resources, patient safety, and drug dosage in CRC treatments [167].

Conclusion

In the era of precision medicine, multisectorial collaborations are important to unify all current knowledge about CRC biology and treatment. There is the need to link sectors not only for funds but also to create a common goal to benefit all socioeconomic groups. In addition, large-scale projects worldwide have studied the multi-omics landscape of CRC by implementing the CMS classification and generating new therapeutic targets related to different populations worldwide. Developed countries might incorporate racial/ethnic minority populations in future cancer researches and clinical trials, and developing countries might invest in obtaining a database of genomic profiles of their populations with the overall objective of linking pharmacogenomics in clinical practice and public health policies.

Data availability

All data generated or analyzed during this study are included in this published article (and its Supplementary Information).

Acknowledgements Universidad UTE and the Latin American Society of Pharmacogenomics and Personalized Medicine (SOLFAGEM) supported this research.

Funding This work was co-funded by Universidad UTE and Project 219RT0572, Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo (CYTED).

Author contributions ALC and NWS conceived the subject and wrote the paper. ALC, GJK, DPIB, JGC, PEL, IAC and PGR did data curation and supplementary data. ALCa, SG, CPyM, LAQ and JPC made a substantial contribution to the discussion of content. All authors reviewed and/or edited the article before submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Disclaimer The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Puccini A, Lenz H-J. Colorectal cancer in 2017: practice-changing updates in the adjuvant and metastatic setting. Nat Rev Clin Oncol. 2017;15:2–3.
3. Sabarinathan R, Pich O, Martincorena I, Rubio-Perez C, Juul M, Wala J, et al. The whole-genome panorama of cancer drivers. 2017. https://www.biorxiv.org/content/10.1101/190330v1.
4. López-Cortés A, Guerrero S, Redal MA, Alvarado AT, Quiñones LA. State of art of cancer pharmacogenomics in Latin American populations. Int J Mol Sci. 2017;18:pii: E639.
5. Gupta PD. Pharmacogenetics, pharmacogenomics and ayurgenomics for personalized medicine: a paradigm shift. Indian J Pharm Sci. 2015;77:135–41.
6. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018;17:183–196.
7. López-Cortés A, Paz-y-Miño C, Guerrero S, Cabrera-Andrade A, Barigye SJ, Munteanu CR, et al. OncoOmics approaches to reveal essential genes in breast cancer: a panoramic view from pathogenesis to precision medicine. bioRxiv. 2019. https://www.biorxiv.org/content/10.1101/638866v1.
8. Wilke RA, Lin DW, Roden DM, Watkins PB, Flockhart D, Zineh I, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. Nat Rev Drug Discov. 2007;6:904–16.
9. Sadanandam A, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nat Med. 2013;19:619–25.
10. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319:525–32.
11. Strimpakos AS, Syrigos KN, Saif MW. Pharmacogenetics and biomarkers in colorectal cancer. Pharmacogenomics J. 2009;9:147–60.
12. Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol. 2009;27:3117–25.
13. Van Dongen S. Graph clustering via a discrete uncoupling process. SIAM J Matrix Anal Appl. 2008;30:121–41.
14. Enright AJ, Van Dongen S, Ouzounis CA. An efficient algorithm for large-scale detection of protein families. Nucleic Acids Res. 2002;30:1575–84.
15. Marisa L, de Reynies A, Duval A, Selves J, Gaub MP, Vescovo L, et al. Gene Expression classification of CRC into molecular subtypes: characterization, validation, and prognostic value. PLoS Med. 2013;10:e1001453.
16. García-cárdenas JM, Guerrero S, López-cortés A, Armendáriz-castillo I, Guevara-ramírez P, Pérez-villa A, et al. Post-transcriptional regulation of colorectal cancer: a focus on RNA-binding proteins. Front Mol Biosci. 2019;6:1–18.
17. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer. 2017;17:79–92.

18. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, et al. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014;158:929–44.
19. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21:1350–6.
20. Guerrero S, López-Cortés A, Indacochea A, García-Cárdenas JM, Zambrano AK, Cabrera-Andrade A, et al. Analysis of racial/ethnic representation in select basic and applied cancer research studies. Sci Rep. 2018;8:13978.
21. The Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487:330–7.
22. Budinska E, Popovici V, Tejpar S, D'Ario G, Lapique N, Sikora KO, et al. Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer. J Pathol. 2013;231:63–76.
23. Schlicker A, Beran G, Chresta CM, McWalter G, Pritchard A, Weston S, et al. Subtypes of primary colorectal tumors correlate with response to targeted treatment in colorectal cell lines. BMC Med Genom. 2012;5:66.
24. Perez-Villamil B, Romera-Lopez A, Hernandez-Prieto S, Lopez-Campos G, Calles A, Lopez-Asenjo J-A, et al. Colon cancer molecular subtypes identified by expression profiling and associated to stroma, mucinous type and different clinical behavior. BMC Cancer. 2012;12:260.
25. Isella C, Brundu F, Bellomo SE, Galimi F, Zanella E, Porporato R, et al. Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer. Nat Commun. 2017;8:1–16.
26. Rodriguez-Salas N, Dominguez G, Barderas R, Mendiola M, García-Albéniz X, Maurel J, et al. Clinical relevance of colorectal cancer molecular subtypes. Crit Rev Oncol/Hematol. 2017;109:9–19.
27. Calon A, Lonardo E, Berenguer-Llergo A, Espinet E, Hernando-Momblona X, Iglesias M, et al. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer. Nat Genet. 2015;47:320–9.
28. Widder M, Luetzkendorf J, Caysa H, Unverzagt S, Wickenhauser C, Benndorf RA, et al. Multipotent mesenchymal stromal cells promote tumor growth in distinct colorectal cancer cells by a β1-integrin-dependent mechanism. Int J Cancer. 2015;138:964–75.
29. Tamborero D, Gonzalez-Perez A, Perez-llamas C, Deu-Pons J, Kandoth C, Reimand J, et al. Comprehensive identification of mutational cancer driver genes across 12 tumor types. Sci Rep. 2013;3:2650.
30. López-cortés A, Leone PE, Freire-paspuel B, Arcos-villacís N, Guevara-ramírez P, Rosales F, et al. Mutational analysis of oncogenic AKT1 gene associated with breast cancer risk in the high altitude ecuadorian mestizo population. Biomed Res Int. 2018;2018:7463832.
31. López-Cortés A, Cabrera-Andrade A, Oña-Cisneros F, Rosales F, Ortiz M, Tejera E, et al. Breast cancer risk associated with genotype polymorphisms of the aurora kinase a gene (AURKA): a case-control study in a high altitude ecuadorian mestizo population. Pathol Oncol Res. 2017;24:457–65.
32. Paz-Y-Miño C, Robles P, Salazar C, Leone PE, García-Cárdenas JM, Naranjo M, et al. Positive association of the androgen receptor CAG repeat length polymorphism with the risk of prostate cancer. Mol Med Rep. 2016;14:1791–8.
33. López-Cortés A, Jaramillo-Koupermann G, Muñoz MJ, Cabrera A, Echeverría C, Rosales F, et al. Genetic polymorphisms in MTHFR (C677T, A1298C), MTR (A2756G) and MTRR (A66G) genes associated with pathological characteristics of prostate cancer in the ecuadorian population. Am J Med Sci. 2013;346:447–54.
34. Paz-y-Miño C, Muñoz MJ, López-Cortés A, Cabrera A, Palacios A, Castro B, et al. Frequency of polymorphisms pro198leu in GPX-1 gene and ile58thr in MnSOD gene in the altitude Ecuadorian population with bladder cancer. Oncol Res. 2010;18:395–400.
35. Paz-y-Miño C, López-Cortés A, Muñoz MJ, Cabrera A, Castro B, Sánchez ME. Incidence of the L858R and G719S mutations of the epidermal growth factor receptor oncogene in an Ecuadorian population with lung cancer. Cancer Genet Cytogenet. 2010;196:201–3.
36. Reddy EP, Reynolds RK, Santos E, Barbacid M. A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. Nature. 1982;300:149–52.
37. Tabin CJ, Bradley SM, Bargmann CI, Weinberg RA, Papageorge AG, Scolnick EM, et al. Mechanism of activation of a human oncogene. Nature. 1982;300:143–9.
38. Rubio-Perez C, Tamborero D, Schroeder MP, Antolín AA, Deu-Pons J, Perez-Llamas C, et al. In silico prescription of anticancer drugs to cohorts of 28 tumor types reveals targeting opportunities. Cancer Cell. 2015;27:382–96.
39. Bailey MH, Tokheim C, Porta-Pardo E, Sengupta S, Bertrand D, Weerasinghe A, et al. Comprehensive characterization of cancer driver genes and mutations. Cell 2018;173:371–385.e18.
40. Sondka Z, Bamford S, Cole CG, Ward SA, Dunham I, Forbes SA. The COSMIC Cancer Gene Census: describing genetic dysfunction across all human cancers. Nat Rev Cancer. 2018;18:696–705.
41. Tamborero D, Rubio-Perez C, Deu-Pons J, Schroeder MP, Vivancos A, Rovira A, et al. Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations. Genome Med. 2018;10:1–8.
42. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;0:mdw235.
43. Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu R, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer; A JSMO - ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol J Eur Soc Med Oncol. 2017;29:2–70.
44. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) colon cancer. Natl Compr Cancer Netw. 2018;1:1–180.
45. Mehmood RK. Review of Cisplatin and oxaliplatin in current immunogenic and monoclonal antibody treatments. Oncol Rev. 2014;8:256.
46. Thavaneswaran S, Rath E, Tucker K, Joshua AM, Hess D, Pinese M, et al. Therapeutic implications of germline genetic findings in cancer. Nat Rev Clin Oncol. 2019;16:386–96.
47. Friedberg EC. Nucleotide excision repair in eukaryotes. eLS. 2001;36:1–8.
48. McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. Mol Cancer Ther. 2009;8:10–6.
49. Kumamoto K, Ishibashi K, Okada N, Tajima Y, Kuwabara K, Kumagai Y, et al. Polymorphisms of GSTP1, ERCC2 and TS-3'UTR are associated with the clinical outcome of mFOLFOX6 in colorectal cancer patients. Oncol Lett. 2013;6:648–54.
50. Inada M, Sato M, Morita S, Kitagawa K, Kawada K, Mitsuma A, et al. Associations between oxaliplatin-induced peripheral neuropathy and polymorphisms of the ERCC1 and GSTP1 genes. Int J Clin Pharm Ther. 2010;48:729–34.

51. Kap EJ, Richter S, Rudolph A, Jansen L, Ulrich A, Hoffmeister M, et al. Genetic variants in the glutathione S-transferase genes and survival in colorectal cancer patients after chemotherapy and differences according to treatment with oxaliplatin. Pharmacogenet Genom. 2014;24:340–7.
52. McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. J Clin Oncol. 2010;28:3227–33.
53. Takenaka T, Yano T, Kiyohara C, Miura N, Kouso H, Ohba T, et al. Effects of excision repair cross-complementation group 1 (ERCC1) single nucleotide polymorphisms on the prognosis of non-small cell lung cancer patients. Lung Cancer. 2010;67:101–7.
54. Ma S-C, Zhao Y, Zhang T, Ling X-L, Zhao D. Association between the ERCC1 rs11615 polymorphism and clinical outcomes of oxaliplatin-based chemotherapies in gastrointestinal cancer: a meta-analysis. Onco Targets Ther. 2015;8:641–8.
55. Yin M, Yan J, Martinez-Balibrea E, Graziano F, Lenz H-J, Kim H-J, et al. ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: a systemic review and meta-analysis. Clin Cancer Res. 2011;17(Mar):1632–40.
56. Chen J, Xie F, Chen K, Wang D, Jiang H, Li J, et al. ERCC5 promoter polymorphisms at -763 and +25 predict the response to oxaliplatin-based chemotherapy in patients with advanced colorectal cancer. Cancer Biol Ther. 2009;8:1424–30.
57. Zaanan A, Dalban C, Emile J-F, Blons H, Fléjou J-F, Goumard C, et al. ERCC1, XRCC1 and GSTP1 single nucleotide polymorphisms and survival of patients with colon cancer receiving oxaliplatin-based adjuvant chemotherapy. J Cancer. 2014;5:425–32.
58. Di Francia R, Siesto RS, Valente D, Del Buono A, Pugliese S, Cecere S, et al. Current strategies to minimize toxicity of oxaliplatin: selection of pharmacogenomic panel tests. Anti-Cancer Drugs. 2013;24:1069–78.
59. Ruzzo A, Graziano F, Galli F, Giacomini E, Floriani I, Galli F, et al. Genetic markers for toxicity of adjuvant oxaliplatin and fluoropyrimidines in the phase III TOSCA trial in high-risk colon cancer patients. Sci Rep. 2014;4:6828.
60. Sullivan I, Salazar J, Majem M, Pallarés C, Del Río E, Páez D, et al. Pharmacogenetics of the DNA repair pathways in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. Cancer Lett. 2014;353:160–6.
61. Artac M, Bozcuk H, Pehlivan S, Akcan S, Pehlivan M, Sever T, et al. The value of XPD and XRCC1 genotype polymorphisms to predict clinical outcome in metastatic colorectal carcinoma patients with irinotecan-based regimens. J Cancer Res Clin Oncol. 2010;136:803–9.
62. Cecchin E, D'Andrea M, Lonardi S, Zanusso C, Pella N, Errante D, et al. A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. Pharmacogenom J 2013;13:403–9.
63. Huang T, Shu Y, Cai Y-D. Genetic differences among ethnic groups. BMC Genomics 2015;16:1093.
64. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, et al. A global reference for human genetic variation. Nature. 2015;526:68–74.
65. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005;27:23–44.
66. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3:330–8.
67. Loganayagam A, Arenas Hernandez M, Corrigan A, Fairbanks L, Lewis CM, Harper P, et al. Pharmacogenetic variants in the DPYD, TYMS, CDA and MTHFR genes are clinically significant predictors of fluoropyrimidine toxicity. Br J Cancer. 2013;108:2505–15.
68. Toffoli G, Giodini L, Buonadonna A, Berretta M, De Paoli A, Scalone S, et al. Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. Int J Cancer. 2015;137:2971–80.
69. Galván CA, Elbarcha OC, Fernández EJ, Beltramo DM, Soria NW. Genetic profiling of GSTP1, DPYD, FCGR2A, FCGR3A and CCND1 genes in an Argentinian population. Clin Biochem. 2011;44:1058–61.
70. Koumarianou A, Tzeveleki I, Mekras D, Eleftheraki AG, Bobos M, Wirtz R, et al. Prognostic markers in early-stage colorectal cancer: significance of TYMS mRNA expression. Anticancer Res. 2014;34:4949–62.
71. Rosmarin D, Palles C, Pagnamenta A, Kaur K, Pita G, Martin M, et al. A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. Gut. 2015;64:111–20.
72. López-Cortés A, Echeverría C, Oña-Cisneros F, Sánchez ME, Herrera C, Cabrera-Andrade A, et al. Breast cancer risk associated with gene expression and genotype polymorphisms of the folate-metabolizing MTHFR gene: a case-control study in a high altitude Ecuadorian mestizo population. Tumour Biol. 2015;36:6451–61.
73. Funke S, Brenner H, Chang-Claude J. Pharmacogenetics in colorectal cancer: a systematic review. Pharmacogenomics. 2008;9:1079–99.
74. García-González X, Cortejoso L, García MI, García-Alfonso P, Robles L, Grávalos C, et al. Variants in CDA and ABCB1 are predictors of capecitabine-related adverse reactions in colorectal cancer. Oncotarget. 2015;6:6422–30.
75. Gonzalez-Haba E, García MI, Cortejoso L, López-Lillo C, Barrueco N, García-Alfonso P, et al. ABCB1 gene polymorphisms are associated with adverse reactions in fluoropyrimidine-treated colorectal cancer patients. Pharmacogenomics. 2010;11:1715–23.
76. Huang L, Chen F, Chen Y, Yang X, Xu S, Ge S, et al. Thymidine phosphorylase gene variant, platelet counts and survival in gastrointestinal cancer patients treated by fluoropyrimidines. Sci Rep. 2014;4:5697.
77. Jennings BA, Kwok CS, Willis G, Matthews V, Wawruch P, Loke YK. Functional polymorphisms of folate metabolism and response to chemotherapy for colorectal cancer, a systematic review and meta-analysis. Pharmacogenet Genom. 2012;22:290–304.
78. Teh LK, Hamzah S, Hashim H, Bannur Z, Zakaria ZA, Hasbullani Z, et al. Potential of dihydropyrimidine dehydrogenase genotypes in personalizing 5-fluorouracil therapy among colorectal cancer patients. Ther Drug Monit. 2013;35:624–30.
79. Afzal S, Jensen SA, Vainer B, Vogel U, Matsen JP, Sørensen JB, et al. MTHFR polymorphisms and 5-FU-based adjuvant chemotherapy in colorectal cancer. Ann Oncol. 2009;20:1660–6.
80. Absenger G, Benhaim L, Szkandera J, Zhang W, Yang D, Labonte MJ, et al. The cyclin D1 (CCND1) rs9344 G>A polymorphism predicts clinical outcome in colon cancer patients treated with adjuvant 5-FU-based chemotherapy. Pharmacogenom J. 2014;14:130–4.
81. Armand JP, Ducreux M, Mahjoubi M, Abigerges D, Bugat R, Chabot G, et al. CPT-11 (irinotecan) in the treatment of colorectal cancer. Eur J Cancer. 1995;31A:1283–7.
82. Ando Y, Hasegawa Y. Clinical pharmacogenetics of irinotecan (CPT-11). Drug Metab Rev. 2005;37:565–74.

83. Innocenti F, Kroetz DL, Schuetz E, Dolan ME, Ramírez J, Relling M, et al. Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. J Clin Oncol. 2009;27:2604–14.
84. Liu X, Xu W. UGT1A1*28 polymorphisms: a potential pharmacological biomarker of irinotecan-based chemotherapies in colorectal cancer. Pharmacogenomics. 2014;15:1171–4.
85. Maeda H, Hazama S, Shavkat A, Okamoto K, Oba K, Sakamoto J, et al. Differences in UGT1A1, UGT1A7, and UGT1A9 polymorphisms between Uzbek and Japanese populations. Mol Diagn Ther 2014;18:333–42.
86. Yao L, Qiu L-X, Yu L, Yang Z, Yu X-J, Zhong Y, et al. The association between TA-repeat polymorphism in the promoter region of UGT1A1 and breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 2010;122:879–82.
87. Cecchin E, Innocenti F, D'Andrea M, Corona G, De Mattia E, Biason P, et al. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. J Clin Oncol. 2009;27:2457–65.
88. Sai K, Saito Y, Maekawa K, Kim S-R, Kaniwa N, Nishimaki-Mogami T, et al. Additive effects of drug transporter genetic polymorphisms on irinotecan pharmacokinetics/pharmacodynamics in Japanese cancer patients. Cancer Chemother Pharmacol 2010;66:95–105.
89. Cha P-C, Mushiroda T, Zembutsu H, Harada H, Shinoda N, Kawamoto S, et al. Single nucleotide polymorphism in ABCG2 is associated with irinotecan-induced severe myelosuppression. J Hum Genet. 2009;54:572–80.
90. Huang L, Zhang T, Xie C, Liao X, Yu Q, Feng J, et al. SLCO1B1 and SLC19A1 gene variants and irinotecan-induced rapid response and survival: a prospective multicenter pharmacogenetics study of metastatic colorectal cancer. PLoS One. 2013;8:e77223.
91. Yamanaka H, Nakajima M, Katoh M, Hara Y, Tachibana O, Yamashita J, et al. A novel polymorphism in the promoter region of human UGT1A9 gene (UGT1A9*22) and its effects on the transcriptional activity. Pharmacogenetics. 2004;14:329–32.
92. Teft WA, Welch S, Lenehan J, Parfitt J, Choi Y-H, Winquist E, et al. OATP1B1 and tumour OATP1B3 modulate exposure, toxicity, and survival after irinotecan-based chemotherapy. Br J Cancer. 2015;112:857–65.
93. Kubo T, Kim S-R, Sai K, Saito Y, Nakajima T, Matsumoto K, et al. Functional characterization of three naturally occurring single nucleotide polymorphisms in the CES2 gene encoding carboxylesterase 2 (HCE-2). Drug Metab Dispos. 2005;33:1482–7.
94. Swami U, Goel S, Mani S. Therapeutic targeting of CPT-11 induced diarrhea: a case for prophylaxis. Curr Drug Targets. 2013;14:777–97.
95. Marsh S, Hoskins JM. Irinotecan pharmacogenomics. Pharmacogenomics. 2010;11:1003–10.
96. Bignucolo A, De Mattia E, Cecchin E, Roncato R, Toffoli G. Pharmacogenomics of targeted agents for personalization of colorectal cancer treatment. Int J Mol Sci. 2017;18:pii: E1522.
97. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. Ann Pharmacother. 2004;38:1258–64.
98. Zhang W, Azuma M, Lurje G, Gordon MA, Yang D, Pohl A, et al. Molecular predictors of combination targeted therapies (cetuximab, bevacizumab) in irinotecan-refractory colorectal cancer (BOND-2 study). Anticancer Res. 2010;30:4209–17.
99. Brat DJ, Bellail AC, Van Meir EG. The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis. Neuro Oncol. 2005;7:122–33.
100. Loupakis F, Cremolini C, Yang D, Salvatore L, Zhang W, Wakatsuki T, et al. Prospective validation of candidate SNPs of VEGF/VEGFR pathway in metastatic colorectal cancer patients treated with first-line FOLFIRI plus bevacizumab. PLoS One. 2013;8:e66774.
101. Kim JC, Ha YJ, Roh SA, Choi EY, Yoon YS, Kim KP, et al. Feasibility of proposed single-nucleotide polymorphisms as predictive markers for targeted regimens in metastatic colorectal cancer. Br J Cancer. 2013;108:1862–9.
102. Formica V, Palmirotta R, Del Monte G, Savonarola A, Ludovici G, De Marchis ML, et al. Predictive value of VEGF gene polymorphisms for metastatic colorectal cancer patients receiving first-line treatment including fluorouracil, irinotecan, and bevacizumab. Int J Colorectal Dis. 2011;26:143–51.
103. Sibertin-Blanc C, Mancini J, Fabre A, Lagarde A, Del Grande J, Levy N, et al. Vascular Endothelial Growth Factor A c.*237C>T polymorphism is associated with bevacizumab efficacy and related hypertension in metastatic colorectal cancer. Dig Liver Dis. 2015;47:331–7.
104. Wang J, Guo C, Liu S, Qi H, Yin Y, Liang R, et al. Annexin A11 in disease. Clin Chim Acta 2014;431:164–8.
105. Gerger A, El-Khoueiry A, Zhang W, Yang D, Singh H, Bohanes P, et al. Pharmacogenetic angiogenesis profiling for first-line Bevacizumab plus oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Clin Cancer Res. 2011;17:5783–92.
106. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2015;26:13–21.
107. Waring P, Tie J, Maru D, Karapetis CS. RAS mutations as predictive biomarkers in clinical management of metastatic colorectal cancer. Clin Colorectal Cancer. 2015;15:95–103.
108. Pander J, Gelderblom H, Antonini NF, Tol J, van Krieken JHJM, van der Straaten T, et al. Correlation of FCGR3A and EGFR germline polymorphisms with the efficacy of cetuximab in KRAS wild-type metastatic colorectal cancer. Eur J Cancer. 2010;46:1829–34.
109. Bonin S, Donada M, Bussolati G, Nardon E, Annaratone L, Pichler M, et al. A synonymous EGFR polymorphism predicting responsiveness to anti-EGFR therapy in metastatic colorectal cancer patients. Tumour Biol. 2015;37:7295–303.
110. Lurje G, Nagashima F, Zhang W, Yang D, Chang HM, Gordon MA, et al. Polymorphisms in cyclooxygenase-2 and epidermal growth factor receptor are associated with progression-free survival independent of K-ras in metastatic colorectal cancer patients treated with single-agent cetuximab. Clin Cancer Res. 2008;14:7884–95.
111. Lu X, Chen X, Sun J, Gao P, Song Y, Huang X, et al. Polymorphism in epidermal growth factor is related to clinical outcomes of metastatic colorectal cancer patients treated with cetuximab: a systematic review and meta-analysis. Int J Clin Exp Med. 2015;8:10929–37.
112. Ogino S, Nosho K, Kirkner GJ, Shima K, Irahara N, Kure S, et al. PIK3CA mutation is associated with poor prognosis among patients with curatively resected colon cancer. J Clin Oncol. 2009;27:1477–84.
113. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26:5705–12.
114. Oikonomou E, Koustas E, Goulielmaki M, Pintzas A. BRAF vs RAS oncogenes: are mutations of the same pathway equal? Differential signalling and therapeutic implications. Oncotarget. 2014;5:11752–77.

115. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, et al. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene. 2006;366:2–16.
116. Wieduwilt MJ, Moasser MM. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci. 2008;65:1566–84.
117. Hu-Lieskovan S, Vallbohmer D, Zhang W, Yang D, Pohl A, Labonte MJ, et al. EGF61 polymorphism predicts complete pathologic response to cetuximab-based chemoradiation independent of KRAS status in locally advanced rectal cancer patients. Clin Cancer Res. 2011;17:5161–9.
118. Baines AT, Xu D, Der CJ. Inhibition of Ras for cancer treatment: the search continues. Future Med Chem. 2011;3:1787–808.
119. Fiala O, Pesek M, Finek J, Topolcan O, Racek J, Minarik M, et al. High serum level of C-reactive protein is associated with worse outcome of patients with advanced-stage NSCLC treated with erlotinib. Tumour Biol. 2015;36:9215–22.
120. Alderson KL, Sondel PM. Clinical cancer therapy by NK cells via antibody-dependent cell-mediated cytotoxicity. J Biomed Biotechnol. 2011;2011:379123.
121. Calemma R, Ottaiano A, Trotta AM, Nasti G, Romano C, Napolitano M, et al. Fc gamma receptor IIIa polymorphisms in advanced colorectal cancer patients correlated with response to anti-EGFR antibodies and clinical outcome. J Transl Med. 2012;10:232.
122. Etienne-Grimaldi M-C, Bennouna J, Formento J-L, Douillard J-Y, Francoual M, Hennebelle I, et al. Multifactorial pharmacogenetic analysis in colorectal cancer patients receiving 5-fluorouracil-based therapy together with cetuximab-irinotecan. Br J Clin Pharmacol. 2012;73:776–85.
123. Bibeau F, Lopez-Crapez E, Di Fiore F, Thezenas S, Ychou M, Blanchard F, et al. Impact of Fc{gamma}RIIa-Fc{gamma}RIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. J Clin Oncol. 2009;27:1122–9.
124. Borrero-Palacios A, Cebrián A, Gómez del Pulgar MT, García-Carbonero R, García P, Aranda E, et al. Combination of KIR2DS4 and FcγRIIa polymorphisms predicts the response to cetuximab in KRAS mutant metastatic colorectal cancer. Sci Rep. 2019;9:2589.
125. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. J Clin Oncol. 2010;28:1075–83.
126. Katz M, Amit I, Yarden Y. Regulation of MAPKs by growth factors and receptor tyrosine kinases. Biochim Biophys Acta. 2007;1773:1161–76.
127. Punt CJA, Koopman M, Vermeulen L. From tumour heterogeneity to advances in precision treatment of colorectal cancer. Nat Rev Clin Oncol. 2017;14:235–46.
128. Pelizzo MR, Dobrinja C, Casal Ide E, Zane M, Lora O, Toniato A, et al. The role of BRAF(V600E) mutation as poor prognostic factor for the outcome of patients with intrathyroid papillary thyroid carcinoma. Biomed Pharmacother = Biomédecine pharmacothérapie. 2014;68:413–7.
129. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.
130. Agúndez JAG, Blanca M, Cornejo-García JA, García-Martín E. Pharmacogenomics of cyclooxygenases. Pharmacogenomics. 2015;16:501–22.
131. Papafili A, Hill MR, Brull DJ, McAnulty RJ, Marshall RP, Humphries SE, et al. Common promoter variant in cyclooxygenase-2 represses gene expression: evidence of role in acute-phase inflammatory response. Arterioscler Thromb Vasc Biol. 2002;22:1631–6.
132. de Vries N, Swets M, Vahrmeijer A, Hokland M, Kuppen P. The Immunogenicity of Colorectal Cancer in Relation to Tumor Development and Treatment. Int J Mol Sci. 2016;17:1030.
133. Riley JM, Cross AW, Paulos CM, Rubinstein MP, Wrangle J, Camp ER. The clinical implications of immunogenomics in colorectal cancer: a path for precision medicine. Cancer. 2018;124:1650–9.
134. Thorsson V, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH, et al. The immune landscape of cancer. Immunity. 2018; 48:812–30.
135. Passardi A, Canale M, Valgiusti M, Ulivi P. Immune checkpoints as a target for colorectal cancer treatment. Int J Mol Sci. 2017;18:pii: E1324.
136. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252–64.
137. Wu X, Zhang H, Xing Q, Cui J, Li J, Li Y, et al. PD-1(+) CD8 (+) T cells are exhausted in tumours and functional in draining lymph nodes of colorectal cancer patients. Br J Cancer. 2014;111:1391–9.
138. Rosenbaum MW, Bledsoe JR, Morales-Oyarvide V, Huynh TG, Mino-Kenudson M. PD-L1 expression in colorectal cancer is associated with microsatellite instability, BRAF mutation, medullary morphology and cytotoxic tumor-infiltrating lymphocytes. Mod Pathol. 2016;29:1104–12. In:
139. Wang HB, Yao H, Li CS, Liang LX, Zhang Y, Chen YX, et al. Rise of PD-L1 expression during metastasis of colorectal cancer: implications for immunotherapy. J Dig Dis. 2017;18:574–81.
140. Goswami S, Basu S, Sharma P. A potential biomarker for anti-PD-1 immunotherapy. Nat Med. 2018;24:123–4.
141. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol. 2017;18:153–67.
142. Singh PP, Sharma PK, Krishnan G, Lockhart AC. Immune checkpoints and immunotherapy for colorectal cancer. Gastroenterol Rep. 2015;3:gov053.
143. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16:908–18.
144. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35.
145. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20.
146. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res. 2013;19:462–8.
147. Llosa NJ, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov. 2015;5:43–51.
148. Gatalica Z, Snyder C, Maney T, Ghazalpour A, Holterman DA, Xiao N, et al. Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomark Prev. 2014;23:2965–70.
149. Tauriello DVF, Palomo-ponce S, Iglesias M, Stork D, Sevillano M, Berenguer-llergo A, et al. TGF-beta drives immune evasion in genetically reconstituted colon cancer metastasis. Nature. 2018;554:538–43.
150. Cantelli G, Crosas-Molist E, Georgouli M, Sanz-Moreno V. TGFB-induced transcription in cancer. Semin Cancer Biol. 2017;42:60–9.

151. Colak S, ten Dijke P. Targeting TGF-β signaling in cancer. Trends Cancer. 2017;3:56–71.
152. Ding L, Bailey MH, Porta-Pardo E, Thorsson V, Colaprico A, Bertrand D, et al. Perspective on oncogenic processes at the end of the beginning of cancer genomics. Cell. 2018;173:305–320. e10.
153. Huang KL, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, et al. Pathogenic germline variants in 10,389 adult cancers. Cell. 2018;173:355–70.
154. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature.2016;536:285–91.
155. Carvalho-Silva D, Pierleoni A, Pignatelli M, Ong CK, Fumis L, Karamanis N, et al. Open Targets Platform: New developments and updates two years on. Nucleic Acids Res. 2019;47: D1056–65.
156. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, et al. STRINGv10: protein–protein interaction networks, integrated over the tree of life. Nucleic Acids Res. 2015;43:D447–52.
157. López-Cortés A, Paz-y-Miño C, Cabrera-Andrade A, Barigye SJ, Munteanu CR, González-Díaz H, et al. Gene prioritization, communality analysis, networking and metabolic integrated pathway to better understand breast cancer pathogenesis. Sci Rep. 2018;8:16679.
158. Thorn CF, Klein TE, Altman RB. PharmGKB: the pharmacogenomics knowledge base. Methods Mol Biol. 2013;1015:311–20.
159. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther. 2018;103:210–6.
160. Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc. 2009;4:44–57.
161. Saito Y, Stamp LK, Caudle KE, Hershfield MS, McDonagh EM, Callaghan JT, et al. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin Pharmacol Ther. 2016;99:36–7.
162. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte—an update of guidelines. Clin Pharmacol Ther. 2011;89:662–73.
163. Ross CJD, Visscher H, Sistonen J, Brunham LR, Pussegoda K, Loo TT, et al. The Canadian pharmacogenomics network for drug safety: a model for safety pharmacology. Thyroid. 2010;20:681–7.
164. Zambrano AK, Gaviria A, Cobos-Navarrete S, Gruezo C, Rodríguez-Pollit C, Armendáriz-Castillo I, et al. The three-hybrid genetic composition of an Ecuadorian population using AIMs-InDels compared with autosomes, mitochondrial DNA and Y chromosome data. Sci Rep. 2019;9:9247.
165. Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature. 2019;570:514–8.
166. Quinones L, Lavanderos M, Cayun J, Garcia-Martin E, Agundez J, Caceres D, et al. Perception of the usefulness of drug/gene pairs and barriers for pharmacogenomics in Latin America. Curr Drug Metab. 2014;15:202–8.
167. Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease–implications for personalized medicine. Pharmacol Rev. 2013;65:987–1009.