Treatment optimisation and pharmacogenetics of systemic and intraperitoneal chemotherapy in colorectal cancer

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PART II

Discovery and validation of genetic biomarkers for hyperthermic intraperitoneal chemotherapy (HIPEC)

CHAPTER 5

Genetic variants in DNA repair pathways as potential biomarkers in predicting treatment outcome of intraperitoneal chemotherapy in patients with colorectal peritoneal metastasis: A systematic review

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ABSTRACT

Background

The introduction of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with either oxaliplatin or mitomycin C for patients with colorectal peritoneal metastasis (CPM) has resulted in a major increase in overall survival. Nonetheless, despite critical patient selection, the majority of patients will develop recurrent disease within one year following CRS+HIPEC. Therefore, improvement of patient and treatment selection is needed and may be achieved by the incorporation of genetic biomarkers. This systematic review aims to provide an overview of genetic biomarkers in the DNA repair pathway that are potentially predictive for treatment outcome of patients with colorectal peritoneal metastases treated with CRS+HIPEC with oxaliplatin or mitomycin C.

Methods

A systematic review was conducted according to the PRISMA guidelines. Given the limited number of genetic association studies of intraperitoneal mitomycin C and oxaliplatin in patients with CPM, we expanded the review and extrapolated the data from biomarker studies conducted in colorectal cancer patients treated with systemic mitomycin C and oxaliplatin-based chemotherapy

Results

In total, 43 papers were included in this review. No study reported potential pharmacogenomic biomarkers in patients with colorectal cancer undergoing mitomycin c-based chemotherapy. For oxaliplatin-based chemotherapy, a total of 26 genetic biomarkers within 14 genes were identified that were significantly associated with treatment outcome. The most promising genetic biomarkers were *ERCC1* rs11615, *XPC* rs1043953, *XPD* rs13181, *XPG* rs17655, *MNAT* rs3783819/ rs973063/rs4151330, MMR status, ATM protein expression, *HIC1* tandem repeat D17S5 and *PIN1* rs2233678.

Conclusion

Several genetic biomarkers have proven predictive value for the treatment outcome of systemically administered oxaliplatin. By extrapolation, these genetic biomarkers may also be predictive for the efficacy of intraperitoneal oxaliplatin. This should be the subject of further investigation

INTRODUCTION

Colorectal peritoneal metastasis (CPM) is associated with a poor prognosis and affects approximately 10–20% of colorectal cancer patients [1–4]. The introduction of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with either oxaliplatin or mitomycin C for patients with isolated CPM has led to a major increase in overall survival and even cure in up to 15% of patients [5, 6]. Therefore CRS + HIPEC is at present considered standard of care for patients with limited peritoneal metastases. Currently, patient selection for CRS + HIPEC is mainly based on the peritoneal carcinomatosis index (PCI) and performance status [7–9]. In addition, several clinical and pathological prognostic biomarkers have been identified, including completeness of cytoreduction, locoregional lymph node status and signet ring cell differentiation [10]. Nonetheless, despite critical patient selection, the majority of patients will develop recurrent disease within one year following CRS + HIPEC [11, 12]. In addition, post-operative surgical complications following CRS + HIPEC are frequent, including mortality in about 1–2% of patients [13].

Knowledge of genetic biomarkers that are predictive or prognostic for treatment outcome may be of additional value in patient and treatment selection, allowing further improvement of treatment outcome for the individual patient. In contrast to thousands of pharmacogenetic association studies that have been conducted in cancer patients treated with systemic chemotherapy, almost no data exist of genetic biomarkers in patients treated with intraperitoneal chemotherapy. Following intraperitoneal administration, oxaliplatin and mitomycin exert their anti-tumor effect locally at the tumor site. Both drugs share a comparable mechanism of action in that they both interfere with DNA synthesis and repair. Thereby, genetic variation in genes involved in DNA repair may reduce the functional activity of certain DNA repair genes, making tumor cells more susceptible for drug-induced DNA damage and hence increased drug efficacy [14, 15]. The DNA repair system is divided into six major DNA repair pathways, i.e. base-excision repair (BER), nucleotide-excision repair (NER), mismatch repair (MMR), homologous recombination (HR), nonhomologous end joining (NHEJ), and translesion DNA synthesis (TLS). In addition, pathways on damage response and DNA synthesis exist [15].

Notwithstanding the in general increasingly applied knowledge of genetic biomarkers in cancer therapy as a proven tool for patient and treatment selection, almost no predictive or prognostic data of genetic biomarkers for treatment outcome exist in patients with CPM treated with intraperitoneal chemotherapy. Therefore, we conducted a systematic review to provide an overview of genetic biomarkers in the DNA repair pathway that are potentially predictive for treatment outcome of patients with colorectal peritoneal metastases treated with CRS + HIPEC with oxaliplatin or mitomycin C.

METHODS

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Of the studies on the use of mitomycin C and oxaliplatin in HIPEC treatment, only two studies were found that have reported biomarkers related to DNA repair [17, 18]. Data obtained from genetic association studies conducted in other than CPM patients treated with oxaliplatin or mitomycin C may potentially be extrapolated to patients with CPM. Therefore, we expanded this review with studies investigating the association between genetic biomarkers related to DNA repair and treatment outcome in patients with colorectal cancer undergoing mitomycin C and oxaliplatin-based chemotherapy.

We searched PubMed until February 2020 without any limitations on publication year using the following search terms: "biomarker", "oxaliplatin", "mitomycin C", "colorectal cancer" and "treatment outcome". The full search string is provided in the supplementary material. In addition, reference lists in original articles and review articles were manually searched to identify additional potentially relevant publications. Literature was reviewed by two independent reviewers (LL and EH). In case of inconsistencies, results were discussed with a third reviewer (MD).

All publications were screened on title and abstract. Only studies that included patients with colorectal cancer were included and studies that were retracted, studies that did not provide original data or case-reports were excluded. The remaining publications were assessed based on screening of the full text. Only studies that reported on the association between genetic biomarkers related to DNA repair and treatment outcome undergoing mitomycin C- and oxaliplatin-based chemotherapy were included. To provide a total overview of the available evidence we included studies on various types of genetic biomarkers including genetic polymorphism, mRNA expression and protein expression. Treatment outcome had to be reported as overall survival (OS), progression-free survival (PFS), disease-free survival (DFS).

Risk of bias assessment was performed and adapted from the Q-genie tool and was based on the following bias items: clear phenotype and outcome definition, and correct nomenclature of genotype. We decided not to exclude studies because of small sample size, ethnic differences, differences in treatment regimens or type of biomarker, or no correction for covariates affecting treatment outcome due to scarcity of data.

All identified genetic biomarkers were subdivided into either one of the six described major DNA-repair pathways [19], i.e. NER, BER, MMR, HR, NHEJ, TLS, or otherwise into a category of genes involved in DNA damage response and DNA synthesis [15]. Results were summarized and presented per gene including a mechanistic background for the drug-gene interaction. The following information per study or genetic biomarker was reported: sample size, CRC type, treatment schedule, biomarker, type of sample, type of assay, rs number (if applicable), reference group and comparator group, and treatment outcome. Treatment outcomes were expressed as hazard ratios, relative risks or differences in median survival with 95% confidence intervals and p-values whichever was available.

The most promising genetic biomarkers were extracted from the results and summarized in a table. Evidence for these biomarkers had to meet the following 2 criteria: 1] no or almost none conflicting data and 2] an association with treatment outcome was reported in at least 2 studies or in one study with sufficient power (arbitrarily defined in this review as a minimum number of 300 patients), or the study included a control group with non-oxaliplatin based-chemotherapy in which no association or an association in the opposite direction was seen compared to the group with oxaliplatin-based chemotherapy.

RESULTS

Study selection

The search string in the PubMed database resulted in a total of 346 identified articles. **Figure 5.1** provides the selection procedure of relevant articles. An additional 17 studies were added that were identified from meta-analyses. After screening the title and abstract, 122 studies were excluded leaving 241 articles for further evaluation. After reviewing the full-text, 198 articles were excluded, resulting in a total of 43 studies that were included in this systematic review. The percent agreement between the two reviewers was 97% and Cohen's kappa was 0.87.

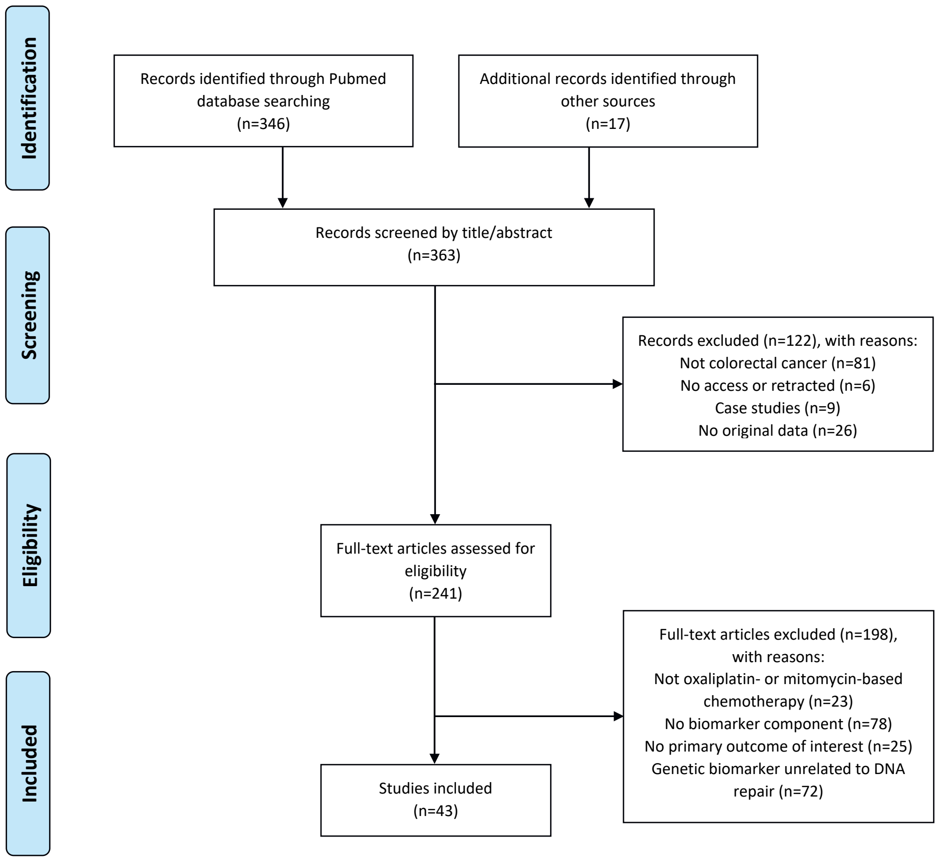

Figure 5.1: Flow chart of selection procedure literature.

Main results

The identified potential genetic biomarkers for treatment outcome of oxaliplatin-based chemotherapy could be divided over 4 out of the 6 major DNA-repair pathways, i.e. NER, BER, MMR and HR or were involved in DNA damage response or DNA synthesis, respectively. No studies were identified that reported on the association between genetic biomarkers and treatment outcome of mitomycin C-based chemotherapy in CRC patients. From all eligible studies, a total of 26 genetic biomarkers within 14 genes were identified in which at least one study had reported a significant association with treatment outcome. The most promising genetic biomarkers belonged to the NER, MMR or DNA damage response pathway and are summarized in **Table 5.1** and explained in more detail below; in contrast to biomarkers that belong to the BER, HR or DNA synthesis pathway which seem less promising due to lack of evidence or conflicting results The results from all included studies are summarized in

Figure 5.2, discussed per gene below and reported in detail in the **Supplementary material – Table S5.1-S5.10**.

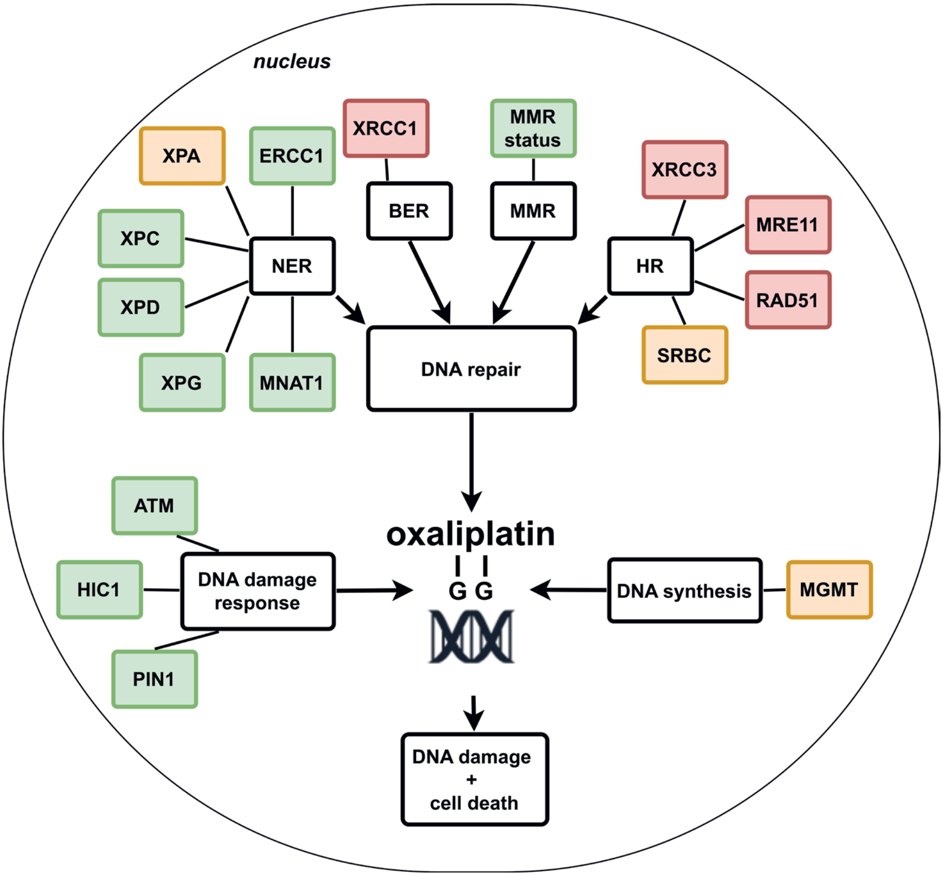

Figure 5.2: Schematic overview of potential genetic biomarkers within DNA repair pathways for treatment outcome of systemic oxaliplatin in colorectal cancer patients.
Green: no or almost none conflicting results and significant association with treatment outcome in ≥2 studies, or in 1 study with a sample size of ≥300, or inclusion of a non-oxaliplatin-based chemotherapy control group in which no association or an association in the opposite direction was seen compared to the group with oxaliplatin-based chemotherapy.
Orange: significant association with treatment outcome in 1 study.
Red: conflicting results or no significant association with treatment outcome.

NER pathway

ERCC1

Oxaliplatin DNA-adducts are mainly removed by the NER pathway [20].Excision repair cross-complementation group 1 (ERCC1) is a key protein in the NER pathway that is encoded by the *ERCC1* gene. Together with xeroderma pigmentosum complementation group F (XPF), ERCC1 forms a heterodimer complex that can incise damaged DNA strands at the 5' side of the lesion [21]. In addition to their involvement in the NER pathway, the XPF/ERCC1 complex is also involved in double strand break repair (DSBR) [22]. Therefore, the expression of *ERCC1* is potentially associated with treatment outcome of oxaliplatin in CRC patients.

In two preclinical studies, elevated ERCC1 protein level was suggested to correlate with oxaliplatin-resistance in cells [23, 24]. Alteration in single nucleotide polymorphisms (SNPs) are expected to have an effect in gene expression level and function. Several *ERCC1* SNPs have been evaluated for their association with treatment outcome of oxaliplatin in CRC patients (**Supplementary material – Table S5.1**). The most commonly investigated nucleotide polymorphism is rs11615 [25–42]. A total of 10 studies showed a significant association between this polymorphism and treatment outcome [25–27, 31, 33–36, 39, 40]. Most studies, six out of 10, reported the mutant CC genotype to be the favorable genotype, with significantly better DFS, PFS, and OS [25, 27, 31, 35, 36, 39]. However, a few studies showed contradictory results. Three studies [26, 33, 34] reported that patients with the CC genotype had a worse treatment outcome in terms of PFS and OS. Another contradicting result was reported by Ruzzo et al. [40] where the rs11615 TT genotype was associated with prolonged PFS in univariate analysis and shorter PFS in multivariate analyses.

Two other reported polymorphisms of *ERCC1* are at codon 259 and 504 [38, 43]. Both polymorphisms showed no significant association with the treatment outcome. Moreover, 2 [26, 44] out of 5 [45–47] studies based on mRNA or protein expression level of ERCC1 showed a significant association between low ERCC1 expression and prolonged PFS and OS.

XPC

Xeroderma pigmentosum group C (XPC), located at chromosome 3p25, encodes for another important protein in the early steps of the NER pathway. XPC binds to RAD23B to form the heterodimeric complex, which is the first NER factor to facilitate the recognition of DNA damage and the initiation of DNA repair [48]. As DNA damage recognition is the rate-limiting step in the NER pathway, the XPC protein plays a critical role in proper DNA repair. Therefore, genetic biomarkers in *XPC* may have potential value in predicting response for oxaliplatin-based chemotherapy.

In **Table S5.3** (Supplementary material), three SNPs in the *XPC* gene that are potentially predictive of treatment response to oxaliplatin-based therapy in CRC patients are reported [49–51]. Only one SNP was significantly associated with survival. In the study by Kap et al. [50], patients carrying the variant allele rs1043953 had a longer OS after treatment with oxaliplatin-based chemotherapy compared to non-carriers after adjusting for multiple testing, while the opposite association was found in patients who were treated with non-oxaliplatin based-chemotherapy.

XPD/ERCC2

The *xeroderma pigmentosum group D (XPD)*, or *excision repair cross complementation group 2* (*ERCC2*) gene, encodes for a helicase protein of 761 amino acids located on chromosome 19q13.3 [52]. The XPD protein is a part of the general transcription factor IIH complex, which is involved in the NER pathway by opening DNA double helix after damage recognition by XPC-RAD23B [53]. SNPs in *XPD* gene can alter the efficiency of DNA repair capacity and could thus be used as a predictive factor for oxaliplatin-based chemotherapy.

SNPs affecting codons 156, 312, and 751 (rs238406, rs1799793 and rs13181, respectively) proved to be extensively studied for their predictive value in CRC treatment (**Supplementary material – Table S5.4**). *XPD* rs238406 SNP was significantly associated with treatment outcome in one [54] out of three studies [31, 55]. The second SNP, rs1799793, was also significantly associated with treatment outcome in one [56] out of three studies [40, 55]. The wild type GG genotype seemed to be the favorable genotype. Sixteen studies assessed the predictive value of *XPD* rs13181polymorphism. In most studies a worse treatment outcome was observed in C allele carriers [31, 33, 36, 40, 42, 55, 57, 58]. Le Morvan et al. compared oxaliplatin treatment with irinotecan treatment and reported that the CC genotype was associated with a lower OS in patients treated with oxaliplatin, in contrast this was not observed in the same patient category treated with irinotecan [57]. However, the opposite association was observed in three studies [27, 28, 59], and five studies did not find significant associations with treatment outcome [25, 34, 41, 43, 60]. Lastly, one study assessed mRNA expression level of *XPD* for its association with treatment outcome, no significant association was observed [44].

XPG/ERCC5

The *xeroderma pigmentosum group G* (*XPG*) gene, also known as *ERCC5* (*Excision repair cross complementation group 5*), is one of the eight core functional genes in the NER pathway. The *XPG* gene, located at chromosome 13q32-33, encodes for a structure specific endonuclease protein that cleaves the 3' side of the damaged nucleotide during NER [61]. The low expression level of *XPG* has been shown to be associated with response to platinum-based chemotherapy in ovarian cancer [62, 63].

Four studies reported on the association between four different SNPs in the *XPG* gene and treatment outcome of oxaliplatin-based chemotherapy in CRC patients (**Supplementary material – Table S5.5**). The -763A>G and +25A>G polymorphisms in the promoter region of *ERCC5* were significantly associated with PFS and OS in patients treated with oxaliplatin [64]. Also, SNPs in rs1047768 and rs17655 were significantly associated with treatment outcome [43, 49, 65].

MNAT1

The *MNAT1* gene encodes for the ménage à trois-1 (MAT1) enzyme that is involved in the assembly of the cyclin dependent kinase-activating kinase (CAK) complex. Together with XPD and other subunits, the CAK-complex forms the TFIIH complex that is involved in the NER pathway [66].

Kap et al. [50] found three predictive SNPs, rs3783819, rs973063 and rs4151330 of the *MNAT1* gene for OS in CRC patients treated with oxaliplatin-based chemotherapy compared to CRC patients with non-oxaliplatin based chemotherapy (**Supplementary material – Table S5.6**). All three SNPs are in high linkage disequilibrium and p-values were corrected for multiple testing. Compared to non-carriers, carriership of these genetic variants was associated with longer OS, but not in patients who received non-oxaliplatin-based chemotherapy.

MMR pathway

MMR status

The DNA mismatch repair (MMR) system recognizes and repairs genetic mismatches that occur during DNA replication and DNA damage. MMR status is defined as deficient (dMMR) when one or more MMR protein (*MLH1*, *MSH2*, *PMS2*, and *MSH6*) expression is lost [67]. Germline mutations in MMR genes were found to be the driving mechanism for Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) [68]. A defective MMR system will result in DNA replication errors, particularly in the short tandem repeat of DNA sequences of the genome referred to as microsatellites, which may lead to microsatellite instability (MSI). It has been suggested that MSI positively affects the clinical outcome of CRC. Mechanistically, oxaliplatin treatment is expected to be more effective in patients with defective MMR protein status as platinum adducts formed by oxaliplatin cannot be repaired.

A total of three studies, evaluating the predictive ability of MMR status in relation to oxaliplatin-based treatment, are included in **Table S5.9** (Supplementary material). In two out of three studies, OS was significantly higher in multivariate analysis in dMMR patients treated with oxaliplatin-based therapy [46, 69]. In contrast, Kim et al. did not find an association between dMMR and treatment outcome of oxaliplatin-based chemotherapy [70].

DNA damage response

ATM

Ataxia telangiectasia mutated (ATM) is a serine/threonine protein kinase that is recruited and activated by the MRN complex during DNA DSBR [71]. The activation of the *ATM* gene leads to the phosphorylation of several key proteins that mediates the effect of ATM protein on DNA repair, cell cycle arrest or apoptosis [72]. Loss of *ATM* in preclinical models seems to increase sensitivity to DNA damaging agents, including platinum-based chemotherapy and ATM inhibitors [73].

Two studies reported a significant association of *ATM* with treatment outcome of oxaliplatin in CRC patients (**Supplementary material – Table S5.10**) [65, 74]. Sundar et al. [74] reported that loss of ATM protein expression in CRC resulted in favorable OS when treated with first line oxaliplatin chemotherapy (49 vs. 32 months; HR: 2.52 [1.00–6.37]). Important to note, loss of ATM expression did not result in favorable OS among patients treated with first line irinotecan-based therapy (24 vs. 33 months; HR: 0.72 [0.28–1.84]). In addition, the explorative study by Kweekel et al. [65] found a significantly shorter PFS for homozygous carriers of the *ATM* rs1801516 SNP, for OS no differences were found.

HIC1

The hypermethylated in cancer 1 (HIC1) protein plays an important role in the DNA repair through its direct binding to the Sirtuin 1 (SIRT1) promoter, thereby suppressing its transcription. SIRT1 is a deacetylase of XPA protein, a component of the NER pathway [75]. Since the variable number of tandem repeats near the promoter lesion of HIC1, which is associated with *HIC1* gene expression, there is a potential value of *HIC1* as a predictive biomarker for oxaliplatin efficacy.

In a study by Okazaki et al. [76], shown in **Table S5.10** (Supplementary material), patients treated with oxaliplatin-based chemotherapy with at least 5 tandem repeats of *HIC1*, in both alleles of the *HIC1* promoter region, had a significantly shorter PFS. In a control group who received irinotecan-based chemotherapy this difference in PFS was not seen. However, no significant association with OS was found.

PIN1

Peptidyl-prolyl cis/trans isomerase NIMA-interacting 1 (PIN1) is an enzyme encoded by the *PIN1* gene. It interacts with prominent DSBR factors and is involved in the regulation of HR and non-homologous end-joining (NHEJ) of DNA DSBR. Previous study showed that the overexpression of PIN1 suppresses HR and its depletion reduces NHEJ, by promoting CtIP polyubiquitylation and subsequent proteasomal degradation [77].

A study by Suenaga et al. [78], shown in **Table S5.10** (Supplementary material), reported that genetic polymorphism in *PIN1* was associated with treatment outcome of oxaliplatin. Patients treated with oxaliplatin-based chemotherapy carrying the *PIN1* rs2233678 C allele had a shorter PFS and OS compared to wild type patients. For OS this was replicated in a validation cohort. In contrast, in a control group treated with non-oxaliplatin-based chemotherapy patients with a C allele had longer median PFS than wild type patients.

Miscellaneous

Following our selection criteria, for XPA in the NER pathway [31, 43, 51], SRBC in the HR pathway [79] and MGMT in the DNA synthesis pathway [80] results remain inconclusive because the observed associations have not yet been replicated and the studies itself were relatively small (<300 patients).

For XRCC1 in the BER pathway a total of nine studies were identified that assessed the association between the *XRCC1* gene and treatment outcome of oxaliplatin-based chemotherapy in CRC patients, and showed conflicting results [25, 28, 30, 32, 34, 39, 59, 81]. All nine studies investigated the *1196A>G* polymorphism, and three studies showed a significant association [25, 59, 81]. However, two out of three studies [25, 81] found a significantly longer OS for the GG genotype, whereas the other study [59] a longer OS for the AA genotype.

For XRCC3 [34, 40], MRE11 [82] and RAD51 [82] in the HR pathway no significant associations with treatment outcome were reported.

DISCUSSION

The majority of patients with peritoneal metastases of colorectal cancer treated with CRS + HIPEC will develop recurrent disease despite critical patient selection. Therefore, improvement of patient and treatment selection is needed and further investigation of genetic biomarkers that are predictive or prognostic for treatment outcome may be of aid herein. We conducted a systematic review to provide an overview of genetic biomarkers in the DNA repair pathway that are potentially predictive for treatment outcome of patients with colorectal peritoneal metastases treated with CRS + HIPEC with oxaliplatin or mitomycin C.

We expanded our review with studies investigating the association between genetic biomarkers related to DNA repair and treatment outcome in patients with colorectal cancer undergoing systemic chemotherapy, because only two studies could be retrieved that investigated the association of biomarkers related to DNA repair and intraperitoneally administered mitomycin C or oxaliplatin. The most promising genetic biomarkers were *ERCC1* rs11615, *XPC* rs1043953, *XPD* rs13181, *XPG* rs17655, *MNAT* rs3783819/ rs973063/rs4151330, MMR status, ATM protein expression, *HIC1* tandem repeat D17S5 and *PIN1* rs2233678. Combination studies of two DNA repair genes have also been studied and showed significant associations with treatment outcome.

Our findings for *ERCC1* rs11615 and *XPD* rs13181 are supported in 4 meta-analyses [83–86]. The other biomarkers have not been studied as extensively. To our knowledge the current review is the first to summarize the available evidence for these markers.

Our results showed that genetic biomarkers in the DNA repair pathway seem of added value in predicting oxaliplatin treatment outcome in colorectal cancer patients. Since the mechanism of action of oxaliplatin is irrespective of the route of administration, it is assumed very reasonable to extrapolate these associations to patients with colorectal peritoneal metastases treated with CRS + HIPEC. In our opinion, single genetic biomarkers within DNA repair should be incorporated into a polygenic risk profile because the effect of a single gene polymorphism may be partially overcome by compensation mechanisms. Comparable to the study by Kap et al., in which the predictive value of the model significantly improved by including more genetic variants [50]. Moreover, besides DNA repair, other pathways may also be of relevance in predicting treatment outcome, such as genetic variation in pharmacokinetic genes [87].

For some genetic biomarkers conflicting results were reported. This might partially be explained by ethnic discrepancy as has been suggested [83, 86]. In addition, studies with small sample sizes and differences in treatment regimens between studies may also attribute to these conflicting results. However, for the selection of the most promising genetic biomarkers we only selected biomarkers for which no or almost none conflicting data existed and results had to be replicated in at least 2 studies or in one study with sufficient power (>300 patients) or the study had to have a control group with non-oxaliplatin based chemotherapy.

Moreover, genetic variants in the DNA repair pathway seem to affect cancer susceptibility, prognosis and treatment outcome [88]. Therefore, it is difficult to distinguish between prognostic effects of these genetic variants or predictive effects on treatment outcome of oxaliplatin. To differentiate between these prognostic effects and predictive effects, a control group consisting of a patient cohort treated with non-oxaliplatin based chemotherapy should be added. Most of the studies that were included had no control group. Nonetheless, the studies that did include a control group with non-oxaliplatin based-chemotherapy did find differences in the association between the genetic biomarker (*XPC* rs1043953, *XPD* rs13181, *MNAT* rs3783819/ rs973063/rs4151330, ATM protein expression, *HIC1* tandem repeat D17S5 and *PIN1* rs2233678) and treatment outcome of oxaliplatin-based chemotherapy and non-oxaliplatin based-chemotherapy, thereby suggesting these biomarkers to be more likely predictive than prognostic.

In addition, we included various types of biomarkers such as genetic polymorphism, mRNA expression and protein expression, these are quite different assays and normally we would not pile together these various types of biomarkers. However, our aim was to give a complete overview of all genetic biomarkers, in order to provide a selection of potential promising genetic biomarkers for further research.

As data scarcity and sparsity was encountered we decided to expand our search from intra-peritoneal chemotherapy to systemic chemotherapy. No formal search in other databases than PubMed was conducted, since it was assumed that the majority of relevant literature was identified using this database. However, this might be considered a limitation of our study. Moreover, the addition of grey literature could have been of added value in terms of data scarcity and publication bias. Nonetheless, grey literature is mostly not peer-reviewed and not always traceable. In addition, the quality of data could potentially be improved by applying a standardized tool for the risk of bias assessment. However, as described in the methods section, a customized assessment of bias was performed which was mainly based on the Q-genie tool.

Lastly, not all studies corrected for additional covariates affecting treatment outcome such as clinical, molecular and pathological patient and tumor characteristics. This might have influenced the effect of the genetic biomarkers on treatment outcome. Therefore, additional prospective research including a multivariate analysis is needed, especially in patients with colorectal peritoneal metastases treated with CRS + HIPEC as literature is scarce in this population.

In this review, several genetic biomarkers in the DNA repair pathway were identified that showed promise for predicting outcome in colorectal cancer patients treated with oxaliplatin. These findings might be extrapolated to patients with colorectal peritoneal metastases treated with CRS + HIPEC and should be the subject of further investigation.

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SUPPLEMENTARY METHODS

Search string

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Supplementary Table S5.1: Overview of studies on the association between ERCC1 biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis			Multivariate analysis		
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	PFS	DFS	OS
Rao et al., 2019 [26]	24	Stage II–III mCRC	CAPOX or FOLFOX	ERCC1-118	n.a.	Blood	Protein expression	**Underexpression +normal (11)** overexpression (13)	HR=2.35 (95% CI: 1.00–5.48) p=0.02					
Kassem et al., 2017 [44]	65	Stage III–IV	CAPOX or FOLFOX-4	*ERCC1*	n.a.	Tumor tissue	mRNA expression	**Low (50)** High (15)			HR=2.80 (95% CI: 1.27–6.21) p=0.01			
Basso et al., 2013 [45]	60	mCRC	FOLFOX-6	*ERCC1*	n.a.	Normal and tumor tissue	mRNA expression	**Overexpression (30)** Underexpression (30)	HR=1.09 (95% CI: 0.63–1.95) p=0.71					
Sfakianaki et al., 2019 [46]	246	Stage II–III	CAPOX or FOLFOX	*ERCC1*	n.a.	Tumor tissue	mRNA expression	**Low (118)** High (128)		HR=1.16 (95% CI: 0.61–1.57) p=0.93	HR=1.00 (95% CI: 0.56–1.80) p=0.99			
Li et al., 2014 [47]	112	Stage II–III	FOLFOX-4 or mFOLFOX or CAPOX	*ERCC1*	n.a.	Tumor tissue	mRNA expression	**Low (-)** High (-)		HR=1.05 (95% CI: 0.85–1.30) p=0.64				
Monzo et al., 2007 [43]	42	aCRC	CAPOX	ERCC1-Lys259Thr *c.776A>C*	rs735482	Blood	Polymorphism	A/A (33) A/C (4) + C/C (5)			14.4 mo vs 30.0 mo p=0.55			

Supplementary Table S5.1: *Continued*

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis PFS	Univariate analysis DFS	Univariate analysis OS	Multivariate analysis PFS	Multivariate analysis DFS	Multivariate analysis OS
Huang et al., 2011 [25]	157	mCRC	FOLFOX-4	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (19)** C/T (58 C/C (80)	C/C HR=0.06 (95% CI: 0.01–0.27) p<0.01 C/T HR=0.48 (95% CI: 0.13–1.74) p=0.26		C/C HR=0.07 (95% CI: 0.01–0.38) p<0.01 C/T HR=0.39 (95% CI: 0.08–1.89) p=0.25			
Rao et al., 2019 [26]	97	Stage II–III mCRC	CAPOX or FOLFOX	ERCC1-Asn118= *c.354T>C*	rs11615	Tumor tissue	Polymorphism	C/C (42) T/C (40) T/T (15)	211 days vs 196 days vs 590 days p=0.03					
Li et al., 2012 [27]	335	aCRC	FOLFOX-6	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (166)** T/C (140) C/C (29)			T/C HR=0.87 (95% CI: 0.60–1.26) C/C HR= 0.22 (95% CI: 0.12–0.81)			T/C HR=0.81 (95% CI: 0.52–1.14) p=0.16 C/C HR=0.20 (95% CI: 0.10–0.79) p<0.05
Lamas et al., 2011 [28]	72	aCRC	mFOLFOX-6	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	C/C C/T T/T	9 mo vs 10 mo vs 10 mo p=1.0					

Supplementary Table S5.1 continues on next page.

Supplementary Table S5.1: ***Continued***

									Univariate analysis			Multivariate analysis		
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	PFS	DFS	OS
van Huis-Tanja et al., 2014 [29]	145	aCRC	CAPOX	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (59)** C/T (72) C/C (14)	4.2 mo vs 4.2 mo vs 4.5 mo p=0.19		10.0 mo vs 12.1 mo vs 10.8 mo p=0.19			
Zaanan et al., 2014 [30]	202	Stage III	FOLFOX-4 or FOLFOX-6	ERCC1-Asn118= *c.354T>C*	rs11615	Tumor tissue	Polymorphism	**C/C (49)** C/T (88) + T/T (65)		HR=2.29 (95% CI: 0.97–5.41) p= 0.06				
Stoehlmacher et al., 2004 [31]	106	mCRC	FUOX	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**C/C (30)** C/T (45) T/T (31)	C/T RR=1.24 (95% CI: 0.73– 2.11) T/T RR=1.36 (95% CI: 0.76–2.41) p=0.51		C/T RR=2.29 (95% CI: 1.19–4.41) T/T RR=1.86 (95% CI: 0.91–3.83) p=0.02			C/T + T/T RR=2.05 (95% CI: 1.00–4.20) p=0.04
Liang et al., 2010 [32]	113	mCRC	mFOLFOX-4 or CAPOX	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**C/C (55)** C/T (43) T/T (15)						C/T HR=1.46 (95% CI: 0.94–2.27) p=0.10 T/T HR=1.66 (95% CI: 0.91–3.01) p=0.10

Supplementary Table S5.1: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis PFS	Univariate analysis DFS	Univariate analysis OS	Multivariate analysis PFS	Multivariate analysis DFS	Multivariate analysis OS
Paré et al., 2008 [33]	106	mCRC	FOLFOX	ERCC1-Asn118= *c.354T>C*	rs11615	Leukocytes	Polymorphism	**T/T (42) + C/T** (52) C/C (24)	10 mo vs 6 mo p<0.001		30 mo vs 11 mo p<0.01			RR=1.8 (CI 95%: 1.1–3.0) p=0.02
Martinez-Balibrea et al., 2008 [34]	47	mCRC	XELOX	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (18)** C/T + C/C (29)	HR=1.13 (95% CI: 0.57–2.24) p=0.74					
Martinez-Balibrea et al., 2008 [34]	49	mCRC	FUOX	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (21)** T/C + C/C (28)	HR=1.96 (95% CI: 0.99–3.92) p=0.05			HR=2.12 (95% CI: 1.05–4.28) p=0.04		
Chang et al., 2009 [35]	168	mCRC	FOLFOX-4	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**T/T (21) + C/T** (67) C/C (80)	7 vs 13 mo p<0.01		16 mo vs 25 mo p<0.01			
Chen et al., 2010 [36]	166	mCRC	FOLFOX-4	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**C/C (78)** C /T + T/T (88)						HR=3.15 (95% CI: 1.89–5.23) p<0.01
Nishina et al., 2013 [38]	68	aCRC and/or recurrent CRC	mFOLFOX-6 + bevacizumab	ERCC1-Asn118= c.354T>C	rs11615	Blood	Polymorphism	**C/C (29)** C/T + T/T (39)	13.5 mo vs 12.6 mo HR=1.08 p=0.80					

Supplementary Table S5.1 continues on next page.

Supplementary Table S5.1: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis			Multivariate analysis		
									PFS	DFS	OS	PFS	DFS	OS
Chua et al., 2009 [39]	115	mCRC	FOLFOX	ERCC1-Asn118= *c.354T>C*	rs11615	Tumor tissue	Polymorphism	**C/C (10)** C/T (64) T/T (41)	C/T HR=2.68 (95% CI: 1.15–6.23) p=0.02 T/T HR=2.54 (95% CI: 1.07–6.04) p=0.04 C/T + T/T HR=2.62 (95% CI: 1.14–6.02) p=0.02		C/T HR=1.88 (95% CI: 0.75–4.71) p=0.20 T/T HR=1.55 (95% CI: 0.60–4.00) p=0.40 C/T + T/T HR=1.74 (95% CI: 0.70–4.30) p=0.20	C/T + T/T HR=2.16 (95% CI: 0.94–4.97) p=0.07		
Ruzzo et al., 2007 [40]	166	mCRC	FOLFOX-4	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**C/C (31)** C/T (85) T/T (50)	C/T HR=1.23 (95% CI: 0.78–1.94) p=0.27 T/T HR=0.53 (95% CI: 1.51–4.25) p<0.01			C/T HR=1.32 (95% CI: 0.78–2.24) p=0.29 T/T HR=2.34 (95% CI: 1.28–4.27) p<0.01		

Supplementary Table S5.1: ***Continued***

									Univariate analysis			Multivariate analysis		
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	PFS	DFS	OS
Sarasqueta et al., 2011 [41]	48	Stage III	CAPOX or FOLFOX	ERCC1-Asn118= *c.354T>C*	rs11615	Normal tissue	Polymorphism	**T/T -** T/C - C/C -					T/C HR=0.67 (95% CI: 0.23–1.89) p=0.45 C/C HR=0.94 (95% CI: 0.26–3.36) p=0.92	
Kumamoto et al., 2013 [42]	63	n.s.	mFOLFOX-6	ERCC1-Asn118= *c.354T>C*	rs11615	Blood	Polymorphism	**C/C (30)** C/T (23) T/T (10)	9.9 mo vs 8.1 mo vs 8.3 mo p=0.63		27.4 mo vs 22.5 mo vs 32.9 mo p=0.38			
Nishina et al., 2013 [38]	68	aCRC and/or recurrent CRC	mFOLFOX-6 + bevacizumab	ERCC1-Gln504Lys *c.1516C>A*	rs3212986	Blood	Polymorphism	**C/C (41)** C/A + A/A (27)	13.8 mo vs 12.6 mo HR=1.18 p=0.71					
Huang et al., 2011 [25]	157	mCRC	FOLFOX-4	ERCC1-Asn118= c.354T>C and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Blood	Polymorphism	2 favorable genotypes (ERCC1 C/C and XRCC1 G/G) - vs ≤1 favorable genotype -			25 mo vs 16.5 mo p<0.01			

Supplementary Table S5.1 continues on next page.

Supplementary Table S5.1: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis PFS	Univariate analysis DFS	Univariate analysis OS	Multivariate analysis PFS	Multivariate analysis DFS	Multivariate analysis OS
Liang et al., 2010 [32]	113	mCRC	Modified FOLFOX-4 or CAPOX	ERCC1-Asn118= *c.354T>C* and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Blood	Polymorphism	**2 favorable genotypes (*XRCC1* A/A and *ERCC1* C/C) 38** vs 1 favorable genotype 40 vs 0 favorable genotype 35						1 HR=2.25 (95% CI: 1.38–3.67) p=0.01 0 HR=2.60 (95% CI: 1.56–4.31) p<0.01
Zaanan et al., 2014 [30]	210	Stage III	FOLFOX-4 or FOLFOX-6	ERCC1-Asn118= *c.354T>C* and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Tumor tissue	Polymorphism	**≥1 favorable genotype (*ERCC1* C/C and/ or *XRCC1* G/G + G/A)** vs 0 favorable genotype		HR=2.42 (95% CI: 1.16–5.03) p=0.02			HR=2.03 (95% CI: 0.96–4.28) p=0.06	

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CI = confidence interval, *ERCC1 = excision repair cross-complementing group 1*, DFS = disease-free survival, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, mo = months, n.a. = not applicable, n.s. = not specified, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RR = relative risk, *XRCC1 = X-ray repair cross-complementation group 1*. * Reference group in **bold**.

Table S5.2: Overview of studies on the association between XPA biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	DFS	OS
Hu et al., 2019 [51]	580	aCRC	FOLFOX4 or CAPOX	XPA *g.100452435C>T*	rs2808668	Blood	Polymorphism	**C/C -** TT + C/T -				HR=1.19 (95% CI: 0.90–1.57) p=0.22	HR=1.17 (95% CI: 0.88–1.54) p=0.28
Hu et al., 2019 [51]	580	Stage III–IV	FOLFOX4 or CAPOX	XPA *g.100462409T>C*	rs10817938	Blood	Polymorphism	**T/T (306)** C/C + C/T (274)		46 mo vs 48 mo p=0.06	55 mo vs 62 mo p<0.01	HR=0.79 (95% CI: 0.63–1.00) p=0.05	HR=0.73 (95% CI: 0.58–0.92) p=0.01
Stoehlmacher et al., 2004 [31]	93	rCRC	FUOX	*XPA c.-4A>G*	rs1800975	Blood	Polymorphism	**G/G (24)** A/G (53) A/A (16)	A/G RR=1.24 (95% CI: 0.70–2.18) A/A RR=1.37 (95% CI: 0.66–2.84) p=0.61		A/G RR=0.88 (95% CI: 0.47–1.62) A/A RR=1.13 (95% CI: 0.49–2.45) p=0.76		
Monzo et al., 2007 [43]	42	aCRC	CAPOX	*XPA c.-4A>G*	rs1800975	Blood	Polymorphism	A/A (17) G/A (20) + A/A (5)			19.2 mo vs 18.1 mo p=0.29		
Monzo et al., 2007 [43]	42	aCRC	CAPOX	XPG-His46= *c.138T>C* and *XPA c.-4A>G*	rs1047768 + rs1800975	Blood	Polymorphism	**Favorable genotype (*XPG* (C/C) + *XPA* (G/A or G/G))** vs unfavorable genotype			49.6 mo vs 14.0 mo p<0.01		RR=34 (95% CI: 6.3–183) p<0.01

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CI = confidence interval, DFS = disease-free survival, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, mo = months, OS = overall survival, PFS = progression-free survival, rCRC = refractory colorectal cancer, RR = relative risk, *XPA = xeroderma pigmentosum complementation group A*, *XPG = xeroderma pigmentosum complementation group G*. * Reference group in **bold**.

Table S5.3: Overview of studies on the association between XPC biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis	Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	OS	DFS	OS
Liu et al., 2012 [49]	432	n.s.	CAPOX or FOLFOX	XPC-Gln939Lys *c.2815C>A*	rs2228001	Blood	Polymorphism	**A/A -** A/C + C/C -	HR=0.97 (95% CI: 0.75–1.32) p=0.99		
Kap et al., 2015 [50]	201	Stage II–IV	Oxaliplatin-based chemotherapy	*XPC c.*463A>G*	rs1043953	Blood/ saliva	Polymorphism	**AA -** AG + GG -	HR=0.45 (95%CI: 0.29–0.70) p<0.01		
Hu et al., 2019 [51]	580	Stage III–IV	CAPOX or FOLFOX4	*XPC c.-27G>C*	rs2607775	Blood	Polymorphism	**C/C -** C/G + G/G		HR=0.91 (95% CI: 0.70–1.17) p=0.44	HR=0.91 (95% CI: 0.70–1.17) p=0.46

Abbreviations: CAPOX = capecitabine and oxaliplatin, CI = confidence interval, CRC = colorectal cancer, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, HR = hazard ratio, n.s. = not specified, OS = overall survival, PFS = progression-free survival, **XPC = xeroderma pigmentosum complementation group C**. * Reference group in **bold**.

Table S5.4: Overview of studies on the association between XPD biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Kassem et al., 2017 [44]	64	Stage III–IV	CAPOX or FOLFOX	XPD	n.a.	Tumor tissue	mRNA expression	**Low (48)** High (16)		HR=1.36 (95% CI: 0.59–3.14) p=0.47			
Kjersem et al., 2015 [54]	508	mCRC	FOLFOX or Nordic FLOX + cetuximab	XPD-Arg156= *c.468A>C*	rs238406	Blood	Polymorphism	C/C (173) + C/A (233) A/A (102)	7.8 mo vs 9.1 mo p<0.01	23.4 mo vs 20.3 mo p=0.33			
Stoehlmacher et al., 2004 [31]	103	rCRC	FUOX	XPD-Arg156= *c.468A>C*	rs238406	Blood	Polymorphism	**A/A (14)** C/A (59) C/C (30)	C/A RR=0.81 (95% CI: 0.44–1.49) C/C RR=0.73 (95% CI: 0.36–1.48) p=0.64	C/A RR=1.22 (95% CI: 0.55–2.75) C/C RR=1.18 (95% CI: 0.49–2.82) p=0.88			
Park et al., 2001 [55]	69	rCRC	FUOX	XPD-Arg156= *c.468A>C*	rs238406	Blood	Polymorphism	**C/C (22)** C/A (38) A/A (9)		11.7 mo vs 13.2 mo vs 8.5 mo C/A RR=0.94 A/A RR=1.60 p=0.50			

Supplementary Table S5.4 continues on next page.

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Liu et al., 2019 [56]	106	Stage IV	mFOLFOX4 or CAPOX	XPD-Asp312Asn *c.934G>A*	rs1799793	Blood	Polymorphism	**G/G (49)** G/A (42) A/A (15)		G/A HR=1.26 (95% CI: 0.83–1.91) p=0.28 A/A HR=1.65 (95% CI: 0.92–2.97) p=0.09 G/A + A/A HR=1.34 (95% CI: 0.91–1.98) p=0.14			G/A HR=1.51 (95% CI: 0.98–2.34) p=0.06 A/A HR=2.43 (95% CI: 1.31–4.53) p<0.01
Park et al., 2001 [55]	59	rCRC	FUOX	XPD-Asp312Asn *c.934G>A*	rs1799793	Blood	Polymorphism	**A/A (7)** G/A (24) G/G (28)		Not reached 9.2 mo vs 26.5 mo G/A RR=2.17 G/G RR=1.29 p=0.27			

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Ruzzo et al., 2007 [40]	165	mCRC	FOLFOX-4	XPD-Asp312Asn *c.934G>A*	rs1799793	Blood	Polymorphism	**G/G (57)** G/A (86) A/A (22)	G/A HR=1.02 (95% CI: 0.62–1.69) p=0.93 A/A HR=1.40 (95% CI: 0.83–2.37) p=0.21		G/A HR=1.13 (95% CI: 0.73–1.78) p=0.58 A/A HR=1.65 (95% CI: 0.73–3.21) p=0.12		
Sarasqueta et al., 2011 [41]	43	Stage III	CAPOX or FOLFOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Normal tissue	Polymorphism	**A/A -** A/C - C/C -				AC HR=0.65 (95% CI: 0.24–1.8) p=0.41 CC HR=0.73 (95% CI: 0.13–4.11) p=0.72	
Lamas et al., 2011 [28]	72	aCRC	mFOLFOX-6	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	A/A 28 A/C 33 C/C 11	8 mo vs 16 mo vs 10 mo p=0.02				

Supplementary Table S5.4 continues on next page.

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Gan et al., 2012 [59]	289	aCRC	FOLFOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (138)** A/C (125) C/C (26)		A/C HR=0.91 (95% CI: 0.66–1.87) C/C HR=0.51 (95% CI: 0.33–0.94)			
Li et al., 2012 [27]	335	aCRC	FOLFOX-6	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (153)** A/C (150) C/C (32)		A/C HR=0.88 (95% CI: 0.61–1.28) C/C HR=0.52 (95% CI: 0.23–1.09)			A/C HR=0.86 (95% CI: 0.56–1.20) p=0.48 C/C HR=0.48 (95% CI: 0.19–0.97) p<0.05
Huang et al., 2011 [25]	157	mCRC	FOLFOX-4	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**C/C (1)** A/C (19) A/A (137)	A/C HR=0.76 (95% CI: 0.09–6.58) p=0.81 A/A HR=0.28 (95% CI: 0.03–2.38) p=0.24	A/C HR=0.86 (95% CI: 0.10–7.74) p=0.86 A/A HR=0.30 (95% CI: 0.03–2.82) p=0.30			

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Le Morvan et al., 2007 [57]	59	mCRC	Oxaliplatin-based chemotherapy	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	A/C (33) + C/C (6) A/A (20)		15.6 mo vs 26.3 mo p=0.02			
Stoehlmacher et al., 2004 [31]	106	rCRC	FUOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (40)** A/C (53) C/C (13)	A/C RR=1.13 (95% CI: 0.72–1.78) C/C RR=1.25 (95% CI: 0.59–2.67) p=0.76	A/C RR=1.87 (95% CI: 1.06–3.31) C/C RR=2.44 (95% CI: 1.09–5.44) p=0.05			A/C RR=1.50 (95% CI: 0.79–2.87) C/C RR=3.33 (95% CI: 1.39–7.99) p=0.04
Paré et al., 2008 [33]	121	mCRC	FOLFOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Leukocytes	Polymorphism	**A/A (52)** A/C (45) + C/C (24)	12 mo vs 8 mo p<0.01	41 mo vs 17 mo p=0.02	RR=1.7 (95% CI: 1.1–2.8) p=0.02		RR=1.6 (95% CI: 1.1–2.5) p=0.03
Martinez-Balibrea et al., 2008 [34]	47	mCRC	CAPOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (20)** A/C (21) C/C (6)	A/C HR=1.05 (95% CI: 0.51–2.15) C/C HR=0.54 (95% CI: 0.19–1.52) p=0.39				

Supplementary Table S5.4 continues on next page.

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Martinez-Balibrea et al., 2008 [34]	48	mCRC	FUOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (22)** A/C (19) C/C (8)	A/C HR=0.94 (95% CI: 0.45–1.97) C/C HR=1.50 (95% CI: 0.61–3.69) p=0.61				
Chen et al., 2010 [36]	166	mCRC	FOLFOX-4	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (139)** A/C (27)					HR=4.41 (95% CI: 2.51–7.75) p<0.01
Etienne-Grimaldi et al., 2010 [60]	115	aCRC	mFOLFOX7	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	A/A (41) A/C (58) C/C (16)	6.4 mo vs 8.0 mo vs 6.4 mo p=0.33				
Lai et al., 2009 [58]	188	mCRC	FOLFOX-4	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	A/A (158) A/C (30)	11 mo vs 7 mo p<0.01	22 mo vs 14 mo p<0.01			
Park et al., 2001 [55]	71	mCRC	FUOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (22)** A/C (39) C/C (10)		17.4 mo vs 12.8 mo vs 3.3 mo A/C RR=1.31 C/C RR=4.01 p<0.01			

Table S5.4: ***Continued***

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis		
									PFS	OS	PFS	DFS	OS
Monzo et al., 2007 [43]	42	aCRC	CAPOX	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	A/A (21) A/C (17) + C/C (4)	14.4 mo vs 19.2 mo p=0.83	8.3 mo vs 8.4 mo, p=0.54			
Ruzzo et al., 2007 [40]	165	mCRC	FOLFOX-4	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (43)** A/C (97) C/C (25)	A/C HR=1.67 (95% CI: 0.96–2.89) p=0.06 C/C HR=1.79 (95% CI: 1.13–3.09) p=0.03		A/C HR=1.81 (95% CI: 1.01–3.25) p=0.04 C/C HR=2.21 (95% CI: 1.17–4.17) p=0.01		
Kumamoto et al., 2013 [42]	63	n.s.	mFOLFOX-6	XPD-Lys751Gln *c.2251A>C*	rs13181	Blood	Polymorphism	**A/A (58)** A/C (5)	10.3 mo vs 6.1 mo p=0.05	25.5 mo vs 29.2mo p=0.26			

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CI = confidence interval, DFS = disease-free survival, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FLOX = 5-fluorouracil and folinic acid, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, mCRC = metastatic colorectal cancer, mo = months, n.s. = not specified, OR = odds ratio, OS = overall survival, PFS = progression-free survival, rCRC = refractory colorectal cancer, RR = relative risk, *XPG = xeroderma pigmentosum complementation group G*. * Reference group in **bold**.

Table S5.5: Overview of studies on the association between XPG biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis		Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	PFS	OS	PFS	OS
Monzo et al., 2007 [43]	42	aCRC	CAPOX	XPG-His46= *c.138T>C*	rs1047768	Blood	Polymorphism	C/C (19) C/T (19) + TT (4)		32.2 mo vs 12.0 mo $p<0.01$		
Kweekel et al., 2009 [65]	91	aCRC	CAPOX	XPG-His46= *c.138T>C*	rs1047768	Blood	Polymorphism	**T/T (28)** T/C (46) C/C (17)		No difference	T/C HR=1.71 (95% CI: 0.98–2.98) C/C HR=2.85 (95% CI: 1.42–5.71) $p<0.01$	
Chen et al., 2016 [64]	170	aCRC	FOLFOX	*XPG +25A>G*	n.s.	Blood	Polymorphism	**AA (32) + AG (83)** GG (55)	HR=1.59 (95% CI: 1.14–2.22) $p<0.01$	HR=1.58 (95% CI: 1.14–2.22) $p<0.01$	HR=1.50 (95% CI: 1.07–2.11) $p=0.02$	HR=1.68 (95% CI: 1.18–2.39) $p<0.01$
Liu et al., 2012 [49]	432	n.s.	CAPOX or FOLFOX	XPG-Asp1104His *c.3310G>C*	rs17655	Blood	Polymorphism	**G/G** G/C + C/C		HR=1.43 (95% CI: 1.01–2.00) $p=0.04$		HR 1.69 (95% CI: 1.20–2.38) $p<0.01$

Table S5.5: *Continued*

									Univariate analysis		Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	PFS	OS	PFS	OS
Chen et al., 2016 [64]	170	aCRC	FOLFOX	*XPG* -763A>G	n.s.	Blood	Polymorphism	**GG (35) + GA (78)** AA (57)	HR=1.75 (95% CI: 1.14–2.22) p<0.01	HR=1.73 (95%CI: 1.24–2.40) p<0.01	HR=1.72 (95% CI: 1.23–2.41) p<0.01	HR=1.88 (95% CI: 1.33–2.66) p<0.01
Monzo et al., 2007 [43]	42	aCRC	CAPOX	XPG-His46= *c.138T>C* and *XPA* *c.-4A>G*	rs1047768 and rs1800975	Blood	Polymorphism	**Favorable genotype (XPG (C/C) + XPA (G/A or G/G)** vs unfavorable genotype		49.6 mo vs 7.8 mo p<0.01		RR=34 (95% CI: 6.3–183) p<0.01

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, FOLFOX = 5-fluorouracil; leucovorin and oxaliplatin, HR = hazard ratio, mo = months, n.s. = not specified, OS = overall survival, OR = odds ratio, PFS = progression-free survival, *XPA = xeroderma pigmentosum complementation group A*, *XPG = xeroderma pigmentosum complementation group G*. * Reference group in **bold**.

Table S5.6: Overview of studies on the association between MNAT1 biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	Univariate analysis OS
Kap et al., 2015 [50]	192	Stage II–IV	Oxaliplatin-based chemotherapy	*MNAT1 c.688-30168A>G*	rs3783819	Bblood/saliva	Polymorphism	**A/A -** vs G/A + G/G -	HR=0.51 (95% CI: 0.36–0.73) p<0.01
Kap et al., 2015 [50]	201	Stage II–IV	Oxaliplatin-based chemotherapy	*MNAT1 c.562-88A>G*	rs973063	Blood/saliva	Polymorphism	**A/A -** vs G/A + G/G -	HR=0.52 (95% CI: 0.37–0.72) p<0.01
Kap et al., 2015 [50]	201	Stage II–IV	Oxaliplatin-based chemotherapy	*MNAT1 c.809+24992A>G*	rs4151330	Blood/saliva	Polymorphism	**A/A -** vs G/A + G/G -	HR=0.53 (95% CI: 0.38–0.75) p<0.01

Abbreviations: CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, OS = overall survival. * Reference group in **bold**.

Table S5.7: Overview of studies on the association between XRCC1 biomarkers and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	DFS	OS
Huang et al., 2011 [25]	157	mCRC	FOLFOX-4	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	**A/A (10)** G/A (57) G/G (90)	G/G HR=0.31 (95% CI: 0.10–0.91) p=0.03 G/A HR=1.25 (95% CI: 0.51–3.07) p=0.62		G/G HR=0.15 (95% CI: 0.04–0.57) p<0.01 G/A HR=0.63 (95% CI: 0.22–1.76) p=0.38		
Suh et al., 2006 [81]	51	aCRC	mFOLFOX-4	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Tumor tissue	Polymorphism	G/G (31) G/A (16) A/A (4)			30.0 mo vs 16.5 mo vs 12.8 mo p=0.02		
Lamas et al., 2011 [28]	72	aCRC	FUOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	A/A - G/A – G/G -	6 mo vs 10 mo vs 12 mo p=0.67				
Zaanan et al., 2014 [30]	207	Stage III	FOLFOX-4 or FOLFOX-6	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Tumor tissue	Polymorphism	**G/G (94) + G/A (80)** A/A (33)		HR=1.61 (95% CI: 0.82-3.12) p=0.16			

Supplementary Table S5.7 continues on next page.

Table S5.7: ***Continued***

									Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	DFS	OS
Stoehlmacher et al., 2004 [31]	105	rCRC	FUOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	**G/G (44)** G/A (51) A/A (10)	G/A RR=0.95 (95% CI: 0.60–1.51) A/A RR=0.99 (95% CI: 0.47–2.09) p=0.97		G/A RR=1.07 (95% CI: 0.63–1.80) A/A RR=1.58 (95% CI: 0.71–3.55) p=0.50		
Liang et al., 2010 [32]	113	mCRC	mFOLFOX-4 or CAPOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	**A/A (61)** A/G (39) G/G (13)					A/G HR=1.09 (95% CI: 0.57–2.08) p=0.80 G/G HR=1.31 (95% CI: 0.53–3.25) p=0.57
Gan et al., 2012 [59]	289	aCRC	FOLFOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	**G/G (149)** G/A (88) A/A (51)			G/A HR=0.85 (95% CI: 0.51–1.23) A/A HR=0.66 (95% CI: 0.36–0.95)		

Table S5.7: ***Continued***

									Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	DFS	OS
Chua et al., 2009 [39]	115	mCRC	FOLFOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Tumor tissue	Polymorphism	**G/G (39)** A/G (61) A/A (15)	A/G HR=0.57 (95% CI: 0.28–1.19) p=0.10 A/A HR=1.01 (95% CI: 0.39–2.60) p=1.0 A/G + A/A HR=0.66 (95% CI: 0.34–1.28) p=0.20		A/G HR=0.92 (95% CI: 0.58–1.45) p=0.70 A/A HR=0.52 (95% CI: 0.24–1.14) p=0.10 A/G + A/A HR=0.83 (95% CI: 0.53–1.29) p=0.40		
Martinez-Balibrea et al., 2008 [34]	47	mCRC	CAPOX	XRCC1-Gln399Arg *c.1196A>G*	rs25487	Blood	Polymorphism	**G/G (19)** G/A (19) A/A (9)	G/A HR=0.82 (95% CI: 0.39–1.71) A/A HR=0.65 (95% CI: 0.25–1.66) p=0.64				
Martinez-Balibrea et al., 2008 [34]	48	mCRC	FUOX	XRCC1-Gln399Arg **c.1196A>G**	rs25487	Blood	Polymorphism	**G/G (21)** G/A (20) A/A (7)	G/A HR=0.85 (95% CI: 0.42–1.73) A/A HR=0.96 (95% CI: 0.31–3.00) p=0.90				

Supplementary Table S5.7 continues on next page.

Table S5.7: ***Continued***

									Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	PFS	DFS	OS	DFS	OS
Huang et al., 2011 [25]	157	mCRC	FOLFOX-4	ERCC1-Asn118= *c.354T>C* and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Blood	Polymorphism	2 favorable genotypes (ERCC1 C/C and XRCC1 G/G) - vs ≤1 favorable genotype -			25 mo vs 16.5 mo $p<0.01$		
Liang et al., 2010 [32]	113	mCRC	Modified FOLFOX-4 or CAPOX	ERCC1-Asn118= *c.354T>C* and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Blood	Polymorphism	**2 favorable genotypes (XRCC1 A/A and ERCC1 C/C) 38** vs 1 favorable genotype 40 vs 0 favorable genotype 35					1 favorable genotype HR=2.25 (95% CI: 1.38–3.67) $p<0.01$ 0 favorable genotype HR=2.60 (95% CI: 1.56–4.31) $p<0.01$
Zaanan et al., 2014 [30]	210	Stage III	FOLFOX-4 or FOLFOX-6	ERCC1-Asn118= *c.354T>C* and XRCC1-Gln399Arg *c.1196A>G*	rs11615 and rs25487	Tumor tissue	Polymorphism	**≥ 1 favorable genotype (ERCC1 C/C and/ or XRCC1 G/G + G/A) 179** vs 0 favorable genotype 21		HR=2.42 (95% CI: 1.16–5.03) p=0.02		HR=2.03 (95% CI: 0.96–4.28) p=0.06	

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CRC = colorectal cancer, CI = confidence interval, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, mo = months, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, rCRC = refractory colorectal cancer. * Reference group in **bold**.

Table S5.8: Overview of studies on the association between biomarkers in the HR pathway and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

									Univariate analysis	Multivariate analysis
Author, year	N	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	PFS	PFS
Martinez-Balibrea et al., 2008 [34]	47	mCRC	CAPOX	XRCC3-Thr241Met *c.722C>T*	rs861539	Blood	Polymorphism	**C/C (23)** C/T (18) T/T (6)	C/T HR=0.91 (95% CI: 0.43–1.9) T/T HR=1.8 (95% CI: 0.66–4.95) p=0.48	
Martinez-Balibrea et al., 2008 [34]	48	mCRC	FUOX	XRCC3-Thr241Met *c.722C>T*	rs861539	Blood	Polymorphism	**C/C (18)** C/T (20) T/T (10)	C/T HR=1.22 (95% CI: 0.58–2.6) T/T HR=1.33 (95% CI: 0.54–3.29) p=0.80	
Ruzzo et al., 2007 [40]	165	mCRC	FOLFOX-4	XRCC3-Thr241Met *c.722C>T*	rs861539	Blood	Polymorphism	**T/T (31)** C/T (71) C/C (63)	C/T HR=1.41 (95% CI: 0.89–2.24) p=0.12 C/C HR=0.87 (95% CI: 0.54–1.38) p=0.54	C/T HR=1.67 (95% CI: 0.96–2.89) p=0.07 C/C HR=0.99 (95% CI: 0.57–1.71) p=0.96

Supplementary Table S5.8 continues on next page.

Table S5.8: ***Continued***

									Univariate analysis	Multivariate analysis
Author, year	N	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/comparator (n)	PFS	PFS
Ihara et al., 2016 [82]	78	mCRC or rCRC	mFOLFOX or CAPOX ±bevacizumab	MRE11	n.a.	Tumor tissue	Protein expression	Positive expression (48) Negative expression (30)	11.3 mo vs 11.8 mo p=0.50	
Ihara et al., 2016 [82]	78	mCRC or rCRC	mFOLFOX or CAPOX ±bevacizumab	RAD51	n.a.	Tumor tissue	Protein expression	**Positive expression (40)** Negative expression (38)	9.7 mo vs 13.5 mo p=0.04	HR 0.80 (95% CI: 0.35–1.83) p=0.60
Ihara et al., 2016 [82]	78	mCRC or rCRC	mFOLFOX or CAPOX ±bevacizumab	MRE11 + RAD51	n.a.	Tumor tissue	Protein expression	MREE1 and/or RAD51: **Positive expression 47** Negative expression 31	10.1 mo vs 13.2 mo p=0.02	HR 1.39 (95%CI: 0.58–3.34) p=0.50
Moutinho et al., 2014 [79] discovery cohort	131	Stage IV	FUOX–based chemotherapy	*SRBC*	n.a.	Tumor tissue	DNA methylation status	**Unmethylated (92)** Methylated (39)	HR=1.83 (95% CI: 1.15–2.92) p= 0.01	
Moutinho et al., 2014 [79] validation cohort	58	Stage IV	FUOX–based chemotherapy	*SRBC*	n.a.	Tumor tissue	DNA methylation status	**Unmethylated (44)** Methylated (14)	HR=1.90 (95% CI: 1.01–3.60) p= 0.05	

Abbreviations: CAPOX = capecitabine and oxaliplatin, CRC = colorectal cancer, CI = confidence interval, DFS = disease-free survival, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, mo = months, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, rCRC = refractory colorectal cancer. * Reference group in **bold**.

Table S5.9: Overview of studies on the association between biomarkers in the MMR pathway and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

								Univariate analysis			Multivariate analysis	
Author, year	n	CRC type	Treatment	Biomarker	Type of sample	Type of assay	Comparator*/reference (n)	PFS	DFS	OS	DFS	OS
Kim et al., 2010 [70]	115	Stage II–IV	FOLFOX	MMR status	Tumor tissue	Protein expression	**pMMR (104)** dMMR (11)		HR=0.69 (0.24–1.97) p=0.49	HR=1.31 (0.17–9.98) p=0.79		
Sfakianaki et al., 2019 [46]	235	Stage II–III	FOLFOX or CAPOX	MMR status	Tumor tissue	Polymorphism	**dMMR (35)** pMMR (200)		HR=1.72 (95% CI: 1.29–3.51) p=0.03	HR=1.38 (95% CI: 1.04–2.71) p=0.04	HR=1.78 (95% CI: 1.34–3.01) p<0.01	HR=1.58 (95% CI: 1.24–3.00) p=0.02
Gallois et al., 2018 [69]	1867	Stage III	FOLFOX4 ± cetuximab	MMR status	Tumor tissue	Polymorphism	**dMMR (172)** pMMR (1560)					HR=1.80 (95% CI: 1.16–2.81) p<0.01

Abbreviations: aCRC = advanced colorectal cancer, CAPOX = capecitabine and oxaliplatin, CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, dMMR = deficient mismatch repair, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HR = hazard ratio, MMR = mismatch repair, mo = months, n.s. = not specified, OS = overall survival, PFS = progression-free survival, pMMR = proficient mismatch repair. * Reference group in **bold**.

Table S5.10: Overview of studies on the association between biomarkers in DNA damage response and DNA synthesis and treatment outcome of oxaliplatin-based chemotherapy in CRC patients

Author, year	N	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis	
									PFS	OS	PFS	OS
Sundar et al., 2018. [74]	121	mCRC	CAPOX± bevacizumab or FOLFOX± bevacizumab/ cetuximab	ATM	n.a.	Ttumor tissue	Protein expression	**Loss (9)** Proficient (113)		HR=2.52 (95% CI: 1.00–6.37) p=0.05		
Kweekel et al., 2009 [65]	91	aCRC	CAPOX	ATM-Asp1853Asn *c.5557G>A*	rs1801516	Blood	Polymorphism	**G/G (63)** G/A (24) A/A (4)		No difference	G/A HR=0.72 (95% CI: 0.43–1.21) A/A HR=4.25 (95% CI: 1.45–12.44) p<0.01	
Okazaki et al., 2017 [76]	218	mCRC	Oxaliplatin-based chemotherapy	*HIC1* *Tandem repeat D17S5 loci*	n.a.	Blood	Polymorphism	**S/S (≤4TRs in both alleles) 179 + S/L (≤4TRs in one allele) 19** L/L(≥5TRs in both alleles) 20	HR=1.93 (95% CI: 1.11–3.35) p=0.01	HR=1.25 (95% CI: 0.74–2.10) p=0.40	HR=2.00 (95% CI: 1.13–3.54) p=0.02	HR=1.20 (95% CI: 0.71–2.04) p=0.50

Table S5.10: ***Continued***

Author, year	N	CRC type	Treatment	Biomarker	rs number	Type of sample	Type of assay	Reference*/ comparator (n)	Univariate analysis		Multivariate analysis	
									PFS	OS	PFS	OS
Suenaga et al., 2018 [78]	143	mCRC	FOLFOX ± bevacizumab	*PIN1* *NC_000019.9:g.9945179G>C*	rs2233678	Blood	Polymorphism	**G/G (129)** G/C (13) + C/C (1)	HR=3.24 (95% CI: 1.60–6.54) p<0.01	HR=2.38 (95% CI: 1.32–4.30) p<0.01	HR= 2.67 (95% CI: 1.28–5.57) p<0.01	HR=1.91 (95%CI: 1.02–3.59) p=0.04
Suenaga et al., 2018 [78]	70	mCRC	FOLFOX or CAPOX + bevacizumab	*PIN1* *NC_000019.9:g.9945179G>C*	rs2233678	Blood	Polymorphism	**G/G (64)** G/C (6)	HR=1.11 (95% CI: 0.43–2.82) p=0.83	HR=2.43 (95% CI: 0.83–7.15) p=0.09	HR=1.15 (95% CI: 0.44–2.98) p=0.78	HR=3.01 (95% CI: 0.98–9.20) p=0.05
Park et al., 2010 [80]	88	mCRC	CAPOX or mFOLFOX4	*MGMT* *-535G>T*	rs1625649	Tumor tissue	Polymorphism	**G/G (39) + G/T (39)** T/T (10)	HR=2.65 (95% CI: 1.10–6.39) p=0.03	HR=2.09 (95% CI: 0.59–7.47) p=0.26	HR=3.14 (95% CI: 1.42–6.91) p<0.01	HR=2.06 (95% CI: 0.74–5.75) p=0.17

Abbreviations: *ATM = ataxia-telangiectasia mutated*, CAPOX = capecitabine and oxaliplatin, CRC = colorectal cancer, CI = confidence interval, FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin, FUOX = 5-fluorouracil and oxaliplatin, HIC1 = hypermethylated in cancer 1, HR = hazard ratio, *MGMT = Human O6-alkylguanine-DNA alkyltransferase*, mo = months, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, *PIN1 = peptidyl-prolyl cis/trans isomerase NIMA-interacting 1*, TR = tandem repeat. * Reference group in **bold**.