National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[B1] Use of molecular biomarkers to guide systemic therapy

NICE guideline TBC

Evidence reviews

July 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Molecular biomarkers to guide systemic therapy for colorectal cancer

This evidence review supports recommendation 1.4.1.

Review question

Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Introduction

Systemic therapy for colorectal cancer includes a number of different chemotherapy drugs, including irinotecan, oxaliplatin and oral fluoropyrimidines as well as anti–EGFR targeted therapy with cetuximab and panitumumab. However, while some drugs offer benefits to certain patients, other patients may experience toxicity instead. Despite the range of options for systemic management, the effectiveness of specific treatments for individual patients has not been thoroughly assessed. Predictive biomarkers provide information about the effect of a therapeutic intervention on an outcome and therefore provide valuable insight to guide treatment decision making. Therefore, the aim of this review was to determine which predictive biomarkers should be used in the systemic management of colorectal cancer patients.

Summary of the protocol

Please see Table 1 for a summary of the population, prognostic/predictive factors, and outcomes (PFO) characteristics of this review.

Table 1: Summary of the PFO table

Population	Adults with primary colorectal cancer (colon or rectal cancer) Stratification: • Right colon versus left colon or rectum • Cancer stage ○ Stage 4 versus others
Predictive factors	Use of molecular biomarkers to guide choice of systemic therapy Predictive biomarkers in colorectal cancer: • *RAS/KRAS/NRAS* • *BRAF* V600E • *PIK3CA* status • *MMR/MSI* • *CD3/CD8* (Immunoscore) • *PD1/PD-L1* • ColDX • Oncotype DX
Outcomes	**Critical** • Response to systemic therapy (as reported in the paper; advanced diseases)

	• Progression-free survival (PFS) • Disease-free survival (DFS; adjuvant treatments) **Important** • Overall survival (OS)

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; KRAS: Kirsten rat sarcoma virus oncogene homolog; MMR: mismatch repair; MSI: microsatellite instability; NRAS: neuroblastoma rat sarcoma virus oncogene homolog; PD(-L)1: programmed death(-ligand) 1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAS: rat sarcoma virus oncogene homolog

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Twenty five studies were identified for this review, 9 systematic reviews (Dahabreh 2011, Des Guetz 2009, Huang 2014, Petrelli 2013, Shen 2019, Sorich 2015, Sun 2019, Yuan 2013, Zhu 2016) and 16 observational analyses of randomised controlled trials (RCTs) which were used to update the systematic reviews (Bertagnolli 2009, Gray 2011, Guren 2017, Hegeswich-Becker 2018, Hutchins 2011, Kennedy 2011, Modest 2016, Niedzwiecki 2016, Ogino 2009,Seligman 2016, Sinicrope 2011, Sinicrope 2015, Taib 2017, Vernook 2013, Yothers 2013, Zaanan 2018).

The included studies are summarised in Table 2.

Seven studies compared *KRAS* mutant versus wildtype (Dahabreh 2011, Hutchins 2011 Petrelli 2013, Modest 2016, Ogino 2009, Sinicrope 2011, Taib 2017).

Three studies compared *RAS* mutant versus wildtype (Guren 2017, Hegeswich-Becker 2018, Sorich 2015).

Eight studies compared *BRAF* mutant versus wildtype (Guren 2017, Hutchins 2011, Modest 2016, Sinicrope 2015, Seligman 2016, Taib 2017, Yuan 2013, Zhu 2016).

One study compared *PIK3CA* mutant versus wildtype (Huang 2014).

Five studies compared deficient versus proficient mismatch repair status (Bertagnolli 2009, Des Guetz 2009, Hutchins 2011, Sinicrope 2011, Zaanan 2018).

One study compared high versus low Immunoscore (Sun 2019).

Two studies compared high versus low ColDX risk (Kennedy 2011, Niedzwiecki 2016).

Three studies compared high versus low Oncotype-DX recurrence risk score (Gray 2011, Vernook 2013, Yothers 2013).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Comparison	Systemic treatment	Outcomes
Bertagnolli 2009 RCT[1] USA	Stage II-III colon cancer	*dMMR/MSI-H* versus *pMMR/MSS*	Chemotherapy	• DFS; N=706
Dahabreh 2011 Systematic review	Metastatic colorectal cancer	*KRAS* mutant versus wildtype	Anti-EGFR ± chemotherapy	• Response; 22 studies; N=2242 • PFS; 16 studies; N=1945 • OS; 13 studies; N=1695
Des Guetz 2009 Systematic review	Metastatic colorectal cancer	*dMMR/MSI-H* versus *pMMR/MSS*	Chemotherapy	• Response; 5 studies; N=860
Gray 2011 RCT[1] UK	Stage II colon cancer	Oncotype-DX recurrence score higher versus lower	Surgery ± chemotherapy	• DFS; N=1436
Guren 2017 RCT[1] Nordic countries	Metastatic colorectal cancer	*BRAF* mutant versus wildtype *RAS* mutant versus *RAS/BRAF* wildtype	Chemotherapy ± Anti-EGFR	• OS; N=457 • Response; N=457
Hegeswich-Becker 2018 RCT[1] Germany	Metastatic colorectal cancer	*RAS* mutant versus *RAS/BRAF* wildtype	Bevacizumab + chemotherapy	• OS; N=567
Huang 2014 Systematic review	Metastatic colorectal cancer	*PIK3CA* mutant versus wildtype (in *KRAS* wildtype)	Anti-EGFR ± chemotherapy	• Response; 9 studies; N=693 • OS; 3 studies; N=508 • PFS; 4 studies; N=526

Study	Population	Comparison	Systemic treatment	Outcomes
Hutchins 2011 RCT[1] UK	Stage II right sided colon cancer	*BRAF* mutant versus wildtype *dMMR/MSI-H* versus *pMMR/MSS* *KRAS* mutant versus wildtype	Chemotherapy	• DFS; N=250
Kennedy 2011 Retrospective cohort study UK	Stage II colon cancer	ColDX high versus low risk	None - surgery alone	• DFS; N=144
Modest 2016 5 RCTs[1] Germany	Metastatic colorectal cancer	*BRAF* mutant versus wildtype *KRAS* mutant versus wildtype	Bevacizumab + chemo Chemo alone	• PFS; 5 studies; N=829 • OS; 5 studies; N=829
Niedzwiecki 2016 RCT[1] USA	Stage II colon cancer	ColDX high versus low risk	Surgery ± edrecolomab	• DFS; N=393
Ogino 2009 RCT[1] USA	Stage II-III colorectal cancer	*KRAS* mutant versus wildtype	Chemotherapy	• DFS; N=508 • OS; N=508
Petrelli 2013 Systematic review	Metastatic colorectal cancer	*KRAS* mutant versus wildtype	Bevacizumab + chemotherapy	• Response; 12 studies; N=2266 • PFS; 12 studies; N=2266 • OS; 12 studies; N=2266
Seligman 2016 2 RCTs[1] UK	Metastatic colorectal cancer	*BRAF* mutant versus wildtype	Chemotherapy	• Response; 2 studies; N=1541 • PFS; 2 studies; N=1283 • OS; 2 studies; N=1541
Shen 2019 Systematic review	Stage I-IV colorectal cancer	*PD-L1* positive versus negative	Chemotherapy	• OS; 10 studies; N=3481
Sinicrope 2011 5 RCTs[1] USA	Stage II-III colon cancer	*dMMR/MSI-H* versus *pMMR/MSS*	Chemotherapy	• DFS; 5 studies; N=2141 • OS; 5 studies; N=2141
Sinicrope 2015 RCT[1]	Stage III colon cancer	*BRAF* mutant versus wildtype *KRAS* mutant versus wildtype	Chemotherapy ± Anti-EGFR	• DFS; N=2720

Study	Population	Comparison	Systemic treatment	Outcomes
USA				
Sorich 2015 Systematic review	Metastatic colorectal cancer	New *RAS* mutant versus all *RAS* wildtype	Anti-EGFR ± chemotherapy	• PFS; 9 studies; N=5948 • OS; 9 studies; N=5948
Sun 2019 Systematic review	Stage I-III colorectal cancer Metastatic colorectal cancer	Immunoscore low versus high	Not reported	• DFS; 5 studies; N=3992 • OS; 6 studies; N=4188
Taib 2017 RCT[1] Europe	Stage III colon cancer	*BRAF* mutant versus wildtype *KRAS* mutant versus wildtype	Chemotherapy ± Anti-EGFR	• DFS; N=783 • OS; N=192
Vernook 2013 RCT[1] USA	Stage II colon cancer	Oncotype-DX recurrence score higher versus lower	Surgery ± edrecolomab	• DFS; N=690
Yothers 2013 RCT[1] USA	Stage II colon cancer	Oncotype-DX recurrence score higher versus lower	Chemotherapy	• DFS; N=892 • OS; N=892
Yuan 2013 Systematic review	Metastatic colorectal cancer	*BRAF* mutant versus wildtype	Anti-EGFR ± chemotherapy	• Response; 21 studies; N=4203 • PFS; 21 studies; N=4203 • OS; 21 studies; N=4203
Zaanan 2018 2 RCTs[1] USA & Europe	Stage III colon cancer	*dMMR/MSI-H* versus *pMMR/MSS*	Chemotherapy	• DFS; 2 studies; N=2501
Zhu 2016 Systematic review	Stage II-III colorectal cancer	*BRAF* mutant versus wildtype	Chemotherapy ± Anti-EGFR	• DFS; 7 studies; N=1035 • OS; 7 studies; N=1035

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; DFS: disease-free survival; dMMR: deficient mismatch repair; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma virus oncogene homolog; MSI-H: high microsatellite instability; MSS: microsatellite stability; N: number of patients; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; pMMR: proficient mismatch repair; RAS: rat sarcoma virus oncogene homolog; RCT: randomised controlled trial

1 Prognostic or predictive data were collected during the course of a randomised trial. The study design was therefore observational for the prognostic or predictive analyses.

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Comparison 1: KRAS mutant versus wildtype

Anti-EGFR targeted therapy

Critical outcomes

Response to systemic therapy

- High quality evidence from 22 observational studies (N=2242) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *KRAS* mutations had poorer response to systemic therapy than patients with wildtype *KRAS.*

Progression-free survival with anti-EGFR targeted therapy

- High quality evidence from 16 observational studies (N=1945) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *KRAS* mutations had poorer progression-free survival than patients with wildtype *KRAS.*

Disease-free survival with adjuvant anti-EGFR targeted therapy

- High quality evidence from 1 observational study (N=783) showed that in patients with stage II or III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy, those with *KRAS* mutations had poorer disease-free survival than patients with wildtype *KRAS.*

Important outcomes

Overall survival with anti-EGFR targeted therapy

- High quality evidence from 13 observational studies (N=1695) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *KRAS* mutations had poorer overall survival than patients with wildtype *KRAS.*

- High quality evidence from 1 observational study (N=783) showed that in patients with stage II or III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy, those with *KRAS* mutations had poorer overall survival than patients with wildtype *KRAS.*

Bevacizumab

Critical outcomes

Response to systemic therapy

- High quality evidence from 12 observational studies (N=2266) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *KRAS* mutations had poorer response to systemic therapy than patients with wildtype *KRAS.*

Progression-free survival with bevacizumab

- High quality evidence from 17 observational studies (N=3095) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *KRAS* mutations had poorer progression-free survival than patients with wildtype *KRAS.*

Disease-free survival with bevacizumab

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with bevacizumab

- High quality evidence from 17 observational studies (N=3095) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *KRAS* mutations had poorer overall survival than patients with wildtype *KRAS.*

Chemotherapy

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival with chemotherapy

- High quality evidence from 5 observational studies (N=410) showed that in patients with metastatic colorectal cancer treated with chemotherapy, there was no important difference between the progression-free survival of those with *KRAS* mutations and those with wildtype *KRAS.*

Disease-free survival with chemotherapy

- High quality evidence from 1 observational study (N=784) showed that in patients with right sided stage II colorectal cancer treated with chemotherapy, those with

KRAS mutations had poorer disease-free survival than patients with wildtype *KRAS..*

Important outcomes

Overall survival with chemotherapy

- High quality evidence from 5 observational studies (N=410) showed that in patients with metastatic colorectal cancer treated with chemotherapy, there was no important difference between the overall survival of those with *KRAS* mutations and those with wildtype *KRAS.*
- High quality evidence from 1 observational study (N=508) showed that in patients with stage II colorectal cancer treated with 5-FU based chemotherapy, there was no important difference between the overall survival of those with *KRAS* mutations and those with wildtype *KRAS.*

Comparison 2: RAS mutant versus wildtype

Anti-EGFR targeted therapy

Critical outcomes

Response to systemic therapy

- High quality evidence from 1 observational study (N=457) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *RAS* mutations had poorer response to systemic therapy than patients with wildtype *RAS.*

Progression-free survival with anti-EGFR targeted therapy

- High quality evidence from 9 observational studies (N=5948) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *RAS* mutations had poorer progression-free survival than patients with wildtype *RAS.*

Disease-free survival with adjuvant anti-EGFR targeted therapy

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with anti-EGFR targeted therapy

- High quality evidence from 10 observational studies (N=6405) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *RAS* mutations had poorer overall survival than patients with wildtype *RAS.*

Bevacizumab

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival with bevacizumab

No evidence was identified to inform this outcome.

Disease-free survival with bevacizumab

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with bevacizumab

- High quality evidence from 1 observational study (N=597) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *RAS* mutations had poorer overall survival than patients with wildtype *RAS.*

Comparison 3: BRAF mutant versus wildtype

Anti-EGFR targeted therapy

Critical outcomes

Response to systemic therapy

- High quality evidence from 22 observational studies (N=4660) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *BRAF* mutations had poorer response to systemic therapy than patients with wildtype *BRAF.*

Progression-free survival with anti-EGFR targeted therapy

- High quality evidence from 21 observational studies (N=4203) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *BRAF* mutations had poorer progression-free survival than patients with wildtype *BRAF.*

Disease-free survival with adjuvant anti-EGFR targeted therapy

- High quality evidence from 9 observational studies (N=3947) showed that in patients with stage II or III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy, those with *BRAF* mutations had poorer disease-free survival than patients with wildtype *BRAF.*

Important outcomes

Overall survival with anti-EGFR targeted therapy

- High quality evidence from 22 observational studies (N=4660) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *BRAF* mutations had poorer overall survival than patients with wildtype *BRAF.*
- High quality evidence from 8 observational studies (N=1227) showed that in patients with stage II or III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy, those with *BRAF* mutations had poorer overall survival than patients with wildtype *BRAF.*

Bevacizumab

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival with bevacizumab

- High quality evidence from 5 observational studies (N=829) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *BRAF* mutations had poorer progression-free survival than patients with wildtype *BRAF,* although there was uncertainty in the effect size.

Disease-free survival with bevacizumab

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with bevacizumab

- High quality evidence from 5 observational studies (N=829) showed that in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy, those with *BRAF* mutations had poorer overall survival than patients with wildtype *BRAF.*

Chemotherapy

Critical outcomes

Response to systemic therapy

- High quality evidence from 2 observational studies (N=1541) showed that in patients with metastatic colorectal cancer treated with chemotherapy, there was no clinically important difference between the response rates of those with *BRAF* mutations and those with wildtype *BRAF.*

Progression-free survival with chemotherapy

- High quality evidence from 7 observational studies (N=1693) showed that in patients with metastatic colorectal cancer treated with chemotherapy, there was no clinically important difference between the progression-free survival of those with *BRAF* mutations and those with wildtype *BRAF.*

Progression-free survival with chemotherapy

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with chemotherapy

- High quality evidence from 7 observational studies (N=1951) showed that in patients with metastatic colorectal cancer treated with chemotherapy, those with *BRAF* mutations had poorer overall survival than patients with wildtype *BRAF.*

Comparison 4: PIK3CA mutant versus wildtype

Critical outcomes

Response to systemic therapy

- Moderate quality evidence from 9 observational studies (N=693) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *PIK3CA* mutations had poorer response to systemic therapy than patients with wildtype *PIK3CA.*

Progression-free survival with anti-EGFR targeted therapy

- Moderate quality evidence from 4 observational studies (N=526) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *PIK3CA* mutations had poorer progression-free survival than patients with wildtype *PIK3CA.*

Disease-free survival with anti-EGFR targeted therapy

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with anti-EGFR targeted therapy

- Moderate quality evidence from 3 observational studies (N=508) showed that in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy, those with *PIK3CA* mutations had poorer overall survival than patients with wildtype *PIK3CA.*

Comparison 5: deficient versus proficient mismatch repair status (dMMR versus pMMR)

Critical outcomes

Response to systemic therapy

- High quality evidence from 5 observational studies (N=693) showed that in patients with metastatic colorectal cancer, there was no clinically important

difference in response to chemotherapy between those with *dMMR* and those with *pMMR.*

Progression-free survival with chemotherapy

No evidence was identified to inform this outcome.

Disease-free survival with chemotherapy

- High quality evidence from 8 observational studies (N=5348) showed that in patients with metastatic colorectal cancer treated with chemotherapy, those with *dMMR* had better disease-free survival than patients with *pMMR.*

Important outcomes

Overall survival with chemotherapy

- High quality evidence from 5 observational studies (N=2141) showed that in patients with metastatic colorectal cancer treated with chemotherapy, those with *dMMR* had better overall survival than patients with *pMMR.*

Comparison 6: Immunoscore (high versus low)

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival

No evidence was identified to inform this outcome.

Disease-free survival

- Low quality evidence from 5 observational studies (N=3992) showed that in patients with stage I to III colorectal cancer, those with high Immunoscore had poorer disease-free survival than patients with a low Immunoscore.

Important outcomes

Overall survival

- Low quality evidence from 5 observational studies (N=4188) showed that in patients with stage I to III colorectal cancer, those with high Immunoscore had poorer overall survival than patients with a low Immunoscore.
- Low quality evidence from 2 observational studies (N=612) showed that in patients with metastatic colorectal cancer, those with high Immunoscore had poorer overall survival than patients with a low Immunoscore.

Comparison 7: PD-L1 positive versus negative

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival

No evidence was identified to inform this outcome.

Disease-free survival

No evidence was identified to inform this outcome.

Important outcomes

Overall survival with chemotherapy

- Moderate quality evidence from 10 observational studies (N=3481) showed that patients with *PD-L1* positive colorectal cancer had poorer overall survival than patients with *PD-L1* negative status.

Comparison 8: ColDX high risk versus low risk

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival

No evidence was identified to inform this outcome.

Disease-free survival

- Low quality evidence from 2 observational studies (N=537) showed that in patients with stage II colon cancer, those with high ColDX risk score had poorer disease-free survival than patients with a low risk score.

Important outcomes

Overall survival

- Low quality evidence from 2 observational studies (N=537) showed that in patients with stage II colon cancer, those with high ColDX risk score had poorer overall survival than patients with a low risk score.

Comparison 9: Oncotype-DX higher versus lower recurrence score

Critical outcomes

Response to systemic therapy

No evidence was identified to inform this outcome.

Progression-free survival

No evidence was identified to inform this outcome.

Disease-free survival

- Moderate quality evidence from 3 observational studies (N=3018) showed that in patients with stage II colon cancer, those with higher Oncotype-DX recurrence score risk score had poorer disease-free survival than patients with a lower recurrence risk score.

Important outcomes

Overall survival

- High quality evidence from 1 observational studies (N=892) showed that in patients with stage II colon cancer treated with adjuvant chemotherapy, those with higher Oncotype-DX recurrence score risk score had poorer overall survival than patients with a lower recurrence risk score.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Response to systemic therapy was a critical outcome for this question because biomarkers could help identify patients most likely to benefit from systemic treatment. Similarly progression-free survival (for those with metastatic disease) and disease-free survival (for those with non-metastatic disease) were critical because effective systemic treatment should influence these outcomes. Overall survival was an important outcome because the relationship between biomarkers, the choice of systemic therapy and overall survival is less clear. This is because biomarkers may be also prognostic factors which identify patients with poor outcomes regardless of which systemic therapy they receive.

The quality of the evidence

Evidence was available on all predictive biomarkers of interest. The quality of the evidence was assessed using modified GRADE and varied from low to high quality. Evidence was downgraded due to incomplete reporting of attrition rates and adjustment for confounders. In some evidence was downgraded because systemic therapy was not given or was not relevant to current practice. There was a potential selection bias in some studies due to the inclusion of only the subset of patients whose tumour tissue could be retrieved for biomarker tests.

Benefits and harms

The evidence showed that *RAS* and *BRAF* V600E mutations were predictive of response to anti-EGFR targeted therapy in people with metastatic colorectal cancer. In this group, people with *RAS* or *BRAF* V600E mutations also had poorer progression-free and overall survival than those without such mutations. By using biomarkers to identify patients unlikely to benefit from anti-EGFR targeted therapy, patients can be spared the side-effects associated with the treatment.

In patients with *KRAS* wildtype metastatic disease the evidence indicated *PIK3CA* was a potential predictive biomarker of response to anti-EGFR targeted therapy but

with a much smaller body of evidence than for *RAS* and *BRAF* the committee were not confident to make a recommendation for *PIK3CA* testing given it is not current practice.

The evidence showed that people with non-metastatic colorectal cancer with *RAS* or *BRAF* V600E mutations who were treated with anti-EGFR targeted therapy had poorer disease-free and overall survival than those without such mutations. The committee did not recommend *RAS* or *BRAF* testing in this group, however, because evidence does not support the use of adjuvant anti-EGFR targeted therapy in non-metastatic disease.

There was consistent evidence that disease-free and overall survival were better in those patients receiving chemotherapy with non-metastatic colorectal cancer and deficient mismatch repair (*dMMR*) when compared to those with proficient mismatch repair (*pMMR*). The committee considered that mismatch repair status could help guide treatment decisions, however NICE diagnostic guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer (DG27) already recommends testing for mismatch repair status in all people with colorectal cancer. For this reason the committee did not make a separate recommendation about mismatch repair testing but instead referred to the existing diagnostics guidance.

Evidence showed that Immunoscore and PD-L1 were associated with overall survival but given the lack of evidence about their association with response rate or progression-free survival the committee did not think there was strong enough evidence about its use to guide systemic treatment decisions and did not make a recommendation about it.

Evidence about CoIDX or Oncotype DX testing was limited to studies reporting overall and disease-free survival in stage II colon cancer. The committee considered that while these may be prognostic markers it was not appropriate to recommend their use for guiding systemic therapy choices.

Cost effectiveness and resource use

The committee considered the resource impact of their recommendations would be minimal as *RAS* testing is current practice and the additional *BRAF* V600E test can be done as part of the extended colorectal cancer molecular test panel.

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Shen Z, Gu L, Mao D, et al. (2019) Clinicopathological and prognostic significance of PD-L1 expression in colorectal cancer: a systematic review and meta-analysis. World Journal of Surgical Oncology 17(1): 4

Sinicrope 2011

Sinicrope F, Foster N, Thibodeau S, et al. (2011) DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. Journal of the National Cancer Institute 103(11): 863-875

Sinicrope 2015

Sinicrope F, Shi Q, Smyrk T, et al, (2015) Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes. Gastroenterology 148(1): 88-99

Sorich 2015

Sorich M, Wiese M, Rowland A, et al. (2015), Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Annals of Oncology 26(1): 13-21

Sun 2019

Sun G, Dong X, Tang X, et al. (2019) The prognostic value of immunoscore in patients with colorectal cancer: A systematic review and meta-analysis. Cancer Medicine 8(1): 182-189

Taieb 2017

Taieb J, Balogoun R, Le Malicot K, et al. (2017) Adjuvant FOLFOX +/- cetuximab in full RAS and BRAF wildtype stage III colon cancer patients. Annals of Oncology 28(4): 824-830

Venook 2013

Venook A, Niedzwiecki D, Lopatin M, et al. (2013) Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. Journal of Clinical Oncology 31(14): 1775-1781

Yothers 2013

Yothers G, O'Connell M, Lee M, et al. (2013) Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in patients with stage

II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. Journal of Clinical Oncology 31(36): 4512-4519

Yuan 2013

Yuan Z, Wang X, Qin Q, et al. (2013) The prognostic role of BRAF mutation in metastatic colorectal cancer receiving anti-EGFR monoclonal antibodies: a meta-analysis. PLoS ONE 8(6): e65995

Zaanan 2018

Zaanan A, Shi Q, Taieb J, et al. (2018) Role of deficient DNA mismatch repair status in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy a pooled analysis from 2 randomized clinical trials. Journal of the American Medical Association - Oncology 4(3): 379-383

Zhu 2016

Zhu L, Dong C, Cao Y, et al. (2016) Prognostic Role of BRAF Mutation in Stage II/III Colorectal Cancer Receiving Curative Resection and Adjuvant Chemotherapy: A Meta-Analysis Based on Randomized Clinical Trials. PLoS ONE 11(5) e0154795

Appendices

Appendix A – Review protocol

Review protocol for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Table 3: Review protocol for use of predictive biomarkers in systemic management of colorectal cancer patients

Field (based on PRISMA-P)	Content
Review question in guideline	Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?
Type of review question	Predictive / prognostic
Objective of the review	To determine which predictive biomarkers should be used in the systemic management of colorectal cancer patients.
Eligibility criteria – population/disease/condition/issue/domain	Adults with primary colorectal cancer (colon or rectal cancer) Stratification: • Right colon versus left colon or rectum • Cancer stages ○ Stage 4 versus others
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Predictors** Use of molecular biomarkers to guide choice of systemic therapy Predictive biomarkers in colorectal cancer: • *RAS/KRAS/NRAS* • *BRAF* V600E • *PIK3CA* status • *MMR/MSI* • *CD3/CD8* (Immunoscore) • *PD1/PD-L1* • ColDX • Oncotype DX
Eligibility criteria – comparator(s)/control or reference (gold) standard	Not applicable
Outcomes and prioritisation	**Critical:** • Response to systemic therapy (as reported in the paper; • Progression-free survival (advanced disease) • Disease-free survival (adjuvant treatments) **Important:** • Overall survival

	MIDs: statistical significance
Eligibility criteria – study design	• Systematic reviews of population-based registry studies • Population-based registry studies • Prospective or retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post-2000 Studies conducted post-2000 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 2000 would no longer be relevant.
Proposed sensitivity/sub-group analysis, or meta-regression	All studies should include multivariate analysis controlling for the following confounding factors: • Line of treatment • Combinations • Single agent • Testing methods (if reported) • Scope
Selection process – duplicate screening/selection/analysis	The quality of the evidence will be assessed on a per study basis using the tools specified in the Methods for assessing bias at outcome/study level section of the protocol. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Analyses will be performed using Cochrane Review Manager (RevMan5) where possible if studies have adjusted for the same confounding factors. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 2000
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to	For details please see section 4.5 of Developing NICE guidelines: the manual

previous protocol	
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • CHARMS checklist for systematic reviews of risk prediction modelling studies • QUIPS tool for prognostic factor studies • PROBAST tool for risk prediction modelling studies • CASP checklist for clinical prediction rule The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE modified for prognostic/predictive reviews.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Odds ratios and hazard ratios will be calculated where appropriate. **Minimally important differences**: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual.

authors and guarantor	Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CASP: Critical Appraisals Skills Programme; CCTR: Cochrane Controlled Trials Register; CDSR: Cochrane Database of Systematic Reviews; CHARMS: Checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies; DARE: Database of Abstracts and Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; KRAS: Kirsten rat sarcoma virus oncogene homolog; MID: minimally important difference; MMR: mismatch repair; MSI: microsatellite instability; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NRAS: neuroblastoma rat sarcoma virus oncogene homolog; PD(-L)1: programmed death(-ligand) 1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; PROBAST: Prediction Model Risk of Bias Assessment Tool; QUIPS: Quality in Prognosis Studies; RAS: rat sarcoma virus oncogene homolog

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: Which predictive biomarkers 3 should be used in the systemic management of colorectal cancer patients?

4 Databases: Embase/Medline

5 Last searched on: 31/10/2018

#	Search
1	exp colorectal neoplasms/ use ppez
2	(exp colorectal cancer/ or exp colon tumor/ or exp rectum tumor/) use emez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	exp *antineoplastic agent/ use emez or exp *antineoplastic agents/ use ppez
6	exp *Antineoplastic Protocols/ use ppez
7	exp *chemotherapy/ use emez
8	Cancer Vaccines/ use ppez
9	cancer vaccine/ use emez
10	cancer immunotherapy/ use emez
11	exp *antibodies, monoclonal/ use ppez
12	*monoclonal antibody/ use emez
13	((anti canc* or anticanc* or anticarcinogen* or anti neoplas* or antineoplas* or cytotoxic*) adj2 (agent* or drug* or protocol* or regimen* or treatment* or therap*)).ti.
14	(SACT or chemotherap* or immunotherap* or biological agent* or biological therap*).ti.
15	systemic therap*.tw.
16	or/5-15
17	exp *Ras proteins/ use ppez
18	(ras protein/ or k ras protein/ or oncogene n ras/) use emez
19	(((ras or kras or k ras or nras or n ras) adj2 (wildtype or wild type or wt or mutant or mutat* or protein or gene)) and (predict* or prognos*)).tw.
20	*Proto-oncogene proteins B-Raf/ use ppez
21	*B raf kinase/ use emez
22	((Braf or b raf) adj3 v600e).tw.
23	exp *Phosphatidylinositol 3-Kinases/ use ppez
24	*phosphatidylinositol 3 kinase/ use emez
25	(PIK3CA and (predict* or prognos*)).tw.
26	DNA mismatch repair/ use ppez
27	*Mismatch repair/ use emez
28	((mismatch or MMR) adj3 (deficien* or deficit* or proficien*)).tw.
29	((Mismatch repair or MMR-d or MMR-p or dMMR or pMMR) and (predict* or prognos*)).tw.
30	*Microsatellite Instability/ use ppez or *microsatellite instability/ use emez
31	(microsatellite instability or microsatellite unstable or MSI-H).tw.
32	(MSI adj2 (cancer* or tumo?r* or test* or status)).tw.
33	exp *cd3 complex/ use ppez
34	*cD3 antigen/ use emez
35	*Cd8 antigens/ use ppez
36	*CD8 antigen/ use emez
37	(((cd3 or cd8) adj3 (antigen* or protein* or complex or immunoscore or immuno score)) and (predict* or prognos*)).tw.

#	Search
38	Programmed Cell Death 1 Receptor/ use ppez
39	programmed death 1 receptor/ use emez
40	B7-H1 Antigen/ use ppez
41	programmed death 1 ligand 1/ use emez
42	((PD1 or PD-1 or PDL-1 or PDL1 or PD-L1) and (predict* or prognos*)).tw.
43	(coldx or col dx or oncotype dx).tw.
44	or/17-43
45	4 and 16 and 44
46	Letter/ use ppez
47	letter.pt. or letter/ use emez
48	note.pt.
49	editorial.pt.
50	Editorial/ use ppez
51	News/ use ppez
52	exp Historical Article/ use ppez
53	Anecdotes as Topic/ use ppez
54	Comment/ use ppez
55	Case Report/ use ppez
56	case report/ or case study/ use emez
57	(letter or comment*).ti.
58	or/46-57
59	randomized controlled trial/ use ppez
60	randomized controlled trial/ use emez
61	random*.ti,ab.
62	or/59-61
63	58 not 62
64	animals/ not humans/ use ppez
65	animal/ not human/ use emez
66	nonhuman/ use emez
67	exp Animals, Laboratory/ use ppez
68	exp Animal Experimentation/ use ppez
69	exp Animal Experiment/ use emez
70	exp Experimental Animal/ use emez
71	exp Models, Animal/ use ppez
72	animal model/ use emez
73	exp Rodentia/ use ppez
74	exp Rodent/ use emez
75	(rat or rats or mouse or mice).ti.
76	or/63-75
77	45 not 76
78	limit 77 to (yr="2000 - current" and english language)
79	remove duplicates from 78

1 **Database: Cochrane Library**

2 Last searched on: 31/10/2018

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees

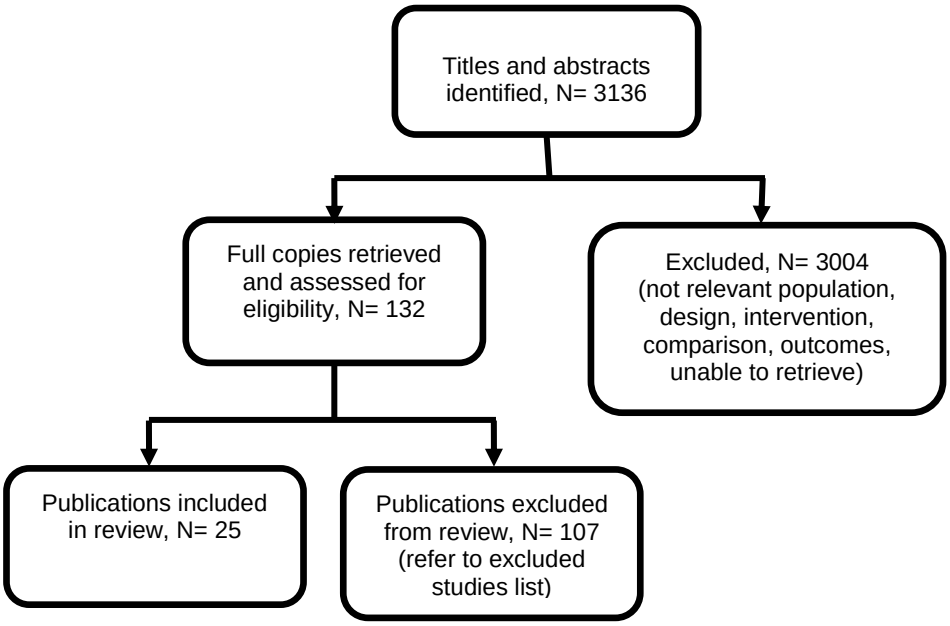
#	Search
2	(((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*))):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Antineoplastic Agents] explode all trees
5	MeSH descriptor: [Antineoplastic Protocols] explode all trees
6	MeSH descriptor: [Cancer Vaccines] explode all trees
7	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
8	((anti canc* or anticanc* or anticarcinogen* or anti neoplas* or antineoplas* or cytotoxic*) near/2 (agent* or drug* or protocol* or regimen* or treatment* or therap*)):ti,ab,kw
9	((chemotherap* or SACT or immunotherap* or biological agent* or biological therap*)):ti
10	(systemic therap*):kw,ab,ti
11	{or #4-#10}
12	MeSH descriptor: [ras Proteins] explode all trees
13	MeSH descriptor: [Genes, ras] this term only
14	((((ras or kras or k ras or nras or n ras) near/2 (wildtype or wild type or wt or mutant or mutat* or protein or gene)) and (predict* or prognos*))):ti,ab,kw
15	MeSH descriptor: [Proto-Oncogene Proteins B-raf] this term only
16	(((Braf or b raf) near/3 v600e)):ti,ab,kw
17	MeSH descriptor: [Phosphatidylinositol 3-Kinases] explode all trees
18	((PIK3CA and (predict* or prognos*))):ti,ab,kw
19	MeSH descriptor: [DNA Mismatch Repair] explode all trees
20	(((mismatch or MMR) near/3 (deficien* or deficit* or proficien*))):ti,ab,kw
21	(((Mismatch repair or MMR-d or MMR-p or dMMR or pMMR) and (predict* or prognos*))):ti,ab,kw
22	MeSH descriptor: [Microsatellite Instability] explode all trees
23	((microsatellite instability or microsatellite unstable or MSI-H)):ti,ab,kw
24	((MSI near/2 (cancer* or tumo?r* or test* or status))):ti,ab,kw
25	MeSH descriptor: [CD3 Complex] explode all trees
26	MeSH descriptor: [CD8 Antigens] explode all trees
27	((((cd3 or cd8) near/3 (antigen* or protein* or complex or immunoscore or immuno score)) and (predict* or prognos*))):ti,ab,kw
28	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees
29	MeSH descriptor: [B7-H1 Antigen] this term only
30	(((PD1 or PD-1 or PDL-1 or PDL1 or PD-L1) and (predict* or prognos*))):ti,ab,kw
31	((coldx or col dx or oncotype dx)):ti,ab,kw
32	{or #12-#31}
33	#3 and #11 and #32 with Cochrane Library publication date Between Jan 2000 and Dec 2018

1

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Table 4: Clinical evidence tables

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Full citation: Bertagnolli, M. M., Redston, M., Compton, C. C., Niedzwiecki, D., Mayer, R. J., Goldberg, R. M., Colacchio, T. A., Saltz, L. B., Warren, R. S., Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer--a study of CALGB 9581 and 89803, Journal of Clinical Oncology, 29, 3153-3162, 2011 **Study type:** RCT **Study dates:** Not reported Analysis in 2008 **Country/ies where the study was carried out:** US **Source of funding:** Supported by Grant No.CA31946 and Grant No.	**Sample size:** N=1264 N=723 analysed **Characteristics:** Stage III colon cancer **Inclusion criteria:** Stage III colon cancer patients enrolled onto trial CALGB protocol 89803 **Exclusion criteria:** Not reported	**Systemic therapy** After complete surgical resection weekly bolus FU/leucovorin (LV) or weekly bolus irinotecan, FU, and LV (IFL) **Biomarkers** dMMR versus pMMR **Biomarker measurement methods** Tumour expression of the MMR proteins, MLH1 and MSH2, was determined by immunohistochemistry (IHC). DNA microsatellite instability was also assessed using a panel of mono- and dinucleotide markers. Tumours with MMR defects were those demonstrating dMMR and/or MSI-H genotype.	**Follow-up** Median 6 years **Outcomes** Disease-free survival **Results** dMMR/MSI-H versus pMMR/MSS in Stage II to III colon cancer. Adjuvant chemotherapy : Disease-free survival HR=0.77 (0.53,1.12) Prevalence of dMMR: 88/399 in right colon; 8/297 in left colon or rectum.	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low risk 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear risk

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
CA33601 from the National Cancer Institute.		**Details of prognostic/predictive model** Cox proportional hazards model was used to make survival comparisons controlling for treatment and other clinicopathologic factors.		3. Measurement. Prognostic factor is adequately measured in study participants to sufficiently limit potential bias. Low risk 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. low risk 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low risk Overall judgement: Low risk Other information

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Full citation Dahabreh, I. J., Terasawa, T., Castaldi, P. J., Trikalinos, T. A., Systematic review: Anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer, Annals of Internal Medicine, 154, 37-49, 2011 **Study type** Systematic review **Study dates** Search date 2010 **Country/ies where the study was carried out** International **Source of funding** Agency for Healthcare Research and Quality	**Sample size** 45 studies included (study size ranged from 12 to 440 patients) **Characteristics** Most patients had received previous treatment with at least 1 chemotherapy regimen; both the number and types of treatment regimens administered varied across studies. Mean or median participant age was 65 years or older in 6 of 40 studies that reported relevant information, and 60 years or older in 31 of 42 studies that reported relevant information. **Inclusion criteria** Studies that reported on at least 10 patients with metastatic colorectal cancer who received treatment with anti-EGFR antibodies alone or in combination with cytotoxic chemotherapy, used genotyping methods to identify KRAS mutations, and reported the outcomes of interest stratified by mutational status.	**Systemic therapy** Anti-EGFR antibodies alone or in combination with cytotoxic chemotherapy **Biomarkers** KRAS MT versus WT. **Biomarker measurement methods** Genotyping methods were used to identify KRAS mutations. Most studies only assessed codons 12 and 13 of the KRAS gene, using direct sequencing or allele-specific methods. **Details of prognostic/predictive model** Meta-analysis of adjusted and unadjusted effect estimates. Covariates used in the study multivariate analyses not always reported.	**Follow-up** Median range from 8 to 94 months where reported **Outcomes** Overall survival Progression-free survival Response to treatment **Results** KRAS MT versus WT in Metastatic. Anti-EGFR targeted therapy : Response rate OR=0.13 (0.08,0.21) KRAS MT versus WT in Metastatic colorectal cancer. Anti-EGFR targeted therapy : Progression-free survival HR=2.11 (1.75,2.55) KRAS MT versus WT in Metastatic colorectal cancer. Anti-EGFR targeted therapy : Overall survival HR=1.79 (1.48,2.17)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
	Exclusion criteria Non English-language, neoadjuvant or adjuvant setting			accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk Other information
Full citation Des Guetz, G., Uzzan, B., Nicolas, P., Schischmanoff, O., Morere, J. F., Microsatellite instability: A predictive marker in metastatic colorectal cancer?, Targeted Oncology, 4, 57-62, 2009 **Study type** Systematic review **Study dates** Search date 2008	**Sample size** 5 studies (860 patients) **Characteristics** Metastatic colorectal cancer. Mean age 63 years; 87 MSI-H; 733 MSS tumours **Inclusion criteria** Studies (any design) in metastatic colon or rectum cancer and assessing	**Systemic therapy** Chemotherapy: FOLFIRI, FOLFOX, XELOX or 5-FU **Biomarkers** MSI-H versus MSS **Biomarker measurement methods** Immunohistochemistry of MLH1, MSH2 or molecular	**Follow-up** Not reported **Outcomes** Treatment response **Results** dMMR/MSI-H versus pMMR/MSS in Metastatic colorectal cancer. 5-FU, oxaliplatin or capeciatbine based : Response rate OR=0.83 (0.66,1.05)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Country/ies where the study was carried out International **Source of funding** No funds received	the relationships between MSI, chemotherapy and response rate (RR). **Exclusion criteria** Lack of survival data in study,	methods (number and type of MSI). **Details of prognostic/predictive model** Covariates not reported		outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				invalid or spurious results. Low Overall judgement. Unclear risk Other information
Full citation Gray RG, Quirke P, Handley K, Lopatin M, Magill L, Baehner FL, Beaumont C, Clark-Langone KM, Yoshizawa CN, Lee M, Watson D, Shak S, Kerr DJ., Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer, Journal of Clinical Oncology, 29, 4611-4619, 2011 **Study type** RCT - retrospective analysis **Study dates** Not reported **Country/ies where the study was carried out** UK **Source of funding** United Kingdom Medical Research Council, Cancer Research UK, and Genomic Health.	**Sample size** N=1436 **Characteristics** Stage II colon cancer, **Inclusion criteria** Patients with stage II colon cancer, enrolled in the QUASAR trial with available FFPE tumour tissue. **Exclusion criteria** Not reported	**Systemic therapy** Adjuvant fluorouracil/folinic acid or no systemic therapy **Biomarkers** Multigene recurrence risk score (Oncotype DX) **Biomarker measurement methods** Multigene RT-PCR based gene expression assay. Recurrance score was calculated from calculated from prespecified algorithms. Cut points for low, intermediate, and high recurrence risk groups were: RS < 30, 30 to 40, and > 40 respectively. **Details of prognostic/predictive model**	**Follow-up** 3 years **Outcomes** Recurrence free interval **Results** Oncotype-DX high versus low score in Stage II colon cancer. Surgery ± adjuvant chemotherapy : Disease-free survival HR=1.29 (1.09,1.52)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
		Cox regression with tumour location, T stage, grade, nodes examined, lymphovascular invasion, MMR, age, and recurrence score included in the model.		measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Low risk Other information
Full citation Guren, T. K., Thomsen, M., Kure, E. H., Sorbye, H., Glimelius, B., Pfeiffer, P., Osterlund, P., Sigurdsson, F., Lothe, I. M. B., Dalsgaard, A. M.,	**Sample size** N=566 **Characteristics**	**Systemic therapy** Patients were randomised to cetuximab plus continuous or intermittent fluorouracil, folinic acid, and oxaliplatin.	**Follow-up** Up to 96 months **Outcomes**	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Skovlund, E., Christoffersen, T., Tveit, K. M., Cetuximab in treatment of metastatic colorectal cancer: final survival analyses and extended RAS data from the NORDIC-VII study, British Journal of Cancer, 116, 1271-1278, 2017 **Study type** RCT **Study dates** 2005 - 2007 **Country/ies where the study was carried out** Norway **Source of funding** Grants and personal fees from Novartis, Ipsen, Amgen, Merck, Nordic Drugs, Celgene, Bayer, Roche, Pfizer, Sanofi Oncology, Eli Lilly, and Baxalta/Shire.	59% colon cancer, 41% rectal cancer. Median age 62 years. All had metastatic disease **Inclusion criteria** Patients enrolled in the NORDIC-VII study - previously untreated metastatic colorectal cancer. **Exclusion criteria** Not reported	**Biomarkers** Extended RAS MT versus RAS/BRAF WT BRAF MT versus RAS/BRAF WT **Biomarker measurement methods** KRAS Mutation Analysis Kit for Real-Time PCR (exons 2, 3, and 4) by EntroGen. NRAS Mutation Analysis Kit (exons 2, 3, and 4) EntroGen. BRAF - not reported **Details of prognostic/predictive model** Cox proportional hazards model was used. Separate univariable analyses of the effect of the WHO performance status, alkaline phosphatase, and RAS and BRAF mutation status was done. Only variables statistically significant in that univariable analyses were included in the multivariable analyses.	Response to treatment Overall survival **Results** RAS MT versus RAS/BRAF WT in Metastatic colorectal cancer. Anti-EGFR targeted therapy : Response rate OR=0.75 (0.62,0.92) RAS MT versus RAS/BRAF WT in Metastatic colorectal cancer. Anti-EGFR targeted therapy : Overall survival HR=1.26 (1.02,1.55) BRAF MT versus WT in Metastatic colorectal cancer (K)RAS-WT. Anti-EGFR therapy : Response rate OR=0.35 (0.2,0.61) BRAF MT versus WT in Metastatic colorectal cancer (K)RAS-WT. Anti-EGFR therapy : Overall survival HR=2.7 (1.99,3.67)	population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk of bias Other information
Full citation Hegewisch-Becker, S., Nopel-Dunnebacke, S., Hinke, A., Graeven, U., Reinacher-Schick, A., Hertel, J., Lerchenmuller, C. A., Killing, B., Depenbusch, R., Al-Batran, S. E., Lange, T., Dietrich, G., Tannapfel, A., Arnold, D., Impact of primary tumour location and RAS/BRAF mutational status in metastatic colorectal cancer treated with first-line regimens containing oxaliplatin and bevacizumab: Prognostic factors from the AIO KRK0207 first-line and maintenance therapy trial, European Journal of Cancer, 101, 105-113, 2018 **Study type**	**Sample size** N=825 (567 had known status for both RAS & BRAF) **Characteristics** Metastatic colorectal cancer **Inclusion criteria** Patients enrolled in AIO KRK0207 RCT (further criteria not reported - see original trial report) **Exclusion criteria** Not reported	**Systemic therapy** First line bevacizumab + oxaliplatin **Biomarkers** RAS MT versus WT BRAF MT versus WT **Biomarker measurement methods** Mutational analysis was performed stepwise using the pyrosequencing technique. In the first step, the mutational status of the codon 12 and 13 of the KRAS gene was determined. In the second	**Follow-up** Up to 80 months **Outcomes** Overall survival **Results** Prevalence of RAS MT: 85/229 in right colon; 191/525 in left colon or rectum. Prevalence of BRAF MT: 39/229 in right colon; 12/525 in left colon or rectum. RAS MT versus RAS/BRAF WT in Metastatic colorectal	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
RCT **Study dates** Not reported **Country/ies where the study was carried out** Germany **Source of funding** Roche Pharma AG and the AIO Studien gGmbH		step, the mutational status of codons 59, 61, 117 and 146 and the mutation hotspots of the NRAS gene in exons 2 to 4 were analysed **Details of prognostic/predictive model** Cox proportional hazards model, including covariates found to be statistically significant on univariate analysis.	cancer.Bevacizumab + oxaliplatin regimen : Overall survival HR=1.22 (0.98,1.52)	sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk of bias

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				Other information
Full citation Huang, L., Liu, Z., Deng, D., Tan, A., Liao, M., Mo, Z., Yang, X., Anti-epidermal growth factor receptor monoclonal antibody-based therapy for metastatic colorectal cancer: A meta-analysis of the effect of PIK3CA mutations in KRAS wild-type patients, Archives of Medical Science, 10, 1-9, 2014 **Study type** Systematic review **Study dates** Search date 2013 **Country/ies where the study was carried out** International **Source of funding** Grants from the National Natural Science Foundation of China (81060234, 81160072), Key Program and University Talents Highland Innovation Team of Guangxi (2012012D003, GJR201147-09), Chairman Science and Technology Fund and Tackle Pro- gram of Guangxi (1116-03, GKG1298003-07-01), Guangxi Science Fund for	**Sample size** 11 studies included (N=864 patients) **Characteristics** Median age 56 to 66 years. All KRAS wildtype, metastaticcolorectal cancer **Inclusion criteria** Studies in KRAS wildtype, metastatic colorectal cancer, exploring the relation between PIK3CA mutations and clinical outcome. **Exclusion criteria** Not reported	**Systemic therapy** Anti-epidermal growth factor receptor monoclonal antibody-based therapy - with or without chemotherapy. **Biomarkers** PIK3CA MT versus WT (in KRAS WT patients) - subgroup analysis by exon. **Biomarker measurement methods** Direct sequencing (6 studies), DxS PI3K Mutation Test Kit (3 studies), Sanger sequencing (1 study) and allelic discrimination (1 study) **Details of prognostic/predictive model** Not reported	**Follow-up** Not reported **Outcomes** Response rate Progression-free survival Overall survival **Results** PIK3CA MT versus WT (in KRAS WT) in Metastatic. Anti-EGFR therapy : Response rate OR=0.42 (0.24,0.75) PIK3CA MT versus WT (in KRAS WT) in Metastatic. Anti-EGFR therapy : Progression-free survival HR=1.54 (1.13,2.09) PIK3CA MT versus WT (in KRAS WT) in Metastatic. Anti-EGFR therapy : Overall survival HR=1.4 (1.03,1.91)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders.

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Distinguished Young Scholars (2012jjFA40011) and the Guangxi Natural Science Fund (2010GXNSFB013064, 2010GXNSFA013181).				Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Unclear risk Other information
Full citation Hutchins, G., Southward, K., Handley, K., Magill, L., Beaumont, C., Stahlschmidt, J., Richman, S., Chambers, P., Seymour, M., Kerr, D., Gray, R., Quirke, P., Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in	**Sample size** N=2857 Analysis N=2008 **Characteristics** Stage II or III colorectal cancer: 91% stage II disease. **Inclusion criteria**	**Systemic therapy** Patients were randomised between FU-based treatment and observation **Biomarkers** dMMR, KRAS, and BRAF	**Follow-up** Up to 10 years **Outcomes** Disease-free survival **Results** Prevalence of KRAS MT: 226/569 in right colon;	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
colorectal cancer, Journal of Clinical Oncology, 29, 1261-1270, 2011 **Study type** RCT **Study dates** Not reported in this publication **Country/ies where the study was carried out** UK **Source of funding** Genomic Health and Roche	Patients in the Quick and Simple and Reliable (QUASAR) trial. Postcurative resection for colon or rectal cancer, **Exclusion criteria** Not reported	**Biomarker measurement methods** dMMR status based on hMLH1 and hMSH2 expression as determined using immunohistochemical techniques. KRAS & BRAF - status determined using PCR & pyrosequencing. **Details of prognostic/predictive model** Univariate analysis of prognostic factors	277/887 in left colon or rectum. Prevalence of BRAF MT: 98/570 in right colon; 10/516 in left colon or rectum. KRAS MT versus WT in Stage II right sided colon cancer. Adjuvant chemotherapy : Disease-free survival HR=1.53 (1.11,2.11) BRAF MT versus WT in Stage II right sided colon cancer. Adjuvant chemotherapy : Disease-free survival HR=0.56 (0.25,1.23) dMMR/MSI-H versus pMMR/MSS in Stage II right sided colon cancer. Adjuvant chemotherapy : Disease-free survival HR=0.36 (0.2,0.65)	observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk of bias Other information
Full citation Kennedy 2011 **Study type** Retrospective cohort study **Study dates** Not reported **Country/ies where the study was carried out** UK **Source of funding** Supported by Almac Diagnostics.	**Sample size** 144 **Characteristics** **Inclusion criteria** Stage II colon adenocarcinoma; patient age 45 years or older at time of primary surgery; six or more regional lymph nodes assessed; a minimum of 50% tumour cells present in the tissue section; no family history of colon cancer; no preoperative or postoperative cancer therapy within 1 year of surgery (although therapy given after recurrence was acceptable) **Exclusion criteria**	**Systemic therapy** None **Biomarkers** ColDX high versus low risk. **Biomarker measurement methods** ColDx gene expression signature was used to classify patients as low or high risk for recurrence by computing a signature score. Score > 0.465 was high risk. **Details of prognostic/predictive model** Multivariate Cox proportional hazards regression using ColDX dichotomised risk together with tumour stage,	**Follow-up** 5 years **Outcomes** Disease-free survival and overall survival **Results** ColDX high versus low risk in Stage II colon cancer : Disease-free survival HR=2.55 (1.47,4.42) ColDX high versus low risk in Stage II colon cancer : Overall survival HR=2.21 (1.23,3.97)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. High risk 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
	Patients with local disease recurrence were excluded as this could be due to residual local disease.	patient tumour grade, tumour location, patient age, patient sex, mucinous/ non-mucinous subtype, and number of lymph nodes retrieved.		outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement High risk Other information
Full citation	**Sample size**	**Systemic therapy**	**Follow-up** Up to 5 years	**Limitations** QUIPs checklist:

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Modest, D. P., Ricard, I., Heinemann, V., Hegewisch-Becker, S., Schmiegel, W., Porschen, R., Stintzing, S., Graeven, U., Arnold, D., von Weikersthal, L. F., et al.,, Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group, Annals of Oncology, 27, 1746-1753, 2016 **Study type** Meta-analysis of 5 RCTs **Study dates** Not reported **Country/ies where the study was carried out** Germany **Source of funding** Merck, Pfizer, Roche and Sanofi	N=1239 patients from five randomized trials (FIRE-1, FIRE-3, AIOKRK0207, AIOKRK0604, RO91) **Characteristics** Metastatic colorectal cancer, first line systemic therapy. **Inclusion criteria** Not reported in this publication (see original trial reports) **Exclusion criteria** Not reported in this publication (see original trial reports)	FUFIRI, mIROX, FOLFIRI+bevacizumab, CAPOX+bevacizumab. CAPIRI+bevacizumab, bevacizumab, FP+bevacizumab, CAPOX/FUFOX. Subgroup analysis for chemo with & without bevacizumab **Biomarkers** KRAS, NRAS and BRAF **Biomarker measurement methods** Methods of testing not reported (were reported in previous publications). **Details of prognostic/predictive model** Multivariate tests were carried out using the Cox models adjusted for study treatment, ECOG, sex, adjuvant chemotherapy, liver-limited disease and number of involved organs.	**Outcomes** Progression-free survival and overall survival **Results** KRAS MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Progression-free survival HR=1.33 (1.07,1.65) KRAS MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Overall survival HR=1.51 (1.2,1.9) BRAF MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Progression-free survival HR=1.58 (0.99,2.51) BRAF MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Overall survival HR=3.67 (2.39,5.63) KRAS MT versus WT in Metastatic colorectal	1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Unclear (reported in previous papers) 4. Confounders. Important potential confounders are appropriately

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
			cancer. Chemotherapy : Progression-free survival HR=1.05 (0.79,1.39) KRAS MT versus WT in Metastatic colorectal cancer. Chemotherapy : Overall survival HR=1.28 (0.95,1.73) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Progression-free survival HR=1.55 (0.86,2.78) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Overall survival HR=2.05 (1.09,3.86)	accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk Other information
Full citation Niedzwiecki, D., Frankel, W. L., Venook, A. P., Ye, X., Friedman, P. N., Goldberg, R. M., Mayer, R. J., Colacchio, T. A., Mulligan, J. M., Davison, T. S., et al.,, Association Between Results of a Gene Expression Signature Assay and Recurrence-Free Interval in Patients With Stage II Colon Cancer in Cancer and Leukemia Group B 9581 (Alliance), Journal of Clinical Oncology, 34, 3047-3053, 2016	**Sample size** N=941 393 analysed **Characteristics** Stage II colon cancer, median age 64 years, 53% male. **Inclusion criteria** Patients enrolled in the Cancer and Leukemia Group B (CALGB), randomized clinical	**Systemic therapy** Edrecolomab (in 49% of patients only) **Biomarkers** ColDX high versus low risk. **Biomarker measurement methods** ColDx gene expression signature was used to classify patients as low or high risk for	**Follow-up** Median 8.1 years **Outcomes** Recurrence free survival **Results** ColDX high versus low risk in Stage II colon cancer : Disease-free survival HR=2.13 (1.3,3.5)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Study type RCT **Study dates** Not reported **Country/ies where the study was carried out** USA **Source of funding** Bayer Healthcare Pharmaceuticals, Onyx Pharmaceuticals, Genentech, Roche, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Sanofi (Inst), Bayer AG (Inst), Immunomedics (Inst), Merck (Inst)	trial (C9581). With FFPE tissue available. **Exclusion criteria** Not reported	recurrence by computing a signature score. Score > 0.4377 was high risk. **Details of prognostic/predictive model** Weighted Cox proportional hazards model adjusted for standard prognostic variables.	ColDX high versus low risk in Stage II colon cancer : Overall survival HR=1.74 (0.98,3.1)	outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				invalid or spurious results. Low Overall judgement. Low risk Other information
Full citation Ogino, S., Meyerhardt, J. A., Irahara, N., Niedzwiecki, D., Hollis, D., Saltz, L. B., Mayer, R. J., Schaefer, P., Whittom, R., Hantel, A., et al.,, KRAS mutation in stage III colon cancer and clinical outcome following intergroup trial CALGB 89803, Clinical Cancer Research, 15, 7322-7329, 2009 **Study type** RCT **Study dates** RCT ran from 1999-2001 **Country/ies where the study was carried out** USA **Source of funding** Pfizer, Roche, Genentech, Bristol Myers Squibb, Imclone, and Amgen	**Sample size** N=1264; 508 included in analysis **Characteristics** Stage III colorectal cancer, mean age 60 years, 54% male, 58% right colon cancer **Inclusion criteria** Patients enrolled in a randomized adjuvant chemotherapy trial CALGB 89803. Those with FFPE tissue available. **Exclusion criteria** Not reported	**Systemic therapy** Adjuvant 5-fluorouracil, leucovorin with or without irinotecan **Biomarkers** KRAS MT versus WT **Biomarker measurement methods** PCR and pyrosequencing spanning KRAS codons 12 and 13. **Details of prognostic/predictive model** Cox proportional hazard models assessed the prognostic significance of KRAS mutation and adjusted for potential confounders including age, sex, tumour location, tumour/node stage, performance status, adjuvant	**Follow-up** Median 6.2 years **Outcomes** Disease-free survival, overall survival **Results** Prevalence of KRAS MT: 100/291 in right colon; 76/212 in left colon or rectum. KRAS MT versus WT in Stage III colorectal cancer. Adjuvant chemotherapy. 5-FU based : Overall survival HR=0.9 (0.64,1.27)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
		chemotherapy arm, and microsatellite instability status.		measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement. Unclear Other information
Full citation Petrelli, F., Coinu, A., Cabiddu, M., Ghilardi, M., Barni, S., KRAS as prognostic biomarker in metastatic colorectal cancer patients treated with	**Sample size** 12 studies (N=2266 patients) **Characteristics**	**Systemic therapy** Chemotherapy + bevacizumab as first line therapy. Chemotherapy was: oxaliplatin-based (5 studies),	**Follow-up** Not reported **Outcomes**	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
bevacizumab: A pooled analysis of 12 published trials, Medical Oncology, 30 (3) (no pagination), 2013 **Study type** Systematic review **Study dates** Search done in 2013 **Country/ies where the study was carried out** International **Source of funding** Not reported	Metastatic CRC **Inclusion criteria** English language studies of patients with metastatic colorectal cancer treated with chemotherapy + bevacizumab as first line therapy. **Exclusion criteria** Studies were excluded if they included associated treatment with other targeted therapies or radiotherapy. So only bevacixumab+chemotherapy alone arms were considered in RCTs.	irinotecan-based (1 study), oxaliplatin or irinotecan-based (3 studies), triplet combinations (3 studies) and capecitabine +/- mitomycin C (1 study). **Biomarkers** KRAS MT versus WT **Biomarker measurement methods** Not reported **Details of prognostic/predictive model** Not reported	Response rate, progression-free survival , overall survival **Results** KRAS MT versus WT in Metastatic. Bevacizumab based therapy [Relative risk] : Response rate OR=0.7 (0.52,0.95) KRAS MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Progression-free survival HR=1.18 (1.02,1.36) KRAS MT versus WT in Metastatic colorectal cancer. Bevacizumab based therapy : Overall survival HR=1.54 (1.09,2.18)	population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Unclear 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Unclear Overall judgement: High risk Other information
Full citation Seligmann, J. F., Fisher, D., Smith, C. G., Richman, S. D., Elliott, F., Brown, S., Adams, R., Maughan, T., Quirke, P., Cheadle, J., Seymour, M., Middleton, G., Investigating the poor outcomes of BRAF-mutant advanced colorectal cancer: Analysis from 2530 patients in randomised clinical trials, Annals of Oncology, 28, 562-568, 2017 **Study type** Meta-analysis of 3 RCTs (FOCUS COIN, PICCOLO) **Study dates**	**Sample size** N=2530 **Characteristics** Advanced colorectal cancer. **Inclusion criteria** Patients enrolled in standard cytotoxic chemotherapy (without targeted therapy) arms of three large randomised trials (FOCUS COIN, PICCOLO) **Exclusion criteria**	**Systemic therapy** Standard cytotoxic chemotherapy (without targeted therapy). First line OxFU or IrFU (COIN, FOCUS), second line irinotecan (PICCOLO). **Biomarkers** BRAF-mutant versus wildtype **Biomarker measurement methods** Methods for DNA extraction and genotyping for mutations including BRAF V600E - not	**Follow-up** Not reported **Outcomes** Response rate, progression-free survival and overall survival **Results** Prevalence of BRAF MT: 133/710 in right colon; 87/1698 in left colon or rectum. BRAF MT versus WT in Metastatic colorectal	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
NR in this publication **Country/ies where the study was carried out** UK **Source of funding** Cancer Research UK and Yorkshire Cancer Research	Not reported	reported in this publication (refer to original trial reports) **Details of prognostic/predictive model** Cox proportional hazards modelling adjusted for factors known to be prognostic or likely to interact with BRAF-status. In COIN and FOCUS: WHO performance status (2 versus 0/1); primary tumour resected (yes versus no); PTL (right colon versus other); platelet count; peritoneal metastases (present versus absent) and MMR status. In PICCOLO, adjustment was made for: response to previous therapy; performance status; peritoneal metastases; primary tumour resected and PTL.	cancer. Chemotherapy : Progression-free survival HR=1.14 (0.92,1.42) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Overall survival HR=1.51 (1.19,1.91) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Response rate OR=0.79 (0.56,1.11) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Progression-free survival HR=1.07 (0.69,1.67) BRAF MT versus WT in Metastatic colorectal cancer. Chemotherapy : Overall survival HR=1.44 (1.04,2)	characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Unclear 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				Overall judgement: Low Other information
Full citation Shen Z, Gu L, Mao D, Chen M, Jin R. Clinicopathological and prognostic significance of PD-L1 expression in colorectal cancer: a systematic review and meta-analysis. World J Surg Oncol. 2019 Jan 4;17(1):4.. **Study type** Systematic review **Study dates** Search date 2018 **Country/ies where the study was carried out** International **Source of funding** Key Research and Development Project of Shandong Science and Technology Department, Grant/Award Number: 2016GSF201010, 2017GSF218034	**Sample size** 10 studies (N= 3481 patients) **Characteristics** Stage II-III colorectal cancer (1 study), stage I-IV colorectal cancer (5 studies), stage III colorectal cancer (1 study) and stage not reported (3 studies). Median age where reported ranged from 59 to 70 years. **Inclusion criteria** Studies with complete clinical and pathological data, in patients with colorectal cancer where PD-L1 expression in colorectal cancer tissues was determined by immunohistochemical staining; reporting the relationship between PD-L1 expression and overall survival . **Exclusion criteria** Listed criteria	**Systemic therapy** Not fully reported – 1 study had preoperative chemotherapy and 4 studies involved adjuvant chemotherapy **Biomarkers** PD-L1 expression **Biomarker measurement methods** PD-L1 expression in colorectal cancer tissues was determined by immunohistochemical staining **Details of prognostic/predictive model** Not reported	**Follow-up** Median 36 to 96 months **Outcomes** Overall survival **Results** Prevalence of PD-L1+: 711/1260 in right colon; 916/1873 in left colon or rectum. PD-L1 positive versus negative in : Overall survival HR=1.22 (1.01,1.47)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Low risk Other information SR assessed study quality using Newcastle Ottawa scale
Full citation Sinicrope, F. A., Foster, N. R., Thibodeau, S. N., Marsoni, S., Monges, G., Labianca, R., Yothers, G., Allegra, C., Moore, M. J.,	**Sample size** N=2141 **Characteristics**	**Systemic therapy** 5-FU-based adjuvant therapy. **Biomarkers**	**Follow-up** Not reported **Outcomes** Disease-free survival, overall survival	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Gallinger, S., Sargent, D. J., DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy, Journal of the National Cancer Institute, 103, 863-875, 2011 **Study type** Combined analysis of 5 RCTs **Study dates** Not reported **Country/ies where the study was carried out** International **Source of funding** National Cancer Institute (CA104683-02 and 1 K05 CA142885-01 to FAS); Mayo Clinic Cancer Center (CA15083)	Stage II or III colon cancer. Mean age 60 years **Inclusion criteria** Stage II and III colon carcinoma patients who were treated in randomized trials of 5-FU-based adjuvant therapy. With FFPE tissue available. **Exclusion criteria** Not reported	dMMR versus pMMR **Biomarker measurement methods** Immunohistochemistry was used to detect expression of MLH1 and MSH2 proteins. MSI was analysed using PCR. In tumours, dMMR was defined by the presence of MSI-H if greater than 30% of the microsatellite markers showed instability and/or by loss of MLH1 or MSH2 or MSH6 protein expression. The pMMR tumours were defined as MSI-L (ie, instability at <30% of loci screened), MSS, and/or by intact MMR protein expression. **Details of prognostic/predictive model** Cox proportional hazards models were used to explore the association of MMR status, treatment, and site of recurrence with disease-free survival and overall survival and were stratified by adjuvant study.	**Results** Prevalence of dMMR: 269/981 in right colon; 69/1128 in left colon or rectum. dMMR/MSI-H versus pMMR/MSS in Stage II to III colon cancer. Adjuvant chemotherapy : Disease-free survival HR=0.8 (0.64,1) dMMR/MSI-H versus pMMR/MSS in Stage II to III colon cancer. Adjuvant chemotherapy. 5-FU based : Overall survival HR=0.79 (0.63,0.99)	population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Low Other information
Full citation Sinicrope, F. A., Shi, Q., Smyrk, T. C., Thibodeau, S. N., Dienstmann, R., Guinney, J., Bot, B. M., Tejpar, S., Delorenzi, M., Goldberg, R. M., et al., Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes, Gastroenterology, 148, 88-99, 2015 **Study type** RCT - retrospective analysis **Study dates** Not reported **Country/ies where the study was carried out** USA	**Sample size** N=2720 **Characteristics** Stage III colon cancer **Inclusion criteria** Patients with resected, stage III (any T, N1 or N2, M0) colonic adenocarcinomas enrolled in a trial of mFOLFOX6 or mFOLFOX6 + cetuximab (NCCTG N0147). Those with complete data on all tumour markers were included.	**Systemic therapy** Adjuvant mFOLFOX6 or mFOLFOX6 + cetuximab (both arms were pooled for the analysis). **Biomarkers** BRAF V600E mutation versus wildtype KRAS mutation versus wildtype **Biomarker measurement methods** Testing for the BRAF V600E mutation in exon 15 was done using a multiplex allele-	**Follow-up** Median 5 years **Outcomes** Disease-free survival, overall survival **Results** Prevalence of KRAS MT: 540/1348 in right colon; 389/1332 in left colon or rectum. Prevalence of BRAF MT: 140/1348 in right colon;	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Source of funding Grants from the National Cancer Institute to the North Central Cancer Treatment Group (CA-25224), the NCCTG Biospecimen Resource (CA-114740), the Alliance for Clinical Trials in Oncology (CA31946), and the Alliance Statistics and Data Center (CA33601), and in part by unrestricted support from Sanofi US, Pfizer, Inc. and Imclone Systems, Inc	**Exclusion criteria** Not reported	specific, real- time PCR based assay and an automated sequencing technique. KRAS mutation status in exon 2 was analyzed in using the DxS mutation test kit, assessing for 7 different mutations in codons 12 and 13. MMR protein (MLH1, MSH2, and MSH6) expression was analysed using immunohistochemistry. **Details of prognostic/predictive model** Multivariable Cox models were used, all models were adjusted for stratification factors selected a priori.	45/1332 in left colon or rectum. Prevalence of dMMR: 231/1348 in right colon; 18/1332 in left colon or rectum. KRAS MT versus WT in Stage III colon cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy : Disease-free survival HR=1.48 (1.27,1.74) BRAF MT versus WT in Stage II-III colorectal cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy: Disease-free survival HR=1.4 (1.06,1.85)	sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Low risk

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				Other information
Full citation Sorich, M. J., Wiese, M. D., Rowland, A., Kichenadasse, G., McKinnon, R. A., Karapetis, C. S., Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials, Annals of Oncology, 26, 13-21, 2015 **Study type** Systematic review **Study dates** Search date 2014 **Country/ies where the study was carried out** International **Source of funding** Not reported	**Sample size** 9 RCTS (N=5948 patients) **Characteristics** Metastatic colorectal cancer **Inclusion criteria** Randomized trials comparing anti-EGFR mAb (either as monotherapy or in combination with chemotherapy) to an alternative therapy in metastatic colorectal cancer; study participants genotyped for at least one of the following in addition to KRAS exon 2: KRAS mutations in exon 3 (codon 59, 61) or exon 4 (codons 117, 146), or NRAS mutations in exon 2, 3 or 4 and follow-up for progression-free survival and/or overall survival **Exclusion criteria** Not reported	**Systemic therapy** Seven studies compared the addition of an anti-EGFR targeted therapy to standard care (FOLFOX, FOLFIRI, irinotecan, oxaliplatin and fluoropyrimidine chemotherapy, or best supportive care), and two studies compared the addition of anti-EGFR mAb or bevacizumab to chemotherapy (FOLFOX or FOLFIRI). **Biomarkers** New RAS MT versus wildtype. New RAS was KRAS exons 3+4 and NRAS exons 2,3+4 **Biomarker measurement methods** Other than the COIN study (which genotyped only KRAS codon 61, and NRAS codons 12 and 61), all studies genotyped the majority of the new RAS codons. The methods used to detect KRAS and NRAS mutations varied	**Follow-up** Not reported **Outcomes** Progression-free survival , OS **Results** New RAS MT versus all RAS WT in Metastatic. Anti-EGFR targeted therapy : Progression-free survival HR=1.67 (1.34,2.08) New RAS MT versus all RAS WT in Metastatic. Anti-EGFR targeted therapy : Overall survival HR=1.39 (1.08,1.79)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders.

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
		between studies, and included bidirectional Sanger sequencing, pyrosequencing, MALDI-ToF analysis and WAVE- based SURVEYOR analysis **Details of prognostic/predictive model** Studies generally reported HRs derived using Cox proportional hazards models stratified according to randomization factors (e.g. ECOG performance status).		Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Low Other information
Full citation Sun G, Dong X, Tang X, Qu H, Zhang H, Zhao E. The prognostic value of immunoscore in patients with colorectal cancer: A systematic review and meta-analysis. Cancer Med. 2019 Jan;8(1):182-189. **Study type** Systematic review	**Sample size** 8 Studies (N=4689 patients) **Characteristics** Stage I-III colorectal cancer (4 studies), stage I-IV rectal cancer (1 study), stage I-III colon cancer (1 study) and stage IV colorectal cancer (2	**Systemic therapy** Not reported **Biomarkers** Immunoscore **Biomarker measurement methods** Immunoscore algorithm: value is based on the density of CD3 + and CD8 + lymphocytes in the CT and IM	**Follow-up** Median 36 to 96 months **Outcomes** Disease-free survival, overall survival **Results**	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Study dates Search date 2018 **Country/ies where the study was carried out** International **Source of funding** Key Research and Development Project of Shandong Science and Technology Department, Grant/Award Number: 2016GSF201010, 2017GSF218034	studies). Median age where reported ranged from 59 to 70 years. **Inclusion criteria** Studies of Immunoscore reported in English articles in patients pathologically diagnosed colorectal cancer; with overall survival or disease-free survival of colorectal cancer as the research focus; and reporting hazard ratio estimates with their corresponding 95% CI (or sufficient data to calculate of these effect measures) **Exclusion criteria** Abstracts were excluded.	regions of tumours. Patients are stratified from I0 to I4 according to the immunoscore, based on the total number of observed high densities (CD3 + cells and CD8 + cells in the tumor regions) **Details of prognostic/predictive model** HR ratios were from adjusted Cox regression analyses in 6/8 studies and unadjusted analyses in 2/8 studies.	Immunoscore high versus low in Stage I-III colorectal cancer: Disease-free survival HR=1.80 (1.6,2.02) Immunoscore high versus low in Stage I-III colorectal cancer: Overall survival HR=1.65 (1.31,2.08) Immunoscore high versus low in Metastatic colorectal cancer Overall survival HR=3.61 (1.75,7.44)	observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Unclear Other information
Full citation Taieb, J., Balogoun, R., Le Malicot, K., Tabernero, J., Mini, E., Folprecht, G., Van Laethem, J. L., Emile, J. F., Mulot, C., Fratte, S., Levache, C. B., Saban-Roche, L., Thaler, J., Petersen, L. N., Bridgewater, J., Perkins, G., Lepage, C., Van Cutsem, E., Zaanan, A., Laurent-Puig, P., Adjuvant FOLFOX +/- cetuximab in full RAS and BRAF wildtype stage III colon cancer patients, Annals of Oncology, 28, 824-830, 2017 **Study type** RCT **Study dates** 2005-2009 **Country/ies where the study was carried out** France	**Sample size** N=2559; 1900 analysed **Characteristics** Stage III colon cancer **Inclusion criteria** Patients with stage III colon cancer enrolled in the PETACC8 trial, with sufficient tumour material for analysis and who consented for the additional analysis. **Exclusion criteria** Not reported	**Systemic therapy** Adjuvant FOLFOX +/- cetuximab **Biomarkers** KRAS mutant versus wildtype BRAF mutant versus wildtype Extended RAS mutations also analysed **Biomarker measurement methods** Next generation sequencing was used for exons 2, 3 and 4 of KRAS and NRAS, as well as BRAF exons 11 and 15, using the Ampliseq colon–lung cancer panel version 2. **Details of prognostic/predictive model**	**Follow-up** At least 5 years **Outcomes** Disease-free survival, OS **Results** Prevalence of RAS MT: 427/755 in right colon; 515/1114 in left colon or rectum. Prevalence of BRAF MT: 149/755 in right colon; 63/1114 in left colon or rectum. KRAS MT versus WT in Stage III colon cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy : Disease-free survival HR=1.72 (1.4,2.12)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Source of funding Merck KGaA and Sanofi-Aventis		Multivariate analyses including the treatment group and baseline prognostic factors that were clinically relevant or significant in univariate analysis: tumour grade, pT stage, pN stage, venous embolism, lymphatic invasion, bowel obstruction/ perforation and tumour location.	KRAS MT versus WT in Stage III colon cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy : Overall survival HR=1.55 (1.23,1.96) BRAF MT versus WT in Stage II-III colorectal cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy : Disease-free survival HR=1.56 (1.14,2.14) BRAF MT versus WT in Stage II to III colorectal cancer. Adjuvant chemotherapy y± Anti-EGFR targeted therapy : Overall survival HR=1.83 (1.29,2.6)	3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk Other information
Full citation Venook, A. P., Niedzwiecki, D., Lopatin, M., Ye, X., Lee, M.,	**Sample size** N=1713; 690 analysed	**Systemic therapy** Adjuvant edrecolomab or observation	**Follow-up** 5 years	**Limitations** QUIPs checklist:

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Friedman, P. N., Frankel, W., Clark-Langone, K., Millward, C., Shak, S., et al.,, Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581, Journal of Clinical Oncology, 31, 1775-1781, 2013 **Study type** RCT **Study dates** Not reported **Country/ies where the study was carried out** USA **Source of funding** Grants No. CA31946 from the National Cancer Institute to the Alliance for Clinical Trials in Oncology for CALGB 9581 (M.M.B.) and No. CA33601 to the Alliance Statistics and Data Center.	**Characteristics** Stage II colon cancer **Inclusion criteria** Patients with stage II colon cancer enrolled in CALGB 9581 randomised trial, with available tissue for analysis. All patients with recurrence and a random sample of those without recurrence were targeted for inclusion. **Exclusion criteria** Patients with highest risk for recurrence, such as obstruction or perforation.	**Biomarkers** Oncotype DX Colon Cancer Recurrence Score **Biomarker measurement methods** RNA was extracted and analyzed by reverse transcriptase polymerase chain reaction. The 12-gene recurrence score was calculated by using the prespecified genes and algorithm. **Details of prognostic/predictive model** A weighted Cox proportional hazards model evaluated the association between RS and recurrence-free interval.	**Outcomes** Recurrence free interval **Results** Oncotype-DX high versus low score in 1Stage II colon cancer. Surgery ± adjuvant edrecolomab : Disease-free survival HR=1.68 (1.19,2.38)	1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement: Unclear risk Other information
Full citation Yothers, G., O'Connell, M. J., Lee, M., Lopatin, M., Clark-Langone, K. M., Millward, C., Paik, S., Sharif, S., Shak, S., Wolmark, N., Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin, Journal of Clinical Oncology, 31, 4512-4519, 2013 **Study type**	**Sample size** N=892 **Characteristics** Stage II and III colon cancer **Inclusion criteria** Patients with stage II and III colon cancer randomly assigned and treated with FU/LV or FU/LV + oxaliplatin in NSABP C-07 with available tumor tissue and clinical follow-	**Systemic therapy** Adjuvant FU/LV or FU/LV + oxaliplatin **Biomarkers** 12-Gene Colon Cancer Recurrence Score (Oncotype-DX) **Biomarker measurement methods** RNA was extracted quantified, and analysed by RT-PCR. Recurrence Score values	**Follow-up** Up to 10 years **Outcomes** Recurrence free interval **Results** Oncotype-DX high versus low score in 1Stage II colon cancer. Adjuvant chemotherapy : Disease-free survival HR=1.6 (1.29,1.99)	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
RCT **Study dates** 2011 **Country/ies where the study was carried out** USA **Source of funding** Public Health Service Grants No. U10-CA-12027, U10-CA- 69651, U10-CA-37377, and U10-CA- 69974 from the National Cancer Institute, Department of Health and Human Services, and Sanofi-Synthelabo.	up. A 50% sample of patients was randomly selected. **Exclusion criteria** Not reported	were calculated using the pre-specified genes and algorithm. Pre-specified RS groups were as follows: low (score, < 30), intermediate (score, 30 to 40), and high (score, > 40) **Details of prognostic/predictive model** Cox proportional hazards regression with adjustment for stage (II, IIIA/B, or IIIC) and randomly assigned treatment was used to evaluate the association between continuous RS and outcomes	Oncotype-DX high versus low score in 1Stage II colon cancer. Adjuvant chemotherapy : Overall survival HR=1.89 (1.46,2.44)	follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				Overall judgement: Low risk Other information
Full citation Yuan, Z. X., Wang, X. Y., Qin, Q. Y., Chen, D. F., Zhong, Q. H., Wang, L., Wang, J. P., The prognostic role of BRAF mutation in metastatic colorectal cancer receiving anti-EGFR monoclonal antibodies: a meta-analysis, PLoS ONE [Electronic Resource], 8, e65995, 2013 **Study type** Systematic review **Study dates** Search date 2013 **Country/ies where the study was carried out** International **Source of funding** National Natural Science Foundation of China (NSFC) and supported by Chinese Ministry of Education's ''Doctor Station'' Foundation.	**Sample size** 21 trials included with 5229 patients **Characteristics** Metastatic colorectal cancer **Inclusion criteria** Studies of patients with metastatic colorectal cancer treated with cetuximab or panitumumab based therapy; evaluating BRAF mutations in the majority of patients; reporting one or more of OR, progression-free survival and overall survival ; comparing the prognosis of patients with WT BRAF to those with MT BRAF **Exclusion criteria** Not reported	**Systemic therapy** 6 trials used anti- EGFR MoAbs therapy as the first line, 8 as second line or higher, 3 as first or higher. 15 trials used cetuximab based therapy, one panitumumab and 5 both. The commonest regimen was cetuximab + irinotecan (11 trials). **Biomarkers** BRAF MT versus WT. The mutated site was mostly V600E mutation at the extron 15 of the BRAF gene. **Biomarker measurement methods** Not reported **Details of prognostic/predictive model** Adjusted HRs were used where reported.	**Follow-up** Not reported **Outcomes** Response, progression-free survival, overall survival **Results** BRAF MT versus WT in Metastatic colorectal cancer. (K)RAS-WT. Anti-EGFR therapy : Response rate OR=0.31 (0.18,0.53) BRAF MT versus WT in Metastatic colorectal cancer. KRAS-any. Anti-EGFR therapy : Response rate OR=0.76 (0.43,1.33) BRAF MT versus WT in Metastatic. Anti-EGFR therapy : Progression-free survival HR=3.45 (2.26,5.26) BRAF MT versus WT in Metastatic. Anti-EGFR therapy : Progression-free survival	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
			HR=2.63 (2.01,3.45) BRAF MT versus WT in Metastatic colorectal cancer. (K)RAS-WT. Anti-EGFR therapy : Overall survival HR=3.85 (2.96,5) BRAF MT versus WT in Metastatic colorectal cancer. KRAS-any. Anti-EGFR therapy : Overall survival HR=2.86 (2.37,3.45)	sufficiently limit potential bias. Unclear 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Unclear Overall judgement: Unclear risk Other information
Full citation Zaanan, A., Shi, Q., Taieb, J., Alberts, S. R., Meyers, J. P., Smyrk, T. C., Julie, C., Zawadi, A., Tabernero, J., Mini, E., Goldberg, R. M., Folprecht, G., Van Laethem, J. L., Le Malicot, K.,	**Sample size** N=2636; 2501 analysed **Characteristics**	**Systemic therapy** Adjuvant FOLFOX **Biomarkers** dMMR versus pMMR	**Follow-up** 5 years **Outcomes** Disease-free survival	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
Sargent, D. J., Laurent-Puig, P., Sinicrope, F. A., Role of deficient DNA mismatch repair status in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy a pooled analysis from 2 randomized clinical trials, JAMA Oncology, 4, 379-383, 2018 **Study type** Meta-analysis of 2 RCTs **Study dates** 2004 - 2009 **Country/ies where the study was carried out** USA and France **Source of funding** French National Society of Gastroenterology, Fédération Francophone de Cancérologie Digestive (FFCD). Merck KGaA and Sanofi-Aventis. National Institutes of Health under Award Numbers U10CA025224, the NCCTG Biospecimen Resource (U24CA114740), and the Alliance for Clinical Trials in Oncology (U10CA031946, U10CA033601, U10CA1808821 and U10CA180882). Bristol-Myers Squibb.	Stage III colon cancer. Median age 59 years **Inclusion criteria** Patient with resected stage III colon adenocarcinoma enrolled in the NCCTG N0147 and PETACC8 adjuvant RCTs who had signed biological informed consent and whose tumour blocks were available for analysis. Only those in the FOLFOX treatment arms were included. **Exclusion criteria** Not reported	**Biomarker measurement methods** Mismatch repair (MMR) tumour status was determined by immunohistochemicalanalysis or by MSI testing when IHC findings were indeterminate. **Details of prognostic/predictive model** Multivariable analyses were performed on MMR phenotype adjusted for patient age, sex, tumour grade, ECOG performance status, pT/pN stage, primary tumour location, and BRAF V600E mutational status.	**Results** Prevalence of dMMR: 213/1109 in right colon; 34/1348 in left colon or rectum. dMMR/MSI-H versus pMMR/MSS in Stage II to III colon cancer. Adjuvant chemotherapy : Disease-free survival HR=0.73 (0.55,0.97)	interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Low 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome. Low 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Low 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Low

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Low Overall judgement Low risk Other information
Full citation Zhu, L., Dong, C., Cao, Y., Fang, X., Zhong, C., Li, D., Yuan, Y., Prognostic Role of BRAF Mutation in Stage II/III Colorectal Cancer Receiving Curative Resection and Adjuvant Chemotherapy: A Meta-Analysis Based on Randomized Clinical Trials, PLoS ONE [Electronic Resource], 11, e0154795, 2016 **Study type** Systematic review **Study dates** Search date 2015 **Country/ies where the study was carried out**	**Sample size** 7 RCTs included with 1035 patients **Characteristics** Stage II or III colorectal cancer **Inclusion criteria** Randomized trials of stage II/III colorectal cancer undergoing curative resection, followed by adjuvant chemotherapy, with sufficient quantitative data of the prognosis according to BRAF mutation status. **Exclusion criteria** Not reported	**Systemic therapy** Adjuvant FU/LV, FLOX, mFOLFOX6, FOLFIRI, IFL, mFOLFOX6 +/- cetuximab, FOLFOX4 **Biomarkers** BRAF MT versus WT **Biomarker measurement methods** BRAF V600E mutation was assessed using PCR and sequencing or pyrosequencing	**Follow-up** Not reported **Outcomes** Disease-free survival, overall survival **Results** BRAF MT versus WT in Stage II-III colorectal cancer. Adjuvant chemotherapy± Anti-EGFR targeted therapy : Disease-free survival HR=1.26 (1.07,1.48) BRAF MT versus WT in Stage II to III colorectal cancer. Adjuvant	**Limitations** QUIPs checklist: 1. Participation. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome. Unclear 2. Attrition. Loss to follow-up is not associated with key characteristics sufficient to limit

Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
International **Source of funding** Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-year Plan Period (2014BAI09B07), Training Program of the Major Research Plan of the National Natural Science Foundation of China (91229104), The National High Technology Research and Development Program of China (863 Program) (2012AA02A506),		**Details of prognostic/predictive model** Not reported	chemotherapy y± Anti-EGFR targeted therapy : Overall survival HR=1.42 (1.25,1.61)	potential bias to the observed relationship between PF and outcome. Unclear 3. Measurement. PF is adequately measured in study participants to sufficiently limit potential bias. Unclear 4. Confounders. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome. Unclear 5. Analysis. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results. Unclear Overall judgement: Unclear

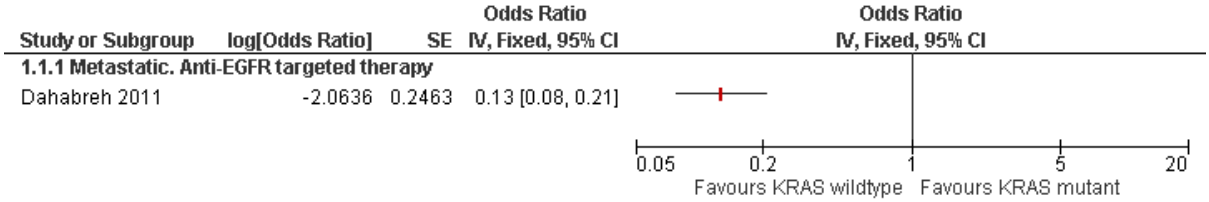
Study details	Participants	Biomarkers and systemic therapies	Outcomes and Follow-up	Comments
				Other information

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; dMMR: deficient MMR; ECOG: Eastern Co-Operative Oncology Group; EGFR: epidermal growth factor receptor; FFPE: formalin-fixed, paraffin-embedded; HR: hazard ratio; IHC: immunohistochemical; KRAS: Kirsten rat sarcoma virus oncogene homolog; MID: minimally important difference; MMR: mismatch repair; MSI: microsatellite instability; MSI-H: high microsatellite instability; MSS: microsatellite stable; MT: mutant type; N: number; NRAS: neuroblastoma rat sarcoma virus oncogene homolog; OR: odds ratio; (RT-)PCR: (reverse transcriptase) polymerase chain reaction; PD(-L)1: programmed death(-ligand) 1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PF: prognosis factor; pMMR: proficient MMR; QUIPS: Quality in Prognosis Studies; RAS: rat sarcoma virus oncogene homolog; RCT: randomised controlled trial; RR: relative risk; RS: recurrence score; WT: wildtype; 5-FU: 5-fluorouracil

Appendix E – Forest plots

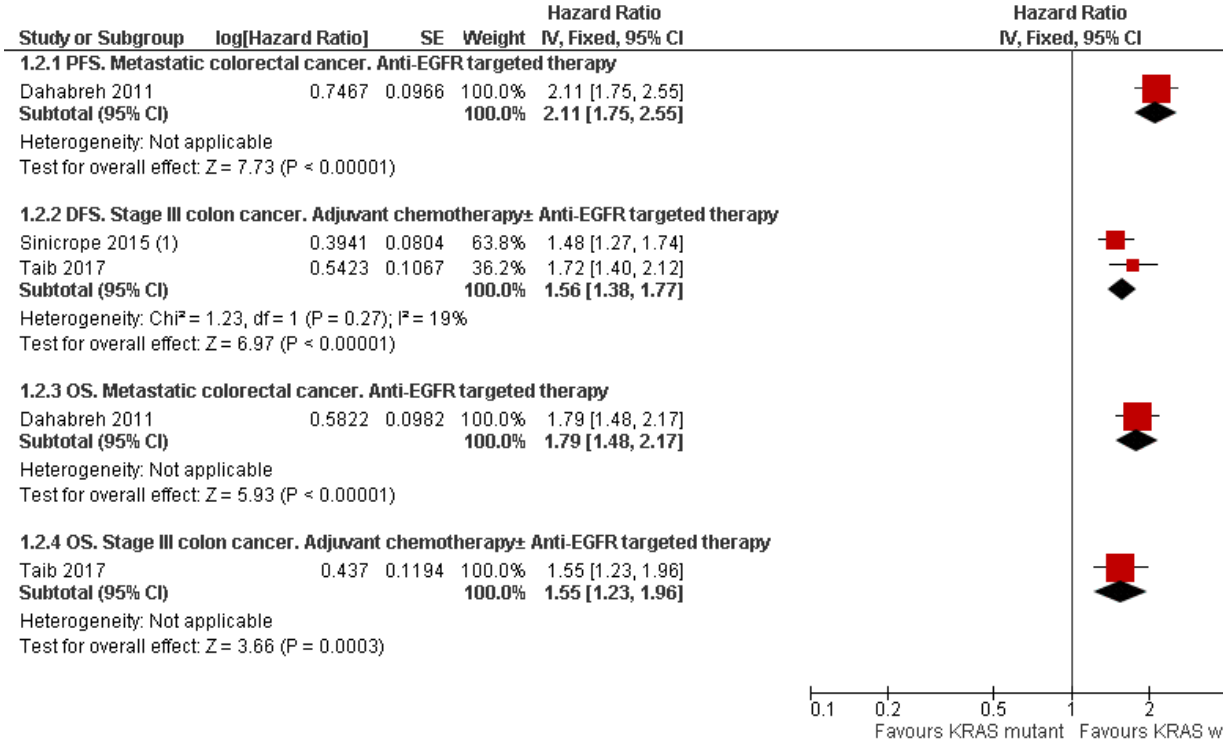
Forest plots for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Figure 2: Comparison 1: KRAS mutant versus KRAS wildtype – response to systemic therapy



CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; SE: standard error

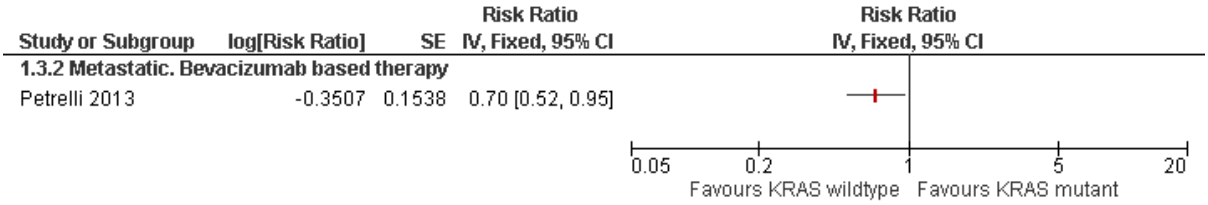
Figure 3: Comparison 1: KRAS mutant versus KRAS wildtype – survival outcomes with anti-EGFR targeted therapy



Footnotes
(1) pMMR only

CI: confidence interval; DFS: disease free survival; EGFR: epidermal growth factor receptor; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; OS: overall survival; PFS: progression-free survival; pMMR: proficient mismatch repair; SE: standard error

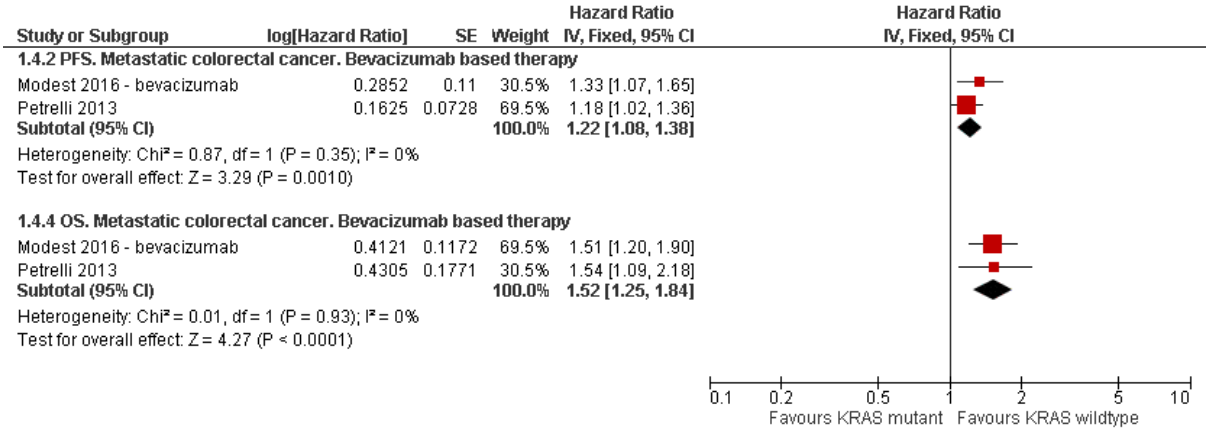
Figure 4: Comparison 1: KRAS mutant versus KRAS wildtype – response to bevacizumab based therapy



CI: confidence interval; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; SE: standard error

1

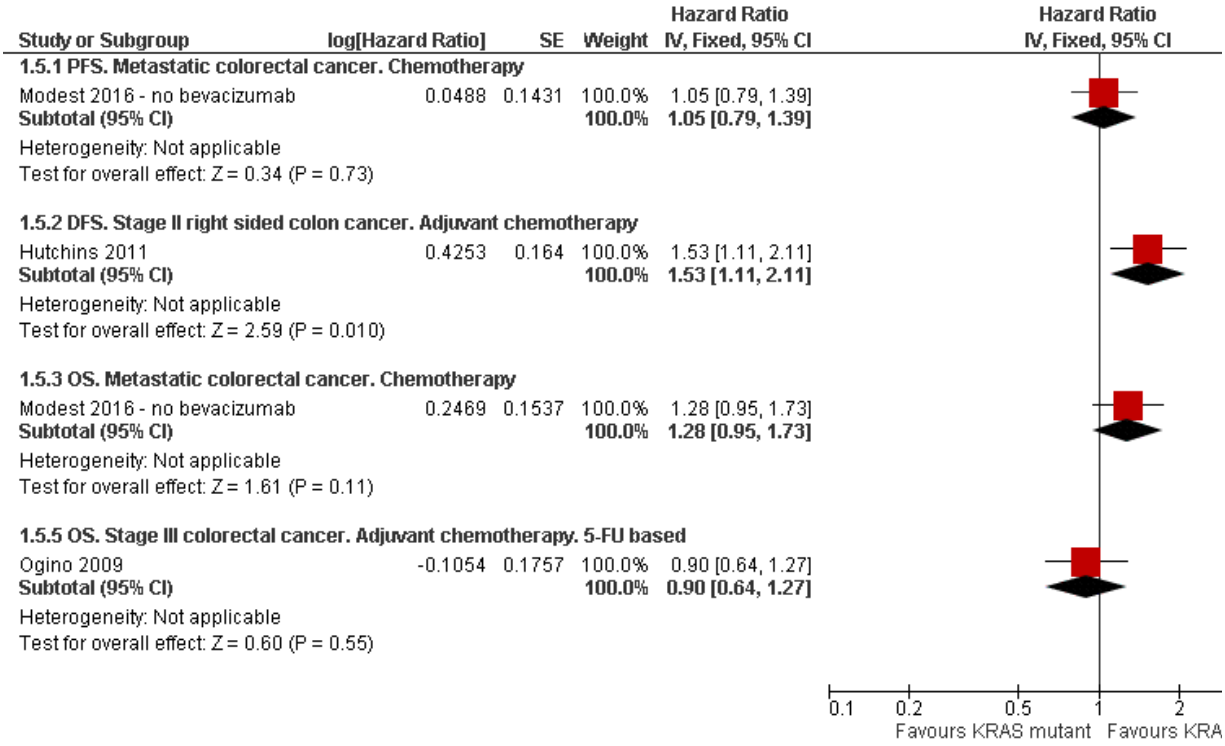
Figure 5: Comparison 1: KRAS mutant versus KRAS wildtype –survival outcomes with bevacizumab based therapy



CI: confidence interval; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; OS: overall survival; PFS: progression-free survival; SE: standard error

2

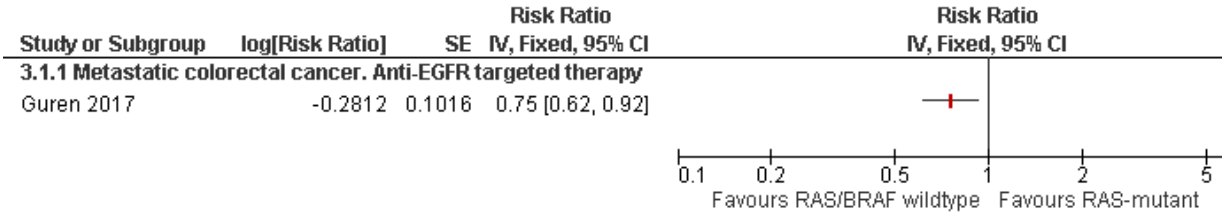
Figure 6: Comparison 1: KRAS mutant versus KRAS wildtype –survival outcomes with chemotherapy



CI: confidence interval; DFS: disease free survival; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog ;OS: overall survival; PFS: progression free survival; SE: standard error; 5-FU: 5 fluorouracil

1

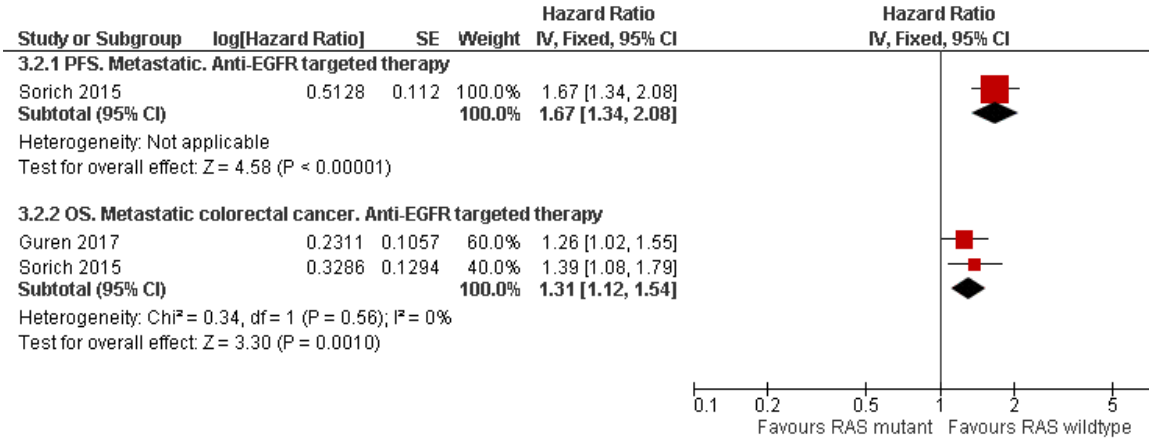
Figure 7: Comparison 2: RAS mutant versus RAS wildtype – response to anti-EGFR targeted therapy



BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; RAS: rat sarcoma virus oncogene homolog; SE: standard error

2

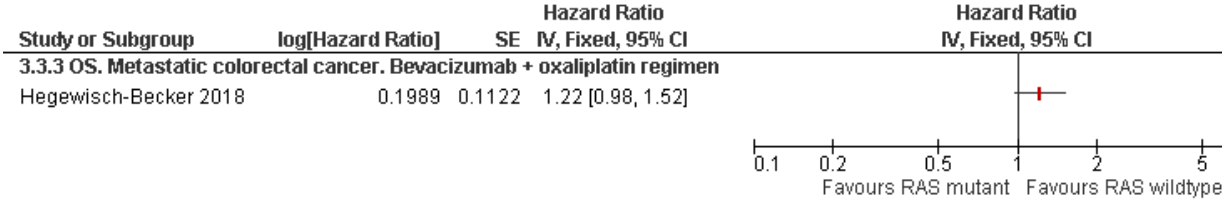
Figure 8: Comparison 2: RAS mutant versus RAS wildtype –survival outcomes with anti-EGFR targeted therapy



CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; OS: overall survival; PFS: progression free survival; RAS: rat sarcoma virus oncogene homolog; SE: standard error

1

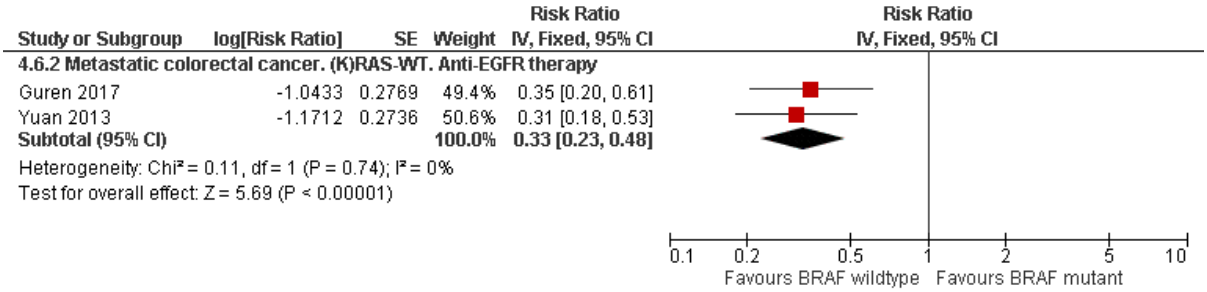
Figure 9: Comparison 2: RAS mutant versus RAS wildtype – survival with bevacizumab based therapy



CI: confidence interval; IV: inverse variance; OS: overall survival; RAS: rat sarcoma virus oncogene homolog; SE: standard error

2
3

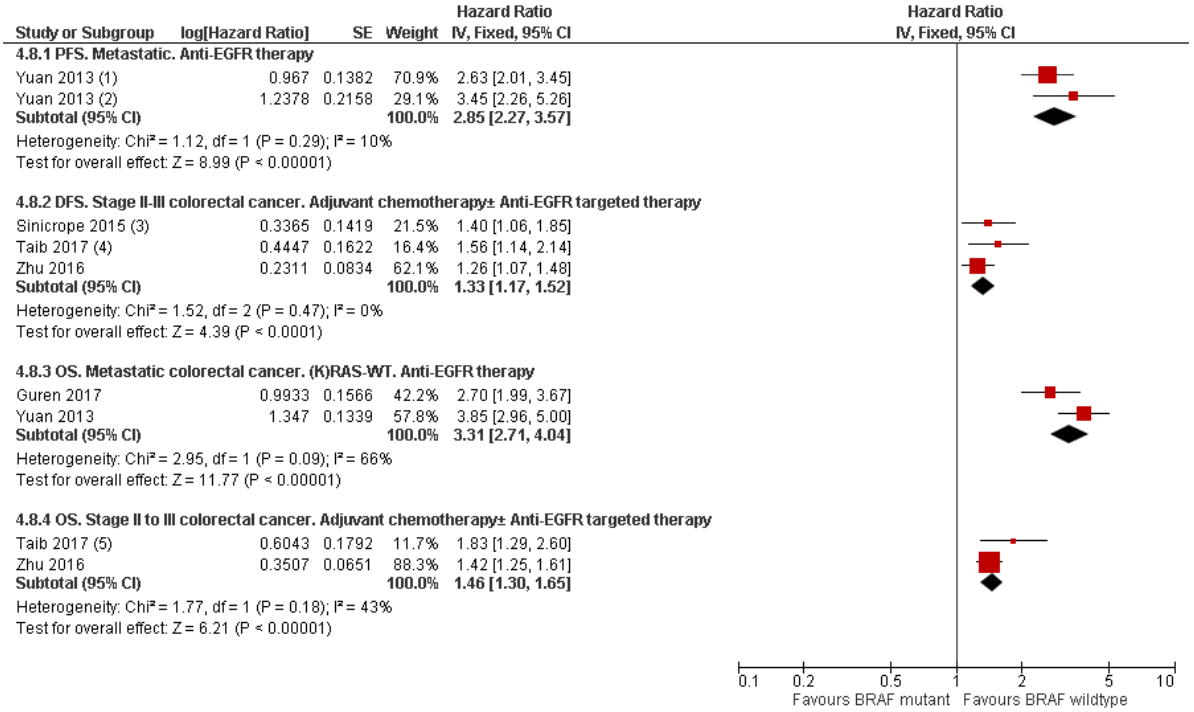
Figure 10: Comparison 3: BRAF mutant versus BRAF wildtype – response to anti-EGFR targeted therapy



BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; (K)RAS(-WT): (Kirsten) rat sarcoma virus oncogene homolog (– wildtype); SE: standard error

4
5

Figure 11: Comparison 3: BRAF mutant versus BRAF wildtype –survival outcomes with anti-EGFR targeted therapy

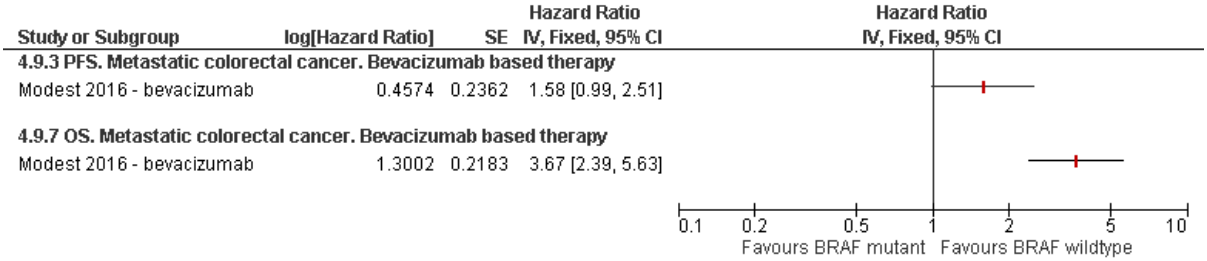


Footnotes
(1) KRAS mutant
(2) KRAS wildtype
(3) pMMR only. Stage III colon cancer,
(4) Stage III colon cancer,
(5) Stage III colon cancer,

BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; DFS: disease free survival; EGFR: epidermal growth factor receptor; IV: inverse variance; (K)RAS(-WT): (Kirsten) rat sarcoma virus oncogene homolog (– wildtype); OS: overall survival; PFS: progression free survival; pMMR: proficient mismatch repair; SE: standard error

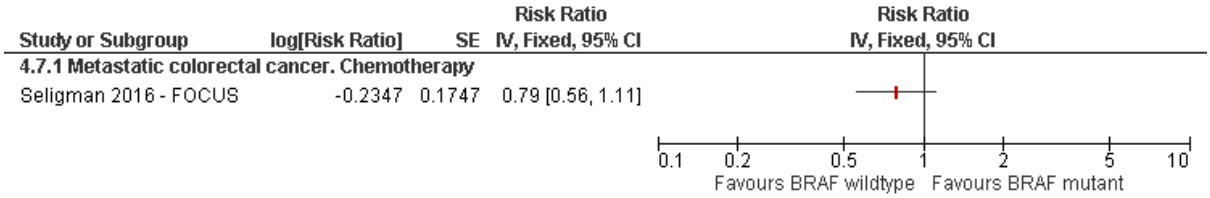
1

Figure 12: Comparison 3: BRAF mutant versus BRAF wildtype –survival outcomes with bevacizumab based therapy



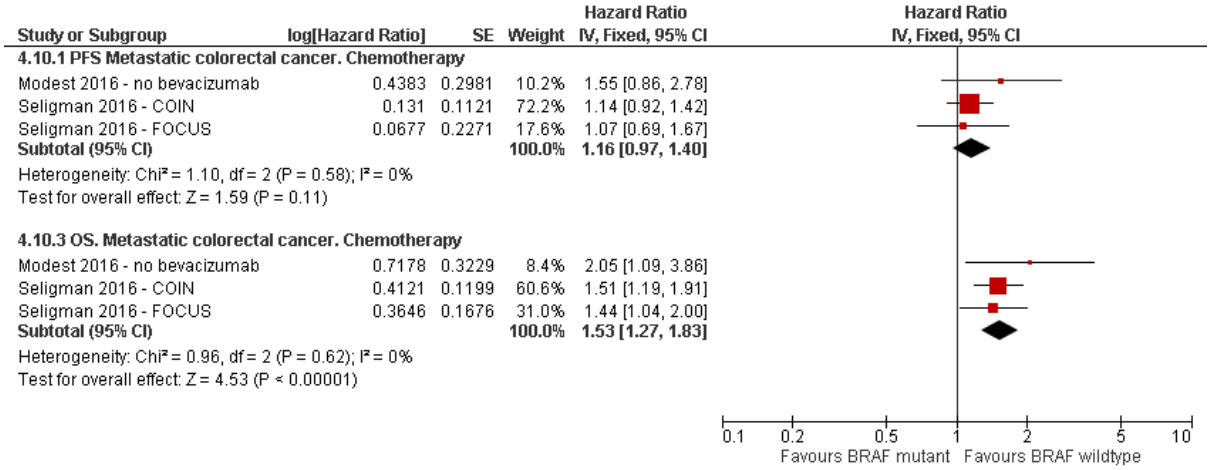
BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; IV: inverse variance; OS: overall survival; PFS: progression free survival; SE: standard error

Figure 13: Comparison 3: BRAF mutant versus BRAF wildtype – response to chemotherapy



BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; IV: inverse variance; SE: standard error

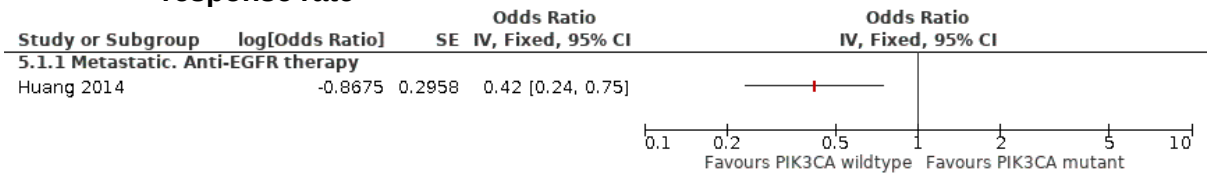
Figure 14: Comparison 3: BRAF mutant versus BRAF wildtype – survival outcomes with chemotherapy



BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; IV: inverse variance; OS: overall survival; PFS: progression free survival; SE: standard error

1

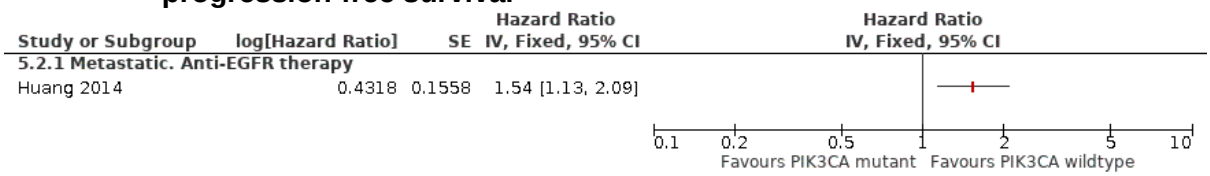
Figure 15: Comparison 4: PIK3CA mutant versus PIK3CA wildtype (in KRAS wildtype) – response rate



CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SE: standard error

2

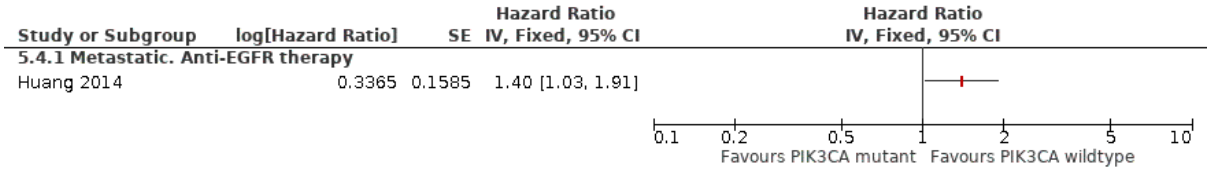
Figure 16: Comparison 4: PIK3CA mutant versus PIK3CA wildtype (in KRAS wildtype) – progression-free survival



CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SE: standard error

1

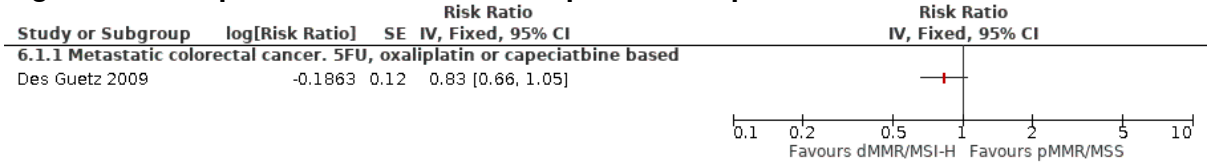
Figure 17: Comparison 4: PIK3CA mutant versus PIK3CA wildtype (in KRAS wildtype) : overall survival



CI: confidence interval; EGFR: epidermal growth factor receptor; IV: inverse variance; KRAS: Kirsten rat sarcoma virus oncogene homolog; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SE: standard error

2

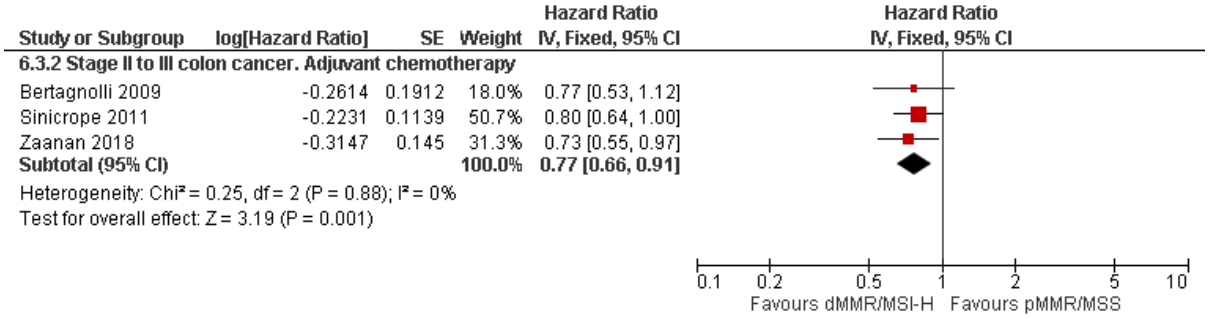
Figure 18: Comparison 5: dMMR versus pMMR – response rate



CI: confidence interval; dMMR: deficient mismatch repair; IV: inverse variance; MSI-H: high microsatellite instability; MSS: microsatellite stable; pMMR: proficient mismatch repair; SE: standard error; 5-FU: 5-fluorouracil

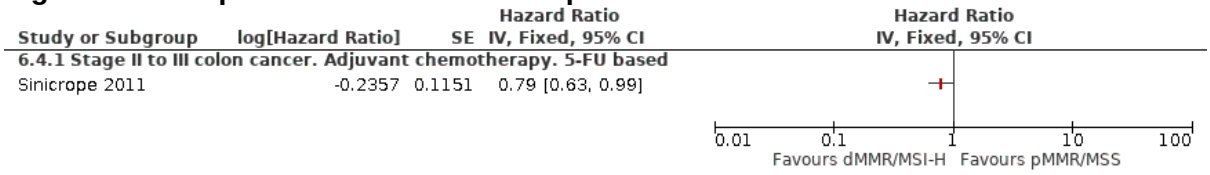
3

Figure 19: Comparison 5: dMMR versus pMMR – disease-free survival



4 *CI: confidence interval; dMMR: deficient mismatch repair; IV: inverse variance; MSI-H: high microsatellite*
5 *instability; MSS: microsatellite stable; pMMR: proficient mismatch repair; SE: standard error*

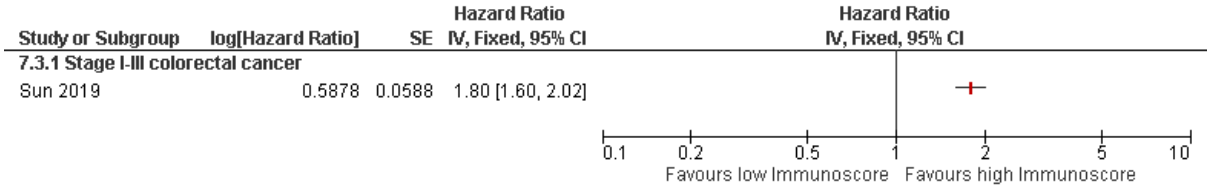
Figure 20: Comparison 5: dMMR versus pMMR – overall survival



CI: confidence interval; dMMR: deficient mismatch repair; IV: inverse variance; MSI-H: high microsatellite instability; MSS: microsatellite stable; pMMR: proficient mismatch repair; SE: standard error; 5-FU: 5-fluorouracil

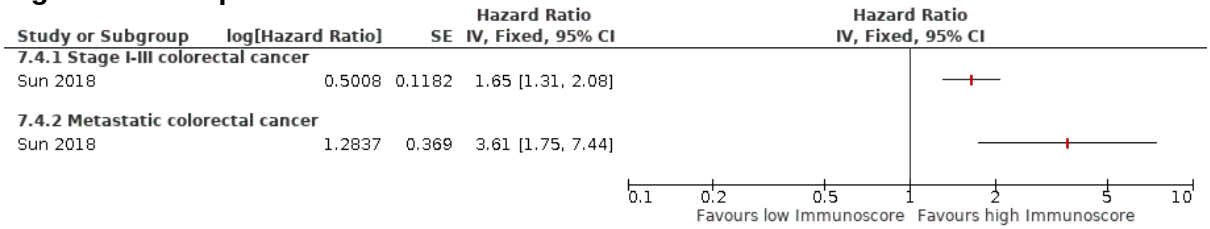
6
7

Figure 21: Comparison 6: Immunoscore – disease free survival



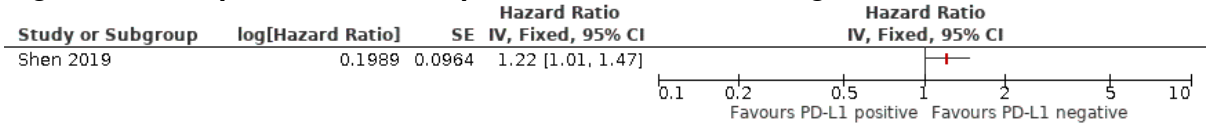
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 22: Comparison 6: Immunoscore – overall survival



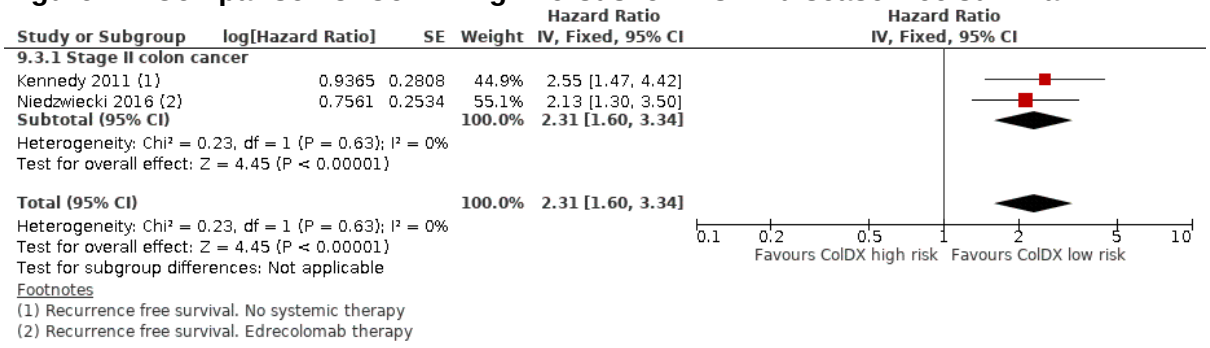
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 23: Comparison 7: PD-L1 positive versus PD-L1 negative – overall survival



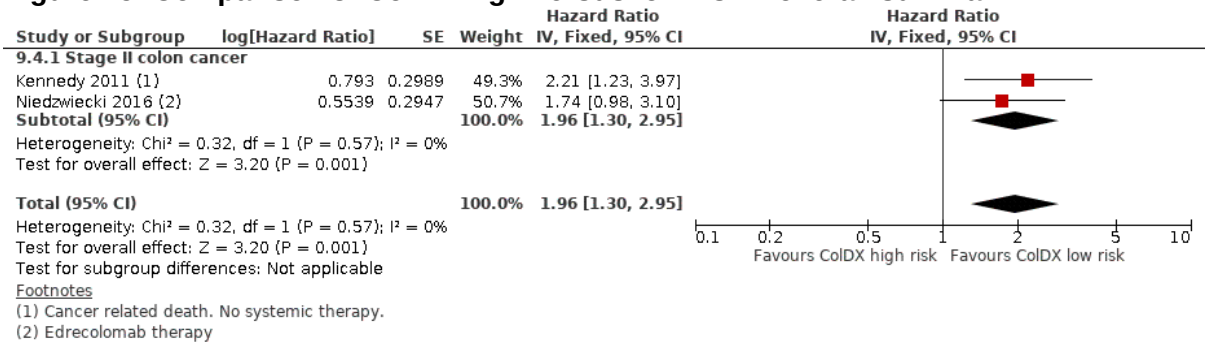
CI: confidence interval; IV: inverse variance; PD-L1: programmed death-ligand 1; SE: standard error

Figure 24: Comparison 8: ColDX high versus low risk – disease-free survival



CI: confidence interval; IV: inverse variance; SE: standard error

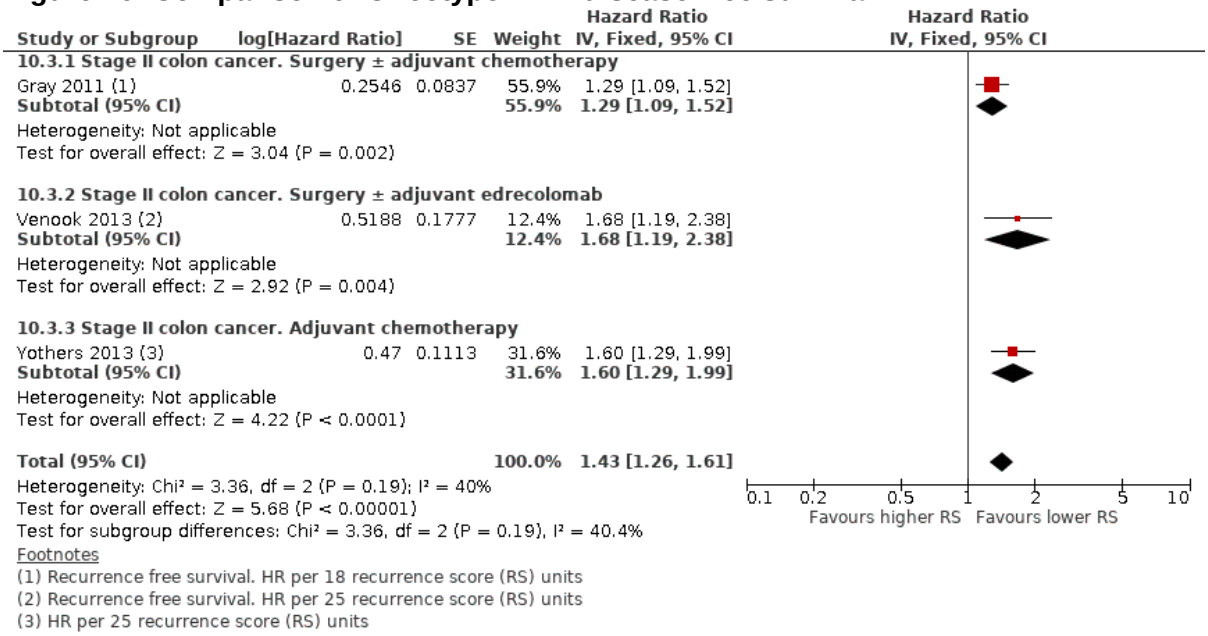
Figure 25: Comparison 8: ColDX high versus low risk – overall survival



CI: confidence interval; IV: inverse variance; SE: standard error

1

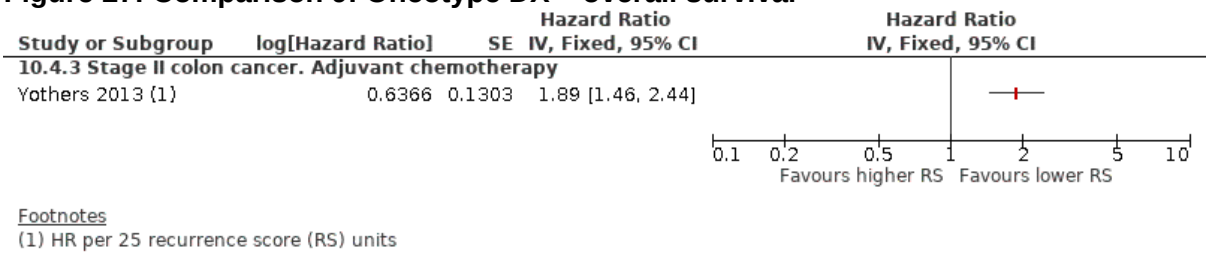
Figure 26: Comparison 9: Oncotype DX – disease-free survival



CI: confidence interval; HR: hazard ratio; IV: inverse variance; SE: standard error

2

Figure 27: Comparison 9: Oncotype DX – overall survival



CI: confidence interval; HR: hazard ratio; IV: inverse variance; SE: standard error

3

Appendix F – GRADE profiles

GRADE profiles for the review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

Table 5: Clinical evidence profile for comparison 1: *KRAS* mutant versus wildtype

Quality assessment								Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N participants	Relative (95% CI)	Absolute	Quality	Importance
Anti-EGFR targeted therapy											
Response to anti-EGFR targeted therapy (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
22	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2242	OR 0.13 (0.08 to 0.21)	-	HIGH	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
16	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1945	HR 2.11 (1.75 to 255)	-	HIGH	CRITICAL
Disease-free survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy)											
2	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3503	HR 1.56 (1.38 to 1.77)	-	HIGH	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
13	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1695	HR 1.79 (1.48 to 2.17)	-	HIGH	IMPORTANT
Overall survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy)											
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	783	HR 1.55 (1.23 to 1.96)	-	HIGH	IMPORTANT
Bevacizumab											
Response to bevacizumab (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy) 2266											
12	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2266	RR 0.70 (0.52 to 0.95)	-	HIGH	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy)											
17	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3095	HR 1.22 (1.08 to 1.38)	-	HIGH	CRITICAL

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy)											
17	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3095	HR 1.52 (1.25 to 1.84)	-	HIGH	IMPORTANT
Chemotherapy											
Response to chemotherapy											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
5	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	410	HR 1.05 (0.79 to 1.39)		HIGH	CRITICAL
Disease-free survival (in patients with stage II right sided colorectal cancer treated with chemotherapy)											
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	784	HR 1.53 (1.11 to 2.11)	-	HIGH	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with chemotherapy)											
5	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	410	HR 1.28 (0.95 to 1.73)	-	HIGH	IMPORTANT
Overall survival (in patients with stage II colorectal cancer treated with 5-FU based chemotherapy)											
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	508	HR 0.90 (0.64 to 1.27)	-	HIGH	IMPORTANT

CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; KRAS: Kirsten rat sarcoma virus oncogene; OR: odds ratio; RR: relative risk

Table 6: Clinical evidence profile for comparison 2: *RAS* mutant versus wildtype

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Anti-EGFR targeted therapy											
Response to anti-EGFR targeted therapy (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	457	RR 0.75 (0.62 to 0.92)	-	HIGH	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
9	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	5948	HR 1.67 (1.34 to 2.08)	-	HIGH	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
10	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	6405	HR 1.31 (1.12 to 1.54)	-	HIGH	IMPORTANT
Bevacizumab											
Response to bevacizumab											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy)											
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	567	HR 1.22 (0.98 to 1.52)	-	HIGH	IMPORTANT

1 *CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; RAS: rat sarcoma virus oncogene; RR: relative risk*

Table 7: Clinical evidence profile for comparison 3: *BRAF* mutant versus wildtype

Quality assessment								Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N participants	Relative (95% CI)	Absolute	Quality	Importance
Anti-EGFR targeted therapy											
Response to anti-EGFR targeted therapy (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
22	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4660	RR 0.33 (0.23 to 0.48)	-	HIGH	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
21	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4203	HR 2.85 (2.27 to 3.57)	-	HIGH	CRITICAL
Disease-free survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy)											
9	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3947	HR 1.33 (1.17 to 1.52)	-	HIGH	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
22	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4660	HR 3.31 (2.71 to 4.04)	-	HIGH	IMPORTANT
Overall survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy ± anti-EGFR targeted therapy)											
8	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1227	HR 1.46 (1.30 to 1.65)	-	HIGH	IMPORTANT
Bevacizumab											
Response to bevacizumab											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy)											
5	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	829	HR 1.58 (0.99 to 2.51)	-	HIGH	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy)											
5	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	829	HR 3.67 (2.39 to 5.63)	-	HIGH	IMPORTANT
Chemotherapy											

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Response to chemotherapy (in patients with metastatic colorectal cancer treated with chemotherapy)											
2	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1541	RR 0.79 (0.56 to 1.11)	-	HIGH	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with chemotherapy)											
7	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1693	HR 1.16 (0.97 to 1.40)	-	HIGH	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with chemotherapy)											
7	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1951	HR 1.53 (1.27 to 1.83)	-	HIGH	IMPORTANT

1 *BRAF: v-raf murine sarcoma b-viral oncogene homolog B1; CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; RR: relative risk*

2 **Table 8: Clinical evidence profile for comparison 4: *PIK3CA* mutant versus wildtype**

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Response anti-EGFR targeted therapy (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
9	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	693	OR 0.42 (0.24 to 0.75)	-	MODERATE	CRITICAL
Progression-free survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
4	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	526	HR 1.54 (1.13 to 2.09)	-	MODERATE	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with metastatic colorectal cancer treated with anti-EGFR targeted therapy ± chemotherapy)											
3	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	508	HR 1.40 (1.03 to 1.91)	-	MODERATE	IMPORTANT

CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; OR: odds ratio; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
1 Downgraded by 1 level due to unclear risk of bias due to attrition and unclear which confounders had been accounted for in the primary studies.

Table 9: Clinical evidence profile for comparison 5: deficient versus proficient mismatch repair (*dMMR* versus *pMMR*)

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Response to chemotherapy (in patients with metastatic colorectal cancer treated with chemotherapy)											
5	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	860	RR 0.83 (0.66 to 1.05)	-	HIGH	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy)											
8	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	5348	HR 0.77 (0.66 to 0.91)	-	HIGH	CRITICAL
Overall survival (in patients with stage II to III colorectal cancer treated with adjuvant chemotherapy)											
5	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2141	HR 0.79 (0.63 to 0.99)	-	HIGH	IMPORTANT

CI: confidence interval; dMMR: deficient mismatch repair; HR: hazard ratio; pMMR: proficient mismatch repair; RR: relative risk

Table 10: Clinical evidence profile for comparison 6: Immunoscore high risk versus low risk

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Response to therapy											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival (in patients with stage I-III colorectal cancer)											

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
5	Observational	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	3992	HR 1.80 (1.60 to 2.02)	-	LOW	CRITICAL
Overall survival (in patients with stage I-III colorectal cancer)											
6	Observational	No serious risk of bias	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	4188	HR 1.65 (1.31 to 2.08)	-	LOW	IMPORTANT
Overall survival (in patients with metastatic colorectal cancer)											
2	Observational	No serious risk of bias	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	612	HR 3.61 (1.75 to 7.44)	-	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio
1 Downgraded one level due to uncertainty about QUIPS participation and attrition domains.
2 Downgraded one level due lack of information about systemic therapies received.

Table 11: Clinical evidence profile for comparison 7: *PD-L1* positive versus negative

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Response to therapy											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (in patients with stage I-IV colorectal cancer receiving chemotherapy)											
10	Observational	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	None	3481	HR 1.22 (1.01 to 1.47)	-	MODERATE	IMPORTANT

CI: confidence interval; HR: hazard ratio; PD-L1: programmed death-ligand 1

1 Downgraded one level due to incomplete reporting of systemic therapy used in the included studies.

Table 12: Clinical evidence profile for comparison 8: ColDX high risk versus low risk

Quality assessment								Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**		
Response to therapy											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival (in patients with stage II colorectal cancer)											
2	Observational	No serious risk of bias	No serious inconsistency	Very serious indirectness[1]	No serious imprecision	None	537	HR 2.31 (1.60 to 3.34)	-	LOW	CRITICAL
Overall survival (in patients with stage II colorectal cancer)											
2	Observational	No serious risk of bias	No serious inconsistency	Very serious indirectness[1]	No serious imprecision	None	537	HR 1.96 (1.30 to 2.95)	-	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio
1 Downgraded two levels – patients had either no systemic therapy or edrecolomab.

Table 13: Clinical evidence profile for comparison 9: Oncotype-DX higher versus lower recurrence score

Quality assessment								Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**		
Response to therapy											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival											
0	No evidence available	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival (in patients with stage II colon cancer treated with surgery ± chemotherapy or edrecolomab)											

Quality assessment								Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**N participants**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3	Observational	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	None	3018	HR 1.43 (1.26 to 1.61)	-	MODERATE	CRITICAL
Overall survival (in patients with stage II colon cancer treated with adjuvant chemotherapy)											
1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	892	HR 1.89 (1.46 to 2.44)	-	HIGH	IMPORTANT

1 *CI: confidence interval; HR: hazard ratio*
2 *1 Downgraded one level – some patients had either no systemic therapy or edrecolomab.*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: Which predictive biomarkers 3 should be used in the systemic management of colorectal cancer patients?

4 **Table 14: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Adelstein, B. A., Dobbins, T. A., Harris, C. A., Marschner, I. C., Ward, R. L., A systematic review and meta-analysis of KRAS status as the determinant of response to anti-EGFR antibodies and the impact of partner chemotherapy in metastatic colorectal cancer, European Journal of Cancer, 47, 1343-1354, 2011	Systematic review - includes subset of the studies in Dahabreh 2011 systematic review
Allegra, C. J., Rumble, R. B., Hamilton, S. R., Mangu, P. B., Roach, N., Hantel, A., Schilsky, R. L., Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American society of clinical oncology provisional clinical opinion update 2015, Journal of Clinical Oncology, 34, 179-185, 2016	Evidence based guideline
Amado, R. G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. J., Juan, T., Sikorski, R., Suggs, S., Radinsky, R., et al.,, Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer, Journal of Clinical Oncology, 26, 1626â€• 1634, 2008	Included in Dahabreh 2011 systematic review.
Andre, T., Vernerey, D., Chibaudel, B., Bonnetain, F., Tijeras-Raballand, A., Scriva, A., Hickish, T., Tabernero, J., Van Laethem, J. L., Banzi, M., Maartense, E., Shmueli, E., Carlsson, G. U., Scheithauer, W., Papamichael, D., Moehler, M., Landolfi, S., Demetter, P., Colote, S., Tournigand, C., Louvet, C., Duval, A., Flejou, J. F., De Gramont, A., Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: Updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study, Journal of Clinical Oncology, 33, 4176-4187, 2015	Included in Zhu 2016 systematic review
Arnold, D., Lueza, B., Douillard, J. Y., Peeters, M., Lenz, H. J., Venook, A., Heinemann, V., Van Cutsem, E., Pignon, J. P., Tabernero, J., Cervantes, A., Ciardiello, F., Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials, Annals of Oncology, 28, 1713-1729, 2017	Prognostic and predictive value of primary tumour side in patients who were all RAS wild-type
Baker, J. B., Dutta, D., Watson, D., Maddala, T., Munneke, B. M., Shak, S., Rowinsky, E. K., Xu, L. A., Harbison, C. T., Clark, E. A., Mauro, D. J., Khambata-Ford, S., Tumour gene expression predicts response to cetuximab in patients with KRAS wild-type metastatic colorectal cancer, British Journal of Cancer, 104, 488-495, 2011	Included in Dahabreh 2011 systematic review.
Balko, J. M., Black, E. P., A gene expression predictor of response to EGFR-targeted therapy stratifies progression-	Patients already included in Dahabreh 2011 systematic review

Study	Reason for exclusion
free survival to cetuximab in KRAS wild-type metastatic colorectal cancer, BMC Cancer, 9 (no pagination), 2009	
Barni, S., Ghilardi, M., Borgonovo, K., Cabiddu, M., Zaniboni, A., Petrelli, F., Cetuximab/irinotecan-chemotherapy in KRAS wild-type pretreated metastatic colorectal cancer: A pooled Analysis and review of literature, Reviews on Recent Clinical Trials, 8, 101-109, 2013	Cetuximab/irinotecan-chemotherapy only
Benvenuti, S., Sartore-Bianchi, A., Di Nicolantonio, F., Zanon, C., Moroni, M., Veronese, S., Siena, S., Bardelli, A., Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies, Cancer Research, 67, 2643-8, 2007	Included in Dahabreh 2011 systematic review.
Berger, M. D., Stintzing, S., Heinemann, V., Yang, D., Cao, S., Sunakawa, Y., Ning, Y., Matsusaka, S., Okazaki, S., Miyamoto, Y., Suenaga, M., Schirripa, M., Soni, S., Zhang, W., Falcone, A., Loupakis, F., Lenz, H. J., Impact of genetic variations in the MAPK signaling pathway on outcome in metastatic colorectal cancer patients treated with first-line FOLFIRI and bevacizumab: Data from FIRE-3 and TRIBE trials, Annals of Oncology, 28, 2780-2785, 2017	MAPK not relevant to review protocol
Blons, H., Emile, J. F., Le Malicot, K., Julie, C., Zaanan, A., Tabernero, J., Mini, E., Folprecht, G., Van Laethem, J. L., Thaler, J., et al.,, Prognostic value of KRAS mutations in stage III colon cancer: post hoc analysis of the PETACC8 phase III trial dataset, Annals of Oncology, 25, 2378â€• 2385, 2014	PETACC8 trial included in Zaanan 2018
Bokemeyer, C., Bondarenko, I., Hartmann, J. T., de Braud, F., Schuch, G., Zubel, A., Celik, I., Schlichting, M., Koralewski, P., Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: The OPUS study, Annals of Oncology, 22, 1535-1546, 2011	OPUS study included in Dahabreh 2011 systematic review
Bokemeyer, C., Bondarenko, I., Makhson, A., Hartmann, J. T., Aparicio, J., de Braud, F., Donea, S., Ludwig, H., Schuch, G., Stroh, C., et al.,, Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer, Journal of Clinical Oncology, 27, 663â€• 671, 2009	OPUS study included in Dahabreh 2011 systematic review
Bokemeyer, C., Cutsem, E. V., Rougier, P., Ciardiello, F., Heeger, S., Schlichting, M., Celik, I., Kohne, C. H., Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials, European Journal of Cancer, 48, 1466-1475, 2012	OPUS study included in Dahabreh 2011 systematic review
Bokemeyer, C., Kohne, C. H., Ciardiello, F., Lenz, H. J., Heinemann, V., Klinkhardt, U., Beier, F., Duecker, K., Van Krieken, J. H., Tejpar, S., FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer, European Journal of Cancer, 51, 1243-1252, 2015	Data from OPUS included in Sorich 2015 systematic review
Chen, J., Ye, Y., Sun, H., Shi, G., Association between KRAS codon 13 mutations and clinical response to anti-	Systematic review - KRAS codon 13 mutations only

Study	Reason for exclusion
EGFR treatment in patients with metastatic colorectal cancer: results from a meta-analysis, Cancer Chemotherapy & Pharmacology, 71, 265-72, 2013	
Chuko, J., Yeh, M. K., Chen, B. J., Hu, K. Y., Efficacy of cetuximab on wild-type and mutant KRAS in colorectal cancer: Systematic review and meta-analysis, Journal of Medical Sciences, 30, 189-198, 2010	Systematic review - fewer studies included than Dahabreh 2011.
Clancy, C., Burke, J. P., Coffey, J. C., KRAS mutation does not predict the efficacy of neo-adjuvant chemoradiotherapy in rectal cancer: A systematic review and meta-analysis, Surgical Oncology, 22, 105-111, 2013	Outcomes not in PICO
Cremolini, C., Casagrande, M., Loupakis, F., Aprile, G., Bergamo, F., Masi, G., Moretto, R. R., Pietrantonio, F., Marmorino, F., Zucchelli, G., Tomasello, G., Tonini, G., Allegrini, G., Granetto, C., Ferrari, L., Urbani, L., Cillo, U., Pilati, P., Sensi, E., Pellegrinelli, A., Milione, M., Fontanini, G., Falcone, A., Efficacy of FOLFOXIRI plus bevacizumab in liver-limited metastatic colorectal cancer: A pooled analysis of clinical studies by Gruppo Oncologico del Nord Ovest, European Journal of Cancer, 73, 74-84, 2017	Liver-limited metastases only
Cui, D., Cao, D., Yang, Y., Qiu, M., Huang, Y., Yi, C., Effect of BRAF V600E mutation on tumor response of anti-EGFR monoclonal antibodies for first-line metastatic colorectal cancer treatment: A meta-analysis of randomized studies, Molecular Biology Reports, 41, 1291-1298, 2014	First line treatment only.
De Bruijn, M. T., Raats, D. A. E., Tol, J., Hinrichs, J., Teerenstra, S., Punt, C. J. A., Borel Rinkes, I. H. M., Kranenburg, O., Combined KRAS and TP53 mutation status is not predictive in CAPOX-treated metastatic colorectal cancer, Anticancer Research, 31, 1379-1385, 2011	CAIRO trial included in other systematic reviews
De Roock, W., Claes, B., Bernasconi, D., De Schutter, J., Biesmans, B., Fountzilas, G., Kalogeras, K. T., Kotoula, V., Papamichael, D., Laurent-Puig, P., Penault-Llorca, F., Rougier, P., Vincenzi, B., Santini, D., Tonini, G., Cappuzzo, F., Frattini, M., Molinari, F., Saletti, P., De Dosso, S., Martini, M., Bardelli, A., Siena, S., Sartore-Bianchi, A., Tabernero, J., Macarulla, T., Di Fiore, F., Gangloff, A. O., Ciardiello, F., Pfeiffer, P., Qvortrup, C., Hansen, T. P., Van Cutsem, E., Piessevaux, H., Lambrechts, D., Delorenzi, M., Tejpar, S., Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: A retrospective consortium analysis, The Lancet Oncology, 11, 753-762, 2010	Included in other systematic reviews
De Roock, W., Piessevaux, H., De Schutter, J., Janssens, M., De Hertogh, G., Personeni, N., Biesmans, B., Van Laethem, J. L., Peeters, M., Humblet, Y., Van Cutsem, E., Tejpar, S., KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab, Annals of Oncology, 19, 508-515, 2008	Included in Dahabreh 2011 systematic review.

Study	Reason for exclusion
Des Guetz, G., Lecaille, C., Mariani, P., Bennamoun, M., Uzzan, B., Nicolas, P., Boisseau, A., Sastre, X., Cucherousset, J., Lagorce, C., Schischmanoff, P. O., Morere, J. F., Prognostic impact of microsatellite instability in colorectal cancer patients treated with adjuvant FOLFOX, Anticancer Research, 30, 4297-4301, 2010	Overlap with Des Guetz 2009
Des Guetz, G., Schischmanoff, O., Nicolas, P., Perret, G. Y., Morere, J. F., Uzzan, B., Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis, European Journal of Cancer, 45, 1890-1896, 2009	Systematic review - overlap with studies included in Sinicrope 2011
Di Fiore, F., Blanchard, F., Charbonnier, F., Le Pessot, F., Lamy, A., Galais, M. P., Bastit, L., Killian, A., Sesboue, R., Tuech, J. J., Queuniet, A. M., Paillot, B., Sabourin, J. C., Michot, F., Michel, P., Frebourg, T., Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy, British Journal of Cancer, 96, 1166-1169, 2007	Included in Dahabreh 2011 systematic review.
Di Nicolantonio, F., Martini, M., Molinari, F., Sartore-Bianchi, A., Arena, S., Saletti, P., De Dosso, S., Mazzucchelli, L., Frattini, M., Siena, S., Bardelli, A., Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer, Journal of Clinical Oncology, 26, 5705-5712, 2008	Included in Dahabreh 2011 systematic review.
Díaz-Rubio, E., Gómez-España, A., Massutí, B., Sastre, J., Reboredo, M., Manzano, J. L., Rivera, F., Safont, M. J., Montagut, C., González, E., et al.,, Role of Kras status in patients with metastatic colorectal cancer receiving first-line chemotherapy plus bevacizumab: a TTD group cooperative study, PLoS ONE, 7, e47345, 2012	Included in Petrelli 2013 systematic review.
Douillard, J. Y., Oliner, K. S., Siena, S., Tabernero, J., Burkes, R., Barugel, M., Humblet, Y., Bodoky, G., Cunningham, D., Jassem, J., Rivera, F., Kocakova, I., Ruff, P., Blasinska-Morawiec, M., Smakal, M., Canon, J. L., Rother, M., Williams, R., Rong, A., Wiezorek, J., Sidhu, R., Patterson, S. D., Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer, New England Journal of Medicine, 369, 1023-1034, 2013	Included in Sorich 2015 systematic review.
Douillard, J. Y., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M., Humblet, Y., Bodoky, G., Cunningham, D., Jassem, J., Rivera, F., Kocakova, I., Ruff, P., Blasinska-Morawiec, M., Smakal, M., Canon, J. L., Rother, M., Oliner, K. S., Wolf, M., Gansert, J., Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study, Journal of Clinical Oncology, 28, 4697-705, 2010	Included in Sorich 2015 systematic review.
Douillard, J. Y., Zemelka, T., Fountzilas, G., Barone, C., Schlichting, M., Heighway, J., Eggleton, S. P., Srimuninnimit, V., FOLFOX4 with cetuximab versus. UFOX with cetuximab as first-line therapy in metastatic colorectal cancer: the	Does not report prognostic / predictive analysis. Reports subgroup analysis by KRAS status.

Study	Reason for exclusion
randomized phase II FUTURE study, Clinical Colorectal Cancer, 13, 14â€• 26.e1, 2014	
Fallik, D., Borrini, F., Boige, V., Viguier, J., Jacob, S., Miquel, C., Sabourin, J. C., Ducreux, M., Praz, F., Microsatellite instability is a predictive factor of the tumor response to irinotecan in patients with advanced colorectal cancer, Cancer Research, 63, 5738-5744, 2003	Included in Des Guetz 2009 systematic review.
Freeman, D. J., Juan, T., Reiner, M., Hecht, J. R., Meropol, N. J., Berlin, J., Mitchell, E., Sarosi, I., Radinsky, R., Amado, R. G., Association of K-ras mutational status and clinical outcomes in patients with metastatic colorectal cancer receiving panitumumab alone, Clinical Colorectal Cancer, 7, 184-190, 2008	Included in Dahabreh 2011 systematic review.
Gavin, P. G., Colangelo, L. H., Fumagalli, D., Tanaka, N., Remillard, M. Y., Yothers, G., Kim, C., Taniyama, Y., Kim, S. I., Choi, H. J., Blackmon, N. L., Lipchik, C., Petrelli, N. J., O'Connell, M. J., Wolmark, N., Paik, S., Pogue-Geile, K. L., Mutation profiling and microsatellite instability in stage II and III colon cancer: An assessment of their prognostic and oxaliplatin predictive value, Clinical Cancer Research, 18, 6531-6541, 2012	Included in Zhu 2016 systematic review
Goey, K. K. H., Elias, S. G., Hinke, A., Van Oijen, M. G. H., Punt, C. J. A., Hegewisch-Becker, S., Arnold, D., Koopman, M., Clinicopathological factors influencing outcome in metastatic colorectal cancer patients treated with fluoropyrimidine and bevacizumab maintenance treatment versus observation: An individual patient data metaanalysis of two phase 3 trials, British Journal of Cancer, 117, 1768-1776, 2017	Reports subgroup analysis by RAS/BRAF but does not compare RAS mutant versus wildtype
Goey, K. K. H., Elias, S. G., van Tinteren, H., Lacle, M. M., Willems, S. M., Offerhaus, G. J. A., de Leng, W. W. J., Strengman, E., Ten Tije, A. J., Creemers, G. M., van der Velden, A., de Jongh, F. E., Erdkamp, F. L. G., Tanis, B. C., Punt, C. J. A., Koopman, M., Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 study, Annals of Oncology, 28, 2128-2134, 2017	Does not report prognostic / predictive analysis. Reports subgroup analysis by BRAF/RAS status.
Guastadisegni, C., Colafranceschi, M., Ottini, L., Dogliotti, E., Microsatellite instability as a marker of prognosis and response to therapy: a meta-analysis of colorectal cancer survival data, European Journal of Cancer, 46, 2788-98, 2010	Systematic review - studies included in other reviews. Time to event outcomes not analysed properly.
Hurwitz, H. I., Yi, J., Ince, W., Novotny, W. F., Rosen, O., The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: Analysis of a phase in study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer, Oncologist, 14, 22-28, 2009	Included in Petrelli 2013 systematic review.
Ibrahim, E. M., Zekri, J. M., Bin Sadiq, B. M., Cetuximab-based therapy for metastatic colorectal cancer: A meta-	Systematic review - includes subset of studies in Dahabreh 2011 systematic review.

Study	Reason for exclusion
analysis of the effect of K-ras mutations, International Journal of Colorectal Disease, 25, 713-721, 2010	
Ince, W. L., Jubb, A. M., Holden, S. N., Holmgren, E. B., Tobin, P., Sridhar, M., Hurwitz, H. I., Kabbinavar, F., Novotny, W. F., Hillan, K. J., Koeppen, H., Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab, Journal of the National Cancer Institute, 97, 981-989, 2005	Included in Petrelli 2013 systematic review.
Karapetis, C. S., Jonker, D., Daneshmand, M., Hanson, J. E., O'Callaghan, C. J., Marginean, C., Zalcberg, J. R., Simes, J., Moore, M. J., Tebbutt, N. C., et al.,, PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer--results from NCIC CTG/AGITG CO.17, Clinical Cancer Research, 20, 744â€• 753, 2014	Subgroup analysis of cetuximab versus BSC by BRAF, PIK3CA and PTEN status. Does not report outcomes for mutant versus wildtype.
Khambata-Ford, S., Garrett, C. R., Meropol, N. J., Basik, M., Harbison, C. T., Wu, S., Wong, T. W., Huang, X., Takimoto, C. H., Godwin, A. K., Tan, B. R., Krishnamurthi, S. S., Burris, H. A., 3rd, Poplin, E. A., Hidalgo, M., Baselga, J., Clark, E. A., Mauro, D. J., Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab, Journal of Clinical Oncology, 25, 3230-7, 2007	Included in Dahabreh 2011 systematic review.
Kim, J. E., Hong, Y. S., Ryu, M. H., Lee, J. L., Chang, H. M., Lim, S. B., Kim, J. H., Jang, S. J., Kim, M. J., Yu, C. S., Kang, Y. K., Kim, J. C., Kim, T. W., Association between deficient mismatch repair system and efficacy to irinotecan-containing chemotherapy in metastatic colon cancer, Cancer Science, 102, 1706-1711, 2011	Study included in Sinicrope 2011 systematic review
Kim, S. T., Lee, J., Park, S. H., Park, J. O., Lim, H. Y., Kang, W. K., Kim, J. Y., Kim, Y. H., Chang, D. K., Rhee, P. L., Kim, D. S., Yun, H., Cho, Y. B., Kim, H. C., Yun, S. H., Chun, H. K., Lee, W. Y., Park, Y. S., The effect of DNA mismatch repair (MMR) status on oxaliplatin-based first-line chemotherapy as in recurrent or metastatic colon cancer, Medical Oncology, 27, 1277-85, 2010	Study included in Sinicrope 2011 systematic review
Kim, S. T., Lee, J., Park, S. H., Park, J. O., Lim, H. Y., Kang, W. K., Kim, J. Y., Kim, Y. H., Chang, D. K., Rhee, P. L., Kim, D. S., Yun, H., Cho, Y. B., Kim, H. C., Yun, S. H., Lee, W. Y., Chun, H. K., Park, Y. S., Clinical impact of microsatellite instability in colon cancer following adjuvant FOLFOX therapy, Current Microbiology, 61, 659-667, 2010	Study included in Sinicrope 2011 systematic review
Koopman, M., Kortman, G. A., Mekenkamp, L., Ligtenberg, M. J., Hoogerbrugge, N., Antonini, N. F., Punt, C. J., van Krieken, J. H., Deficient mismatch repair system in patients with sporadic advanced colorectal cancer, British Journal of Cancer, 100, 266â€• 273, 2009	Included in Des Guetz 2009 systematic review.
Laurent-Puig, P., Cayre, A., Manceau, G., Buc, E., Bachet, J. B., Lecomte, T., Rougier, P., Lievre, A., Landi, B., Boige, V., Ducreux, M., Ychou, M., Bibeau, F., Bouche, O., Reid, J., Stone, S., Penault-Llorca, F., Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy	Included in Dahabreh 2011 systematic review.

Study	Reason for exclusion
in wild-type KRAS metastatic colon cancer, Journal of Clinical Oncology, 27, 5924-5930, 2009	
Li, W., Shi, Q., Wang, W., Liu, J., Ren, J., Li, Q., Hou, F., KRAS status and resistance to epidermal growth factor receptor tyrosine-kinase inhibitor treatment in patients with metastatic colorectal cancer: a meta-analysis, Colorectal Disease, 16, O370-8, 2014	Systematic review - less comprehesive than Dahabreh 2011
Lievre, A., Bachet, J. B., Boige, V., Cayre, A., Le Corre, D., Buc, E., Ychou, M., Bouche, O., Landi, B., Louvet, C., Andre, T., Bibeau, F., Diebold, M. D., Rougier, P., Ducreux, M., Tomasic, G., Emile, J. F., Penault-Llorca, F., Laurent-Puig, P., KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab, Journal of Clinical Oncology, 26, 374-379, 2008	Included in Dahabreh 2011 systematic review.
Lin, A. Y., Buckley, N. S., Lu, A. T. T., Kouzminova, N. B., Salpeter, S. R., Effect of KRAS mutational status in advanced colorectal cancer on the outcomes of anti-epidermal growth factor receptor monoclonal antibody therapy: A systematic review and meta-analysis, Clinical Colorectal Cancer, 10, 63-69, 2011	Systematic review - less comprehensive than Dahabreh 2011
Loupakis, F., Pollina, L., Stasi, I., Ruzzo, A., Scartozzi, M., Santini, D., Masi, G., Graziano, F., Cremolini, C., Rulli, E., Canestrari, E., Funel, N., Schiavon, G., Petrini, I., Magnani, M., Tonini, G., Campani, D., Floriani, I., Cascinu, S., Falcone, A., PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer, Journal of Clinical Oncology, 27, 2622-9, 2009	Included in Dahabreh 2011 systematic review.
Loupakis, F., Ruzzo, A., Cremolini, C., Vincenzi, B., Salvatore, L., Santini, D., Masi, G., Stasi, I., Canestrari, E., Rulli, E., Floriani, I., Bencardino, K., Galluccio, N., Catalano, V., Tonini, G., Magnani, M., Fontanini, G., Basolo, F., Falcone, A., Graziano, F., KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer, British Journal of Cancer, 101, 715-721, 2009	Included in Dahabreh 2011 systematic review.
Mao, C., Huang, Y. F., Yang, Z. Y., Zheng, D. Y., Chen, J. Z., Tang, J. L., KRAS p.G13D mutation and codon 12 mutations are not created equal in predicting clinical outcomes of cetuximab in metastatic colorectal cancer: A systematic review and meta-analysis, Cancer, 119, 714-721, 2013	Systematic review - KRAS codon 13 mutations only
Mao, C., Liao, R. Y., Qiu, L. X., Wang, X. W., Ding, H., Chen, Q., BRAF V600E mutation and resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer: a meta-analysis, Molecular Biology Reports, 38, 2219-23, 2011	Systematic review - includes the same studies as Yuan 2013
Mao, C., Yang, Z. Y., Hu, X. F., Chen, Q., Tang, J. L., PIK3CA exon 20 mutations as a potential biomarker for resistance to anti-EGFR monoclonal antibodies in KRAS wild-type metastatic colorectal cancer: A systematic review	Systematic review - superceeded by Huang 2013

Study	Reason for exclusion
and meta-analysis, Annals of Oncology, 23, 1518-1525, 2012	
Maughan, T. S., Adams, R. A., Smith, C. G., Meade, A. M., Seymour, M. T., Wilson, R. H., Idziaszczyk, S., Harris, R., Fisher, D., Kenny, S. L., Kay, E., Mitchell, J. K., Madi, A., Jasani, B., James, M. D., Bridgewater, J., Kennedy, M. J., Claes, B., Lambrechts, D., Kaplan, R., Cheadle, J. P., Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial, The Lancet, 377, 2103-2114, 2011	Included in Sorich 2015 systematic review.
Modest, D. P., Jung, A., Moosmann, N., Laubender, R. P., Giessen, C., Schulz, C., Haas, M., Neumann, J., Boeck, S., Kirchner, T., Heinemann, V., Stintzing, S., The influence of KRAS and BRAF mutations on the efficacy of cetuximab-based first-line therapy of metastatic colorectal cancer: An analysis of the AIO KRK-0104-trial, International Journal of Cancer, 131, 980-986, 2012	Trial included in Yuan 2013 systematic review.
Morgen, E. K., Lenz, H. J., Jonker, D. J., Tu, D., Milano, G., Graziano, F., Zalcberg, J., Karapetis, C. S., Dobrovic, A., O'Callaghan, C. J., Liu, G., Germline polymorphisms as biomarkers of tumor response in colorectal cancer patients treated with anti-EGFR monoclonal antibodies: A systematic review and meta-analysis, Pharmacogenomics Journal, 17, 535-542, 2017	Systematic review - of germline polymorphisms
Ogino, S., Liao, X., Imamura, Y., Yamauchi, M., McCleary, N. J., Ng, K., Niedzwiecki, D., Saltz, L. B., Mayer, R. J., Whittom, R., et al.,, Predictive and prognostic analysis of PIK3CA mutation in stage II colon cancer intergroup trial, Journal of the National Cancer Institute, 105, 1789â€• 1798, 2013	Included in Zhu 2016 systematic review
Ogino, S., Shima, K., Meyerhardt, J. A., McCleary, N. J., Ng, K., Hollis, D., Saltz, L. B., Mayer, R. J., Schaefer, P., Whittom, R., et al.,, Predictive and prognostic roles of BRAF mutation in stage III colon cancer: results from intergroup trial CALGB 89803, Clinical Cancer Research, 18, 890â€• 900, 2012	Study included in Yuan 2013 systematic review.
Park, J. H., Han, S. W., Oh, D. Y., Im, S. A., Jeong, S. Y., Park, K. J., Kim, T. Y., Bang, Y. J., Park, J. G., Analysis of KRAS, BRAF, PTEN, IGF1R, EGFR intron 1 CA status in both primary tumors and paired metastases in determining benefit from cetuximab therapy in colon cancer, Cancer Chemotherapy and Pharmacology, 68, 1045-1055, 2011	Study included in Yuan 2013 systematic review.
Patterson, S. D., Peeters, M., Siena, S., Van Cutsem, E., Humblet, Y., Van Laethem, J. L., Andre, T., Tian, Y., Sidhu, R., Oliner, K. S., Comprehensive analysis of KRAS and NRAS mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408), Journal of Clinical Oncology. Conference, 31, 2013	Included in Sorich 2015 systematic review.
Peeters, M., Douillard, J. Y., Van Cutsem, E., Siena, S., Zhang, K., Williams, R., Wiezorek, J., Mutant KRAS codon	Included in Sorich 2015 systematic review

Study	Reason for exclusion
12 and 13 alleles in patients with metastatic colorectal cancer: Assessment as prognostic and predictive biomarkers of response to panitumumab, Journal of Clinical Oncology, 31, 759-765, 2013	
Peeters, M., Oliner, K. S., Jay Price, T., Cervantes, A., Sobrero, A. F., Ducreux, M., Hotko, Y., Andre, T., Chan, E., Lordick, F., Punt, C. J. A., Strickland, A., Wilson, G., Ciuleanu, T. E., Roman, L., Van Cutsem, E., Tian, Y., Jung, A. S., Sidhu, R., Patterson, S. D., Analysis of KRAS/NRAS mutations in phase 3 study 20050181 of panitumumab (pmab) plus FOLFIRI versus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC), Journal of Clinical Oncology. Conference, 32, 2014	Included in Sorich 2015 systematic review
Peeters, M., Oliner, K. S., Price, T. J., Cervantes, A., Sobrero, A. F., Ducreux, M., Hotko, Y., Andre, T., Chan, E., Lordick, F., Punt, C. J. A., Strickland, A. H., Wilson, G., Ciuleanu, T. E., Roman, L., Van Cutsem, E., He, P., Yu, H., Koukakis, R., Terwey, J. H., Jung, A. S., Sidhu, R., Patterson, S. D., Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer, Clinical Cancer Research, 21, 5469-5479, 2015	Trial 20050181 - included in Sorich 2015 systematic review.
Peeters, M., Price, T. J., Cervantes, A., Sobrero, A. F., Ducreux, M., Hotko, Y., Andre, T., Chan, E., Lordick, F., Punt, C. J., Strickland, A. H., Wilson, G., Ciuleanu, T. E., Roman, L., Van Cutsem, E., Tzekova, V., Collins, S., Oliner, K. S., Rong, A., Gansert, J., Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer, Journal of Clinical Oncology, 28, 4706-13, 2010	Trial 20050181 - included in Sorich 2015 systematic review.
Peng, J., Lin, J., Qiu, M., Zhao, Y., Deng, Y., Shao, J., Ding, P., Zhang, H., Wan, D., Lu, Z., Pan, Z., Oncogene mutation profile predicts tumor regression and survival in locally advanced rectal cancer patients treated with preoperative chemoradiotherapy and radical surgery, Tumor Biology, 39, 2017	Combines all oncogenes into 1 group
Pietrantonio, F., Petrelli, F., Coinu, A., Di Bartolomeo, M., Borgonovo, K., Maggi, C., Cabiddu, M., Iacovelli, R., Bossi, I., Lonati, V., Ghilardi, M., de Braud, F., Barni, S., Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis, European Journal of Cancer, 51, 587-94, 2015	Systematic review - Anti-EGFR versus control for RAS-wt/BRAF-mutant patients.
Prenen, H., De Schutter, J., Jacobs, B., De Roock, W., Biesmans, B., Claes, B., Lambrechts, D., Van Cutsem, E., Tejpar, S., PIK3CA mutations are not a major determinant of resistance to the epidermal growth factor receptor inhibitor cetuximab in metastatic colorectal cancer, Clinical Cancer Research, 15, 3184-3188, 2009	Included in Dahabreh 2011 systematic review.
Price, T. J., Bruhn, M. A., Lee, C. K., Hardingham, J. E., Townsend, A. R., Mann, K. P., Simes, J., Weickhardt, A.,	Reports bevacizumab versus control for RAS

Study	Reason for exclusion
Wrin, J. W., Wilson, K., et al.,, Correlation of extended RAS and PIK3CA gene mutation status with outcomes from the phase III AGITG MAX STUDY involving capecitabine alone or in combination with bevacizumab plus or minus mitomycin C in advanced colorectal cancer, British Journal of Cancer, 112, 963â€• 970, 2015	
Price, T. J., Hardingham, J. E., Lee, C. K., Weickhardt, A., Townsend, A. R., Wrin, J. W., Chua, A., Shivasami, A., Cummins, M. M., Murone, C., Tebbutt, N. C., Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer, Journal of Clinical Oncology, 29, 2675-2682, 2011	Included in Petrelli 2013 SR.
Qiu, L. X., Mao, C., Zhang, J., Zhu, X. D., Liao, R. Y., Xue, K., Li, J., Chen, Q., Predictive and prognostic value of KRAS mutations in metastatic colorectal cancer patients treated with cetuximab: A meta-analysis of 22 studies, European Journal of Cancer, 46, 2781-2787, 2010	Systematic review - includes subset of studies in Dahabreh 2011 systematic review.
Reinacher-Schick, A., Schulmann, K., Modest, D. P., Bruns, N., Graeven, U., Jaworska, M., Greil, R., Porschen, R., Arnold, D., Schmiegel, W., Tannapfel, A., Effect of KRAS codon13 mutations in patients with advanced colorectal cancer (advanced CRC) under oxaliplatin containing chemotherapy. Results from a translational study of the AIO colorectal study group, BMC Cancer, 12, 349, 2012	Included in Petrelli 2013 systematic review.
Ribic, C. M., Sargent, D. J., Moore, M. J., Thibodeau, S. N., French, A. J., Goldberg, R. M., Hamilton, S. R., Laurent-Puig, P., Gryfe, R., Shepherd, L. E., Tu, D., Redston, M., Gallinger, S., Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer, New England Journal of Medicine, 349, 247-257, 2003	included in Sinicrope 2011
Rivera, F., Karthaus, M., Hecht, J. R., Sevilla, I., Forget, F., Fasola, G., Canon, J. L., Guan, X., Demonty, G., Schwartzberg, L. S., Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma, International Journal of Colorectal Disease, 32, 1179-1190, 2017	Data from PEAK trial included in Sorich 2015 meta-analysis
Romiti, A., Rulli, E., Pilozzi, E., Gerardi, C., Roberto, M., Legramandi, L., Falcone, R., Pacchetti, I., Marchetti, P., Floriani, I., Exploring the Prognostic Role of Microsatellite Instability in Patients With Stage II Colorectal Cancer: A Systematic Review and Meta-Analysis, Clinical Colorectal Cancer, 16, e55-e59, 2017	Stage II only
Roth, A. D., Delorenzi, M., Tejpar, S., Yan, P., Klingbiel, D., Fiocca, R., d'Ario, G., Cisar, L., Labianca, R., Cunningham, D., et al.,, Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer, Journal of the National Cancer Institute, 104, 1635â€• 1646, 2012	Included in Zhu 2016 systematic review

Study	Reason for exclusion
Rowland, A., Dias, M. M., Wiese, M. D., Kichenadasse, G., McKinnon, R. A., Karapetis, C. S., Sorich, M. J., Meta-analysis comparing the efficacy of anti-EGFR monoclonal antibody therapy between KRAS G13D and other KRAS mutant metastatic colorectal cancer tumours, European Journal of Cancer, 55, 122-30, 2016	Systematic review - compares anti-EGFR versus control in KRAS subgroups (does not report predictive factor analysis).
Rowland, A., Dias, M. M., Wiese, M. D., Kichenadasse, G., McKinnon, R. A., Karapetis, C. S., Sorich, M. J., Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer, British Journal of Cancer, 112, 1888-1894, 2015	Comment on Pietrantonio systematic review
Rui, Y. Y., Zhang, D., Zhou, Z. G., Wang, C., Yang, L., Yu, Y. Y., Chen, H. N., Can K-ras Gene Mutation Be Utilized as Prognostic Biomarker for Colorectal Cancer Patients Receiving Chemotherapy? A Meta-Analysis and Systematic Review, PLoS ONE, 8 (10) (no pagination), 2013	Systematic review - meta-analysis does not use correct method - checked for relevant studies.
Sargent, D. J., Marsoni, S., Monges, G., Thibodeau, S. N., Labianca, R., Hamilton, S. R., French, A. J., Kabat, B., Foster, N. R., Torri, V., et al.,, Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer, Journal of Clinical Oncology, 28, 3219â€• 3226, 2010	Study included in Sinicrope 2011 systematic review
Sartore-Bianchi, A., Di Nicolantonio, F., Nichelatti, M., Molinari, F., De Dosso, S., Saletti, P., Martini, M., Cipani, T., Marrapese, G., Mazzucchelli, L., Lamba, S., Veronese, S., Frattini, M., Bardelli, A., Siena, S., Multi-determinants analysis of molecular alterations for predicting clinical benefit to EGFR-targeted monoclonal antibodies in colorectal cancer, PLoS ONE [Electronic Resource], 4, e7287, 2009	Included in Dahabreh 2011 systematic review.
Sartore-Bianchi, A., Martini, M., Molinari, F., Veronese, S., Nichelatti, M., Artale, S., Di Nicolantonio, F., Saletti, P., De Dosso, S., Mazzucchelli, L., Frattini, M., Siena, S., Bardelli, A., PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies, Cancer Research, 69, 1851-1857, 2009	Included in Dahabreh 2011 systematic review.
Sasaki, Y., Akasu, T., Saito, N., Kojima, H., Matsuda, K., Nakamori, S., Komori, K., Amagai, K., Yamaguchi, T., Ohue, M., Nagashima, K., Yamada, Y., Prognostic and predictive value of extended RAS mutation and mismatch repair status in stage III colorectal cancer, Cancer Science, 107, 1006-1012, 2016	Subgroup analysis of adjuvant chemo versus no adjuvant chemo by RAS mutation. Cannot extract prognostic outcomes.
Schwartzberg, L. S., Rivera, F., Karthaus, M., Fasola, G., Canon, J. L., Yu, H., Oliner, K. S., Go, W. Y., Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC), Journal of Clinical Oncology. Conference, 31, 2013	Data from PEAK trial included in Sorich 2015 meta-analysis
Sclafani, F., Gonzalez, D., Cunningham, D., Hulkki Wilson, S., Peckitt, C., Giralt, J., Glimelius, B., Rosello Keranen, S., Wotherspoon, A., Brown, G., Tait, D., Oates, J., Chau, I.,	Cannot extract prognostic outcomes

Study	Reason for exclusion
RAS mutations and cetuximab in locally advanced rectal cancer: Results of the EXPERT-C trial, European Journal of Cancer, 50, 1430-1436, 2014	
Seymour, M. T., Brown, S. R., Middleton, G., Maughan, T., Richman, S., Gwyther, S., Lowe, C., Seligmann, J. F., Wadsley, J., Maisey, N., Chau, I., Hill, M., Dawson, L., Falk, S., O'Callaghan, A., Benstead, K., Chambers, P., Oliver, A., Marshall, H., Napp, V., Quirke, P., Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): A prospectively stratified randomised trial, The Lancet Oncology, 14, 749-759, 2013	Included in Sorich 2015 systematic review.
Sinicrope, F. A., Mahoney, M. R., Smyrk, T. C., Thibodeau, S. N., Warren, R. S., Bertagnolli, M. M., Nelson, G. D., Goldberg, R. M., Sargent, D. J., Alberts, S. R., Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy, Journal of Clinical Oncology, 31, 3664-3672, 2013	See Sinicrope 2015, 2017
Sinicrope, F. A., Shi, Q., Allegra, C. J., Smyrk, T. C., Thibodeau, S. N., Goldberg, R. M., Meyers, J. P., Pogue-Geile, K. L., Yothers, G., Sargent, D. J., et al.,, Association of DNA Mismatch Repair and Mutations in BRAF and KRAS With Survival After Recurrence in Stage III Colon Cancers : a Secondary Analysis of 2 Randomized Clinical Trials, JAMA Oncology, 3, 472â€• 480, 2017	Outcome not in PICO. See Taied 2015 pooled analysis of 3934 pts from these PETACC8 and N0147 trials
Smith, J. C., Brooks, L., Hoff, P. M., McWalter, G., Dearden, S., Morgan, S. R., Wilson, D., Robertson, J. D., Jurgensmeier, J. M., KRAS mutations are associated with inferior clinical outcome in patients with metastatic colorectal cancer, but are not predictive for benefit with cediranib, European Journal of Cancer, 49, 2424-2432, 2013	Cediranib therapy - not yet NICE approved
Sohn, B. S., Kim, T. W., Lee, J. L., Ryu, M. H., Chang, H. M., Kang, Y. K., Park, H. S., Na, Y. S., Jang, S. J., Kim, J. C., Lee, J. S., The role of KRAS mutations in predicting the efficacy of cetuximab-plus-irinotecan therapy in irinotecan-refractory Korean metastatic colorectal cancer patients, Oncology, 77, 224-230, 2009	Included in Dahabreh 2011 systematic review.
Song, Q. B., Wang, Q., Hu, W. G., Anti-epidermal growth factor receptor monoclonal antibodies in metastatic colorectal cancer: A meta-analysis, World Journal of Gastroenterology, 21, 4365-4372, 2015	Systematic review - does not analyse prognostic/predictive factors
Sorich, M., Rowland, A., Dias, M., McKinnon, R. A., Kichenadasse, G., Wiese, M., Karapetis, C. S., BRAF V600E and survival benefit of anti-EGFR monoclonal antibody (mAb) therapy for metastatic colorectal cancer (mCRC): A Meta-analysis, Journal of Clinical Oncology. Conference, 33, 2015	Conference abstract
Srivastava, G., Renfro, L. A., Behrens, R. J., Lopatin, M., Chao, C., Soori, G. S., Dakhil, S. R., Mowat, R. B., Kuebler, J. P., Kim, G., Mazurczak, M., Lee, M., Alberts, S. R., Prospective multicenter study of the impact of oncotype DX	Does not report prognostic or predictive results

Study	Reason for exclusion
colon cancer assay results on treatment recommendations in stage II colon cancer patients, Oncologist, 19, 492-7, 2014	
Stremitzer, S., Stift, J., Gruenberger, B., Tamandl, D., Aschacher, T., Wolf, B., Wrba, F., Gruenberger, T., KRAS status and outcome of liver resection after neoadjuvant chemotherapy including bevacizumab, British Journal of Surgery, 99, 1575-1582, 2012	Included in Petrelli 2013 systematic review.
Taieb, J., Malicot, K. L., Penault-Llorca, F. M., Bouche, O., Shi, Q., Thibodeau, S. N., Tabernero, J., Mini, E., Goldberg, R. M., Folprecht, G., Van Laethem, J. L., Sargent, D. J., Alberts, S. R., Laurent-Puig, P., Sinicrope, F. A., American Society of Clinical Oncology Prognostic value of BRAF V600E and KRAS exon 2 mutations in microsatellite stable (MSS), stage III colon cancers (CC) from patients (pts) treated with adjuvant FOLFOX+/-cetuximab: A pooled analysis of 3934 pts from the PETACC8 and N0147 trials, Journal of Clinical Oncology. Conference, 33, 2015	See Zaanan 2018 for pooled analysis of the PETACC8 and N0147 trials
Tol, J., Koopman, M., Cats, A., Rodenburg, C. J., Creemers, G. J., Schrama, J. G., Erdkamp, F. L., Vos, A. H., van Groeningen, C. J., Sinnige, H. A., et al.,, Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer, New England Journal of Medicine, 360, 563â€• 572, 2009	Included in Dahabreh 2011 systematic review.
Tveit, K. M., Guren, T., Glimelius, B., Pfeiffer, P., Sorbye, H., Pyrhonen, S., Sigurdsson, F., Kure, E., Ikdahl, T., Skovlund, E., Fokstuen, T., Hansen, F., Hofsli, E., Birkemeyer, E., Johnsson, A., Starkhammar, H., Yilmaz, M. K., Keldsen, N., Erdal, A. B., Dajani, O., Dahl, O., Christoffersen, T., Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study, Journal of Clinical Oncology, 30, 1755-1762, 2012	Trial included in Yuan 2013 systematic review.
Van Cutsem, E., Kohne, C. H., Lang, I., Folprecht, G., Nowacki, M. P., Cascinu, S., Shchepotin, I., Maurel, J., Cunningham, D., Tejpar, S., Schlichting, M., Zubel, A., Celik, I., Rougier, P., Ciardiello, F., Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status, Journal of Clinical Oncology, 29, 2011-2019, 2011	CRYSTAL trial Included in Sorich 2015 systematic review.
Vincenzi, B., Cremolini, C., Sartore-Bianchi, A., Russo, A., Mannavola, F., Perrone, G., Pantano, F., Loupakis, F., Rossini, D., Ongaro, E., Bonazzina, E., Dell'Aquila, E., Imperatori, M., Zoccoli, A., Bronte, G., De Maglio, G., Fontanini, G., Natoli, C., Falcone, A., Santini, D., Onetti-Muda, A., Siena, S., Tonini, G., Aprile, G., Prognostic significance of K-Ras mutation rate in metastatic colorectal cancer patients, Oncotarget, 6, 31604-12, 2015	KRAS mutation rate (>40% versus <40%)
Wang, L., Sun, Y., Zhao, B., Zhang, H., Yu, Q., Yuan, X., Chemotherapy plus targeted drugs in conversion therapy for potentially resectable colorectal liver metastases: a meta-analysis, Oncotarget, 7, 55732-55740, 2016	Does not report predictive or prognostic factors.

Study	Reason for exclusion
Wang, Q., Hu, W. G., Song, Q. B., Wei, J., BRAF V600E mutation as a predictive factor of Anti-EGFR monoclonal antibodies therapeutic effects in metastatic colorectal cancer: A meta-analysis, Chinese Medical Sciences Journal, 29, 197-203, 2014	Systematic review - includes subset of studies also in Yuan 2013
Webber, E. M., Kauffman, T. L., O'Connor, E., Goddard, K. A. B., Systematic review of the predictive effect of MSI status in colorectal cancer patients undergoing 5FU-based chemotherapy, BMC Cancer, 15 (1) (no pagination), 2015	Systematic review - does not report MSI as a prognostic factor. Subgroup analysis by MSI/MSS reported.
Westwood, M., van Asselt, T., Ramaekers, B., Whiting, P., Joore, M., Armstrong, N., Noake, C., Ross, J., Severens, J., Kleijnen, J., KRAS mutation testing of tumours in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis, Health Technology Assessment (Winchester, England)Health Technol Assess, 18, 1-132, 2014	HTA of different KRAS mutation tests.
Xu, Q., Xu, A. T., Zhu, M. M., Tong, J. L., Xu, X. T., Ran, Z. H., Predictive and prognostic roles of BRAF mutation in patients with metastatic colorectal cancer treated with anti-epidermal growth factor receptor monoclonal antibodies: a meta-analysis, Journal of Digestive Diseases, 14, 409-16, 2013	Systematic review - includes the same studies as Yuan 2013.
Yen, L. C., Uen, Y. H., Wu, D. C., Lu, C. Y., Yu, F. J., Wu, I. C., Lin, S. R., Wang, J. Y., Activating KRAS mutations and overexpression of epidermal growth factor receptor as independent predictors in metastatic colorectal cancer patients treated with cetuximab, Annals of Surgery, 251, 254-260, 2010	Included in Dahabreh 2011 systematic review.
Zhou, M., Yu, P., Hou, K., Fu, L., Chen, Y., Qu, J., Qu, X., Liu, Y., Zhang, J., Effect of RAS status on anti-EGFR monoclonal antibodies + 5-FU infusion-based chemotherapy in first-line treatment of metastatic colorectal cancer: A meta-analysis, Meta Gene, 9, 110-119, 2016	Does not report direct comparison of RAS mutant versus wildtype

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Appendix L – Research recommendations

Research recommendations for review question: Which predictive biomarkers should be used in the systemic management of colorectal cancer patients?

No research recommendations were made for this review question.