Molecular Biomarkers for the Evaluation of Colorectal Cancer

Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association of Molecular Pathology, and American Society of Clinical Pathology

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METHODS USED TO PRODUCE THE GUIDELINE

Panel Composition
The College of American Pathologists (CAP), the American Society for Clinical Pathology (ASCP), the Association For Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO) convened an Expert Panel (EP) consisting of pathologists, geneticists, oncologists, biostatisticians, laboratory technologists, and a methodologist to develop an evidence-based guideline to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for patients. All four organizations appointed a representative to serve as a co-chair, with one taking a leadership role (AS). All four organizations approved the appointment of panel members. The EP and the methodologist performed the systematic evidence review. An advisory panel (AP) of pathologists, oncologists, and patient advocates also helped in the development of the guideline. The role of the AP members was to provide guidance and feedback on the key questions for the literature search, vet the draft guideline statements prior to the public comment period, and to review and provide feedback for the manuscript and supplemental digital content.

Conflict of Interest (COI) Policy
Prior to acceptance on the expert or advisory panel, potential members completed a joint guideline conflict of interest (COI) disclosure process, whose policy and form (in effect July 2011) require disclosure of material financial interest in, or potential for benefit of significant value from, the guideline’s development or its recommendations 12 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Examples of conflicts of interest with relevant commercial entities were provided to the participants using a Conflict of Interest (COI) Policy Supplemental Information Evaluation of KRAS, BRAF and MMR for Colorectal Cancer document.

The ASCP/CAP/AMP/ASCO joint guideline conflicts of interest policy uses the following criteria to define relationships that could be interpreted as constituting an actual, potential, or apparent conflict:
1. Stock options or bond holdings in a relevant commercial entity or self-directed pension plan
2. Research grants from a relevant commercial entity
3. Employment (full or part-time) by a relevant commercial entity
4. Ownership or partnership in relevant corporate entities, including equities and stock options
5. Consulting or advisory fees from relevant commercial entities
6. Other remuneration from relevant commercial entities, including free or discounted products or equipment, trips, accommodations, tickets to sports or entertainment events, etc.
7. Non-remunerative positions of influence in a relevant commercial entity such as officer, board member, trustee, spokesperson, advisor
8. Royalties from relevant commercial entities
9. Intellectual property rights, i.e., patents issued or pending
10. Lecture or speaker fees/honoraria from relevant commercial entities
11. Other relationships, e.g., research collaborations, to be identified with details, as needed

All project participants were required to disclose conflicts prior to beginning and continuously throughout the project’s timeline. All disclosed conflicts were reviewed by a joint COI Review Committee composed of staff officials from each of the respective organizations. The joint COI Review Committee agreed, by majority vote, on any resolution of actual or perceived conflicts of interest.

Only one of the co-chairs could receive research support from a relevant commercial entity (no other relevant relationship was allowed). At least 51% of the Expert Panel had no existing or future relationships planned with relevant commercial entities during the development and publication of the practice guidelines. For the remaining 49%, such relationships did not preclude Expert Panel membership. At the discretion of the Co-Chairs, these individuals were asked to recuse themselves from discussing topics and abstained from voting on any decisions or approvals relevant to their relationships. Expert panel members’ disclosed conflicts are listed in the appendix of the manuscript. Advisory panel
members had a disclosure requirement, but conflicts were not subject to management by the COI Review Committee.

ASCP, CAP, AMP, and ASCO provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist.

**Literature Review and Analysis**

The Expert Panel met 11 times through teleconference webinars from July 27, 2013 to September 24, 2015. Additional work was completed via electronic mail. The panel met in person on three occasions (July 26 and 27, 2013, Houston, Texas; Dec 7 and 8, 2013, San Francisco, California; Feb 14 and 15, 2015, Bethesda, Maryland) to review evidence to date and draft recommendations. Additionally, the panel co-chairs met monthly to monitor the project’s progress.

Prior to the in-person meeting, the expert panel formed the following key questions on which to base the literature search:

I. **What biomarkers are useful to select patients with colorectal cancer (CRC) for targeted and conventional therapies?**
   1. Do **KRAS**, **NRAS**, **BRAF**, **PIK3CA**, **PTEN**, MMR/MSI, **MLH1** methylation, and gene expression profiling, provide independent prognostic information and/or therapeutically predictive response information for colorectal cancer?
   2. Does **KRAS** provide independent prognostic information and/or therapeutically predictive response information?
   3. Is extended **RAS** testing (such as **NRAS**, exons 1-4, including codons 12, 13, 61, 146) indicated for targeted or conventional therapies?
      a. Does the **KRAS** G13D mutation provide therapeutically predictive response information?
   4. Does **BRAF** provide independent prognostic information and/or therapeutically predictive response information?
   5. Does **PIK3CA** provide independent prognostic information and/or therapeutically predictive response information?
   6. Does **PTEN** provide independent prognostic information and/or therapeutically predictive response information?
   7. Does deficient MMR (dMMR) (detected by MSI or IHC) provide independent prognostic information?
      • Does dMMR provide independent prognostic information in metastatic and in Stage II, III, adjuvant therapy setting?
      • Does dMMR provide similar or different independent prognostic information in Lynch and sporadic MSI?
      • Does dMMR/MSI provide therapeutically predictive response information?
      • Does dMMR provide therapeutically predictive response information in metastatic and/or in Stage II, III, adjuvant therapy?
      • Does dMMR provide similar or different therapeutically predictive response information in Lynch and sporadic MSI?
   8. Does **MLH1** methylation provide independent prognostic information and/or therapeutically predictive response information?
   9. Does gene expression profiling provide independent prognostic information and/or therapeutically predictive response information?

II. **How should tissue specimens be processed for biomarker testing for CRC management?**

   10. What is the optimal CRC specimen to be tested?
   11. How should CRC specimens be processed for molecular testing?
   12. What factors should be evaluated in the selection of tissue specimens to be tested?
III. How should biomarker testing for CRC management be performed?

13. What are the minimum analytic requirements for testing for each marker?
14. What is the appropriate algorithm for CRC molecular testing?
15. What additional considerations are there for biomarker testing?

IV. How should molecular testing of CRC be implemented and operationalized?

16. For what biomarkers in addition to MMR status should patients with hereditary nonpolyposis colorectal cancer (HNPCC or Lynch Syndrome) be tested?
17. Are there specific CRC biomarker testing algorithms that should be used?
18. What is the optimal time for CRC molecular biomarker testing results to be reported?

V. Are there emerging genes/biomarkers that should routinely tested in CRC?

19. What is the optimal time for CRC molecular biomarker testing results to be reported?
20. What research is needed to validate their use?

All expert panelists participated in the systematic evidence review (SER). Each level of the SER (title-abstract, full text review, and data extraction) was performed in duplicate by two members of the expert panel. All expert panelists and a methodologist performed adjudication of the conflicts. Articles meeting the inclusion criteria were assessed for strength of evidence, methodological rigor, and confirmation of validity by the methodologist. Supplemental Figure 1 displays the results of the literature review. All articles were available as discussion or background references. All members of the expert panel participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving final recommendations and writing/editing of the manuscript.

Peer Review

A public open comment period was held from March 30 through April 22, 2015. Twenty one draft statements (8 recommendations, 10 expert consensus opinions, and 3 no recommendation) were posted online on the AMP Web site www.amp.org. The open comment period was publicized via joint society communications announcements and the following societies were deemed to have interest:

- American Society for Clinical Pathology (ASCP)
- College of American Pathologists (CAP)
- Association for Molecular Pathology (AMP)
- American Society for Clinical Oncology (ASCO)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Arthur Purdy Stout Society (APSS)
- Association of Pathology Chairs (APC)
- Canadian Association of Pathologists (CAP-APC)
- United States & Canadian Academy of Pathology (USCAP)
- Quality Initiative in Interpretive Pathology (QIIP) Canadian Partnership Against Cancer
- Society to Improve Diagnoses in Medicine (SIDM)
- Roger G Haggitt Gastrointestinal Pathology Society (GIPS)
- European Society for Medical Oncology (ESMO)
- American Association for Clinical Chemistry (AACC)
- American College of Medical Genetics and Genomics (ACMG)
- Association of Community Cancer Centers (ACCC)
- National Comprehensive Cancer Network (NCCN)
- American Cancer Society
- Partnership Against Cancer American Cancer Society
- Cancer Research and Prevention Foundation
- Cancer Leadership Council
- Union for International Cancer Control
• Fight Colorectal Cancer
• Colon Cancer Alliance
• US Food and Drug Administration (FDA)
• Centers for Medicare & Medicaid Services (CMS)
• Centers for Disease Control and Prevention (CDC)
• Veteran’s Affairs (VA) and Department of Defense (DOD)

The website received 248 comments in total (Agree and Disagree responses were also captured). All eight recommendations achieved between 73% to 94% agreement. All ten expert consensus opinion statements achieved between 66% to 90% agreement. Teams of 3 to 4 of expert panel members were assigned 3 to 5 draft recommendations for which to review all comments received and provide an overall summary to the rest of the panel. Following panel discussion, and the final quality of evidence assessment, the panel members determined whether to maintain the original draft recommendation as is, revise it with minor language change, or consider it as a major recommendation change. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (rounds of email discussion and multiple edited recommendations) amongst the panel members. The final recommendations were approved by the expert panel with a formal vote. The panel considered the risks and benefits throughout the whole process in their considered judgment process. Formal cost analysis or cost effectiveness was not performed.

Organizational review was instituted to review and approve the guideline. ASCP assigned the review to a Special Review Panel. For the CAP, an independent review panel (IRP) representing the Council on Scientific Affairs was nominated to review and approve the guideline. The CAP IRP was masked to the expert panel and vetted through a COI process. The AMP approval process required the review of the Publications and Communications Committee Chair and Executive Committee in order to ensure AMP's protection from liability or other problems due to the publication's content. The Publications and Communications Committee Chair enlisted the assistance of any Subdivision Leadership or Board member in this review. Concurrent reviews by the PCC Chair and Executive Committee are permitted but not required. The ASCO approval process required the review and approval of the Clinical Practice Guidelines Committee.

Dissemination Plans
Final dissemination of the guideline will be a joint process between the four organizations. There are plans to host a resource page which will include a link to the manuscript and supplement, summary of the recommendations, social media as well as patient information guides. The guideline will be promoted and presented at various society meetings.

Systematic Evidence Review (SER)
The objective of the SER was to determine to develop an evidence-based guideline to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for patients. If of sufficient quality, findings from this review could provide an evidence base to support the development of the guideline. The scope of the SER and the key questions (KQs) were established by the EP in consultation with the methodologist prior to beginning the literature search.

Search and Selection
A comprehensive search for literature was performed in MEDLINE using the OvidSP (8/1/2013) and PubMed (9/17/2013) interfaces. The initial MEDLINE search encompassed the publication dates of 1/1/2008 to 8/1/2013 (OvidSP) and 1/1/2008 to 9/17/2013 (PubMed). A supplemental literature search was performed utilizing Scopus (9/25/2013) to identify relevant articles published in journals not indexed in MEDLINE and published between 1/1/2008 and 9/25/2013. The literature search of the electronic databases involved two separate searches in each database, the first using MeSH terms and keywords for the concepts “Colorectal Cancer”, “Biomarkers”, “Treatment” and “Treatment Outcomes”, and the second using terms for the concepts “Colorectal Cancer”, “Biomarkers, and “Laboratory Methods”. Limits were set for human studies published in English, and a publication filter was applied to exclude lower levels of evidence such as letters, commentaries, editorials, and case reports. The Ovid search was
rerun on 2/12/2015 to identify articles published since 8/1/2013. The Ovid, PubMed, and Scopus search strategies are included as Supplemental Figure 2.

In addition to the searches of electronic databases, an Internet search of international health organizations, the National Guidelines Clearinghouse, and Guidelines International Network was conducted for existing relevant guidelines or protocols. Guidelines were included if they were published since 2008 in English. The proceedings of the meetings of the American Society of Clinical Oncology (ASCO and ASCO-GI), European Society for Medical Oncology (ESMO), and the American Association for Cancer Research (AACR) from the years 2012 and 2013 were also searched for relevant abstracts.

A focused examination of all systematic reviews retrieved by the initial literature search and retained after full text review was performed to identify primary research studies not already included. In addition, recommendations from the expert panel were reviewed, and the reference lists of all articles deemed eligible for inclusion were scanned for relevant reports. The results of all searches were combined and deduplicated.

Selection at all levels was based on predetermined inclusion/exclusion criteria. Included were:

1. Patients of all ages with colorectal or rectal cancer with a pathology diagnosis of adenocarcinoma or adenocarcinoma with neuroendocrine differentiation, either primary or metastatic
2. Patients of all ages
3. Patients with cancer of any invasive stage
4. Biomarker testing such as KRAS, MMR/MSI, BRAF, NRAS, PIK3CA, PTEN, MLH1 methylation, or gene expression profiles.
5. Comparative studies
6. Human studies
7. Studies published in English

Not included were:

1. All other tumor primaries and types (i.e., non-colorectal or non-rectal cancers, tumor types other than adenocarcinoma or adenocarcinoma with neuroendocrine differentiation)
2. Patients with non-invasive tumors (i.e., intraepithelial, dysplasia, in situ, polyps without carcinoma)
3. Studies of colorectal cancers without biomarker testing, novel biomarkers (e.g., VEG-F, XRCC1, Insulin GroMut-h Factor, E, ERCC, micro-RNA, TS, GCC, LINE, CIMP, HER2, CIN Status (LOH), and germline (genetics only) testing)
4. Non-English language articles
5. Animal studies
6. Studies published prior to 2002
7. Non-comparative studies, letters, commentaries, editorials
8. Studies that did not address at least one of the defined inclusion criteria
9. Studies that did not present new evidence
10. Studies with less than 50 patients per comparison arm

**Outcomes of Interest**
The primary outcomes of interest included survival outcomes and performance characteristics of laboratory testing assays. Survival outcomes included: overall survival (OS), disease-free survival (DFS), progression free survival (PFS), recurrence-free survival, time to recurrence, response to therapy (e.g., complete and partial response). Laboratory data and test performing characteristics included: percent mutation, concordance of detected mutations between primary and metastatic mutations (number of cases (%) with mutations versus number of cases with no mutations in the gene of interest), concordance of mutations (synchronous primary versus metastatic, metachronous primary versus metastatic, between synchronous metastases, between metachronous metastases), sensitivity and specificity of testing methods.

**Data Extraction & Management**
Following the initial search, titles and abstracts of retrieved studies were reviewed by two expert panel members for relevancy. Conflicts were resolved by initial reviewers and further adjudicated by a project co-chair, if necessary. Those deemed relevant to the key questions that met inclusion criteria and none of the exclusion criteria were moved on to full text review. Full text articles were reviewed for relevancy by two expert panel members to determine eligibility, and conflicts were resolved by the initial reviewers and further adjudicated by a project co-chair, if necessary. In cases of duplication of reporting study results, the most inclusive were retained. Data extraction was performed by one expert panel member and audited by a methodologist. Any discrepancies in data extraction were resolved by discussion. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment Methods
An assessment of the quality of the evidence was performed for all retained studies following application of the inclusion and exclusion criteria. Using this method, studies deemed be of low quality would not be excluded from the systematic review, but would be retained and their methodological strengths and weaknesses discussed where relevant. Studies would be assessed by confirming the presence of items related to both internal and external validity, and which are all associated with methodological rigor and a decrease in the risk of bias. These items were assessed as being either yes, no, partial, not reported (NR), or not applicable (N/A) in the following way:

Clinical Practice Guidelines (CPGs) and Systematic Reviews (SRs) were assessed for quality by confirming the following attributes were considered and incorporated in its design as recommended by the Institute of Medicine (IOM).1 (Summarized in Supplemental Table 1)

- Based on a systematic review (this was not assessed for SRs)
- Included a multidisciplinary panel
- Patient preferences were considered
- Important patient sub-types were considered
- Methods were well-described and reproducible
- Information on potential conflicts of interest were gathered and disclosed
- Quality of the evidence was assessed
- Strength of the evidence was rated
- CPG includes a plan for updating
- Sources of funding are disclosed

Meta-analyses (MAs) were assessed in a similar fashion to CPGs according to the following criteria:

- Based on a systematic review
- Methods were well-described and reproducible
- Quality of the evidence was assessed
- Any planned pooling was stated a priori
- Limitations of the analysis are discussed
- Sources of funding are disclosed

Randomized Control Trials (RCTs) and Quasi-RCTs were assessed for quality according to reporting and full description of:

- Randomization method fully-described
- Details on any blinding was provided
- Provided details of all planned analyses
- Stated the expected effect size and described the statistical power calculation
- Reported the length of follow-up
- Provided a description of the baseline characteristics for all patients by treatment/assessment arm
- Sources of funding are disclosed
Non-randomized clinical trials (NRCTs), prospective cohort studies (PCS), and retrospective cohort studies (RCS) were assessed according to:

- Balance between treatment/assessment groups
- Reporting of baseline characteristics
- Reporting if any adjustments were made where baseline differences were detected
- Sources of funding

Supplemental Table 1 summarizes the quality assessment criteria by study design.

Each study was assessed individually, and then each study type was summarized. Finally, a summary of the overall quality of the evidence was given considering the evidence in totality.

**Quality Assessment Results**

A total of 622-63 studies, comprising 39 systematic reviews, with or without meta-analyses, two meta-analyses, one RCT, 9 prospective cohort studies, and 11 retrospective cohort studies were obtained that met the inclusion criteria. Each of the included studies was assessed for quality against specific risk of bias criteria as described in the Methods, and a summary of these assessments appears with each recommendation. The tabulated results of the assessment for each recommendation can be found in Supplemental Tables 2 through 11.

**Assessing the Strength of Recommendations**

The overarching goal of the panel was to develop an evidence-based guideline to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for patients.

Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1) What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.

2) What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as Convincing, Adequate or Inadequate, based on four published criteria (Supplemental Table 12). Strength of evidence is a key element in determining the strength of a recommendation.

3) What is the strength of each recommendation? There are many methods for determining the strength of a recommendation based on the strength of evidence and the magnitude of net benefit or harm. However, such methods have rarely (if ever) been applied to the area of biomarker molecular testing practice for colorectal cancer. Therefore, the method for determining strength of recommendation has been modified for this application (Supplemental Table 11), and is based on the strength of evidence and the likelihood that further studies will change the conclusions. Recommendations not supported by evidence (i.e., evidence was missing or insufficient to permit a conclusion to be reached) were made based on consensus expert opinion. Another potential consideration is the likelihood that additional studies will be conducted that fill gaps in knowledge.

4) What is the net balance of benefits and harms? The consideration of net balance of benefits and harms will focus on the core recommendations to adopt specific biomarker molecular testing for colorectal cancer.
**Supplemental Table 1 – Quality Assessment Criteria by Study Design**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>Based on a systematic review</td>
<td>Clinical Practice Guideline (CPG)/Systematic Review (SR)</td>
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<td>Meta-analyses</td>
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<td></td>
<td>Randomized Control Trial (RCT)/Quasi-randomized Controlled Trial (QRCT)</td>
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<td></td>
<td>Non-randomized Controlled Trial (NRCT)/Prospective Cohort Study (PCS)/Retrospective Control Study (RCS)</td>
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<td>Patient preferences were considered</td>
<td>✓</td>
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<td>Important patient sub-types were considered</td>
<td>✓</td>
</tr>
<tr>
<td>Methods were well-described and reproducible</td>
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<td>Information on potential conflicts of interest were gathered and disclosed</td>
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<td>Provided a description of the baseline characteristics for all patients by treatment/assessment arm</td>
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## Supplemental Table 2 – Quality Assessment Results for Statement 1

<table>
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<th>Author</th>
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<th>Important patient sub-types considered</th>
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<th>COIs are examined</th>
<th>Rated quality of the Evidence</th>
<th>Rated strength of the evidence</th>
<th>Includes a plan for updating</th>
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<th>Overall risk of bias assessment</th>
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### Supplemental Table 3 – Quality Assessment Results for Statement 2

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<th>Rated strength of the evidence</th>
<th>Includes a plan for updating</th>
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**Supplemental Table 5 – Quality Assessment Results for Statement 4**

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Systematic reviews (N=2)

### Supplemental Table 7 – Quality Assessment Results for Statement 6

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**Supplemental Table 8 – Quality Assessment Results for Statement 7**

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**Supplemental Table 9 – Quality Assessment Results for Statement 14**

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<td>N/A</td>
<td>Non-industry</td>
<td>Low</td>
</tr>
<tr>
<td>Chen Y et al</td>
<td>2009</td>
<td>Y</td>
<td>N/A</td>
<td>N/A</td>
<td>Non-industry</td>
<td>Low</td>
</tr>
<tr>
<td>Chow L et al</td>
<td>2012</td>
<td>Y</td>
<td>N/A</td>
<td>N/A</td>
<td>Non-industry</td>
<td>Low</td>
</tr>
<tr>
<td>Sundstrom M et al</td>
<td>2010</td>
<td>Y</td>
<td>N/A</td>
<td>N/A</td>
<td>Industry</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Retrospective Cohort Studies (N=2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nardon E et al</td>
<td>2010</td>
<td>Y</td>
<td>N/A</td>
<td>N/A</td>
<td>Non-industry</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Supplemental Table 11 – Quality Assessment Results for Statement 19

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Provided details on randomization</th>
<th>Provided details on blinding</th>
<th>Provided details on any planned analysis</th>
<th>Expected effect size calculation and power calculation</th>
<th>Reported on length of follow-up</th>
<th>Reported on any differences in patient characteristics</th>
<th>Funding source</th>
<th>Overall risk of bias assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials (N=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vakiani E et al\textsuperscript{54}</td>
<td>2012</td>
<td>Y</td>
<td>N/A</td>
<td>N/A</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Low</td>
</tr>
<tr>
<td>&quot;Douillard JY et al\textsuperscript{55}&quot;</td>
<td>2013</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>Partial industry</td>
<td>Low-moderate</td>
</tr>
</tbody>
</table>
**Supplemental Table 12. Grades for Strength of Evidence**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Requirements</th>
</tr>
</thead>
</table>
| **Convincing** | • Two or more Level 1\(^a\) or 2 studies (study design and execution) that had an appropriate number and distribution of challenges\(^b\) and reported consistent\(^c\) and generalizable\(^d\) results.  
• One Level 1 or 2 study that had an appropriate number and distribution of challenges and reported generalizable results. |
| **Adequate** | • Two or more Level 1 or 2 studies that lacked the appropriate number and distribution of challenges OR were consistent but not generalizable. |
| **Inadequate** | • Combinations of Level 1 or 2 studies that show unexplained inconsistencies OR combinations of one or more lower quality studies (Level 3 or 4) OR expert opinion. |

---

\(^a\) Level 1 studies include systematic reviews of Level 2 studies, Level 2 studies include randomized clinical trials (RCT) of good quality, Level 3 studies include RCTs of poor quality, comparative studies with concurrent controls, and comparative study without concurrent controls. Level 4 studies include case series with either post-test or pre-test/post-test outcomes.

\(^b\) Based on number of possible response categories and required confidence in results.

\(^c\) Consistency can be assessed formally by testing for homogeneity, or, when data are limited, less formally using central estimates and range of values.

\(^d\) Generalizability is the extension of findings and conclusions from one study to other settings.

---

**Supplemental Table 13: Grades for Strength of Recommendations**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Recommendation</td>
<td>Recommend for or against a particular molecular testing practice for colorectal cancer (Can include must or should)</td>
<td>Supported by convincing or adequate strength of evidence, high or intermediate quality of evidence and clear benefit that outweighs any harms</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Recommend for or against a particular molecular testing practice for colorectal cancer (Can include should or may)</td>
<td>Some limitations in strength of evidence (adequate or inadequate), and quality of evidence (intermediates or low), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation</td>
</tr>
<tr>
<td>Expert Consensus Opinion</td>
<td>Recommend for or against a particular molecular testing practice for colorectal cancer (Can include should or may)</td>
<td>Serious limitations in strength of evidence (inadequate or insufficient), quality of evidence (inadequate or low), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary</td>
</tr>
<tr>
<td>No Recommendation</td>
<td>No recommendation for or against a particular molecular testing practice for colorectal cancer</td>
<td>Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation</td>
</tr>
</tbody>
</table>

Data derived from Guyatt, et al.65
### Supplemental Table 14. Summary of Studies

<table>
<thead>
<tr>
<th>Study type and evidence</th>
<th>Number of studies (Number of patients n(N))</th>
<th>Comparison</th>
<th>Tests used*</th>
<th>Overall Survival (OS)</th>
<th>Progression Free Survival (PFS)</th>
<th>Overall Response Rate (ORR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS</strong></td>
<td>311(74,546)</td>
<td>KRAS Mut + versus KRAS Mut-</td>
<td>PCR (including qPCR, PCR, AS-PCR, PCR-RFLP), direct sequencing, pyro-sequencing, FISH, CISH, Sanger, surveyor analysis, SISH, ARMS, Scorpion, hybridization, topographic, genotypic, AD, melting curve analysis, TTGE, HPLC, capillary sequencing, allelic discrimination, SSCP, ASO, MALDI-ToF analysis and WAVE-based SURVEYOR analysis, Luminex xMAP</td>
<td>21 pooled OS: 14 found significant differences</td>
<td>21 pooled PFS: 20 found significant differences</td>
<td>16 pooled ORR: 14 found significant differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-anti-EGFR inhibitor to wild-type patients</td>
<td><strong>KRAS</strong> wild-type &gt; KRAS mutation (N=6)</td>
<td><strong>KRAS</strong> wild-type + anti-EGFR inhibitor &gt; KRAS mutation given CT alone (N=4)</td>
<td>anti-EGFR inhibitor to CT for KRAS wild-type patients &gt; CT alone (N=15), although one of these found the difference in 3rd-line patients only (1413), and one found a disadvantage for patients with the <strong>PIK3CA</strong> exon 20 mutation (869)</td>
<td>adding an anti-EGFR inhibitor + CT in wild-types patients &gt; CT alone (N=8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-anti-EGFR inhibitor treatment independent of KRAS status</td>
<td><strong>G13D</strong> &gt; codon 12 (N=1)</td>
<td><strong>G13D</strong> &gt; other mutations (N=1)</td>
<td><strong>KRAS</strong> wild-type patients &gt; mutation patients (N=4)</td>
<td><strong>G13D</strong> mutations &gt; codon 12 mutations (N=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G13D versus 12, 13 versus other, 13D versus other, high EGFR Gene Copy Number (GCN) versus low EGFR-GCN</td>
<td><strong>G13D</strong> &gt; other mutations (N=1)</td>
<td>high EGFR GCN with anti-EGFR inhibitors &gt; low EGFR GCN (N=1)</td>
<td><strong>G13D</strong> mutation &gt; other mutation (N=1)</td>
<td>codon 13 &gt; other mutations (N=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCR (including qPCR, PCR, AS-PCR, PCR-RFLP), direct sequencing, pyro-sequencing, FISH, CISH, Sanger, surveyor analysis, SISH, ARMS, Scorpion, hybridization, topographic, genotypic, AD, melting curve analysis, TTGE, HPLC, capillary sequencing, allelic discrimination, SSCP, ASO, MALDI-ToF analysis and WAVE-based SURVEYOR analysis, Luminex xMAP</td>
<td>21 pooled OS: 14 found significant differences</td>
<td>21 pooled PFS: 20 found significant differences</td>
<td>16 pooled ORR: 14 found significant differences</td>
<td>adding an anti-EGFR inhibitor &gt; BSC alone in wild-type patients (N=1)</td>
</tr>
<tr>
<td>BRAF</td>
<td>8 SRs, 1 PCS, 1 RCS</td>
<td>BRAF Mut+ patients with BRAF Mut- patients (N=3)</td>
<td>BRAF Mut+ BRAF Mut– CT +/- anti-EGFR MoAbs (N=1)</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=4)</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=4)</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=5)</td>
</tr>
<tr>
<td>------</td>
<td>------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>118(16,477**)</td>
<td>direct sequencing (N=2), pyro-sequencing (N=2), AS, AD, PCR amplification, qPCR, Sanger, rTPCR, genotyping+DS, PCR clamping, melting curve analysis, allele-specific PCR, DNA sequencing, Taqman SNP assay</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=4)</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=4)</td>
<td>BRAF wild-type patients &gt; BRAF mutations (N=5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIK3CA</th>
<th>5 SRs, 1 RCS</th>
<th>PIK3CA Mut+ versus Mut - (N=4)</th>
<th>Direct sequencing (N=3)</th>
<th>4 pooled OS: 3 found significant differences</th>
<th>4 pooled PFS: 3 found significant differences</th>
<th>2 pooled ORR: 1 found significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30(2613)</td>
<td>exon 20 mutations</td>
<td>pyro sequencing (N=3)</td>
<td></td>
<td></td>
<td>Exon 9 &gt; exon 20</td>
</tr>
<tr>
<td>versus no exon 20 mutations (N=1)</td>
<td>Sanger (N=2)</td>
<td>Exon 9 &gt; exon 20 mutations (N=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Mut - versus BRAF Mut+ and PIK3CA Mut +(N=1)</td>
<td>allelic discrimination (N=1)</td>
<td>PIK3CA Mut - &gt; PIK3CA Mut + (N=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR amplification, AS+PCR, genotyping, rtPCR, DNA sequencing, Luminex xMAP</td>
<td>PIK3CA Mut - &gt; PIK3CA Mut + (N=2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PTEN**

<table>
<thead>
<tr>
<th>4 SRs</th>
<th>31(2545)</th>
<th>loss of PTEN expression compared with normal PTEN expression (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHC (N=3)</td>
<td>3 pooled OS: 1 found significant differences normal PTEN expression &gt; loss of PTEN expression (N=1)</td>
</tr>
<tr>
<td></td>
<td>FISH (N=2)</td>
<td>3 pooled PFS: 2 found significant differences normal PTEN expression &gt; loss of PTEN expression (N=2)</td>
</tr>
</tbody>
</table>

**MSI/MSS**

<table>
<thead>
<tr>
<th>4 SRs</th>
<th>127(27,044)</th>
<th>MSI with MSS (N=3) positive with negative MLH1 promoter methylation (N=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHC (N=1)</td>
<td>2 pooled OS: 1 found significant differences MSS&gt;MSI (N=1)</td>
</tr>
<tr>
<td></td>
<td>PCR (N=1)</td>
<td>2 pooled PFS: 1 found significant differences MSS&gt;MSI (N=1)</td>
</tr>
<tr>
<td></td>
<td>flow cytometry (N=1)</td>
<td>1 pooled ORR: No significant differences found</td>
</tr>
<tr>
<td></td>
<td>image analysis</td>
<td></td>
</tr>
<tr>
<td>CTC^a, ^b</td>
<td>(N=1)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>2 SRs</td>
<td>23(2,487)</td>
<td></td>
</tr>
<tr>
<td>CTC vs no-CTC</td>
<td>(N=2)</td>
<td></td>
</tr>
<tr>
<td>RT-PCT</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>IMP</td>
<td>1 pooled DFS:</td>
<td></td>
</tr>
<tr>
<td>(N=1)</td>
<td>1 found significant difference</td>
<td></td>
</tr>
<tr>
<td>ICS</td>
<td>No-CTC &gt; CTC</td>
<td></td>
</tr>
<tr>
<td>(N=1)</td>
<td>(N=1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Allelic Discrimination PCR; ARMS, Amplification Refractory Mutation System; ASO, Allele-Specific Oligonucleotide; AS-PCR, Allele-Specific-Polymerase Chain Reaction; BRAF, proto-oncogene B-Raf/v-Raf murine sarcoma viral oncogene homolog B; BSC, Best Supportive Care; CISH, Chromogenic In Situ Hybridization; CT, chemotherapy; CTC, Circulating Tumor Cells; EGFR, Epidermal Growth Factor Receptor; FISH, Fluorescence In Situ Hybridization; HPLC, High-Performance Liquid Chromatography; HTA, Health Technology Assessment; IHC, Immunohistochemistry; KRAS, Kirsten RAt Sarcoma viral oncogene homolog; M-A, meta-analysis; MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization-Time of Flight; MLH1, MutL homolog 1; MoAbs, monoclonal antibodies; MSI, MicroSatellite Instability; MSS, Microsatellite Stable; Mut+, mutation positive; Mut-, mutation negative; n, number of studies, N, number of patients; NR, Not Reported; ORR, Objective Response Rate; OS, Overall Survival; PCR, Polymerase Chain Reaction; PCR-RFLP, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; PFS, progression-Free Survival; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic subunit Alpha; PTEN, Phosphatase and TENsin homolog; qPCR, quantitative PCR; RCS, retrospective cohort study; RCT, randomized controlled trials; SISH, Silver In Situ Hybridization; SSCP, Single-Strand Conformation Polymorphism; SR, systematic review; TTGE, Tissue TransGlutaminase Enzyme; xMAP, Multiplex assay

^Codons studied for KRAS: G13D, 13, 12, 59, 61, 117, 146; for BRAF: V600/V600E (N=10), D549C, 599, K601E, 466, 469, MLH1 (N=1) exon 15/codon 11 (N=1); for PIK3CA: Exon 9 (N=6), Exon 20 (N=5), Exon 7 (N=1), Exon 8 (N=1), Exon 18 (N=1), Exon 19 (N=1); for PTEN: not reported.

**Yang et al^f1: Total number of patients not reported
### Supplemental Table 15. Emerging evidence on prognostic and predictive colorectal molecular markers

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Title</th>
<th>Markers studied/ Assays used</th>
<th>Prognostic or predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akiyoshi T et al, 2012</td>
<td>Predicting the response to preoperative radiation or chemoradiation by a microarray analysis of the gene expression profiles in rectal cancer.</td>
<td>Microarray data</td>
<td>Predictive of response to CRT</td>
</tr>
<tr>
<td>Bertagnolli MM et al, 2009</td>
<td>p27Kip1 in stage III colon cancer: implications for outcome following adjuvant chemotherapy in cancer and leukemia group B protocol 89803.</td>
<td>p27Kip1 IHC</td>
<td>Prognostic</td>
</tr>
<tr>
<td>Guo GF et al, 2011</td>
<td>Autophagy-related proteins Beclin-1 and LC3 predict cetuximab efficacy in advanced colorectal cancer.</td>
<td>Beclin-1 and LC3 IHC</td>
<td>Predictive: Low expression associated with better outcomes of cetuximab treated CRC-</td>
</tr>
<tr>
<td>Kim JC et al, 2009</td>
<td>Chemoresponsiveness associated with canonical molecular changes in colorectal adenocarcinomas.</td>
<td>TGF-beta2 expression</td>
<td>Predictive: Preserved expression associated with response to fluoropyrimidine therapy</td>
</tr>
<tr>
<td>Li P et al, 2013</td>
<td>ERCC1, defective mismatch repair status as predictive biomarkers of survival for stage III colon cancer patients receiving oxaliplatin-based adjuvant chemotherapy.</td>
<td>ERCC1 IHC</td>
<td>Predictive of survival</td>
</tr>
<tr>
<td>Licitra L et al, 2013</td>
<td>Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer; analysis of data from the EXTREME and CRYSTAL studies.</td>
<td>EGFR IHC</td>
<td>Not predictive of response to cetuximab</td>
</tr>
<tr>
<td>Negri FV et al, 2008</td>
<td>Biological predictive factors in rectal cancer treated with preoperative radiotherapy or radiochemotherapy.</td>
<td>TS IHC</td>
<td>Predictive of response to RCT</td>
</tr>
<tr>
<td>Walsh MD et al, 2009</td>
<td>HLA-DR expression is associated with better prognosis in sporadic Australian clinicopathological Stage C colorectal cancers.</td>
<td>HLADR IHC</td>
<td>Prognostic</td>
</tr>
<tr>
<td>Zhang W et al, 2011</td>
<td>A let-7 microRNA-binding site polymorphism in 3'-untranslated region of KRAS gene predicts response in wild-type KRAS patients with metastatic colorectal cancer treated with cetuximab monotherapy.</td>
<td>TG/GG KRAS genotype polymorphism</td>
<td>Predictive of response to cetuximab</td>
</tr>
<tr>
<td>Zlobec I et al, 2010</td>
<td>TIA-1 cytotoxic granule-associated RNA binding protein improves the prognostic performance of CD8 in mismatch repair-proficient colorectal cancer.</td>
<td>IHC</td>
<td>Prognostic</td>
</tr>
<tr>
<td>Diehl F et al, 2008</td>
<td>Circulating mutant DNA to assess tumor dynamics.</td>
<td>ctDNA</td>
<td>Prognostic</td>
</tr>
</tbody>
</table>
Supplemental Figure 1. Literature Review Flow Diagram

Records identified through database searching (n = 3930)

Additional records identified through other sources (n = 479)

Records after duplicates removed (n = 4197)

Records screened (n = 4197)

Full-text articles assessed for eligibility (n = 866)

Studies included for data extraction (n = 154)

Studies included for data extraction and qualitative analysis (n = 123)

Studies included for data extraction and qualitative assessment (n = 62)

Records excluded (n = 3331)

Full-text articles excluded, with reasons* (n = 712)

Data extraction articles excluded, with reasons** (n = 31)

Studies included during qualitative analysis, with reasons** (n = 61)

*Excluded based on expert opinion, did not fall within project scope or meet inclusion/exclusion criteria.

**Excluded based on expert opinion, did not meet minimum quality standards, presented incomplete data or data that were not in useable formats.


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Supplemental Figure 2: Literature search strategies

Ovid Search Strings

Concept 1: Colorectal Cancer
1. Colorectal Neoplasms/
2. exp Colonic Neoplasms/
3. exp Colorectal Neoplasms, Hereditary Nonpolyposis/
4. Rectal neoplasms/
5. or/1-4
6. Adenocarcinoma/
7. exp Colon/
8. 6 and 7
9. ((colon or colorectal or rectal) adj3 (cancer or carcinoma or adenocarcinoma or neoplas$ or malignan$ or tumor$)).ti,ab.
10. ((lynch adj4 syndrome) and (colon or colorectal or rectal)).ab,ti.
11. (non?polyposis adj8 (familial or syndrome)).ab,ti.
12. 5 or 8 or 9 or 10 or 11

Concept 2: Biomarkers
1. exp Adaptor Proteins, Signal Transducing/
2. exp Antigens, Neoplasm/
3. Base Pair Mismatch/
4. exp Base Sequence/
5. exp Cell Adhesion Molecules/
6. DNA Mismatch Repair/
7. DNA Methylation/
8. DNA Binding Proteins/
9. DNA, Neoplasm/
10. Gene Amplification/
11. exp Gene Expression/
12. Gene Expression Profiling/
13. Gene Expression Regulation, Neoplastic/
14. Genetic Heterogeneity/
15. Genes, ras/ or Genes, erbB-1/ or Genes, erbB-2/
16. Genetic Markers/
17. Genetic Testing/
18. MicroRNAs/
19. Microsatellite instability/
20. exp Phenotype/
21. exp Phosphatidylinositol 3-Kinases/
22. exp Promoter Regions, Genetic/
23. exp Proto-Oncogene Proteins/
24. PTEN Phosphohydrolase/
25. Proto-Oncogene Proteins B-raf/
26. exp ras Proteins/
27. Receptor, Epidermal Growth Factor/
28. exp RNA, Messenger/
29. exp Tumor Markers, Biological/
30. B?raf.ab. /freq=2
31. K?ras.ab. /freq=2
32. MMR.ab. /freq=2
34. (mismatch adj3 repair).ab. /freq=2
35. PIK3CA.ab. /freq=2
36. (microRNA$ or miRNA$).ab. /freq=2
37. biomarker$.ab. /freq=2
38. (tumor adj3 marker$).ab. /freq=2
39. germ$. mutation.ab. /freq=2
40. (genom$ adj3 (analysis$ or rearrangement? or sequenc$)).ab. /freq=2
41. ((cpg or dna) adj3 methy$).ab. /freq=2
42. cimp.ab. /freq=2
43. transcriptome.ab. /freq=2
44. interactome.ab. /freq=2
45. (GCC adj2 expression).ab. /freq=2
46. "guanylyl cyclase c".ab,ti.
47. ("long interspersed nuclear element?1" or LINE?1).ti,ab.
48. (microarray adj5 analysis).ab. /freq=2
49. ("microsatellite instability" or MSI$).ab. /freq=2
50. PTEN.ab. /freq=2
51. (VEGF$ or XRCC1 or EGFR or HER?2 or MIR?21 or "insulin growth factor$" or ERCC?1 or "long non?coding" or MLH?1 or "MutL homolog").ab. /freq=2
52. (gene adj3 (expression$ or signature$)).ab. /freq=2
53. (predictive adj2 marker$).ab. /freq=2
54. (somatic adj3 mutation$).ab. /freq=2
55. (germ$ adj2 polymorphism).ti,ab.
56. "copy number variation$".ti,ab.
57. (("CIN status" or "chromosomal instability") and (LOH or "loss of heterozygosity")).ti,ab.
58. or/1-57

Concept 3: Outcomes
1. Analysis of Variance/
2. Cluster Analysis/
3. Decision Support Techniques/
4. Diagnosis, Differential/
5. Disease Progression/
6. Disease-Free Survival/
7. Drug Resistance, Neoplasm/
8. exp Early Diagnosis/
9. Kaplan-Meier Estimate/
10. Multivariate Analysis/
11. "Predictive Value of Tests"/
12. Prognosis/
13. Risk Assessment/
15. exp Survival Analysis/
16. Survival Rate/
17. exp Treatment Outcome/
18. ((improve$ or overall or disease$ or time) adj3 survival).ab,ti.
19. ((prognos$ or predict$ or therap$ or treatment) adj3 (marker$ or value or respons$)).ab,ti.
20. ((progression$ or recurrence$) adj3 (time or survival)).ab,ti.
22. non?respon$.ab,ti.
23. ("clinical usefulness" or (prediction adj3 ability)).ab,ti.
24. (statistical$ adj3 significan$).ab,ti.
25. prognos$.ab. /freq=3
26. RECIST.ab,ti.
27. or/1-26

**Concept 4: Treatment**
1. Antibodies, Monoclonal/
2. Antibodies, Monoclonal, Humanized/
3. Antimetabolites, Antineoplastic/
4. Antineoplastic Agents/
5. Antineoplastic Combined Chemotherapy Protocols/
6. exp Combined Modality Therapy/
7. Fluorouracil/
8. Leucovorin/
9. Camptothecin/
10. Chemotherapy, Adjuvant/
11. Combined Modality Therapy/
12. Drug Therapy, Combination/
13. Drug Combinations/
14. Phenylurea Compounds/
15. Molecular Targeted Therapy/
16. Neoadjuvant Therapy/
17. Organoplatinum Compounds/
18. Oxonic Acid/
19. Protein Kinase Inhibitors/
20. Tegafur/
21. Pyridines/
22. Individualized Medicine/
23. Anti-Inflammatory Agents, Non-Steroidal/
24. Aspirin/
25. (chemotherap$ or chemoradiotherap$ or chemoradiation or chemosensitivit$).ti,ab.
26. ((personal$ or individual$) adj (medicine or treatment or therapy)).ab,ti.
27. (cetuximab$ or ?folfox$ or folfiri$ or bevacizumab$ or benzimidazole$ or 5?fluorouracil$ or 5?FU or camptothecin$ or irinotecan$ or regorafenib$ or capecitabine$ or panitumumab$ or oxaliplatin$ or S?1 or tegafur$ or oteracil$ or gimeracil$ or avastin$ or fluorouracil$ or trastuzumab$).ab,ti.
28. (*MEK inhibitor$ or TKI$ or PKI$).ab,ti.
29. (anti?egfr or (EGFR adj3 antibody)).ab,ti.
30. (adjuvant or neoadjuvant or epigenetic).ti,ab.
31. ((EGFR or kinase) adj3 inhibitor$).ab,ti.
32. (drug adj5 respons$).ab,ti.
33. (aspirin or NSAID$ or COX2).ab. /freq=2
34. (target$ or therap$ or agent$ or treatment$).ab. /freq=3
35. or/1-34

**Concept 5: Laboratory Testing Methods**
1. *DNA mutational analysis/
2. *High-Throughput Nucleotide Sequencing/
3. *Oligonucleotide Array Sequence Analysis/
4. *Molecular Diagnostic Techniques/
5. exp *Molecular Typing/
6. *Neoplastic Cells, Circulating/
7. *Comparative Genomic Hybridization/
8. *nucleic acid denaturation/
9. exp *Polymerase Chain Reaction/
10. exp *Sequence Analysis, DNA/
11. *immunohistochemistry/
12. *fluorescent antibody technique/
13. *fluorescent antibody technique, direct/
14. *fluorescent antibody technique, indirect/
15. *Genome-Wide Association Study/
16. exp *Nucleic Acid Amplification Techniques/
17. fixatives/
18. formaldehyde/
19. paraffin embedding/
20. tissue fixation/
21. exp *Transfection/
22. *Radioimmunoassay/
23. exp *Enzyme-Linked Immunosorbent Assay/
24. *Chromatography, High Pressure Liquid/
25. exp *Molecular Probe Techniques/
26. exp *Molecular Probes/
27. *Polymorphism, Restriction Fragment Length/
29. ((real?time or reverse or chain) adj3 polymerase).ab,ti.
30. (HPLC or HRMA or RFLP or smart?amplification or sequencing or pyrosequencing or PNA?enriched or RT?PCR or PCR?invader or TaqMan or multiplexing or "laser capture").ab. /freq=2
31. ((melting or sequence or chain) adj2 analysis).ab. /freq=2
32. (("gene expression" or mutation$) adj3 (analys#s or status or profiling)).ab. /freq=2
33. (formalin or paraffin or FFPE or PCR).ab. /freq=2
34. (test$ adj3 (implementation or validat$)).ti,ab.
35. (analytic$ adj3 (method$ or sensitivity or requirement$)).ab,ti.
36. ("life technologies" or quantstudio or agilent or raindance or qiagen or bio?rad or "ion torrent" or illumina or roche or fluidigm or snapshot or mi?seq or hi?seq or high?seq).ab. /freq=2
37. "tumor cell enrichment".ab,ti.
38. (ChIP?seq$ or ChIP?array$ or microarray or "Sanger seq$").ab. /freq=2
39. ((Parallel or next?gen$ or target$ or deep or multiplex) adj3 seq$).ab. /freq=2
40. (DNA adj3 extract$).ab. /freq=2
41. (Circulating adj (tumor cells or nucleic acid or DNA)).ab,ti.
42. (probe adj2 amplification).ab,ti.
43. (macro?dissection or micro?dissection or "laser capture" or fresh?frozen or immunohistochem$ or IHC or "in situ hybridization" or FISH).ab. /freq=2
44. or/1-43

Publication Filter:
1. Meta-Analysis as Topic/
2. meta analysis.pt.
3. meta?analy$.tw.
4. (pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
9. (study adj selection).ab.
10. 8 or 9
11. review.pt.
12. 10 and 11
13. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
14. (randomized controlled trial or clinical trial, phase?III or clinical trial, phase?IV).pt.
15. random allocation/ or double blind method/ or single blind method/
16. (randomized trial? or rct or phase?I or phase?II or phase?III or phase?IV or phase?1 or phase?2 or phase?3 or phase?4).tw.
17. or/13-16
18. exp clinical trial/ or exp clinical trial as topic/
19. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
20. 18 or 19
21. ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw.
22. (allocated adj3 random).tw.
23. (clinical$ adj3 trial$1).tw.
24. ((experimental or study or research) adj3 design).tw.
25. placebos/
26. or/21-25
27. practice guidelines/
28. (practice adj3 guideline?).tw.
29. practice guideline.pt.
30. or/27-29
32. consensus development conference.pt.
34. evaluation studies.pt.
35. or/31-34
36. research support, nih, extramural.pt.
37. research support, nih, intramural.pt.
38. research support, non us gov't.pt.
39. research support, us gov't, non phs.pt.
40. research support, us gov't, phs.pt.
41. or/36-40
42. 7 or 12 or 17 or 20 or 26 or 30 or 35 or 41
43. (comment or interview or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
44. 42 not 43
45. (colon or colorectal or rectal).ab,ti.
46. 44 and 45

Search #1: Concepts 1, 2, 3, 4 and publication filter.
Search #2: Concepts 1, 2, 5 and publication filter.

Both searches were run and duplicates were removed. Limits were set for human-only studies [NOT (animal NOT human)], studies published in English only, and with the publication dates 1/1/2008 – 8/1/2013. Unique references from both searches were pooled for title/abstract review. The searches were rerun on 2/12/2015 to identify articles published since 8/1/2013.
PubMed – Search #1

PubMed Search #2

(((Clinical Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp]) OR Evaluation Studies[ptyp]) OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]) OR Research Support, N I H, Extramural[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Practice Guideline[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Research Support, Non U S Gov't[ptyp] OR Research Support, U S Gov't, Non P H S[ptyp] OR Research Support, U S Gov't, P H S[ptyp] OR Review[ptyp] OR systematic[sb] OR Validation Studies[ptyp]) AND ((("colorectal neoplasms"[MeSH Terms:noexp] OR "colonic neoplasms"[MeSH Terms]) OR "colorectal neoplasms, hereditary nonpolyposis"[MeSH Terms]) OR "rectal neoplasms"[MeSH Terms:noexp]) OR ("adenocarcinoma, mucinous"[MeSH Terms:noexp] OR "adenocarcinoma"[MeSH Terms:noexp]) AND "colon"[MeSH Terms]) AND ((((((((("analysis of variance"[MeSH Terms:noexp] OR "cluster analysis"[MeSH Terms:noexp]) OR "decision support techniques"[MeSH Terms:noexp]) OR "diagnosis, differential"[MeSH Terms:noexp]) OR "disease progression"[MeSH Terms:noexp]) OR "disease-free survival"[MeSH Terms:noexp]) OR "drug resistance, neoplasm"[MeSH Terms:noexp]) OR "early diagnosis"[MeSH Terms]) OR "kaplan-meier estimate"[MeSH Terms]) OR "multivariate analysis"[MeSH Terms:noexp]) OR "predictive value of tests"[mh:noexp]) OR "prognosis"[MeSH Terms:noexp]) OR "risk assessment"[MeSH Terms:noexp]) OR "sensitivity and specificity"[mh:noexp]) OR "survival analysis"[MeSH Terms]) OR "survival rate"[MeSH Terms:noexp]) OR "treatment outcome"[MeSH Terms]) AND ((((((((((((("antibodies, monoclonal"[MeSH Terms:noexp]) OR "antibodies, monoclonal, humanized"[MeSH Terms:noexp]) OR "antitumor, antimetabolites, antineoplastic"[MeSH Terms:noexp]) OR "antineoplastic agents"[MeSH Terms:noexp]) OR "antineoplastic combined chemotherapy protocols"[MeSH Terms:noexp]) OR "combined modality therapy"[MeSH Terms]) OR "fluorouracil"[MeSH Terms:noexp]) OR "leucovorin"[MeSH Terms:noexp]) OR "camptothecin"[MeSH Terms:noexp]) OR "chemotherapy, adjuvant"[mh:noexp]) OR "drug therapy, combination"[MeSH Terms:noexp]) OR "drug combinations"[MeSH Terms:noexp]) OR "organoplatinum compounds"[MeSH Terms:noexp]) OR "oxonic acid"[MeSH Terms:noexp]) OR "protein kinase inhibitors"[MeSH Terms:noexp]) OR "tegafur"[MeSH Terms:noexp]) OR "pyridines"[MeSH Terms:noexp]) OR "individualized medicine"[MeSH Terms:noexp]) OR "anti-inflammatory agents, non-steroidal"[MeSH Terms:noexp]) OR "aspirin"[MeSH Terms:noexp]) AND ("adaptor proteins, signal transducing"[Majr]) OR "antigen, neoplasm"[Majr]) OR "base pair mismatch"[Majr]) OR "base sequence"[Majr]) OR "cell adhesion molecules"[Majr]) OR "dna mismatch repair"[Majr]) OR "DNA methylation"[Majr]) OR "DNA-binding proteins"[Majr]) OR "DNA, neoplasms"[Majr]) OR "gene amplification"[Majr]) OR "gene expression"[Majr]) OR "gene expression profiling"[Majr]) OR "gene expression regulation, neoplastic"[Majr]) OR "genetic heterogeneity"[Majr]) OR "genes, ras"[Majr]) OR "genes, erbb-1"[Majr]) OR "genes, erbb-2"[Majr]) OR ("genetic markers"[Majr]) OR ("genetic testing"[Majr]) OR ("micrornas"[Majr]) OR ("microsatellite instability"[Majr]) OR "phenotype"[Majr]) OR "phosphatidylinositol 3-kinases"[Majr]) OR "promoter regions, genetic"[Majr]) OR "proto-oncogene proteins"[Majr]) OR ("pten phosphohydrolase"[Majr]) OR "proto-oncogene proteins b-ral"[Majr]) OR "ras proteins"[Majr]) OR "receptor, epidermal growth factor"[Majr]) OR "rna, messenger"[Majr]) OR "tumor markers, biological"[Majr]) AND ((("2008/01/01"[PDAT] : "2013/12/31"[PDAT]) NOT "animals"[MeSH Terms:noexp]) AND English[lang])
Scopus Search Strategy

(((TITLE-ABS-KEY(colorectal OR colon OR rectal) AND TITLE-ABS-KEY(cancer OR carcinoma OR neoplasm OR neoplasia))) AND ((TITLE-ABS-KEY(molecular OR biomarker OR KRAS OR BRAF OR MSI OR MMR OR NRAS OR PIK3CA OR PTEN OR MIR21 OR MLH1) AND TITLE-ABS-KEY("laboratory method" OR technique OR validation OR implementation))) AND (guideline OR metaanalysis OR systematic OR "randomized controlled" OR "clinical trial") AND NOT (mouse OR mice OR animal OR murine OR "cell line"))) or (((TITLE-ABS-KEY(colorectal OR colon OR rectal) AND TITLE-ABS-KEY(cancer OR carcinoma OR neoplasm OR neoplasia))) AND ((TITLE-ABS-KEY(molecular OR biomarker OR KRAS OR BRAF OR MSI OR MMR OR NRAS OR PIK3CA OR PTEN OR MIR21 OR MLH1) AND TITLE-ABS-KEY((treatment OR chemotherapy OR therapy) AND (outcome OR survival OR progression OR recurrence))) AND (guideline OR metaanalysis OR systematic OR "randomized controlled" OR "clinical trial") AND NOT (mouse OR mice OR animal OR murine OR "cell line"))) AND ( LIMIT-TO(SUBJAREA,"MEDI") OR LIMIT-TO(SUBJAREA,"BIOC") OR LIMIT-TO(SUBJAREA,"PHAR") OR LIMIT-TO(SUBJAREA,"HEAL") ) AND ( LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011) OR LIMIT-TO(PUBYEAR,2010) OR LIMIT-TO(PUBYEAR,2009) OR LIMIT-TO(PUBYEAR,2008) OR LIMIT-TO(PUBYEAR,2007) )

Unique results published in journals not indexed in MEDLINE were added to the evidence pool.
REFERENCES


61. Yang ZY, Wu XY, Huang YF, et al. Promising biomarkers for predicting the outcomes of patients with KRAS wild-type metastatic colorectal cancer treated with anti-epidermal growth


