Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults

I. Background and Objectives for the Systematic Review

Colorectal cancer (CRC) is the third most common cancer in both men and women, with more than 140,000 cases expected to have occurred in the United States in 2010. These cases predominantly occur in the colon, with only 30 percent of cases occurring in the rectum. More than 50,000 deaths from CRC are expected to have occurred in 2010, representing 9 percent of all the cancer deaths in the United States. Incidence and mortality rates for CRC have declined over the past 2 decades.¹ This decrease has been partially attributed to the use of CRC-screening tests that allow for early detection and treatment of cancer or precancerous colorectal polyps. Self-reported CRC-screening rates have increased from less than 25 percent in the 1980s to 50 to 60 percent in 2005–2006. Multiple patient, clinician, and health care–delivery factors have been found to negatively influence CRC screening, including low socioeconomic or educational status, lack of physician recommendation, and lack of insurance or limited access to health care.²

Most organizations agree that screening is better than not screening for CRC and that the age to begin screening in average-risk adults is 50 years. CRC-screening tests use different approaches, including stool-based tests and direct-visualization methods. Currently, most U.S. guideline organizations, including the U.S. Preventive Services Task Force (USPSTF), agree that the recommended options in screening for CRC include: colonoscopy every 10 years; high-sensitivity guaiac fecal occult-blood testing (FOBT) or fecal immunohistochemical testing (FIT) annually; and flexible sigmoidoscopy every 5 years with or without fecal blood testing (FOBT or FIT).³,⁴ Some disagreement occurs between guideline organizations about screening interventions with less evidence to support their use. These tests include: computerized tomographic colonography, double-contrast barium enema, and fecal or stool-based DNA testing.³

Fecal DNA testing detects molecular alterations associated with CRC development in cellular DNA excreted in stool. CRC screening improves health outcomes by detecting early stage cancer, which has a better prognosis, and by detecting precancerous lesions (i.e., adenomas). It is estimated that up to 50 percent of individuals will develop a colorectal adenoma in their lifetime; however, only 6 percent of these lesions are estimated to later develop into CRC.⁵ Therefore, it is important for a screening test to be able to detect those adenomas that are most likely to develop into cancer. Many markers related to oncogenesis have been described for CRC, including DNA mutations and methylation. These markers have been found to be released into a patient’s stool early during the development of CRC.⁵ In patients with CRC, carcinoma cells are continuously shed into the large bowel and passed into the feces. Only 0.01 percent of DNA in the feces is of human origin; most fecal DNA is acquired through outside sources, including diet and microflora. Once the human DNA is isolated from the stool, mutations related to colorectal adenoma or carcinoma sequences can be identified in the fecal DNA by using a variety of detection methodologies.⁶

Source: www.effectivehealthcare.ahrq.gov
Published Online: May 18, 2011
Currently, there are no fecal DNA tests approved by the U.S. Food and Drug Administration (FDA) for screening or diagnosing CRC. Available fecal DNA tests are instead offered as a direct-to-consumer laboratory-developed test; such tests are currently regulated by the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (Public Law 100-578), excluding the States of Washington and New York, which have State-level licensure programs that are exempt from CLIA Program requirements. Historically, the FDA’s oversight of genetic testing has been focused on commercial test kits. However, the FDA is now engaged in dialogues with manufacturers and the public about how it should develop a consistent, reasonable, and fair approach for laboratory-developed tests to ensure safety and to promote innovation.

Fecal DNA testing may offer advantages for patient adherence and acceptability over direct-visualization CRC-screening modalities as a noninvasive, home-based technique for CRC screening. In addition, proponents point out that fecal DNA testing requires only a single whole-stool sample (when compared with the multiple smear samples from consecutive bowel movements that are required for the FOBT and FIT tests) and no diet or medication restrictions.

Marketing for commercially available fecal DNA testing specifies that the test is intended for individuals who are not eligible (either unable or unwilling) for more invasive CRC screening (i.e., colonoscopy, flexible sigmoidoscopy, or computerized tomographic colonography).

In 2008, the USPSTF found that evidence was insufficient to recommend fecal DNA testing for CRC screening based on a systematic review of new and established CRC-screening modalities. However, the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology collectively recommended fecal DNA testing as an alternative screening method. This recommendation by these groups was based on lower quality evidence that was excluded from the review conducted on behalf of the USPSTF due to its more stringent inclusion and quality criteria (e.g., case-control studies of screening accuracy or lack of a reference standard). The American College of Gastroenterology recognized that fecal DNA testing may offer an alternative form of CRC screening; however, they state that the preferred forms of screening include colonoscopy and FIT, noting the very limited evidence for fecal DNA testing. While adding a noninvasive test to accepted screening strategies may increase patient compliance, the possibility remains to be established. Currently, there is at least one fecal DNA test commercially available in the United States (ColoSure, Exact Sciences Corporation, Madison, WI).

This topic was nominated to the Agency for Healthcare Research and Quality for its Effective Healthcare (EHC) Program by an organization interested in using the proposed review to develop an evidence-based recommendation statement. The proposed Key Questions (KQs) and the Analytic Framework were posted for public comment on the EHC Program Web site from February 7, 2011, through March 7, 2011. No changes to the KQs or Analytic Framework were made on the basis of the public comments. The draft protocol was also reviewed by a Technical Expert Panel. Based on input from our Technical Expert Panel, we made minor changes in the wording of the KQs and changed our contextual question on the analytic validity of currently available fecal DNA assays to a KQ (now KQ 4).

II. The Key Questions

The final KQs for this review are:

Source: www.effectivehealthcare.ahrq.gov
Published Online: May 18, 2011
Question 1: Direct Evidence

What is the effectiveness of fecal DNA testing to screen for colorectal cancer in reducing morbidity (colorectal cancer incidence) or mortality (all-cause or CRC-specific):

a. Alone?
b. In combination with other screening tests?

Question 2: Clinical Validity

a. What are the absolute test-performance characteristics (e.g., sensitivity, specificity) of fecal DNA testing for CRC screening, as compared to colonoscopy?

(1). To detect CRC?
(2). To detect precancerous lesion(s)?

b. What is the relative test performance of fecal DNA testing as compared to other established screening modalities in current practice?

(1). To detect CRC?
(2). To detect precancerous lesion(s)?

Question 3: Interval of Screening

What is the test performance of fecal DNA testing across different screening interval(s)?

Question 4: Analytic Validity

a. What is the analytic validity (analytic sensitivity, specificity, and reproducibility) of currently available fecal DNA assays?

b. What are the important analytic and preanalytic factors that can affect fecal DNA assay validity?

Question 5: Acceptability of Testing

What is the acceptability and adherence of fecal DNA screening in comparison to other stool-based screening tests, or in comparison to more invasive modalities of screening?

Question 6: Harms

What are the potential harms of fecal DNA testing?

In addition, we propose to address the following nonsystematically reviewed contextual question:

Source: www.effectivehealthcare.ahrq.gov
Published Online: May 18, 2011
Contextual Question 1

a. How have fecal DNA assays evolved over time?

b. How similar (or different) are previous versions of assays to currently available fecal DNA assays?

Table 1. PICOTS

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic adults at average risk for CRC, who are age 40 years or older (based on earlier risk of disease in certain racial or ethnic subpopulations).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Fecal DNA assay.</td>
</tr>
<tr>
<td>Comparators</td>
<td>KQs 1 &amp; 2: For studies providing relative test performance, the comparator can be any established CRC-screening modality (i.e., FOBT [high-sensitivity or traditional], FIT, flexible sigmoidoscopy, DCBE, or CT colonography). KQ 2: For studies primarily addressing the absolute test performance of fecal DNA testing for CRC screening, the comparator must be colonoscopy alone or supplemented by another test (i.e., CT colonography).</td>
</tr>
</tbody>
</table>
| Outcomes         | KQ 1: Final Health Outcomes  
|                  | 1) CRC-specific or all-cause mortality  
|                  | 2) CRC incidence  
|                  | KQs 2 & 3: Diagnostic Outcomes  
|                  | 1) Sensitivity, specificity, positive predictive value, negative predictive value, or relative detection rate for:  
|                  | a) CRC, that is, adenocarcinoma or carcinoma in situ (adenomas with severe dysplasia but no invasion into the muscularis mucosa)  
|                  | b) Adenomas (tubular, tubulovillous, or villous histology)  
|                  | c) Composite outcome, that is, advanced neoplasia (adenocarcinoma, adenomas with high-grade dysplasia or villous histology, and large adenomas ≥10 mm in diameter)  
|                  | KQ 4: Analytic Outcomes  
|                  | 1) Analytic sensitivity (lower limit of detection)  
|                  | 2) Analytic specificity  
|                  | 3) Reproducibility  
|                  | KQ 5: Acceptability and Adherence |
1) Patient acceptability
2) Patient adherence

KQ 6: Harms of Fecal DNA Testing

1) Test inaccuracy, that is, false-positive or false-negative results
2) Negative psychological, ethical, legal, or social consequences

<table>
<thead>
<tr>
<th>Timing</th>
<th>We will not exclude studies based on duration of followup. Timing of the application of reference-standard testing will be considered as part of the quality assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Settings</td>
<td>All settings.</td>
</tr>
</tbody>
</table>

Abbreviations: CRC = colorectal cancer; CT colonography = computerized tomographic colonography; DCBE = double-contrast barium enema; FIT = fecal immunohistochemical testing; FOBT = fecal occult-blood testing; PICOTS = population, intervention, comparator, outcome, timing, and setting.
III. Analytic Framework

Figure 1: Draft analytic framework the benefits and harms of Fecal DNA Testing in Screening for Colorectal Cancer

1. Screening
   - Fecal DNA Screening
   - Colorectal Cancer
   - Precancerous Lesion
   - Negative Screening
   - Management / Surveillance

2. Colorectal Cancer
   - Decreased Colorectal Cancer or All-Cause Mortality
   - Decreased Colorectal Cancer Incidence

3. Harms of Screening
4. Asymptomatic adults at average risk for Colorectal Cancer (CRC)
5. Adherence and Acceptability
6. Harms of Treatment

Source: www.effectivehealthcare.ahrq.gov
Published Online: May 18, 2011
IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We have developed a preliminary set of criteria for inclusion and exclusion of studies for KQs 1–5 based on our understanding of the literature (Table 2).

Table 2. Inclusion/Exclusion criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion/Exclusion Criteria</th>
</tr>
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<tbody>
<tr>
<td>Population</td>
<td><strong>KQs 1-6:</strong> Adults ≥40 years old at average risk for CRC. We will exclude studies that exclusively include adults who are at high-risk for CRC and those diagnosed with CRC. Persons at high risk for CRC include persons with a strong family history of CRC including syndrome-related elevated risks (e.g., FAP, HNPCC, Gardener syndrome [FPC], Turcot syndrome, and Peutz-Jeghers syndrome).</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>KQs 1-6:</strong> Fecal assays intended to screen for CRC, though early cancer or precancerous lesions detected by DNA testing including genotyping, gene-expression measurement, and/or methylation detection. Fecal DNA tests may be performed alone or in combination with other CRC-screening tests. <strong>KQ 4:</strong> Tests will be limited to those that are currently available to patients, because the assay technology has changed significantly over time.</td>
</tr>
<tr>
<td>Comparator</td>
<td><strong>KQ 1:</strong> No screening or another established CRC-screening modality (colonoscopy, FOBT [high-sensitivity or traditional], FIT, flexible sigmoidoscopy, barium enema, or CT colonography). <strong>KQ 2:</strong> For absolute test performance: colonoscopy alone or supplemented by another test. For relative test performance: any established CRC-screening modality. <strong>KQ 5:</strong> Any established CRC-screening modality.</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>KQ 1:</strong> CRC incidence (or advanced neoplasia incidence if CRC incidence is not reported), all-cause mortality, and CRC-specific mortality. <strong>KQs 2 &amp; 3:</strong> Absolute or relative test-performance measures, including sensitivity, specificity, PPV, NPV, or relative detection rate: 1. For detection of CRC (adenocarcinoma, carcinoma in situ). 2. For adenomas (any histology). 3. For advanced neoplasia.</td>
</tr>
</tbody>
</table>
KQ 4: Analytic sensitivity (lower limit of detection), analytic specificity, and reproducibility.

KQ 5: Any self-reported or objective measures of patient acceptability of or patient adherence to fecal-DNA screening.

KQ 6: Any reported harms, including test inaccuracy (i.e., false-positive or false-negative results), and negative psychological, ethical, legal, or social consequences.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Setting</td>
<td>KQs 1–6: All settings.</td>
</tr>
<tr>
<td>Study Geography</td>
<td>KQs 1–6: All locations.</td>
</tr>
<tr>
<td>Publication Language</td>
<td>KQs 1–6: English only.</td>
</tr>
<tr>
<td>Study Design</td>
<td>KQs 1–2: Systematic review, randomized or nonrandomized controlled trial, prospective or retrospective cohort, diagnostic accuracy studies, or case-control studies. KQs 3–6: Any study design.</td>
</tr>
<tr>
<td>Followup Duration</td>
<td>KQs 1–6: We will not exclude studies based on duration of followup. Timing of application of reference-standard testing will be considered as part of the quality assessment.</td>
</tr>
<tr>
<td>Sample Size</td>
<td>KQs 1–6: We will not exclude studies based on sample size alone, although it may be considered as part of the quality assessment.</td>
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</table>

Abbreviations: CRC = colorectal cancer; CT colonography = computerized tomographic colonography; FIT = fecal immunohistochemical testing; FOBT = fecal occult-blood testing; FPC = familial polyposis coli; HNPCC = hereditary nonpolyposis colon cancer; KQ = key question; NPV = negative predictive value; PPV = positive predictive value.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The research librarian, in collaboration with the review team, will develop and implement search strategies designed to identify evidence relevant to each KQ. Contextual questions will be will be answered by using nonsystematic review searching of the published literature and expert input. Literature searches will be restricted to the English language and to a start date of 2000. Previous reviews found that published evidence in this area began after 2000. Although the Technical Expert Panel
suggested that there has been investigation on the use of fecal DNA markers in Italy and China, they did not think that we would miss studies that meet our inclusion criteria by restricting our searches to only English-language publications. A search of non-English-language publications since 2000 confirmed that there are a very limited number of abstracts on fecal DNA testing, none of which met the inclusion criteria for our review. A proposed search strategy is shown in Appendix A. Comprehensive searches will be conducted in the following databases:

- MEDLINE
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Database of Abstracts of Reviews of Effects
- Health Technology Assessments Database

Results from the literature searches will be entered into version 11.0.1 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management database. The reference lists of relevant existing systematic reviews and clinical practice guidelines will also be checked to identify potential studies for inclusion. We will also supplement our searches with suggestions from members of the Technical Expert Panel. If additional studies are identified, we will consult with the research librarian to examine why the initial search strategy did not identify the article(s) in question.

In addition to a search of the published literature, the research librarian will perform grey literature searches for this comparative effectiveness review. For the purposes of this review, grey literature comprises information that is not controlled by commercial publishing, including: unpublished data from recent (2009–2011) conference abstracts (e.g., American Association for Cancer Research, American Association for Clinical Chemistry, American College of Gastroenterology, American Society of Clinical Oncology, Digestive Disease Week, Gastrointestinal Cancers Symposium), regulatory documents (e.g., FDA Medical and Statistical Reviews; Authorized Medicines for the European Union), proprietary data via submitted scientific information packets and manufacturer Web sites, and information regarding ongoing and future research via clinical trial registry entries (e.g., ClinicalTrials.gov and WHO Clinical Trials).

We will conduct a bridge search of the published literature upon submission of the draft report and will incorporate newly identified studies as needed (including while the draft report is undergoing review). The report will also be updated with any additional information identified through public and peer review.

A two-step process will be used for study selection. First, each title and abstract (if available) will be independently reviewed by two reviewers to determine if an article may meet the inclusion criteria for study design, population, and intervention (see Section B, Table 1). Each article will be coded as: potentially included (I), excluded (E), or background (X). Next, we will retrieve full-text articles for all the potentially included studies, including those that are questionable based on limited reporting at the abstract stage. Two reviewers will independently assess each full-text article by using a standard form that details the predetermined inclusion and exclusion criteria. Disagreements will be resolved through discussion and consensus or by consulting a third reviewer.
C. Data Abstraction and Data Management

Data from all included studies will be abstracted into standard evidence tables by one reviewer and checked for accuracy and completeness by a second reviewer. The following information will be extracted from each study, where applicable: author identification, year of publication, source of study funding, study design characteristics, recruitment setting/patient-inclusion criteria, sample size, and setting; important study population characteristics (e.g., age, race, sex); fecal DNA test and comparator test (reference standard) characteristics; and outcomes, including harms. We will record details relevant to the technical specification of the fecal DNA assay being conducted, including the gene mutations/expression analyzed, the assay characteristics and laboratory setting, and the technique used for sample analysis (reagents, machinery, quality control). The data-abstraction tables will be tested for completeness on select studies and will be revised as necessary before data extraction is fully performed on all the articles. Authors of included studies may be contacted if clarification of methods or results is needed.

In addition, we will code the reasons for exclusion of articles considered at the full-article review stage. Studies at the abstract and full-article review stages will be managed by using Reference Manager, so that we can easily compile a list of included and excluded articles and the reasons for exclusion. Project staff will meet regularly to discuss the results at each phase, to review studies that are difficult to classify, and to address any questions that the team may have.

D. Assessment of Methodological Quality of Individual Studies

To assess the methodological quality of included studies, we will use the study design-specific quality criteria proposed by the USPSTF. When appropriate, we will supplement these quality criteria with methods from the Evaluation of Genomic Applications in Practice and Prevention Working Group (specific to genetic testing), the Newcastle Ottawa Scale (specific to cohort and case-control studies), and the QUADAS criteria (specific to diagnostic accuracy studies). Two independent reviewers will assign a quality rating of the internal validity for each study. Disagreements will be resolved by discussion and consensus or by consulting a third, independent reviewer. A rating of “good,” “fair,” or “poor” will be assigned by using the predefined criteria for each study design. Good-quality studies generally meet all of the study design-specific quality criteria. Fair-quality studies do not meet all the criteria but do not have any fatal flaws in study design. Poor-quality studies have significant flaws or lack of reporting that imply bias, affecting interpretation of study results. While no articles will be excluded for quality reasons, studies rated as poor in quality will be discussed separately. The quality assessment of adverse effects and harms data will be informed by the methods guidance for comparative effectiveness reviews developed by the Agency for Healthcare Research and Quality. Quality ratings will be recorded in the evidence tables.
E. Data Synthesis

We anticipate that the data obtained from the literature review will not be conducive to meta-analyses and, therefore, will be synthesized qualitatively by KQ. If the data allow, we will analyze findings by sex and race/ethnicity. Results will be displayed in tables, thereby allowing comparison of findings across studies. If we find a sufficient number of similar studies for KQ 1 or 2, we will consult a biostatistician about the quantitative analysis of the most commonly reported outcome measures.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for primary outcomes by using the standard process of the Evidence-based Practice Centers as outlined in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. The grade will be based on four major domains: risk of bias, consistency, directness, and precision of the evidence. We will classify the bodies of evidence pertaining to each primary outcome into four basic grades: high, moderate, low, and insufficient (Table 3). As advised, the number of studies that form the basis of given findings or conclusions will also be recorded. Additional domains—such as dose-response association, plausible confounding, strength of association, and publication bias—will be assessed and reported if applicable.

### Table 3. Strength of evidence grades and definitions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit a conclusion.</td>
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</table>

G. Assessing Applicability

In addition to quality assessment, we will also assess the applicability of studies. Judgments of applicability for each outcome (including harms) will be performed separately from assessments of the other domains of strength of evidence as recommended (see Section F). We will identify and abstract factors in individual
studies that might affect applicability, particularly including factors related to the populations studied (e.g., how highly selected they were [what portion of those eligible were included], how they were recruited) and if the fecal DNA assay is currently available or not (or how similar is the assay to currently available fecal DNA assays). Based on these characteristics, we will note any potential limitations to applicability on the interpretation of each individual study and will conclude with an evaluation of the applicability of the total body of evidence.

V. References


VI. Abbreviations

CLIA = Clinical Laboratory Improvement Amendments
CRC = Colorectal Cancer
CT = Computerized Tomography
DNA = Deoxyribonucleic Acid
FIT = Fecal Immunohistochemical Testing
FOBT = Fecal Occult-Blood Testing
USPSTF = U.S. Preventive Services Task Force

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as
well as identifying particular studies or databases to search. They are selected to provide broad
expertise and perspectives specific to the topic under development. Divergent and conflicted
opinions are common and perceived as health scientific discourse that results in a thoughtful,
relevant systematic review. Therefore study questions, design and/or methodological approaches
do not necessarily represent the views of individual technical and content experts. Technical
Experts provide information to the EPC to identify literature search strategies and recommend
approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of
any kind nor contribute to the writing of the report and have not reviewed the report, except as
given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and
any other relevant business or professional conflicts of interest. Because of their unique clinical
or content expertise, individuals are invited to serve as Technical Experts and those who present
with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or
mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their
clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of
the report are considered by the EPC in preparation of the final draft of the report. Peer
reviewers do not participate in writing or editing of the final report or other products. The
synthesis of the scientific literature presented in the final report does not necessarily represent the
views of individual reviewers. The dispositions of the peer review comments are documented
and will, for CERs and Technical briefs, be published three months after the publication of the
Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and
any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not
have any financial conflict of interest greater than $10,000. Peer reviewers who disclose
potential business or professional conflicts of interest may submit comments on draft reports
through the public comment mechanism.
Appendix A: Example Draft MEDLINE Search Strategy

Draft search strategy for fecal DNA testing (all key questions)

Database(s): Ovid MEDLINE(R)

Search Strategy:

1. ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab.
2. f-dna.ti,ab.
3. sdna.ti,ab.
4. DNA/
5. DNA Methylation/
6. DNA Mutational Analysis/
7. DNA, Neoplasm/
8. 4 or 5 or 6 or 7
9. Feces/
10. 8 and 9
11. 1 or 2 or 3 or 10
12. Colorectal Neoplasms/
13. Colonic Polyps/
14. Colonic Neoplasms/
15. Sigmoid Neoplasms/
16. Rectal Neoplasms/
17. Anus Neoplasms/
18. Anal Gland Neoplasms/
19. Intestinal Polyps/
20. Colon cancer.ti,ab.
22. Colon$ neoplas$.ti,ab.
23. or/12-22
24. 11 and 23