Supplementary Online Content


**eFigure 1.** Search Strategies

**eFigure 2.** Quality assessment summary: review authors’ judgments about each risk of bias item for each included study

**eFigure 3.** Methodological quality of included studies graph: review authors’ judgments about each item presented as percentages across all included studies

**eFigure 4.** Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity of FIT for diagnosis of a) colorectal cancer; b) advanced neoplasia

**eFigure 5.** Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies with low risk of bias or concerns for applicability (QUADAS-2)

**eFigure 6.** Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies using quantitative FIT with cut off value less than 25μg/g only in patients with familial risk of CRC

**eFigure 7.** Fagan’s nomogram plots

**eTable 1.** Synopsis of results from sensitivity analyses depending on risk of bias, patient population and reference standard used for the diagnosis of colorectal cancer and advanced neoplasia

**eTable 2.** Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the quality of the body evidence regarding the diagnostic accuracy of FIT

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2017 American Medical Association. All rights reserved.
Supplementary Online Content

eFigure 1: Search Strategies

eFigure 2: Quality assessment summary: review authors’ judgments about each risk of bias item for each included study.

eFigure 3: Methodological quality of included studies graph: review authors' judgments about each item presented as percentages across all included studies.

eFigure 4: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity of FIT for diagnosis of a) colorectal cancer; b) advanced neoplasia.

eFigure 5: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies with low risk of bias or concerns for applicability (QUADAS-2).

eFigure 6: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies using quantitative FIT with cut off value less than 25μg/g only in patients with familial risk of CRC.

eFigure 7: Fagan’s nomogram plots

eTable 1: Synopsis of results from sensitivity analyses depending on risk of bias, patient population and reference standard used for the diagnosis of colorectal cancer and advanced neoplasia.

eTable 2: Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the quality of the body evidence regarding the diagnostic accuracy of FIT
eFigure 1: Search Strategies

Medline via PubMed

#1 fecal [mh]
#2 fecal [tw]
#3 faecal [mh]
#4 faecal [tw]
#5 feces [mh]
#6 feces [tw]
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 immunochem*[tw]
#9 immunologic*[tw]
#10 #8 OR #9
#11 #7 AND #10
#12 FIT [tw]
#13 iFOBT [tw]
#14 FOB* [tw]
#15 FOBT [tw]
#16 FOB* [tw]
#17 "oc-light" [tw]
#18 "oc light" [tw]
#19 "oc-hemodia" [tw]
#20 "oc hemodia" [tw]
#21 "oc-micro" [tw]
#22 "oc micro" [tw]
#23 "oc-sensor" [tw]
#24 "oc sensor" [tw]
#25 "FOB gold" [tw]
#26 Magstream [tw]
#27 Hemsp [tw]
#28 Hemtube [tw]
#29 Hemosure [tw]
#30 Hemoccult [tw] OR
#31 Hemcheck [tw] OR
#32 Hemochaser [tw] OR
#33 Monohaem [tw] OR
#34 sentiFOB [tw]
#35 flexsure [tw]
#36 immocare [tw]
#37 sentiFIT [tw]
#38 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR
#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR 
#37
#39 #11 OR #38
#40 colorectal neoplasms [mh]
#41 colonic neoplasms [mh]
#42 sigmoid neoplasms [mh]
#43 colonic polyps [mh]
#44 intestinal polyps [mh]
#45 colon* [tw]
#46 colorectal [tw]
#47 sigmoid [tw]
#48 intestinal [tw]
#49 anal [tw]
#50 adenomat* [tw]
#51 adenoma* [tw]
#52 polyps [tw]
#53 polyp [tw]
#54 carcinoma* [tw]
#55 neoplas* [tw]
#56 tumour* [tw]
#57 tumor* [tw]
#58 cancer* [tw]
#59 #45 OR #46 OR #47 OR #48 OR #49 OR #50
#60 #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
#61 #59 AND #60
#62 #40 OR #41 OR #42 OR #43 OR #44 OR #61
#63 "Sensitivity and Specificity" [mh]
#64 "Likelihood Functions" [mh]
#65 "Reproducibility of Results" [mh]
#66 "Area Under Curve" [mh]
#67 "predictive value of tests" [mh]
#68 "false negative reactions" [mh]
#69 "false positive reactions" [mh]
Cochrane library, DARE (Database of Abstracts of Reviews of Effects), NHS EED (NHS Economic Evaluation Database), HTA (Health technology assessments) Database

#1 fecal
#2 faecal
#3 feces
#4 #1 or #2 or #3
#5 immunochem*
#6 immunologic*
#7 #5 or #6
#8 #4 and #7 in Trials
#9 FIT
#10 IFOB*
#11 IFOBT
#12 FOB*
#13 FOBT
#14 Magstream
#15 oc-light
#16 "oc light"
#17 hemosure
#18 oc-hemodia
#19 "oc hemodia"
#20 hemsp
#21 hemtube
#22 hemosure
#23 hemoccult
#24 hemcheck
#25 hemochaser
#26 oc-sensor
#27 "oc censor"
#28 oc-micro
#29 "oc micro"
#30 Monohaem
#31 "FOB Gold"
#32 flexsure
#33 immocare
#34 sentiFIT
#35 sentiFOB
#36 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 in Trials
#37 #8 or #36 in Trials
#38 MeSH descriptor: [Colorectal Neoplasms] explode all trees
#39 MeSH descriptor: [Intestinal Polyps] explode all trees
#40 "colorectal cancer*"
#41 "colorectal neoplas*"
#42 "colorectal tumor*"
#43 "colorectal tumour*"
#44 "colorectal carcinoma*"
#45 "colorectal polyp*"
#46 "colorectal adenoma*"
#47 "colorectal adenocarcinoma"
#48 "colon* neoplas*"
#49 "colon* tumor*"
#50 "colon* cancer*"
#51 "rectal neoplas*"
#52 "rectal cancer*"
#53 "colon* polyp*"
#54 "adenomatous polyp*"
#55 #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
#56 MeSH descriptor: [Sensitivity and Specificity] explode all trees
#57 MeSH descriptor: [False Positive Reactions] explode all trees
#58 MeSH descriptor: [False Negative Reactions] explode all trees
#59 MeSH descriptor: [Likelihood Functions] explode all trees
#60 MeSH descriptor: [Area Under Curve] explode all trees
#61 accurac*
#62 sensitiv*
#63 specificit*
#64 "likelihood ratio**"
#65 "predictive value**"
#66 "false negative**"
#67 "false positive**"
#68 "receiver operat**"
#69 #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68
#70 #37 and #55 and #69 in Trials

Embase via Ovid
#1 fecal.mp.
#2 faecal.mp.
#3 feces.mp.
#4 #1 OR #2 OR #3
#5 exp immunohistochemistry/ OR immunochistoch$.mp.
#6 immunologic$.mp.
#7 immunochem$.mp.
#8 #5 OR #6 OR #7
#9 #4 AND #8
#10 FIT.mp.
#11 iFOBS.mp.
#12 iFOBT.mp.
#13 FOB$.mp.
#14 *occult blood/ OR FOBT.mp.
#15 #10 OR #11 OR #12 OR #13 OR #14
#16 #9 OR #15
#17 "oc-light".mp.
#18 "oc light".mp.
#19 "oc-hemodia".mp.
#20 "oc hemodia".mp.
#21 "oc-micro" .mp.
#22 "oc micro".mp.
#23 "oc-sensor".mp.
#24 "oc sensor" .mp.
#25 "FOB gold" .mp.
#26 Magstream .mp.
#27 Hemsp .mp.
#28 Hemtube.mp.
#29 Hemosure.mp.
#30 Hemoccult .mp.
#31 Hemcheck .mp.
#32 Hemchaser.mp.
#33 Monohaem.mp.
#34 sentiFOB.mp.
#35 flexsure.mp.
#36 immocare.mp.
#37 sentiFIT.mp.
#38 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
#39 #16 OR #38
#40 'colorectal carcinoma'.mp. OR exp colon tumor/ OR exp rectum carcinoma/ OR exp colorectal carcinoma/ OR exp rectum tumor/ OR exp colon carcinoma/
#41 colonic polyps.mp. OR exp colon polyp/
#42 colorectal neoplasm.mp OR exp colorectal tumor/
#43 exp colon cancer/ OR colon cancer.mp.
#44 intestinal polyp.mp. OR exp intestine polyp/
#45 exp rectum cancer/ OR rectum cancer.mp.
#46 exp sigmoid carcinoma/ OR sigmoid cancer
#47 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48 colorect$.mp
#49 colon$.mp.
#50 rect$.mp.
#51 anal$.mp
#52 intestin$.mp
#53 adenomat$.mp
#54 sigmoid.mp
#55 #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
#56 adenoma$.mp
#57 poly$.mp.
#58 carcinoma$.mp
#59 tumo$.mp.
#60 neoplas$.mp.
#61 adenocarcinoma$.mp.
#62 #56 OR #57 OR #58 OR #59 OR #60 OR #61
#63 #55 AND #62
#64 #47 OR #63
#65 #39 AND #64
#66 exp "Sensitivity and Specificity"/
#67 diagnostic error.mp. OR exp "diagnostic errors" /
#68 laboratory diagnosis.mp OR exp laboratory diagnosis/
#69 predictive value/
#70 exp Area Under Curve/
#71 exp Reference Values/
#72 exp diagnostic accuracy/ OR diagnostic accuracy.mp
#73 exp Observer Variation/
#74 exp Reproducibility/
#75 sensitiv$.mp.
#76 specificit$.mp.
#77accurac$.mp.
#78 likelihood ratio$.mp.
#79 false negative$.mp.
#80 false positive$.mp.
#81 predictive value$.mp
#82 roc curve$.mp. OR exp receiver operating characteristic/
#83 "diagnostic odds ratio".mp. OR exp diagnostic value/
#84 #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83
#85 #64 AND #65
#86 limit 85 to human
**eFigure 2: Quality assessment summary: review authors’ judgments about each risk of bias item for each included study.**

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Selection</strong></td>
<td><strong>Index Test</strong></td>
</tr>
<tr>
<td>Antonio 2011</td>
<td>+</td>
</tr>
<tr>
<td>Castro 2014</td>
<td>+</td>
</tr>
<tr>
<td>Gimeno-Garcia 2009</td>
<td>+</td>
</tr>
<tr>
<td>Hazazi 2010</td>
<td>+</td>
</tr>
<tr>
<td>Hunt 1997</td>
<td>-</td>
</tr>
<tr>
<td>Levi 2007</td>
<td>+</td>
</tr>
<tr>
<td>Ng 2013</td>
<td>+</td>
</tr>
<tr>
<td>Otero-Estevez 2015</td>
<td>+</td>
</tr>
<tr>
<td>Quintero 2014</td>
<td>+</td>
</tr>
<tr>
<td>Terhaar 2012</td>
<td>+</td>
</tr>
<tr>
<td>Vleugels 2015</td>
<td>+</td>
</tr>
<tr>
<td>Wong 2015</td>
<td>+</td>
</tr>
</tbody>
</table>

- **High**
- **Unclear**
- **Low**
eFigure 3: Methodological quality of included studies graph: review authors' judgments about each item presented as percentages across all included studies.
eFigure 4: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity of FIT for diagnosis of a) colorectal cancer; b) advanced neoplasia.

Each circle represents a study, with the size being proportional to the study size. The curve represents the summary receiver operating characteristic curve for FIT. The square represents
the summary estimate of test performance and the zone outlines surrounding it represent the 95% confidence and 95% prediction regions of this summary estimate respectively.
eFigure 5: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies with low risk of bias or concerns for applicability (QUADAS-2). a) diagnosis of colorectal cancer; b) diagnosis of advanced neoplasia.
Each circle represents a study, with the size being proportional to the study size. The curve represents the summary receiver operating characteristic curve for FIT. The square represents the summary estimate of test performance and the zone outlines surrounding it represents the 95% confidence and 95% prediction regions of this summary estimate respectively.
eFigure 6: Hierarchical summary receiver operating curve (HSROC) plot of sensitivity versus specificity for performance of FIT in studies used quantitative FIT with cut off value less than 25μg/g only in patients with familial risk of CRC a) diagnosis of colorectal cancer; b) diagnosis of advanced neoplasia.
Each circle represents a study, with the size being proportional to the study size. The curve represents the summary receiver operating characteristic curve for FIT. The square represents the summary estimate of test performance and the zone outlines surrounding it represents the 95% confidence and 95% prediction regions of this summary estimate respectively.
eFigure 7: Fagan’s nomogram plots
Prior Prob (%) = 1
LR_Positive = 10
Post_Prob_Pos (%) = 8
LR_Negative = 0.08
Post_Prob_Neg (%) = 0
Fagan’s nomogram plot to explore the clinical utility of FIT for detection of colorectal cancer and advanced neoplasia in increased-risk individuals with a pre-test probability (prevalence) equal to 0.8% and 10.2% respectively.
eTable 1: Synopsis of results from sensitivity analyses depending on risk of bias, patient population and reference standard used for the diagnosis of colorectal cancer and advanced neoplasia.

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Diagnostic odds ratio (95% CI)</th>
<th>Positive predictive value, % (95% CI)</th>
<th>Negative predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity analysis for FIT for diagnosis of colorectal cancer (CRC), including only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At low risk of bias</strong></td>
<td>5</td>
<td>3580</td>
<td>97(62 to 100)</td>
<td>91(89 to 93)</td>
<td>11.2(8.3 to 15.1)</td>
<td>0.03(0.00 to 0.60)</td>
<td>354(15 to 8139)</td>
<td>8</td>
</tr>
<tr>
<td>Reporting estimates for patients with familial risk of CRC</td>
<td>5</td>
<td>2401</td>
<td>86(31 to 99)</td>
<td>91(89 to 93)</td>
<td>10.0(5.8 to 17.5)</td>
<td>0.16(0.02 to 1.48)</td>
<td>64(4 to 1010)</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>Using colonoscopy as reference standard</strong></td>
<td>6</td>
<td>4152</td>
<td>97(31 to 100)</td>
<td>91(89 to 93)</td>
<td>10.8(8.0 to 14.6)</td>
<td>0.04(0.00 to 2.02)</td>
<td>285(4 to 19329)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Using quantitative FIT with a cut off value &lt;25μg/g in patients with familial risk for CRC</strong></td>
<td>4</td>
<td>1829</td>
<td>91(51 to 99)</td>
<td>92(88 to 94)</td>
<td>10.8(6.6 to 17.8)</td>
<td>0.1(0.01 to 0.8)</td>
<td>112(9 to 1421)</td>
<td>9.4</td>
</tr>
</tbody>
</table>

**Sensitivity analysis for FIT for diagnosis of advanced neoplasia (AN), including only studies**

<p>| At low risk of bias | 5 | 3580 | 44(34 to 53) | 94(92 to 96) | 7.7(5.1 to 11.7) | 0.6(0.5 to 1 to 0.71) | 13(8 to 22) | 45.4 | 93.7 |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting estimates for patients</td>
<td>11</td>
<td>4168</td>
<td>46(37 to 56)</td>
<td>93(90 to 95)</td>
<td>6.6(4.9 to 8.7)</td>
<td>0.58(0.48 to 0.69)</td>
<td>11(8 to 17)</td>
</tr>
<tr>
<td>with familial risk of CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4566</td>
<td>47(37 to 58)</td>
<td>93(91 to 95)</td>
<td>6.9(4.9 to 9.7)</td>
<td>0.56(0.46 to 0.69)</td>
<td>12(8 to 20)</td>
</tr>
<tr>
<td>Using colonoscopy as reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard</td>
<td></td>
<td>2701</td>
<td>47(39 to 55)</td>
<td>94(91 to 96)</td>
<td>8.1(5.9 to 11.2)</td>
<td>0.56(0.49 to 0.65)</td>
<td>14(10 to 20)</td>
</tr>
<tr>
<td>Using quantitative FIT with a cut off</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>value &lt;25 μg/g in patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with familial risk for CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl: confidence interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a post-hoc analysis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### eTable 2: Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the quality of the body evidence regarding the diagnostic accuracy of FIT

**Question 1: Should FIT be used to diagnose colorectal cancer in asymptomatic individuals at increased risk of colorectal cancer?**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study design</th>
<th>Factors that may decrease quality of evidence</th>
<th>Effect per 1,000 patients tested</th>
<th>Test accuracy QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True positives</strong></td>
<td>7 studies (4790 patients) cross-sectional (cohort type accuracy study)</td>
<td>Risk of bias: not serious; Indirectness: very serious; Inconsistency: serious; Imprecision: none</td>
<td>7 (4 to 8)</td>
<td>⬤⬤⬤ ✔️ VERY LOW</td>
</tr>
<tr>
<td><strong>False negatives</strong></td>
<td>7 studies (4790 patients) cross-sectional (cohort type accuracy study)</td>
<td>Risk of bias: not serious; Indirectness: very serious; Imprecision: none</td>
<td>1 (0 to 4)</td>
<td></td>
</tr>
<tr>
<td><strong>True negatives</strong></td>
<td>7 studies (4790 patients) cross-sectional (cohort type accuracy study)</td>
<td>Risk of bias: not serious; Indirectness: not serious; Imprecision: none</td>
<td>903 (883 to 913)</td>
<td>⬤⬤ ○ LOW</td>
</tr>
<tr>
<td><strong>False positives</strong></td>
<td>7 studies (4790 patients) cross-sectional (cohort type accuracy study)</td>
<td>Risk of bias: not serious; Indirectness: not serious; Imprecision: none</td>
<td>89 (79 to 109)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93 (95% CI: 0.53 to 0.99)</td>
<td>0.91 (95% CI: 0.89 to 0.92)</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

CI: confidence interval.

* This domain was downgraded by 2 points due to heterogeneity in population (mixed set of studies including patients with personal and familial risk), index test (one study with qualitative FIT) and reference standard utilized (one study using delayed colonoscopy).
This domain was downgraded by 2 points due to wide variance of point estimates across studies and minimal overlap of confidence intervals.

This domain was downgraded by 1 point, due to the small number of patients with events included (TP+FN). Wide 95% confidence intervals were not considered to contribute to imprecision due to the low prevalence of CRC.
**Question 2:** Should FIT be used to diagnose advanced neoplasia in asymptomatic individuals at increased risk of colorectal cancer?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>0.48 (95% CI: 0.39 to 0.57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>0.93 (95% CI: 0.91 to 0.94)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Factors that may decrease quality of evidence</th>
<th>Effect per 1000 patients tested</th>
<th>Test accuracy QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td>Indirectness</td>
<td>Inconsistency</td>
<td>Imprecision</td>
</tr>
<tr>
<td>True positives</td>
<td>12 studies</td>
<td>6204 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td>False negatives</td>
<td>12 studies</td>
<td>6204 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td>True negatives</td>
<td>12 studies</td>
<td>6204 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td>False positives</td>
<td>63 (54 to 81)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval.
a Based on the Quality Assessment of Diagnostic Accuracy Studies version 2 tool, 6 out of 12 studies were assessed at high risk of bias.
b This domain was downgraded by 2 points due to heterogeneity in population (mixed set of studies including patients with personal and familial risk), index test (4 studies with qualitative FIT) and reference standard utilized (3 studies using delayed colonoscopy).
c This domain was downgraded by 2 points due to wide variance of point estimates across studies and minimal overlap of confidence intervals.
d This domain was downgraded by 1 point due to increased projected range of patients testing as false-negative, when assuming a prevalence of 10.2%.
**Question 3:** Should FIT be used to diagnose colorectal cancer in asymptomatic individuals with familial risk for colorectal cancer?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.86 (95% CI: 0.31 to 0.99)</td>
<td>0.91 (95% CI: 0.89 to 0.93)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

### Factors that may decrease quality of evidence

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Effect per 1,000 patients tested</th>
<th>Test accuracy QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>5 studies 2401 patients</td>
<td>Cross-sectional (cohort type accuracy study)</td>
<td>Serious a</td>
<td>Serious a</td>
<td>Very serious c</td>
<td>Serious d</td>
</tr>
<tr>
<td>False negatives</td>
<td>5 studies 2401 patients</td>
<td>Cross-sectional (cohort type accuracy study)</td>
<td>Serious a</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>True negatives</td>
<td>5 studies 2401 patients</td>
<td>Cross-sectional (cohort type accuracy study)</td>
<td>Serious a</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>False positives</td>
<td>5 studies 2401 patients</td>
<td>Cross-sectional (cohort type accuracy study)</td>
<td>Serious a</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

CI: confidence interval.

a Based on the Quality Assessment of Diagnostic Accuracy Studies version 2 tool, two out of five studies were assessed at high risk of bias.

b This domain was downgraded by 1 point due to heterogeneity in index test (1 study with qualitative FIT) and reference standard utilized (1 study using delayed colonoscopy).

c This domain was downgraded by 2 points due to wide variance of point estimates across studies and minimal overlap of confidence intervals.

d This domain was downgraded by 1 point, due to the small number of patients with events included (TP+FN). Wide 95% confidence intervals were not considered to contribute to imprecision due to the low prevalence of CRC.
Question 4: Should FIT be used to diagnose advanced neoplasia in asymptomatic individuals with familial risk for colorectal cancer?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>0.46 (95% CI: 0.37 to 0.56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>0.93 (95% CI: 0.90 to 0.95)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Factors that may decrease quality of evidence:

- Risk of bias
- Indirectness
- Inconsistency
- Imprecision
- Publication bias

<table>
<thead>
<tr>
<th>True positives</th>
<th>11 studies 4168 patients</th>
<th>cross-sectional (cohort type accuracy study)</th>
<th>very serious (^a)</th>
<th>very serious (^b)</th>
<th>serious (^d)</th>
<th>none</th>
<th>47 (38 to 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False negatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55 (45 to 64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True negatives</th>
<th>11 studies 4168 patients</th>
<th>cross-sectional (cohort type accuracy study)</th>
<th>very serious (^a)</th>
<th>not serious</th>
<th>not serious</th>
<th>none</th>
<th>835 (808 to 853)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63 (45 to 90)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

\(^a\) Based on the Quality Assessment of Diagnostic Accuracy Studies version 2 tool, 6 out of 11 studies were assessed at high risk of bias.

\(^b\) This domain was downgraded by 1 point due to heterogeneity in index test (4 studies with qualitative FIT) and reference standard utilized (3 studies using delayed colonoscopy).

\(^c\) This domain was downgraded by 2 points due to wide variance of point estimates across studies and minimal overlap of confidence intervals.

\(^d\) This domain was downgraded by 1 point due to increased projected range of patients testing as false-negative, when assuming a prevalence of 10.2%.

Question 5: Should FIT be used to diagnose colorectal cancer in asymptomatic individuals with personal history of colorectal cancer?
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study design</th>
<th>Factors that may decrease quality of evidence</th>
<th>Test accuracy QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk of bias</td>
<td>Indirectness</td>
</tr>
<tr>
<td>True</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>False negatives</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>True negatives</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>False positives</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

CI: confidence interval.

\(^{a}\) This domain was downgraded by 1 point because we expect that other studies may have different estimates.
b. This domain was downgraded by 2 points, due to the small number of patients with events included (TP+FN) and small sample size.

c. This domain was downgraded by 2 points due to small sample size.
**Question 6:** Should FIT be used to diagnose advanced neoplasia in asymptomatic individuals with personal history of colorectal cancer?

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>0.32 to 0.76</th>
<th><strong>Prevalence</strong></th>
<th>9.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>0.89 to 0.92</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Factors that may decrease quality of evidence</th>
<th>Test accuracy QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk of bias</td>
<td>Indirectness</td>
</tr>
<tr>
<td><strong>True positives</strong></td>
<td>2 studies (1039 patients)</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td><strong>False negatives</strong></td>
<td>2 studies (1039 patients)</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td><strong>True negatives</strong></td>
<td>2 studies (1039 patients)</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
<tr>
<td><strong>False positives</strong></td>
<td>2 studies (1039 patients)</td>
<td>cross-sectional (cohort type accuracy study)</td>
</tr>
</tbody>
</table>

\(^a\) This domain was downgraded by 1 point due to heterogeneity in population (mixed set of studies including patients with personal history of CRC or advanced adenomas).

\(^b\) This domain was downgraded by 2 points due to wide variance of point estimates across studies and no overlap of confidence intervals.

\(^c\) This domain was downgraded by 2 points due to increased projected range of patients testing as false-negative, when assuming a prevalence of 9.8%, and due to small sample.

\(^d\) This domain was downgraded by 1 point due to small sample size.