Test Characteristics of Fecal Immunochemical Tests for Colorectal Cancer and Advanced Adenomas Based on Location: A Systematic Review

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BACKGROUND

- The fecal immunochemical test (FIT) is the most common test used worldwide for colorectal (CRC) cancer screening.
- Test characteristics for FIT for CRC and advanced adenomas (AA) vary based on threshold / cutoff and may – for any threshold – vary based on location within the colon.
- The published literature on FIT test characteristics for proximal versus distal CRC and AA is both heterogeneous - in terms of specific FIT used and threshold for positivity - and inconsistent.
- Knowing test characteristics by location within the colorectum and individual patient risk factors for advanced neoplasia of the proximal or distal colon could affect both whether FIT is used for an individual patients and its effectiveness in population-based screening.

STUDY OBJECTIVE

- Quantify test characteristics of FIT for both CRC and AA based on location (proximal, distal) within the colorectum

METHODS

- Study design: systematic review and meta-analysis
- Data sources: Ovid, MEDLINE, PubMed, EMBASE, ClinicalTrials.gov, Cochrane Library
  - – From inception to 2/21/22
  - – Reference lists of selected full text and review articles
- Study selection: English language studies quantifying FIT test characteristics in which:
  - – Colonoscopy was the reference standard
  - – FIT test characteristics for CRC and/or AA were available by segment (proximal / distal)
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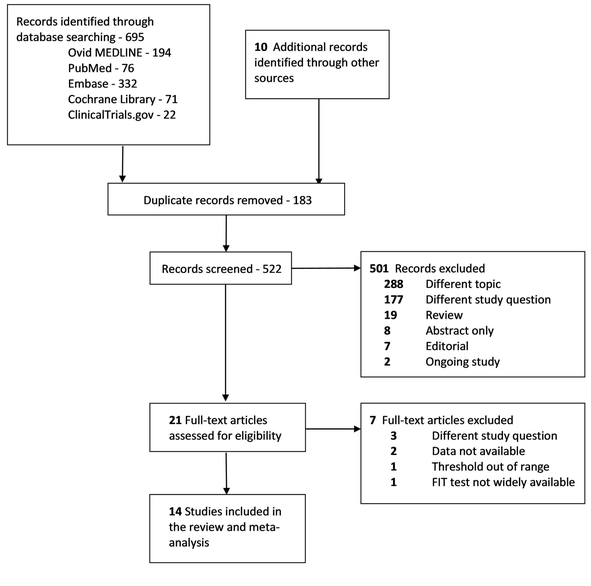
- Two authors independently reviewed all citations to identify relevant studies, abstracted study characteristics and numerical data, and assessed study quality using the QUADAS-2 criteria
  - – All disagreements were resolved after discussion
- Analysis: For all summary-level estimated, we:
  - – Used a univariate generalized linear mixed model to simultaneously estimate pooled measures of sensitivity and specificity
    - Separately for CRC and AA
    - At various thresholds (ug/g)
  - – Compared proximal and distal sensitivity for CRC and AA in pre-specified subgroups
    - Using the “between groups” analysis of variance test

RESULTS

- From 705 titles identified from 5 electronic databases and selected reference lists:
  - – Screened 522 unique citations and abstracts (when available)
  - – Excluded 501 because of unrelated content or absence of original data
  - – Reviewed 21 full text articles
    - Excluded 7 of these for various reasons (see Figure 1 - Flow Diagram)
  - – Selected 14 articles for analysis

Figure 1: Flow Diagram for Study Identification and Inclusion



DESCRIPTIVE RESULTS

- 34,790 participants, 10 FIT tests, 30 FIT analytic groups
- Mean participant age (11 studies) – 59.4 years
- A mean of 64.3% of participants were women
- Excluding 87 participants with CRC and/or AA in both segments resulted in:
  - – 259 with CRC (0.7%) – 94 proximal, 165 distal
  - – 2450 with AA (7.0%) – 1,097 proximal, 1,371 distal

QUALITATIVE RESULTS

- All studies were considered high-quality with low-risk for bias (Figure 2)

Table for Figure 2A.

Q1 Was a consecutive or random sample of patients enrolled?
Q2 Was a case-control design avoided?
Q3 Did the study avoid inappropriate exclusions?
Q6 Were the index test results interpreted without knowledge of the results of the reference standard?
Q7 If a threshold was used, was it pre-specified?
Q10 Is the reference standard likely to correctly classify the target condition?
Q11 Were the reference standard results interpreted without knowledge of the results of the index test?
Q14 Was there an appropriate interval between index test(s) and reference standard?
Q15 Did all patients receive a reference standard?
Q16 Did all patients receive the same reference standard?
Q17 Were all patients included in the analysis?

Figure 2A:

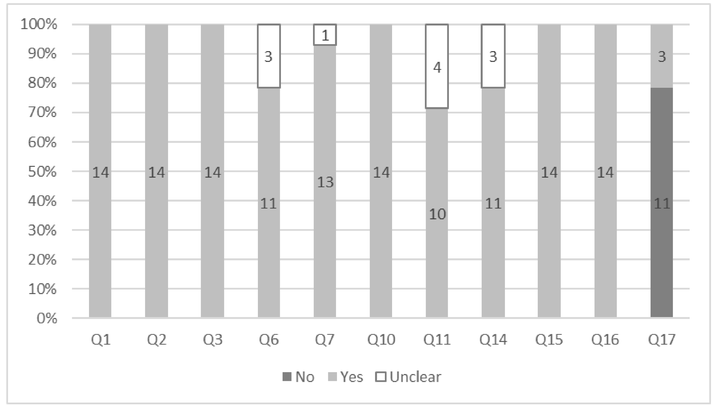
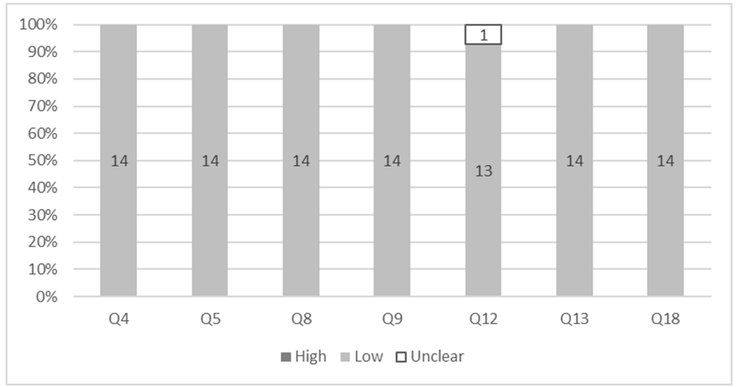


Table for Figure 2B:

Q4 Could the selection of patients have introduced bias?
Q5 Are there concerns that the included patients do not match the review question?
Q8 Could the conduct or interpretation of the index test have introduced bias?
Q9 Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Q12 Could the reference standard, its conduct, or its interpretation have introduced bias?
Q13 Are there concerns that the target condition as defined by the reference standard does not match the review question?
Q18 Could the patient flow have introduced bias?

Figure 2B:



QUANTITATIVE RESULTS – See Table 3

- For SENSITIVITY - I^2 values for heterogeneity were 0% for proximal CRC, and ranged from 0% to 53% for distal CRC, from 57% to 82% for proximal AA, and from 0% to 84% for distal AA.
- For SPECIFICITY – I^2 values were all ≥ 98%
- For both CRC and AA, test characteristics varied by threshold, but not by location for any threshold category.
- For AA sensitivity, there was a 10% absolute difference – higher for distal AAs - for the 10ug/g and ≥ 20ug/g thresholds, the latter of which just missed statistical significance (P=0.0518).

Table 3: Quantitative Results

				Univariate Summary Results for Colorectal Cancer (CRC)						
				Proximal			Distal			P-value[1]
Threshold µg/g	N of Subjects	N of CRC Proximal	N of CRC Distal	N of Studies	Sensitivity [95% CI]	Specificity [95% CI]	N of Studies	Sensitivity [95% CI]	Specificity [95%CI]	Proximal vs distal (sensitivity only)
<10 (all studies)	4074	7	21	3	0.86 [0.42; 0.98]	0.90 [0.82; 0.94]	2	0.76 [0.54; 0.90]	0.91 [0.81; 0.96]	----
<10 excluding Graser 2009)	3789	6	21	2	0.83 [0.37; 0.98]	0.91 [0.81; 0.96]	2	0.76 [0.54; 0.90]	0.91 [0.81; 0.96]	0.71
10 (all studies)	13476	34	85	6	0.74 [0.56; 0.86]	0.93 [0.88; 0.96]	5	0.74 [0.57; 0.86]	0.91 [0.87; 0.94]	----
10 (excluding Levy 2014)	13259	33	85	5	0.76 [0.58; 0.87]	0.91 [0.87; 0.94]	5	0.74 [0.57; 0.86]	0.91 [0.87; 0.94	0.86
11-19	14882	43	104	6	0.8106 [0.52; 0.94]	0.93 [0.88; 0.95]	6	0.81 [0.68; 0.90]	0.93 [0.88; 0.95]	0.99
>=20	18675	81	142	10	0.75 [0.65; 0.83]	0.95 [0.93; 0.97]	10	0.76 [0.68; 0.82]	0.95 [0.93; 0.97]	0.90
				Univariate Summary Results for Advanced Adenoma (AA)						
				Proximal			Distal			
Threshold µg/g	N of Subjects	N of AA Proximal	N of AA Distal	N of Studies	Sensitivity [95%CI]	Specificity [95% CI]	N of Studies	Sensitivity [95% CI]	Specificity [95% CI]	
<10	4074	112	239	3	0.25 [0.14; 0.40]	0.90 [0.82; 0.94]	3	0.32 [0.26; 0.38]	0.90 [0.82; 0.94]	0.38
10	13805	370	552	7	0.21 [0.12; 0.35]	0.94 [0.90; 0.96]	7	0.31 [0.23; 0.40]	0.94 [0.89; 0.96]	0.21
11-19	14882	449	664	6	0.26 [0.17; 0.39]	0.93 [0.88; 0.95]	6	0.32 [0.23; 0.42]	0.939 [0.88; 0.95]	0.51
>=20	19750	942	1172	14	0.14 [0.08; 0.22]	0.95 [0.93; 0.96]	14	0.24 [0.18; 0.32]	0.95 [0.93; 0.96]	0.0518

Note: Univariate summary estimates are shown for both sensitivity and specificity with 95% confidence intervals in brackets. Estimates were obtained using a random effects logistic regression model.
[1]P-value for difference between proximal and distal sensitivity from random effects logistic regression model.

STUDY LIMITATIONS

- Only English language studies were included
- Incomplete reporting limited quality assessment of some studies
- Performance characteristics are for 1-time rather than programmatic testing

CONCLUSION

- In this systematic review of FIT test characteristics for CRC and AA based on location in the colon, we found:
  - – High quality studies
  - – Test characteristics varied by threshold (as expected)
  - – For thresholds of 10 ug/g and ≥ 20 ug/g, AA sensitivity was numerically higher by an absolute difference of 10% for distal AAs, with the latter threshold nearly achieving statistical significance.

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