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Which Fecal Immunochemical Test Should I Choose?

Jeanette M. Daly[1], Yinghui Xu, MS[1], and Barcey T. Levy[1]

Abstract

Objectives: To summarize the fecal immunochemical tests (FITs) available in the United States, the 2014 pathology proficiency testing (PT) program FIT results, and the literature related to the test characteristics of FITs available in the United States to detect advanced adenomatous polyps (AAP) and/or colorectal cancer (CRC). **Methods:** Detailed review of the Food and Drug Administration's Clinical Laboratory Improvement Amendments (CLIA) database of fecal occult blood tests, the 2014 FIT PT program results, and the literature related to FIT accuracy. **Results:** A search of the CLIA database identified 65 FITs, with 26 FITs available for purchase in the United States. Thirteen of these FITs were evaluated on a regular basis by PT programs, with an overall sensitivity of 99.1% and specificity of 99.2% for samples spiked with hemoglobin. Automated FITs had better sensitivity and specificity than CLIA-waived FITs for detection of AAP and CRC in human studies using colonoscopy as the gold standard. **Conclusion:** Although many FITs are available in the United States, few have been tested in proficiency testing programs. Even fewer have data in humans on sensitivity and specificity for AAP or CRC. Our review indicates that automated FITs have the best test characteristics for AAP and CRC.

Keywords

health promotion, fecal immunochemical test, fecal occult blood test, colorectal cancer screening, proficiency testing programs

Introduction

Fecal occult blood tests (FOBTs) are used to detect small amounts of blood in the stool, which can indicate the presence of advanced adenomatous polyps (AAP) or colorectal cancer (CRC).[1,2] Two types of FOBTs are available—guaiac (gFOBT) and fecal immunochemical tests (FITs). There is general agreement that FITs have better test characteristics and are easier for patients to use compared with gFOBTs.[1,3-7] However, the many brands of FIT on the market and limited information on test characteristics for the outcomes of AAP or CRC make it difficult to decide which FIT to choose.

The gFOBT was developed in the 1860s for CRC screening.[8,9] FITs were developed in the 1970s and use antibodies directed against the globin component of hemoglobin to detect blood in the stool.[9-11] The US Preventive Services Task Force, the American College of Gastroenterology, and the American Cancer Society promote the use of FIT over gFOBT in CRC screening.[12-15] FITs are preferred by patients over colonoscopy[3,4] and there are no dietary or medicine restrictions, unlike with the gFOBT.[1,5,6] Modeling studies indicate there is no difference in life-years gained when comparing a CRC screening strategy of annual FIT testing with a colonoscopy every 10 years.[16] FITs use 2 immunoassay techniques: an automated laboratory instrument-based immunoturbidometric test and a lateral flow immunochromatographic analysis for point-of-care testing.[1]

There are numerous FIT products available. The purposes of this research were to summarize: (1) the FITs currently available in the United States based on the Food and Drug Administration (FDA) and product websites, (2) the 2014 pathology proficiency testing (PT) program results regarding FITs, and (3) the literature related to the test characteristics of FITs available in the United States to detect AAP and/or CRC.

[1]The University of Iowa, Iowa City, IA, USA

Corresponding Author:
Jeanette M. Daly, Department of Family Medicine, Carver College of Medicine, The University of Iowa, 01290-F PFP, 200 Hawkins Drive, Iowa City, IA 52242, USA.
Email: jeanette-daly@uiowa.edu

Background

FDA Website and FOBT Approval via the 510(k) Process

The US Department of Health and Human Services FDA website has a section for medical devices, the Clinical Laboratory Improvement Amendments (CLIA) database, that lists the commercially marketed test systems catalogued by the FDA since 2000, as well as those catalogued by the Centers for Disease Control and Prevention prior to that time (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/search.cfm). This database lists FOBTs that have been cleared by the FDA and associated documentation.

FDA FOBT Test Complexity

CLIA legislation passed by Congress in 1988 was established to ensure accuracy, reliability, and timeliness of patient test results regardless of where the test was performed.[17] FOBTs, both waived and moderate complexity, are classified as class II devices. Waived tests are "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result."[17] To perform waived tests, the healthcare provider needs to have a CLIA Certificate of Waiver. Moderate complexity tests have to be analyzed in a certified pathology laboratory. Class indicates the intended use of the device and the risk the device poses to a patient with class I being the least risk and class III the greatest risk. For class II tests, a 510(k) application to the FDA is required for clearance and then marketing.

All certified pathology laboratories are required to participate in a PT program for all analytes they test for. The Centers for Medicare & Medicaid Services (CMS), through CLIA, regulates approximately 252 000 laboratory entities where FOBTs are analyzed.[18]

FDA Document Number

The FDA requires a 510(k) application to be submitted prior to marketing and selling of FOBTs. The 510(k) must demonstrate the FOBT is substantially equivalent to a device already legally marketed. An application submitter must compare their FOBT to one or more similarly marketed devices to support their substantial equivalency claims. The FDA then determines if the data provided supports the claim of substantial equivalence and categorizes the FOBT as a new device, substantially equivalent for marketing in the United States, or as a device modification. Listed on the 510(k) are the predicate device names and numbers, which indicate the device is safe and effective/substantially equivalent to its predicate. Contrary to what one might see on company websites, the FDA does not "approve" any FOBTs, but provides clearance after review of a 510(k) application.

Methods

The University of Iowa Institutional Review Board reviewed this project and determined it was not human subjects research. Data were collected and summarized from the FDA CLIA database, all CMS-approved PT programs in the United States for the calendar year 2014, and a detailed, literature review on FIT characteristics published in the English language where colonoscopy was used as the gold standard.

FDA CLIA Database

The CLIA database was searched and 122 FOBTs were listed as of July 22, 2016. For each FOBT, a search of the Internet using the name of the product and manufacturer, guaiac, fecal immunochemical, and fecal occult blood test was conducted to determine whether the product was a gFOBT or a FIT. If the product could not be found on the Internet, a search of PubMed was conducted.

Proficiency Testing Programs

Pathology laboratories participate in PT programs to ensure that procedures for analyte testing give accurate results. Currently, there are 7 PT programs in the United States that distribute samples for FOBTs.[19] PT program 2014 data were obtained from the programs' Internet posting or customer service. The programs included (1) American Academy of Family Physicians Proficiency Testing (AAFP-PT), (2) American Association of Bioanalysts (AAB) Proficiency Testing Service, (3) American College of Physicians (ACP) Medical Laboratory Evaluation (MLE) Program, (4) American Proficiency Institute (API), (5) the College of American Pathologists (CAP)–Surveys (large laboratories), (6) the CAP External Comparative Evaluation for Laboratories EXCEL (small laboratories), and (7) Wisconsin State Laboratory of Hygiene (WSLH). Results that included specific FOBT test system/manufacturer names were obtained from 6 of the 7 PT programs. The AAFP-PT testing service was only able to provide the data in aggregate for manufacturers. Thus, their results were not included in this analysis.

Data from PT programs did not indicate the superiority or inferiority of instruments, reagents, or other materials.[20] PT is required on all analytes conducted in pathology laboratories that are not waived under CLIA. However, if waived tests are run in a CLIA-certified lab, then it is to the advantage of the laboratories to also test those analytes that are waived.[21] If waived FITs are performed in a physician's office, a CLIA Certificate of Waiver must be obtained and PT is not required.[17]

gFOBTs were eliminated from the PT sensitivity/specificity analysis because FITs are now preferred for CRC

screening.[12,13,15] The PT review included 15 distinct FITs and a total of 12 730 samples.

Literature Review

As of March 11, 2016, there were 447 publications listed in PubMed using the search term "fecal immunochemical test." There were 72 articles for review after excluding those not written in English, non-research articles and research that did not assess FIT accuracy for AAP and/or CRC in human subjects. After reviewing these abstracts, 26 were found to have information on the accuracy of FITs, with all subjects undergoing a colonoscopy or flexible sigmoidoscopy after FOBT collection.[22-47] Two authors (JMD, BTL) reviewed these papers independently to find the results of FIT test accuracy for AAP and/or CRC. After reviewing the articles, those that presented results of FITs no longer on the market, such as FlexSure OBT and HemeSelect, were excluded,[23,24,40,41] not used in the United States,[30,34,35] not named in the paper,[36] and those where colonoscopy was not used on all subjects.[24,36,40,41] For papers presenting sequential results of incremental study populations,[26,31,32,37,39,42,45,46] we chose the paper with the largest subject number[26,39,46] since that provided the most reliable estimates of test accuracy for AAP and/or CRC. Thus, 13 papers were found in the English language on test characteristics of FITs, using colonoscopy as the gold standard.[22,25-29,33,38,39,43,44,46,47]

Data Analysis

The PT programs' results for each FIT brand evaluated in 2014 were reviewed in detail and summarized. At each testing interval, 2 or 3 blinded synthetic fecal samples were sent to participating pathology laboratories and analyzed for the presence of spiked hemoglobin with FITs used in their laboratory. Results were reported back as either positive or negative for hemoglobin. PT programs reported whether the results were correct or incorrect for each FIT and the overall percentages correct/incorrect were tallied across FIT devices. The test system/manufacturer sensitivity and specificity for synthetic fecal samples and the overall sensitivity and specificity for each FIT device across testing programs, along with 95% Agresti-Coull binomial proportion confidence intervals were calculated,[48] using SAS version 9.4 (SAS, Inc, Cary, NC).

Results

FDA CLIA Database

The initial FIT listed in the CLIA database was the SmithKline FlexSure OBT, which is no longer on the market. Historically, CMS reports that early FITs were considered substantially equivalent to the first gFOBT.[49]

Based on the search for FOBTs in the CLIA database, 122 FOBT analytes with 60 distinct 510(k) numbers were retrieved; 65 were FITs, 56 were gFOBT, and one was an orthotolidine reagent method (see Figure 1). Of the 65 FITs listed, 60 are CLIA-waived, and 5 are moderate complexity, non-CLIA-waived (See Table 1). There are 25 distinct 510(k) numbers for the 60 CLIA-waived FITs and 3 distinct 510(K) numbers for the automated FITs. Only 2 automated FITs are sold in the US Test systems with the same 510(k) numbers have the same manufacturer (see Table 1). For example, Immunostics, Inc, is listed as the test system/manufacturer for these 4 FITs, hema-screen SPECIFIC Immunochemical Fecal Occult Blood Test, Consult Diagnostics iFOBT, Henry Schein OneStep+ iFOBT, and Select Diagnostics Immunochemical Fecal Occult Blood Test. These 4 FITs have identical 510(k) numbers but are sold under different labels. Three of these 4 FITs are included in the PT program results.

Of the 60 CLIA-waived FITs, 24 FITs with 16 unique 510(k) numbers are available for purchase in the United States (see Table 2). The 5 moderate complexity FITs have 3 unique 510(k) numbers, but only 2 are available in the United States (OC-Auto Micro 80 and OC-Sensor Diana). These 2 use identical liquid-vial collection containers, reagent, calibrator, and controls, but the analyzers have different throughput rates.

Proficiency Testing Programs' Accuracy of FITs

There were 57 433 synthetic stool samples used for analysis of gFOBTs and FITs for the 7 PT programs in 2014. However, no information is available on the types of FOBTs analyzed for the 2552 AAFP-PT samples, leaving 54 881 samples available from 6 PT programs for analysis. Of these, 12 730 (23%) were FITs and 42 151 (77%) were gFOBTs. Of the 12,730 FIT samples, the following FITs were most frequently evaluated: (1) Hemosure One-Step Immunological Fecal Occult Blood Test (30%), (2) Beckman Coulter Hemoccult ICT (27%), (3) OC-Light iFOB (12%), (4) OC-Auto Micro 80 (12%), and (5) QuickVue IFOB (9%). These 5 tests accounted for 90.7% of the FITs evaluated. PT programs evaluated 13 FITs, 11 (9 distinct 510(k) numbers) of the 24 CLIA-waived FITs and 2 automated FITs (see Table 3).

For the waived FITs, sensitivity ranged from 93.0% for Enterix Insure Fecal Immunochemical Test to 100% for 5 test system/manufacturers and specificity ranged from 96.6% for BTNX, Inc Rapid Response Fecal Occult Blood Test to 100% for 5 test system/manufacturers (see Table 3). The automated FIT, OC-Sensor Diana, had a sensitivity of 100% and specificity of 100%, with similar results for the OC-Auto Micro 80.

Literature Review

As described in the Methods section, 13 studies presented the accuracy of FITs for AAP and/or CRC, using colonoscopy

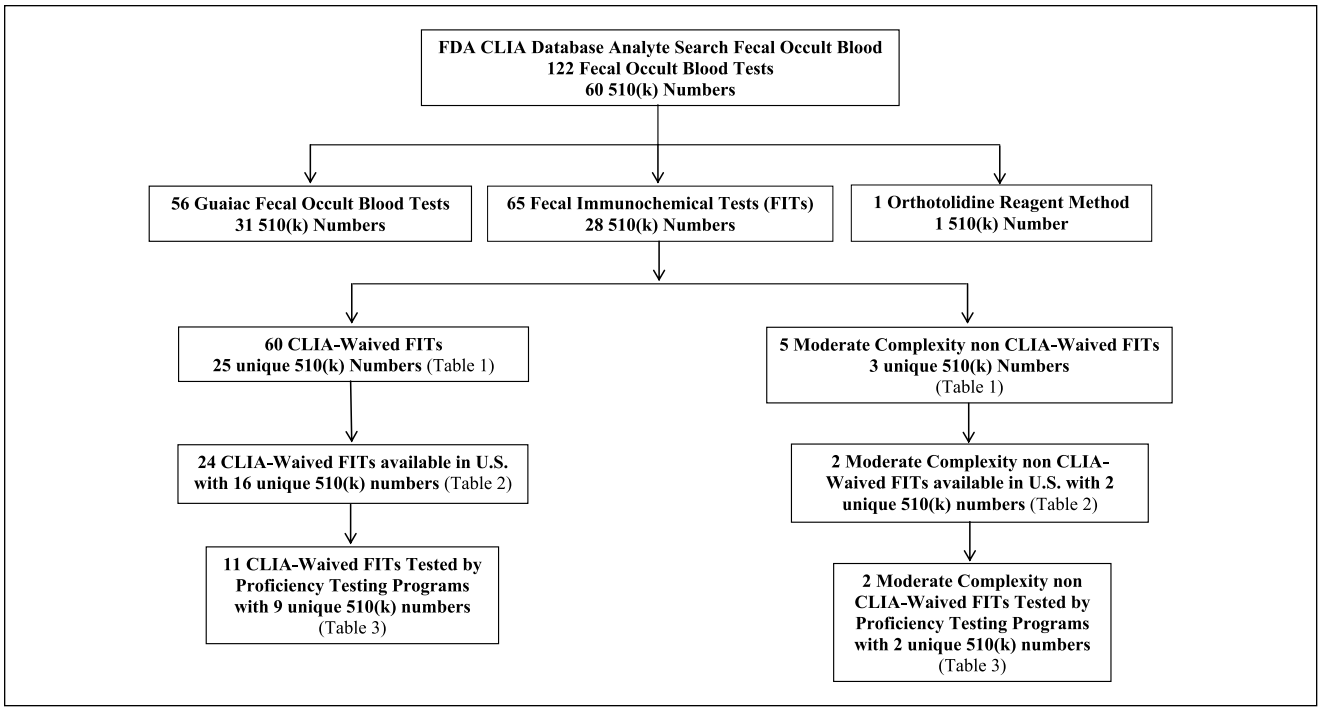

Figure 1. FDA CLIA database fecal occult blood search focusing on distinct FITs available in the United States and number tested by proficiency testing programs. FDA, Food and Drug Administration; CLIA, Clinical Laboratory Improvement Amendments; FIT, fecal immunochemical test.

as the gold standard. Information on FIT accuracy in human studies is available for only 4 CLIA-waived FITs on the US market (see Table 2).[26,27,33,44,46] These studies were heterogeneous, conducted on screening or mixed screening, and high-risk populations in Canada,[44] China,[46] Germany,[26] Taiwan,[27] and the United States.[33] The outcomes differed across studies and were typically either AAP or CRC, or the 2 combined. Table 2 shows which products were tested, the size of the study population, the test detection limits, and the sensitivities, specificities, and positive predictive value for the outcome. In general, the sensitivity for any specific outcome varied within product across studies and by outcome across products. The sensitivity for CRC or AAP reported by Levy, et al[33] was 4.0% for the Polymedco OC-Light, whereas the much larger study by Chiu et al[27] reported 28% sensitivity for AAP and 78.6% for CRC.[27] The Levy, et al study had the FIT mailed in for testing, and the Chiu et al study had the specimen collected the day before the colonoscopy, stored in the refrigerator, and brought into the clinic the day of the colonoscopy which may have affected the results. The sensitivity reported for advanced neoplasms or screening relevant neoplasia for the QuickVue IFOB was 59.6%,[26] for OC-Light FOB was 28%,[27] and for Beckmann Coulter ICT was 23.2%.[44] Corresponding specificities were 70.2%, 93.5%, and 95.8%. There were 2 studies that reported sensitivities separately for AAP and colorectal cancer.[27,46] The Wong et al study using Hemosure One-Step showed sensitivity for CRC of 54.5% and AAP of 33.1%.[46]

For the 2 automated FITs, there were 8 studies assessing FIT accuracy (see Table 2).[22,25,28,29,38,39,43,47] Sensitivity for AAP across studies was highly variable, from 25.7%[25] to 49.5.[28] Sensitivity for colorectal cancer varied from 65%[39] to 92.3.[38] For studies reporting the sensitivity for CRC separately from AAP, sensitivities for colorectal cancer were higher than for AAP.

Discussion

Based on our review of the FDA database, there are 26 unique FITs currently on the U.S. market, with 24 waived under CLIA and two automated tests. FITs comprise 23% of the market based on proficiency testing results, with the rest being gFOBT. The 2 automated tests are used quantitatively in many countries in order to adjust the numbers of individuals sent for diagnostic colonoscopy. These are not approved by the FDA for quantitative analysis in the United States.

Of the 26 FITs on the market, 13 with 11 distinct 510(k) numbers were tested in PT programs. Most FITs tested extremely well with sensitivities for 11 of 13 FITs at 99% or higher and specificities for 10 of the 13 FITs at 99.4% or higher. However, samples used by PT programs are

Table 1. FDA 510(k) Document Number and Test System/Manufacturer[a] for CLIA-Waived and Moderate Complexity FITs.[b]

No. FITs	No. 510(k) numbers	510(k) Document Number	Test System/Manufacturer	Effective Date (mm/dd/yy)
CLIA-waived FITs				
1	1	E990036	Alfa Scientific Designs Instant-View Fecal Occult Blood Test (Cassette)	07/23/1999
2	2	K002457	ENTERIX INSURE FECAL OCCULT BLOOD TEST	01/31/2001
3		K002457	ENTERIX INSURE FECAL IMMUNOCHEMICAL TEST	10/16/2003
4	3	K021423	ALFA SCIENTIFIC DESIGNS - ISCREEN FECAL OCCULT BLOOD TEST	02/25/2005
5		K021423	QuickVue iFOB Test (Immunochemical Fecal Occult Blood) (Cassette)	11/9/2005
6	4	K041202	Clarity Hemosure One-Step Immunological Fecal Occult Blood Test	03/30/2005
7		K041202	HEMOSURE ONE-STEP FECAL OCCULT BLOOD TEST	09/8/2004
8	5	K041297	Clearview Ultra FOB Test	08/18/2004
9		K041297	OC-Light iFOB Test	03/24/2011
10		K041297	POLYMEDCO POLY STAT OC-LIGHT FOB TEST	08/18/2004
11	6	K051806	Care Fecal Occult Blood Test	10/7/2005
12	7	K052598	Care Diagnostic Clarity IFOB Test	01/26/2010
13		K052598	immoCARE Fecal Occult Blood Test	03/22/2006
14	8	K060463	Consult Diagnostics Immunochemical Fecal Occult Blood Test (iFOBT)	07/8/2010
15		K060463	Henry Schein OneStep+ iFOBT	03/5/2009
16		K060463	Immunostics Inc. hema-screen SPECIFIC Immunochemical Fecal Occult Blood Test	06/15/2006
17		K060463	Select Diagnostics Immunochemical Fecal Occult Blood Test	02/8/2007
18	9	K060930	ENTERIX INSURE II FECAL IMMUNOCHEMICAL TEST	08/3/2006
19		K060930	InSure Quik Fecal Immunochemical Test (F.I.T.)	01/26/2007
20	10	K060953	OcculTech Fecal Occult Blood Rapid Test	09/22/2006
21	11	K061065	CLIAwaived Inc. Rapid Fecal Occult Blood Test	11/9/2009
22		K061065	Teco Rapid Fecal Occult Blood (FOB) Card Test	08/9/2006
23		K061065	BTNX Inc. Rapid Response Immunological Fecal Occult Blood Test (IFOBT)	07/22/2008
24	12	K063673	Innovacon FOB Flipcard Fecal Occult Blood Test	03/7/2007
25	13	K063693	Centralcheck iFOBT Complete Fecal Occult Blood Test	11/16/2010
26		K063693	Forsure One Step Fecal Occult Blood (FOB) Screen Card Test	05/16/2007
27		K063693	GERMAINE LABORATORIES AimStep Immunological Fecal Occult Blood Test (iFOBT)	09/9/2009

(continued)

Table 1. (continued)

No. FITs	No. 510(k) numbers	510(k) Document Number	Test System/Manufacturer	Effective Date (mm/dd/yy)
28		K063693	Germaine Laboratories Compliance Gold iFOB (immunological fecal occult blood)Test	07/1/2008
29		K063693	Healthcare Provider Direct OneStep Fecal Occult Blood (FOB) Screen Card Test	07/22/2008
30		K063693	Inverness Medical Clearview iFOBT Complete Fecal Occult Blood Test	03/1/2010
31		K063693	Jant Pharmacal Accutest Immunological Fecal Occult Blood Test (iFOBT)	12/4/2008
32	14	K070660	Alfa Scientific Designs Fecal Occult Blood (FOB) Self-Test	06/28/2007
33		K070660	Alfa Scientific Designs Instant-View Fecal Occult Blood (FOB) Self-Test (Cassette)	06/28/2007
34		K070660	BTNX Inc. Clarity Fecal Occult Blood (FOB) Self Test	10/5/2007
35		K070660	BTNX Inc. Know Fecal Occult Blood (FOB) Self Test	10/5/2007
36		K070660	BTNX Inc. Rapid Response Fecal Occult Blood (FOB) Self Test	10/5/2007
37		K070660	Medline Fecal Occult Blood Test (Cassette)	08/22/2013
38	15	K071242	AmeriTek dBest One Step Occult Blood Test	03/12/2008
39	16	K073431	Jant Pharmacal Accutest Dual Sample Immunological Fecal Occult Blood (iFOB) Test	12/4/2008
40		K073431	Tianjin New Bay Bioresearch Co. Ltd. ForeSure IFOB Dual-Sample Fecal Occult Blood Screen Card Test	02/22/2012
41	17	K080812	BECKMAN COULTER HEMOCCULT ICT	07/1/2008
45	18	K901064	CHEMICON MONOHAEM	05/15/2003
42	19	K961062	SmithKline FlexSure OBT	02/28/1997
43		K961062	BECKMAN COULTER HEMOCCULT ICT	05/26/2004
44		K961062	BECKMAN COULTER HEMOCCULT ICT	06/28/2004
46	20	K100031	American IVD Biotechnology Services Inc. FOB/CRC Advanced+	10/4/2010
47		K100031	BTNX Inc. Rapid Response Fecal Immunochemical Test (FIT)	10/4/2010
48		K100031	IND Diagnostic Inc. One Step Fecal Occult Blood Test	07/28/2010
49		K100031	Medline iFOB One-Step Immunological Fecal Occult Blood Test	04/19/2012
50	21	K100817/ CR140487[c]	Medline iFOB TEST	06/26/2015
51		K100817	Princeton BioMeditech BioSign Immunochemical Fecal Occult Blood Test (iFOBT)	07/8/2010
52		K100817	Status iFOBT	10/19/2011
53		K100817/ CR150328	Sekisui Diagnostics LLC OSOM iFOB Test	07/28/2015
54	22	K102664/ CR160124	Germaine Laboratories Inc. Compliance Gold Fecal Occult Blood Test	04/20/2016

(continued)

Table 1. (continued)

No. FITs	No. 510(k) numbers	510(k) Document Number	Test System/Manufacturer	Effective Date (mm/dd/yy)
55	23	K110309	Orient Gene Biotech - One Step Rapid FOB	09/20/2011
56		K110309	Rapid Response(TM) FIT - Fecal Immunochemical Test	04/22/2014
57		K110309/ CR150438	Tanner Scientific IFOB One Step Rapid Test	09/14/2015
58		K110309/ CR150489	Clarity Diagnostics One-Step Fecal Occult Blood Test	10/6/2015
59	24	K121397	OSOM® iFOB Test OSOM® iFOBT Control Kit	01/3/2013
60	25	K143325/ CR140487	Eiken Chemical Co. LTD OC-Light S FIT	08/24/2015
Moderate Complexity FITs				
61	1	K132167	Boditech Med Inc. i-CHROMA iFOB with i-CHROMA Reader	05/6/2014
62	2	K092330	OC Auto Sensor DIANA iFOB	12/5/2013
63		K092330	OC Auto Micro 80 iFOB	12/5/2013
64	3	K041408	Polymedco OC Auto Micro 80 analyzer	05/23/2005
65		K092330[d]	Polymedco OC-Sensor DIANA iFOB Test	01/20/2010

Abbreviations: FDA, Food and Drug Administration; CLIA, Clinical Laboratory Improvement Amendments; FIT, fecal immunochemical test.
[a]Test System/Manufacturer listed as presented on FDA CLIA Database.
[b]Shading indicates the same test marketed under different names.
[c]On March 21, 2014, CLIA started filing using CR as a prefix, with the Parent Document number with a prefix of K.
[d]The correct document number should be K041408 (Helen Landicho, Senior Vice President of Regulatory Affairs, Polymedco).

Table 2. CLIA-Waived and Moderate Complexity FITs Available for Purchase in United States as of July 22, 2016 With FDA Applicant, Respective 510(k) Document Number, Effective Date, and Accuracy in Human Studies.[a]

No. FITs	No. 510(k) number	Test System/Manufacturer Applicant/(Effective Date)	% of FITs in PT Programs (N = 12 730)	510(k) Document Number	Colonoscopic Histology Results/No. of Subjects in Study	Detection Limits	Sensitivity/ Specificty/PPV
CLIA-waived FITs							
1	1	Enterix Insure Fecal Immunochemical Test[b,c] Enterix, Inc. (10/16/2003)	0.50	K002457			None
2	2	QuickVue IFOB Test[b] Alfa Scientific Designs, Inc. (11/9/2005)	8.90	K021423	Cancer or advanced adenoma/1,330 Cancer or advanced adenoma /86	50 ng/mL Brenner 2010[26] 50 ng/mL Levy 2014[33]	59.6/70.2/18.0 17.0/89.0/10.0
3	3	Hemosure One-Step Immunological Fecal Occult Blood Test[b] WHPM, Inc. (9/8/2004)	30.28	K041202	Cancer Advanced adenoma/ 5,343	100 ng/mL Wong 2015[46]	54.5/90.5/2.3 33.1/91.5/17.2
4	4	OC-Light iFOB Test[b] (8/18/2004 and 3/24/2011) (changing to OC-Light S FIT K143325) (8/24/2015) Polymedco, Inc.	12.04	K041297	Cancer Advanced adenoma/ 18,296 Cancer or advanced adenoma/346	50 ng/mL Chiu 2013[27] 50 ng/mL Levy 2014[33]	78.6/92.8/1.65 28.0/93.5/13.3 4.0/97.0/11.1

(continued)

Table 2. (continued)

No. FITs	No. 510(k) number	Test System/Manufacturer Applicant/(Effective Date)	% of FITs in PT Programs (N = 12 730)	510(k) Document Number	Colonoscopic Histology Results/No. of Subjects in Study	Detection Limits	Sensitivity/ Specificty/PPV
5	5	Care Fecal Occult Blood Test Epitope Diagnostics, Inc. (10/7/2005)	0.00	K051806			None
6	6	Care Diagnostic Clarity iFOB Test[b] Care Diagnostic, Inc. (1/26/2010)	0.61	K052598			None
7	7	Consult Diagnostics Immunochemical fecal occult blood test[b] Immunostics, Inc. (7/8/2010)	1.32	K060463			None
8		Henry Schein OneStep+ iFOBT[b] Immunostics, Inc. (3/5/2009)	0.43	K060463			None
9		Immunostics Inc. hema-screen SPECIFIC Immunochemical Fecal Occult Blood Test[b,c] Immunostics, Inc. (6/15/2006)	4.45	K060463			None
10	8	CLIAwaived Inc. Rapid Fecal Occult Blood Test TECO Diagnostics (11/9/2009)	0.00	K061065			None
11	9	Germaine Laboratories Compliance Gold iFOB Tianjin New Bay Bioresearch Co., Ltd. (9/9/2009)	0.00	K063693			None
12		Forsure One Step Fecal Occult Blood (FOB) Screen Care Test Tianjin New Bay Bioresearch Co., Ltd. (5/16/2007)	0.00	K063693			None
13		Jant Pharmacal Accutest Immunological Fecal Occult Blood Test[b] Tianjin New Bay Bioresearch Co., Ltd. (12/4/2008)	0.15[d]	K063693			None
14	10	Jant Pharmacal Accutest Dual Sample Immunological Fecal Occult Blood Test[b] Tianjin New Bay Bioresearch Co., Ltd. (12/4/2008)		K073431			None
15	11	BTNX, Inc. Rapid Response Fecal Occult Blood Test[b] Alfa Scientific Designs, Inc. (10/5/2007)	0.49	K070660			None
16	12	Medline iFOB Test Princeton BioMeditech Corporation (6/26/2015)	0.00	K100817			None

(continued)

Table 2. (continued)

No. FITs	No. 510(k) number	Test System/Manufacturer Applicant/(Effective Date)	% of FITs in PT Programs (N = 12 730)	510(k) Document Number	Colonoscopic Histology Results/No. of Subjects in Study	Detection Limits	Sensitivity/ Specificty/PPV
17		Status iFOBT Princeton BioMeditech Corporation (10/19/2011)	0.00	K100817			None
18		Princeton BioMeditech BioSign Immunochemical Fecal Occult Blood Test Princeton BioMeditech Corporation (7/8/2010)	0.00	K100817			None
19	13	Germaine Laboratories Inc. Compliance Gold Fecal Occult Blood Test ER Germaine Laboratories Inc. (4/20/2016)	0.00	K102664			None
20	14	Rapid Responses™ FIT Orient Gene Biotech (4/22/2014)	0.00	K110309			None
21		Tanner Scientific iFOB One Step Rapid Test Tanner Scientific (9/14/2015)	0.00	K110309			None
22		Clarity Diagnostics One-Step Fecal Occult Blood Test Clarity Diagnostics (10/6/2015)	0.00	K110309			None
23	15	OSOMÂ® iFOB Test[c] Sekisui Diagnostics, LLC (1/3/2013)	0.00	K121397			None
24	16	Beckman Coulter Hemoccult ICT[b,c] SmithKline Diagnostics, Inc. (2/28/1997)	27.16	K961062	Screening relevant neoplasia/1075	200 ng/mL[e] Wong 2012[44]	23.2/95.8/27.6
Non CLIA-waived FITs							
25	17	Polymedco OC Auto Micro 80 analyzer[b] Polymedco, Inc. (5/23/2005 and 12/5/2013)	12.29	K041408	Cancer Advanced adenoma/1682	≥100 ng/mL Rozen 2010[39]	65.0/94.6/12.7 26.4/96.4/33.3
26	18	Polymedco OC-Sensor DIANA iFOB Test[b] Polymedco, Inc. (1/20/2010 and 12/5/2013)	1.34	K092330	Cancer or advanced neoplasia/1020	≥50 ng/mL Huang 2016[22]	59.6/90.6/26.3
					Cancer Cancer or advanced neoplasms/2235	100 ng/mL Brenner 2013[25]	73.3/95.5/10.0 25.7/97.4/51.8
					Cancer Advanced adenoma/457	75 ng/mL Crouse 2015[28]	82.9/60.0/NA 49.5/62.7/NA
					Cancer Advanced adenoma/1256	≥100 ng/mL de Wijkerslooth 2012[29]	75.0/95.0/8.0 29.0/97.0/46.0

(continued)

Table 2. (continued)

No. FITs	No. 510(k) number	Test System/Manufacturer Applicant/(Effective Date)	% of FITs in PT Programs (N = 12 730)	510(k) Document Number	Colonoscopic Histology Results/No. of Subjects in Study	Detection Limits	Sensitivity/ Specificty/PPV
					Cancer Advanced adenoma/770	≥100 ng/mL Park 2010[38]	92.3/90.1/13.8 33.9/90.6/23.0
					Cancer High risk adenomas/3794	≥100 ng/m Sohn 2005[43]	25.0/NA/NA 6.0/NA/NA
					Cancer Advanced precancerous lesions/9989	≥100 ng/mL Imperiale 2014[47]	73.8/94.9/6.9 23.8/94.9/25.7

Abbreviations: FDA, Food and Drug Administration; CLIA, Clinical Laboratory Improvement Amendments; FIT, fecal immunochemical test; PT, proficiency testing; PPV, positive predictive value; NA, not available.
[a]Shading indicates the same test marketed under different names.
[b]Assessed by Proficiency Testing Programs.
[c]Dry slide collection method.
[d]Proficiency Testing Programs provide only the single sample result.
[e]Taken from manufacturers' product brochure.

Table 3. Proficiency Testing Programs' Fecal Immunochemical Test (FIT) Totals and Accuracy for Spiked Samples by Test System/ Manufacturer for 2014.

Test System/Manufacturer/Sample Size/510(k) Number		Total Correct (Percentage Correct)		Total Incorrect (Percentage Incorrect)		Overall Sensitivity, % (95% CI)	Overall Specificity, % (95% CI)
		Positive	Negative	Positive	Negative		
1	Hemosure One-Step Immunological Fecal Occult Blood Test (n = 3854) (K041202)	2189 (99.5)	1638 (98.9)	10 (0.5)	17 (1.1)	99.2 (98.8-99.5)	99.4 (98.9-99.7)
2	Beckman Coulter Hemoccult ICT (n = 3458) (K961062)	1819 (98.7)	1597 (98.9)	24 (1.3)	18 (1.1)	99.0 (98.5-99.4)	98.5 (97.8-99.0)
3	OC-Light iFOB Test (n = 1533) (K041297)	875 (99.3)	636 (97.5)	6 (0.7)	16 (2.5)	98.2 (97.1-98.9)	99.1 (97.9-99.6)
4	QuickVue IFOB Test (n = 1138) (K021423)	661 (99.5)	472 (99.6)	3 (0.5)	2 (0.4)	99.7 (98.8-100)	99.4 (98.1-99.9)
5	Immunostics Inc. hema-screen SPECIFIC Immunochemical Fecal Occult Blood Test (n = 566) (K060463)	310 (100)	255 (99.6)	0	1 (0.4)	99.7 (98.0-100)	100 (98.2-100)
6	Consult Diagnostics Immunochemical fecal occult blood test (n = 169) (K060463)	113 (99.1)	55 (100)	1 (0.9)	0	100 (96.1-100)	98.2 (89.7-100)
7	Henry Schein OneStep+ iFOBT (n = 55) (K060463)	36 (100)	19 (100)	0	0	100 (88.5-100)	100 (80.2-100)
8	Care Diagnostic Clarity iFOB Test (n = 77) (K052598)	49 (100)	28 (100)	0	0	100 (91.3-100)	100 (85.7-100)
9	Enterix Insure Fecal Immunochemical Test (n = 63) (K002457)	40 (100)	20 (87.0)	0	3 (13.0)	93.0 (80.7-98.3)	100 (81.0-100)

(continued)

Table 3. (continued)

	Test System/Manufacturer/Sample Size/510(k) Number	Total Correct (Percentage Correct)		Total Incorrect (Percentage Incorrect)		Overall Sensitivity, % (95% CI)	Overall Specificity, % (95% CI)
		Positive	Negative	Positive	Negative		
10	BTNX, Inc. Rapid Response Fecal Occult Blood Test (n = 62) (K070660)	33 (97.1)	28 (100)	1 (2.9)	0	100 (87.6-100)	96.6 (81.4-100)
11	Jant Pharmacal Accutest Immunological Fecal Occult Blood Test (n = 19) (K073431)	13 (100)	6 (100)	0	0	100 (73.4-100)	100 (55.7-100)
12	OC-Auto Micro 80[a] (n = 1565) (K041408)	808 (100)	750 (99.1)	0	7 (0.9)	99.1 (98.2-99.6)	100 (99.4-100)
13	OC-Sensor Diana[a] (n = 171) (K092330)	88 (100)	83 (100)	0	0	100 (95.0-100)	100 (94.7-100)
	Total (n = 12 730)	7034	5587	45	64	99.1 (98.9-99.3)	99.2 (98.9-99.4)

(shaded area indicate FITs with same 510(k) number).
[a]Automated FITs.
(shaded area indicate FITs with same 510(k) number).

simulated fecal material spiked with an unknown amount of hemoglobin that is likely not at the lower limits of sensitivity for FIT products being assessed. PT programs will not share how much hemoglobin is in their spiked samples, as that is considered proprietary information. Tests used for CRC screening need to be simple, reliable, and test well under usual conditions.[50] Health care providers and patients deserve to know that the FITs being used provide accurate test results. There is very little published, population-based research on CLIA-waived FITs done at a single point in time, using colonoscopy as the gold standard. Only 5 studies of 4 unique CLIA-waived FITs (out of 16 total) have been conducted.[26,27,33,44,46] The 2 automated FITs have been studied in larger populations than the CLIA-waived FITs and generally have favorable sensitivities and specificities for CRC and/or AAP.[22,25,28,29,38,39,43,47]

Lee et al[51] conducted a systematic review and meta-analysis to assess the diagnostic accuracy of FITs for CRC.[51] Nineteen research studies, 2 from the United States, were included in the study with both qualitative and quantitative FITs. The overall sensitivity for CRC across these 19 studies of 113 360 total patients was 79% and specificity was 94%. Sensitivity and specificity was not studied for AAP.[51] Another review of 21 studies using either CLIA-waived or automated FITs demonstrated that FITs have a sensitivity for CRC ranging from 0.25 to 1.00 and specificity of 0.83 to 0.99.[52] A systematic review and meta-analysis of qualitative FDA-cleared FITs used in US studies would be worthwhile to continue to explore accuracy for CRC and AAP. This cannot be done without more data. Researchers in Germany have evaluated 20 qualitative and 1 quantitative FIT for hemoglobin in spiked samples and determined the detection limits for hemoglobin do not match the manufacturer's specifications.[53] German researches recommend screening programs avoid using qualitative FITs due to differences in detection limits with large variations in sensitivity and specificity.[54]

A good FIT is one that has a high sensitivity and specificity for screening relevant neoplasia. FITs are recommended regularly over time, in order to have the best chance of detecting occult blood. However, in a real-world setting, many issues can affect the sensitivity and specificity of FITs.[33,50,55] There is a seasonal variation in FIT results with lower positivity rates in warmer weather, due to degradation of hemoglobin.[55,56] Allison et al[57] have also recommended all companies use a standard collection device and probe with a known buffer for comparison across studies. There is no accepted international quality control standard for use with FITs.

The AAFP-PT results were excluded because they provided only aggregated data for all FOBTs, thus, it was not known which FITs were evaluated by that program. However, the AAFP-PT was only 4% of the total proficiency tests evaluated. Proficiency testing results do not provide any information on the accuracy of human samples for AAP or CRC. In addition, laboratories performing point-of-care tests are not required to participate in PT programs. This means that there is little to no information on test accuracy for the majority of CLIA-waived tests being used in primary care offices and Federally Qualified Health Centers in the United States.

Based on the 2014 PT program results, the gFOBT accounts for 77% of the FOBTs, even though the FIT has been determined to be a better test for occult blood in the stool. Proficiency test results are a crude measure for determining the percentage of gFOBTs and FITs used in the

United States. Among the FITs, Hemosure One-Step Immunological Fecal Occult Blood Test was evaluated the most with the Beckman Coulter product close behind. The current worldwide use of FITs is primarily automated FITs read with quantitative results.[22,25,29,39,51] In the United States, 122 671 physician office laboratories use the CLIA-waived FOBTs[58] and the quantitative FITs used in other countries are either not available or are only able to report qualitative results because they have not been approved by the FDA to report quantitatively.

The 13 FIT brands tested across the 6 PT programs tested extremely well using spiked samples and might be appropriate to use in CRC screening programs. However, there was published information on only 4 of 24 (16 unique 510(k) numbers) CLIA-waived tests in screening populations and/or populations at higher risk. Given the goal of 80% of individuals screened for colorectal cancer by 2018, it is likely that FITs will need to play a greater role in screening, and an estimated 24 million more Americans will need to be screened.[59] Most developed countries have a systematic CRC screening program that uses mailed automated FITs developed in a central or few locations.[60,61] A comparative effectiveness study of the test characteristics of commonly used FITs with colonoscopy as the gold standard is essential if we are to know which FITs available in the United States have the best test characteristics. Studies conducted on 4 qualitative, CLIA-waived FITs demonstrate widely varying test accuracy.[33] Do the commonly used FIT brands test positive down to the lower limits of hemoglobin specified in their product inserts and under conditions where stool is present? It is critical to determine the FITs with the best test characteristics in order to implement successful FIT-based screening programs.[28,32,62]

To answer the question, "which FIT do I use?" a FIT is recommended in the CRC screening guidelines in preference to gFOBT.[12,13,15] Reviewing the PT program results, 13 FITs evaluated across programs would be appropriate based on spiked samples. However, narrowing the FITs further, based on the studies that conducted a one-time FIT prior to colonoscopy to assess test accuracy for AAP or CRC, the automated FITs (OC-Auto Micro 80 and OC-Sensor Diana), provided the best sensitivities and specificities across studies. Further studies are warranted prior to recommending FITs that are waived under CLIA for private practice offices.

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Author Biographies

Jeanette M. Daly is an associate research scientist in the Department of Family Medicine, Roy J. and Lucille A. Carver College of Medicine. She conducts research regarding colorectal cancer screening, fecal immunochemical tests, and elder abuse.

Yinghui Xu is a biostatistician in the Department of Family Medicine, Roy J. and Lucille A. Carver College of Medicine.

Barcey T. Levy is a professor of Family Medicine, Roy J. and Lucille A. Carver College of Medicine, and professor of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa. She has a strong interest in improving colorectal cancer screening and in understanding which of the numerous fecal immunochemical tests perform well, when compared with colonoscopy.