# The Iowa Experience with CLIA-waived FITs

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## FITs are often used in population-based screening

Purposes of this study:

1. To compare the results of a single sample FIT with colonoscopy, and
2. Compare the odds of a positive test for distal vs. proximal adenomatous polyps or cancer.

## Methods

- Individuals scheduled for a colonoscopy were invited to complete a FIT prior to colonoscopy.
- FIT results were classified as positive, negative, or invalid.
- Colonoscopy reports were reviewed and abstracted.
- Because of product issues, four different FIT manufacturers were used.
- Test characteristics for each FIT manufacturer were calculated for adenomatous polyps or cancer according to broad reason for colonoscopy (screening or surveillance/diagnostic).

## FITs were CLIA-waived

- All FITs used were liquid-based non-automated Clinical Laboratory Improvement Amendment (CLIA) waived tests.
- We chose CLIA-waived tests because many small offices can not afford an automated analyzer.
- In the U.S., small medical offices are able to run "simple" lab tests under a CLIA-waiver, if they have a CLIA-waived certificate.
- Larger pathology labs participate in proficiency testing on all tests they run, including CLIA-waived tests.

## Results

- Invitations were mailed to 2,336 potential subjects, of whom 1,040 (44.5%) completed a FIT and a colonoscopy.
- Fourteen individuals (1.4%) had an invalid result, leaving 1,026 (43.9%) for analysis of test characteristics.
- Median time from FIT collection to testing was 5.0 days (s.d. 2.9 days).

## Demographics (n=1040)

| | |
|---|---|
| Mean age ± s.d. (years) | 56.9 ± 7.6 |
| Percentage female | 59% |
| Percentage married | 70% |
| Percentage white | 94% |
| Percentage African American | 2% |
| Percentage Latino | 1% |
| Percentage with income below USD $40,000 | 34% |
| Percentage with high school education or less | 20% |

## FITs used in this study

| FIT Manufacturer (n) | Test Device | Sensitivity | Dates Used | Reason for FIT Switch |
|---|---|---|---|---|
| Inverness Clearview ULTRA iFOB n =65 | Dipstick test strip | 50 ng/ml 50 µg/g | January to February 2010 | Company changed product to cassette and changed their name to Alere Clearview |
| Alere Clearview iFOB Complete n=529 | Cassette | 50 ng/ml 6 µg/g | March 2010 to March 2011 | Product recall |
| Polymedco OC-Light iFOB n=346 | Dipstick test strip | 50 ng/ml 10 µg/g | April 2011 to September 2011 | Positivity rate significantly lower than the first two FITs used; this product did not test positive at 50 ng hemoglobin/ml in our quality control testing. |
| Quidel QuickVue iFOB n=86 | Cassette | 50 ng/ml 50 µg/g | October 2011 to January 2012 | Grant funding ended |

## Overall results of colonoscopy and FITs

| | n | % |
|---|---|---|
| Men | 424 | 40.8% |
| Women | 616 | 59.2% |
| Adenocarcinoma | 2 | 0.2% |
| Advanced adenoma* and none of the above | 73 | 7.0% |
| Other adenoma (i.e., tubular and <10mm), and none of the above | 267 | 25.7% |
| Hyperplastic polyp and none of the above | 200 | 19.2% |
| Other/No diagnostic abnormality/No histology performed/Lymphoid aggregate and none of the above | 498 | 47.9% |
| Positive FITs | 112 | 10.8% |
| Negative FITs | 914 | 87.9% |
| Invalid FITs | 14 | 1.4% |
| ***Total*** | 1040 | |

*Advanced adenoma was defined as any tubulovillous, villous, serrated, or with high-grade dysplasia or a tubular polyp 10 mm or greater.

## Test Characteristics for Advanced Adenomas or Cancer (n=1,026)

| All Groups (screening + surveillance/diagnostic) | | | | |
|---|---|---|---|---|
| n | Company | Sensitivity | Specificity | Positive Predictive Value |
| 65 | Inverness Clearview | 0.38 (0.09–0.76) | 0.88 (0.76–0.95) | 0.30 (0.07–0.65) |
| 529 | Alere Clearview | 0.24 (0.11–0.42) | 0.85 (0.82–0.88) | 0.10 (0.04–0.18) |
| 346 | Polymedco OC-Light | 0.04 (0.00–0.19) | 0.97 (0.95–0.99) | 0.10 (0.00–0.45) |
| 86 | Quidel QuickVue | 0.17 (0.00–0.64) | 0.89 (0.80–0.95) | 0.10 (0.00–0.45) |
| 1026 | Overall | 0.18 (0.10–0.28) | 0.90 (0.87–0.91) | 0.12 (0.06–0.19) |

## Distal adenomas were more likely than proximal adenomas to test positive

| Model (n=1024) | Adenoma Location | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| **Adenoma Location** | Distal, AA or adenocarcinoma | 2.68 | 1.20 to 5.99 | 0.02 |
| | Proximal, AA or adenocarcinoma | 0.96 | 0.28 to 3.28 | 0.94 |
| | No AA or adenocarcinoma | 1.00 | - | - |

All eligible subjects with valid FIT results included. Two subjects were removed for having missing biopsy location results that were required for analysis. Two subjects with both proximal and distal adenomas were classified according to the location of their most concerning lesion. Controlling for FIT manufacturer (Polymedco, Inverness, Alere, or Quidel).

## Results

- FIT results were **negative** for a total of 36 patients where a positive result would have been expected:
  - Two patients with adenocarcinoma
  - 34 patients with an AA including a patient with an advanced adenoma with high-grade dysplasia.
- Unexpectedly, four different FIT manufacturers had to be used. This could not have been anticipated at the start of the study and calls into question the number of FITs are on the market that may not be providing valid results.

## Discussion

- We assessed the characteristics of a single round of FIT testing with optical colonoscopy as the gold standard.
- The overall sensitivity of single-sample FITs for advanced adenomas and adenocarcinoma was low at 18%, with a specificity of 90%.
- Polymedco OC-Light had a statistically significantly lower test positivity than all other manufacturers.

## Discussion (cont'd)

- The sensitivity of FIT for distal advanced lesions was higher than for proximal advanced lesions.
- The two patients with adenocarcinoma and 34 of 39 with an advanced adenoma tested negative on FIT.
- It is likely that many primary care physicians are not aware of the limitations of CLIA-waived FITs.

## Discussion (cont'd)

- We chose CLIA-waived FITs because many resource-poor settings are not able to provide universal access to colonoscopy and FIT is a logical first step in screening.
- There were multiple issues with FITs that led to using four different FIT manufacturers over this two year study.
- The sensitivity for advanced adenomas of 18% that we found was very close to the sensitivity of 22% estimated by Zauber, et al. (Zauber AG, Ann Intern Med 2008)

## Why was sensitivity so low?

- We used a single sample instead of two or three. A one-time FIT will never be as good as a colonoscopy. FIT must be done regularly over time.
- Our population had been exposed to screening.
- Advanced polyps and cancers not bleeding at the time sampled?
- The antibody/antibodies were not working as claimed?
- Hemoglobin degraded in the buffer due to high temperatures or buffer characteristics?
- RBCs remained intact and hemoglobin was not released (buffer kept hemoglobin too stable?)
- Relatively low numbers of patients with advanced adenomas in this population.

## Recommendations for the FDA

- Manufacturers should be required to show that their product tests down to the level specified in samples spiked with known levels of hemoglobin under various conditions (temperature, humidity, length of time after spiking, presence of fecal matter, etc.).
- Standardize the amount of stool picked up by probe and volume of buffer.
- Manufacturers should demonstrate the characteristics of their product in clinical populations:
  - Screening
  - Those under surveillance
  - Those with known colorectal cancers before treatment is begun.

## Conclusions

- CLIA-waived FITs marketed in the U.S. have not undergone standardized rigorous follow-up testing in real populations. They merely have to show equivalence to similar products.
- Manufacturers of FITs have a responsibility to ensure that their products perform reliably at the level of sensitivity claimed, since many health centers can not afford automated tests, and may not have the resources to follow positivity rates over time.

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Manuscripts from this funding:

- Levy B T, J Med Screen 2014; 21(3): 133-143.
- Daly J M, Prim Care Community Health 2013; 4(4): 245-250.
- Xu Y, BMC Health Services Research 2015; 15(1):175.