Interventions to Improve Follow-up of Positive Results on Fecal Blood Tests

Results of a systematic review, Kaiser experience, and implications for the Canton of Vaud

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Outline

- FIT-based screening programs and problems with follow-up of test-positive patients

- A systematic review of interventions to improve follow-up of positive fecal tests

- How organized programs at Kaiser and other countries follow up test-positive patients

- Implications for CRC screening program in the Canton of Vaud
Fecal immunochemical tests are ideal for mass screening

- RCTs with guaiac FOBT show a 15-33% reduction in CRC-specific mortality
- FIT are both more sensitive and more specific
  - Increased detection of advanced adenomas
- Only one sample, no dietary or medication restrictions
  - RCTs show increased adherence
- Sufficiently stable for mailed outreach
- Quantitative FIT cut-off can be varied
Low rates of follow-up colonoscopy after positive fecal blood tests are a problem

- Real-world efficacy of FIT screening depends on colonoscopy follow-up of positive tests
- Follow-up rates of ~50% in multiple settings in the United States
- Rates of 60-70% in Asia
- Follow-up closer to 70-90% in Canada and Europe: still a problem in many places!
- Challenging: follow-up involves interaction of multiple levels of care
- Patients are often reluctant

Dis Colon Rectum. 2006;49:1002-10
Colonoscopy delays after a positive fecal test are important

Analysis of 70,000+ FIT-positive patients shows an increased risk of CRC, and specifically advanced-stage CRC, when time to colonoscopy is greater than 6 months.

Systematic review objective:

Evaluate interventions to improve rates of follow-up colonoscopy for adults after a positive result on fecal immunochemical tests (FIT) or guaiac fecal occult blood tests (gFOBT)
Methods

Data Sources:

- Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Embase through June 2017
- English-language studies

Study Selection:

- Randomized and nonrandomized studies
- Interventions to improve colonoscopy (or DCBE in older studies) follow-up of positive fecal test results in the screening setting
- Focus on absolute change in colonoscopy completion at 6 months, if available

Data Extraction:

- Two reviewers extracted data and ranked study quality, and then rated overall strength of evidence for each study category

Protocol available: PROSPERO: CRD42016048286
Results

- 23 studies eligible for analysis
- 7 randomized and 16 nonrandomized studies
- Only 3 at low risk of bias
- Number of patients ranged from 14 to 39,105
- 5 of FIT follow-up, 18 of gFOBT follow-up
- No meta analysis performed given significant heterogeneity in outcomes reported
1. Patient-level Interventions

Changes to invitation strategy to screening

- 2 studies, 1 randomized trial at low-risk of bias
- Interventions to increase screening rates don’t worsen follow-up of positive tests

Provision to patients of test results or follow-up appointments

- 4 studies, 1 randomized trial at moderate risk of bias
- Mailing or calling all patients to provide test results or directly providing appointments to discuss follow-up colonoscopy
- RCT: among initial non-responders in Italy, a specialized nurse increased follow-up (+12% (CI 0.5 to 24))
1. Patient-level Interventions - continued

Patient navigation

• 5 studies, 2 randomized trials at low-risk of bias

• RCT 1: Registered nurse patient navigators increased follow-up from 80.8% to 91.0% at 6 months (+ 10.1% (CI -1.5 to 22)). Trial was underpowered

• RCT 2: Patient navigators for multiple cancers using “strengths-based” approach increased from 58% to 79% at 1 year (+ 21% (CI 9.5 to 33))
2. Provider-level Interventions

Provision to providers of reminders and/or performance data

- 5 studies, 2 cluster randomized
- All used electronic algorithms to clearly identify ordering providers / assigned primary care physician
- Remind those with inadequate action after 60 or 90 days
- 4 from integrated systems in the US, generally multi-component interventions, showed positive results (+9 to +25%)
- 1 used centrally generated reports in a provincial screening program, showed no difference (HR 0.95, CI 0.79 to 1.13)
3. System-level Interventions

Automated referral to gastroenterologist
- 2 studies, all positive fecal test results sent directly to gastroenterologists
- Both from VA medical centers, integrated EHR allowed transfer of patient information

Replacement of precolonoscopy visit with telephone call
- 1 study, patients given choice of phone call instead of face-to-face consultation

Registry to track patients with positive results
- 1 study, registry reviewed regularly by nurse manager, +23% improvement over several years (CI 21 to 26)

Multicomponent quality improvement efforts
- 3 studies, all from VA, Pre-post or observational designs, only 6 to 10% improvement
<table>
<thead>
<tr>
<th>Intervention Level and Type</th>
<th>Risk of Bias of Included Studies†</th>
<th>Consistency‡</th>
<th>Directness§</th>
<th>Precision‖</th>
<th>Overall Strength of Evidence¶</th>
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<tbody>
<tr>
<td><strong>Patient-level interventions</strong></td>
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<tr>
<td>Changes to invitation strategy to screening (38, 42)</td>
<td>1 low, 1 high</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
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<td>Provision to patients of test results or follow-up appointments (33, 43, 45, 47)</td>
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<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
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<tr>
<td>Patient navigator (31, 32, 39, 40, 48)</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
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<td><strong>Provider-level interventions</strong></td>
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<tr>
<td>Provision of reminders and/or performance data to providers (30, 35, 41, 49, 50)</td>
<td>3 moderate, 2 high</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
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<td><strong>System-level interventions</strong></td>
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<tr>
<td>Automated referral to gastroenterologist (46, 51)</td>
<td>1 moderate, 1 high</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
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<tr>
<td>Replacement of precolonoscopy visit with telephone call (44)</td>
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<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
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<td>Registry to track patients with positive results (52)</td>
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<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
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<tr>
<td>Multicomponent quality improvement efforts (7, 34, 53)</td>
<td>2 high, 1 moderate</td>
<td>Consistent</td>
<td>Indirect</td>
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</table>
Limitations

- Heterogeneous outcome measurements: no meta analyses
- Colonoscopy completion is an intermediate outcome
- Most U.S. studies (10 of 14) from within the VA
- Cannot rule out publication bias
- Inclusion of non-randomized studies is more complete, but higher risk of bias, may be misleading
Areas for further research

- Need greater standardization of results reporting and more RCTs
- Need for pragmatic trials when implementing new programs
- What is the effect of increased endoscopy capacity?
- Stratifying patient populations to target high-cost interventions
- Can we better engage patients electronically?
Outline

- FIT-based screening programs and problems with follow-up of test-positive patients
- A systematic review of interventions to improve follow-up of positive fecal tests
- How organized programs at Kaiser and in other countries follow up test-positive patients
- Implications for CRC screening program in the Canton of Vaud
Follow-up of positive FIT at Kaiser Permanente Northern California

- KPNC: integrated healthcare system with 4.5 million members
- Mailed FIT outreach since 2006
- Approximately 20,000 positive FIT per year
- Median time to colonoscopy in 2015 of 36 days (IQR 24 to 73), with 83% having had a colonoscopy by 6 months
- How is this being done?
Traditional flow

- FIT read as positive
- Primary care provider (PCP) notified
- Patient given result and appointment scheduled
- Sees GI for colonoscopy
Increasing responsibility assumed by GI to manage FIT positive patients

- FIT read as positive
  - Primary care provider (PCP) notified
    - e-consult
      - GI receives FIT+ patient list and/or e-consult
  - Patient given result and appointment scheduled
    - ‘Navigator’ call to explain colonoscopy logistics, risks and preparation
  - Colonoscopy completed
Overall organization of FIT-positive follow-up within Kaiser Permanente Northern California

FIT read as positive

Primary care provider (PCP) notified

Minimum 3 attempts to contact patient

Registered letter if no phone or e-mail contact

GI receives FIT+ patient list and/or e-consult

Patient given result and appointment scheduled

‘Navigator’ call to explain colonoscopy logistics, risks and preparation

Colonoscopy completed
FIT read as positive

Primary care provider (PCP) notified

Minimum 3 attempts to contact patient

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‘Navigator’ call to explain colonoscopy logistics, risks and preparation

Colonoscopy completed

GI receives FIT+ patient list and/or e-consult

Patient given result and appointment scheduled

Organizational supports in place to ensure success

Adequate colonoscopy capacity (staff and endoscopy suites)

Registry of FIT+ patients with real-time updates (PROMPT)

GI Staff member designated responsible

Frequent feedback of FIT+ follow-up performance

Financial rewards to management for attaining colonoscopy access targets
Examples from other countries

- Ontario, Canada: 75% colonoscopy completion
  - Originally results by letter only to GP
  - Later results sent to patient and reminder / performance letters for GP

- United Kingdom: 80-85% completion
  - Results by letter to patient and GP
  - Call from “Specialist Screening Practitioner”, usually a nurse

- Netherlands: 75-80% completion
  - Results by letter to patient and GP
  - Scheduled pre-colonoscopy appointment at a “colonoscopy center”. Colonoscopy appointments managed centrally

*Curr Oncol.* 2017; 24(1):47-51


*Gastroenterology.* 2017;152(4):767-775
Examples from other countries

- France: 85-90% follow-up.
  - Results by letter to GP and patient. GPs to coordinate referral.
  - If no report of completed colonoscopy, reminders sent at 3 and 6 months, emphasizing need.
  - After 12 months, patient excluded from programme.
  
  \[\textit{British Journal of Cancer}. \, 2013; \, 109:1437-1444\]

- Italy: Long-time program in Veneto region has 90+% follow-up
  - Trained operators contact FIT+ subjects by phone call to communicate result and invite them to colonoscopy. Exam can be scheduled immediately
  - Repeat calls if initial refusal / difficulty with scheduling
  - Emphasize free colonoscopy

  \[\textit{Gut}, \, 2016; \, 0:1-7\]
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Canton of Vaud CRC screening program

- Launched in 2015 with first mailed invitations in 2016
- Target population of 180,000 people aged 50-69, rolling invitations over 5-7 years
- All participants offered choice of FIT and colonoscopy
- Initial projections of participation rates of 30% for FIT and 10-15% for colonoscopy
- Reimbursement without deductible of 90% of cost of appointment for inclusion, test of choice, and follow-up colonoscopy
Population registry from canton

Rolling invitations based on birth year

Invitation letter:
- Information brochure
- Refusal form letter

GP Consultation – specific billing code
Patient entered into central database

No response, no billing receipt received

Repeat invitations after 3 months

Next invitation in 2 years if no answer

Receipt of refusal

FIT
Prescription for pharmacy

Test picked up at the pharmacy.
Test performed by patient at home and sent to central lab.

FIT normal
Next invitation in 2 years

Positive FIT
Return to GP

Colonoscopy
Coordinated by GP

Colonoscopy done by gastroenterologist of choice

Normal exam
Reinvitation in 10 years

Positive colonoscopy.
Pathology results to tumor registry

Temporary or definitive exclusion from the program

FIT, Prescription for pharmacy

Colonoscopy

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Positive colonoscopy
Pathology results to tumor registry

Temporary or definitive exclusion from the program
Handling of positive tests

- Results of positive tests mailed to both the patient and GP, with the GP receiving result 24 hours ahead
- Recommended follow-up is colonoscopy, with 90% of cost reimbursed by the program
- Early indicators show about 90% of test-positive patients have gotten a colonoscopy
- Target: European recommendations of diagnostic colonoscopy within 31 days of referral. Referral within 15 days of a positive FIT.  
  - Acceptable proportion getting colonoscopy: 90%. Desired: 95%
What implications from this research for the Canton of Vaud?

- For now, too early to precisely measure follow-up rates
- Proportion of FIT-positive patients with colonoscopy completed at 6 months should be monitored as a performance measure
- Vaudois program very decentralized – emphasis on GP and gastroenterologist autonomy,
  - Will likely require centralized tracking and individualized reminders
  - Inclusion via GP may be an advantage (clear responsibility)
- Patient navigators have been used successfully in other organized programs and could be considered
Conclusions

1. More work and research are needed in this important area

2. Patient navigators appear to work and are used by many organized screening programs internationally – can be expensive, often require centralized control

3. Provider reminder systems, direct referral to gastroenterologists, and central management of colonoscopy appointments are promising, less labor-intensive interventions
Thank you!

- Doug Corley & research group at Kaiser DOR
- Supporters at University of Lausanne
- Swiss Cancer Research Foundation
Extra slides

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Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection for interventions to improve follow-up of positive fecal blood tests for colorectal cancer screening.

9,054 articles identified with database searching:
- 3,278 Medline
- 5,173 Embase
- 617 CENTRAL

24 studies identified by hand searching bibliographies and clinical trial databases

1,846 duplicates removed

7,232 titles and abstracts screened for eligibility

7,154 excluded based on review of title and abstract

77 full-text articles assessed for eligibility

54 excluded after review of full text:
- 31 had no intervention
- 14 were not a screening population or the study did not separately report fecal test positive patients
- 5 were interventions to increase screening colonoscopy
- 5 were duplicate studies

23 articles included in qualitative synthesis
<table>
<thead>
<tr>
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<th>Study Design Type</th>
<th>Patients, n</th>
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<tr>
<td>Grazzini et al, 2000 (A) (42)</td>
<td>Italy</td>
<td>Nonrandomized trial</td>
<td>278</td>
<td>High</td>
<td>73</td>
<td>91</td>
<td>18 (4.2 to 32)</td>
<td>&lt;0.01</td>
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<td>88</td>
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<td>74</td>
<td>72</td>
<td>1.9 (−11 to 7.4)</td>
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<td>Provision to patients of test results or follow-up appointments</td>
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<td>Cha et al, 2011 (43)</td>
<td>South Korea</td>
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<td>90</td>
<td>High</td>
<td>72</td>
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<td>Stock et al, 2015 (33)</td>
<td>Canada</td>
<td>Pre-post</td>
<td>39 105</td>
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<td>Control Colonoscopy Completion, %</td>
<td>Intervention Colonoscopy Completion, %</td>
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<td>95</td>
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<td>Risk of Bias†</td>
<td>Control Colonoscopy Completion, %</td>
<td>Intervention Colonoscopy Completion, %</td>
<td>Absolute Difference (95% CI), percentage points</td>
<td>P Value</td>
<td>Follow-up Interval†</td>
<td>Change in Percentage of Test-Positive Patients Completing Colonoscopy</td>
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<td>System-level</td>
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<td>Automated referral to gastroenterologist</td>
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<tr>
<td>Humphrey et al, 2011 (51)</td>
<td>United States</td>
<td>Cluster randomized controlled trial with analysis done pre–post</td>
<td>1497</td>
<td>Moderate</td>
<td>26</td>
<td>48</td>
<td>22 (17 to 28)</td>
<td>&lt;0.001</td>
<td>180 d</td>
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<tr>
<td>Van Kleek et al, 2010 (46)</td>
<td>United States</td>
<td>Historically controlled trial</td>
<td>233</td>
<td>High</td>
<td>59</td>
<td>66</td>
<td>6.5 (–6.0 to 19)</td>
<td>0.31</td>
<td>Unspecified</td>
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<tr>
<td>Replacement of precolonoscopy visit with telephone call</td>
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<td>Rodger and Steele, 2008 (44)</td>
<td>United Kingdom</td>
<td>Historically controlled trial</td>
<td>704</td>
<td>High</td>
<td>85</td>
<td>99</td>
<td>14 (10 to 18)</td>
<td>&lt;0.001</td>
<td>Unspecified</td>
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<tr>
<td>Registry to track test-positive patients</td>
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<td>Miglioretti et al, 2008 (52)</td>
<td>United States</td>
<td>Historically controlled trial</td>
<td>8513</td>
<td>High</td>
<td>60</td>
<td>83</td>
<td>23 (21 to 26)</td>
<td>&lt;0.001</td>
<td>1 y</td>
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<td>Multicomponent quality improvement efforts</td>
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<tr>
<td>Powell et al, 2009 (34)</td>
<td>United States</td>
<td>Observational cohort</td>
<td>NA</td>
<td>High</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
<td>60 d</td>
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<tr>
<td>Powell et al. 2011 (7)</td>
<td>United States</td>
<td>Pre–post</td>
<td>16 560</td>
<td>High</td>
<td>37</td>
<td>47</td>
<td>10 (8.4 to 12)</td>
<td>&lt;0.001</td>
<td>1 y</td>
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<tr>
<td>Singh et al, 2009 (53)</td>
<td>United States</td>
<td>Pre–post</td>
<td>749</td>
<td>Moderate</td>
<td>2</td>
<td>8</td>
<td>6.0 (2.7 to 9.2)</td>
<td>&lt;0.001</td>
<td>60 d</td>
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<tr>
<td>Study type</td>
<td>Criteria used</td>
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<tr>
<td>Randomized controlled trial</td>
<td>Considered to be at low risk of bias. Upgraded to moderate risk if there was concern for the following problems in the study design or reporting.</td>
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<tr>
<td></td>
<td>- Lack of allocation concealment</td>
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<td></td>
<td>- Lack of blinding that influences outcomes</td>
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<td></td>
<td>- Incomplete accounting of patients and outcome events</td>
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<td>- Selective outcome reporting bias</td>
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<td></td>
<td>- Recruitment bias in cluster-randomized trials</td>
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<td>Observational study or non-randomized interventional study (for example a pre-post or non-randomized parallel group study design)</td>
<td>Considered to be at high risk of bias. Downgraded to moderate risk if the study design adequately accounted for and reported all of the following elements. Upgraded to very high risk if there were severe or multiple problems with these elements.</td>
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<td></td>
<td>- Development and application of appropriate eligibility criteria</td>
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<td>- Adequate measurement of both exposure and outcome</td>
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<td>- Adequate control for confounding, with both accurate measurement of all known prognostic factors and adjustment for these factors</td>
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<td>- Adequate follow-up of all participants</td>
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