

## Is there a role for quantitative FIT in the U.S. and.... Would the FDA help or hinder?

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## Agenda

- The potential for quantitative FIT (and not just in the U.S.)
  - Why bother?
  - Shouldn't everyone just have colonoscopy?
- Would the FDA help or hinder the approval process for qFIT?
  - "There is no redeeming value"
  - "What *possibly* could a qFIT mean anyway?"

## Test characteristics of qFIT

- 1,000 subjects with symptoms or high-risk for colorectal neoplasia who had colonoscopy.
- 91 individuals had clinically significant neoplasia
  - 17 cancers (16 Dukes A or B); 74 advanced polyps
  - 3 FIT samples provided - OC-MICRO desktop
- Mean (95% CI) f-Hb increased with findings:
  - 35 (25-45) ng/ml for normal colon
  - 79 (44-118) ng/ml for non-advanced adenomas
  - 485 (315-654) ng/ml for advanced adenomas
  - 597 (435-759) ng/ml for all advanced *neoplasia*
  - 1,087 (697-1,477) ng/ml for cancer

Levi Z et al. Ann Intern Med 2007; 146:244-255

## Test Characteristics: Cancer (N=17)

Fecal Hb Threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
≥ 50 ng / ml	100 (84 - 100)	84 (82 - 87)
≥ 75 ng / ml	94 (83 - 100)	88 (85 - 90)
≥ 100 ng / ml	88 (73 - 100)	90 (88 - 92)

## Test Characteristics: CSN (N=91)

Fecal Hb Threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
≥ 50 ng / ml	73 (63 - 82)	89 (87 - 91)
≥ 75 ng / ml	67 (57 - 77)	91 (90 - 93)
≥ 100 ng / ml	62 (52 - 72)	93 (92 - 95)

## Effect of different cutoffs for qFIT

Strategy	# CYs (%)	# CAs (%)	# Advanced polyps (%)	# Advanced Neoplasia
CY only	1000	17 (100)	74 (100)	91 (100)
FIT @ 75 ng/ml	134 (13)	16 (94)	45 (61)	61 (67)
FIT @ 100 ng/ml	116 (12)	15 (88)	41 (55)	56 (62)
FIT @ 50 ng/ml	170 (17)	17 (100)	49 (66)	66 (73)

### Other studies: findings & limitations

1 <sup>st</sup> author, yr	Main findings	Limitations
Ciatto, 2007	Age, lesion size, distal location predict [f-Hb]	All had f-Hb $\geq$ 100 ng/ml; S.D.s wide
Park, 2010	qFIT better than HO II; [f-Hb] of 118 ng/ml had Se=92.3%; Sp=90.9%	Only 13 CRCs (3 advanced), 72 (not 78) ACRNs; 3 qFIT specimens obtained
Chen, 2011	Index qFIT [f-Hb] predicts subsequent "incident" CRN	Includes mostly non-advanced adenomas
Digby, 2013	[f-Hb] is related to severity of neoplasia	Includes only those with [f-hb] $\geq$ 400 ng/ml

### Potential roles for qFIT

#### ■ Societal / health systems

- Adjust the cutoff to tailor % positive based on available resources
- Prioritize who gets colonoscopy sooner / later

#### ■ Patient perspective

- Would providing a number enhance adherence?
- Increase threshold for elderly (300 ng/ml – Levy)
- Tailor interval for retesting
  - High-normal  $\rightarrow$  1-2 years; low-normal  $\rightarrow$  3-4 years
- Incorporate value into a prediction model
  - Tailor screening test / strategy based on risk

### FDA and qFIT

- FDA's role - protect public health
- Safety and efficacy
  - Change of intended use of FIT
  - qFIT association with disease state
  - Practice of medicine using qFIT
- Prevailing attitudes regarding FIT/FOBT
  - Colonoscopy centric – triage unfathomable
  - Colonoscopy good for 10 years

### FDA Questions ???

#### ■ Evidence based approval

- qFIT's value in a normal risk US population
  - FIT positive
  - FIT negative
- qFIT's role in GI pathology (excluding cancer)
  - R/O bleeding from hemorrhoids
  - Repeated qFIT values

### FDA Approval Requirements

- Outcome studies with definitive conclusions supporting the safe and effective use of qFIT in the US
  - Stratification of risk
  - Prediction and health economic models
  - Longitudinal data