

OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING
Saturday, May 19, DDW Washington, 2007
Presenter: Steven Itzkowitz

Improvements in Stool DNA Tests

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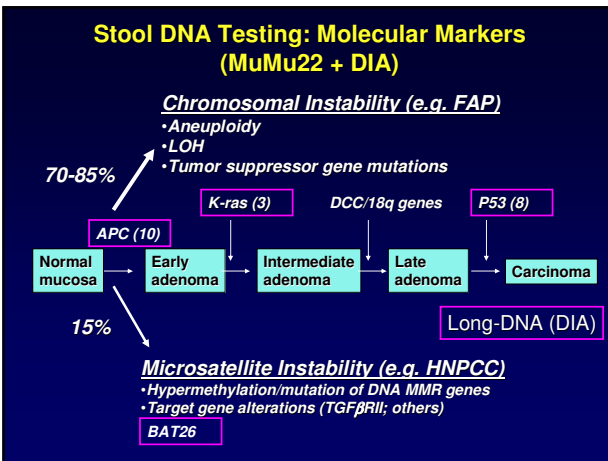
Disclosures

Dr. Itzkowitz receives research support from Exact Sciences Corp.



Background

- Colonoscopy is considered the preferred CRC screening test in the USA.
- However, barriers to colonoscopy include:
 - Organizational: access (USA, abroad); capacity
 - Patient-associated: discomfort, fear, embarrassment, inconvenience (work absence; patient escort; child care)
- **Therefore, non-invasive tests may greatly facilitate CRC screening efforts.**



Stool DNA Testing: Early Studies With Version 1.0

Study	Sensitivity (CRC)	Specificity
Ahlquist '00	91% (20/22)	93% (26/28)
Tagore '00	63% (33/52)	98.2% (111/113)
Syngal '02,'03	62% (40/65)	--
Brand '02	69% (11/16)	--
Calistri '03	62% (33/53)	97% (37/38)
Syngal '06	63% (43/68)	--

These studies analyzed:
 • High risk individuals for sensitivity
 • Stools collected post-colonoscopy
 • Stools that were rapidly frozen

Average-Risk Individuals: Stool DNA is Better than FOBT in

2,507 asymptomatic, average-risk subjects over age 50
 Stool DNA assay (Version 1.0) compared to Hemoccult-II
 All subjects underwent colonoscopy

Results:	sDNA	Hemoccult-II	
Sensitivity (n=31):	51.6 %	12.9%	(p<0.003)
Specificity (n=1423):	94.4%	95.2%	(p=NS)

Conclusions:

- sDNA more sensitive than Hemoccult-II for CRC
- sDNA similar specificity as Hemoccult-II
- But, DIA performance lower than expected (DNA degraded in transit)

Imperiale, Ransohoff, Itzkowitz, et al. NEJM 351:2704, 2004

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**Enhancements to Stool DNA Test:
 "Version 1.1"**

- **Better DNA stabilization**
 - Adding EDTA-containing buffer to stool significantly increases the recovery of DNA ¹
- **Improved DNA extraction method**
 - Gel-based extraction (Effipure®), instead of beads, enhances DNA recovery ²

¹ Olson et al, *Diagn Mol Pathol* 14:183, 2005
² Whitney et al. *J Mol Diagn* 6:386, 2004

Version 1.1 is Better than Version 1.0

	Version 1.0 (Imperiale, <i>NEJM</i> , '04)		Version 1.1 (Itzkowitz, <i>CGH</i> , '07)*	
	No. Positive	% Positive	No. Positive	% Positive
Sensitivity for CRC:				
•All markers	16/31	51.6%	29/40	72.5%
•MuMu22	16/31	51.6%	17/40	42.5%
•DIA	1/31	3.2%	26/40	65.0%

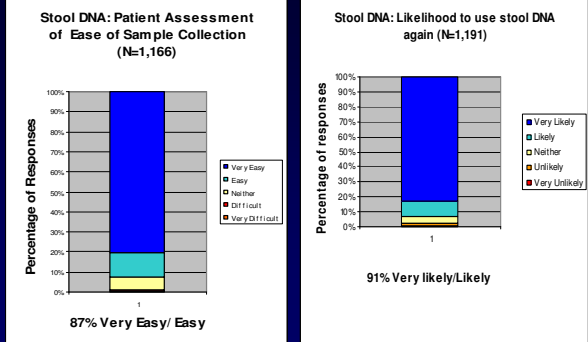
(p<0.0001)

Buffer & Effipure (gel capture) increased sensitivity of

- the original marker panel (51.6% -> 72.5%)
- especially DIA (3.2% -> 65%)
- specificity = 89%

* Itzkowitz et al. *Clin Gastro Hepatol* 5:111, 2007

**Clinical Experience with Version 1.1:
 Patient Preferences**



Berger et al, *Clinical Colorectal Cancer*, Jan. 2006

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Version 2.0 (DIA+Vim) Detected Most CRCs Regardless of Location

	DY	Vim	DY + Vim
Right (n=11)	36.4%	72.7%	90.9%
Left (n=29)	75.9%	72.4%	86.2%
<i>P value</i>	0.03	NS	NS

Patient Satisfaction with Version 2.0

	Percent
Male	41%
Age >60 yrs	40%
Perform the test; easy/very easy	97%
Open the preservative bottle; easy/very easy	96%
Add the preservative to specimen; easy/very easy	100%
Very comfortable performing the test	93%
Would repeat test if doctor recommended it	84%

Conclusions

- A second generation stool DNA test:
- Has high sensitivity with reasonable specificity
 - Uses only two markers (each marker alone performs very well)
 - Has high patient acceptance and satisfaction
 - Is very useful for getting patients screened who might not otherwise get screening.

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Future Directions

Phase 1: (complete) *

- Establish new DIA cut-offs
- Configure Optimal Marker Panel (Vim + DY)
- *45 CRC; 150 Normal colonoscopy*

Phase 2: (ongoing)

- Increase precision of Version-2 results by narrowing 95% CI
- Provide a future validation set of samples
- *80 CRC; 250 Normal colonoscopy*

* Itzkowitz et al. *Clin Gastro Hepatol* 5:111, 2007
