The Future of Colorectal Cancer Screening

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Disclosures

- Exact Sciences (Madison WI)
  - Mayo Clinic
    - Minor equity investor
  - John B. Kisiel
    - Scientific advisor
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    - Potential royalties

Goals and Objectives

- The present:
  - Overview of current recommendations
  - Strengths and weaknesses of colorectal cancer screening tools

- The future:
  - Improve compliance
  - Change the entire screening paradigm

Colorectal Cancer (CRC)

- Remains a major killer worldwide, #2 in USA

- Shift toward right colon
  - Now ~50% R-side in US
  - Olmsted county: ~60% R-side

- Conventional screening tools
  - Reduce mortality
  - Underutilized

- Imperative to improve
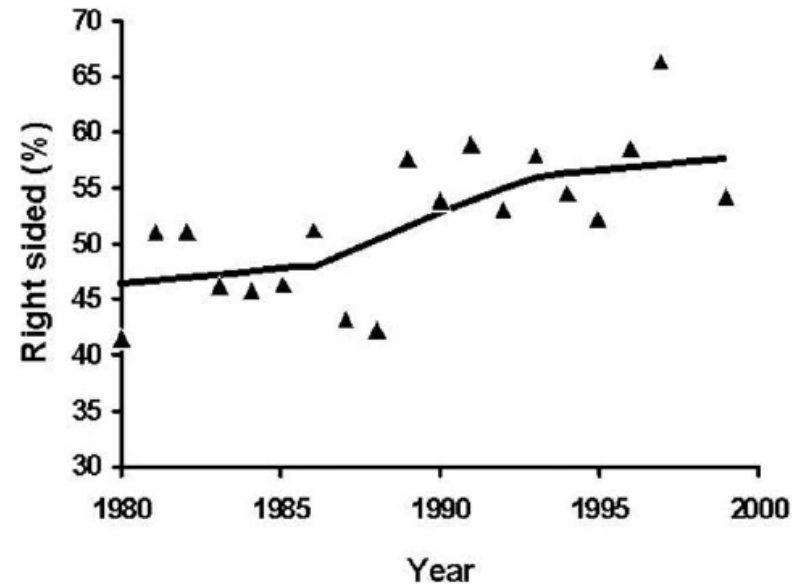
Siegel et al. CA *Cancer J Clin 2015;65:5*
Gupta et al. *Clin Gastroenterol Hepatol*. 2005;3:150
Shapiro et al. *Cancer Epidemiol Biomarkers Prev*. 2012;21:895

American Cancer Society Guidelines

Average-risk adults begin CRC screening at age 50 years with one of the following options:

- Annual high-sensitivity gFOBT or FIT

- Flexible sigmoidoscopy every 5 years

- Colonoscopy every 10 years

- Double-contrast barium enema every 5 years

- CT colonography every 5 years

- sDNA test every 3 years

Smith et al. *CA Cancer J Clin.* 2015;65:30

Effectiveness of CRC Screening Tests

Test (evidence)	Incidence	Mortality	Left side rate	Right side rate	References
FOBT (RCT)	No effect	↓ 14-30%	30% CRC sensitivity	20% CRC sensitivity	Logan.*Gut.* 2012;61:1439 Heresbach. *Euro J Gastroenterol Hepatol* 2006;18:427 Haug. *Br J Cancer.* 2011 ;104:1779
Flex sig (RCT)	↓21-33%	↓26-43%	↓26-43% mortality	↓0% mortality	Atkin. *Lancet.* 2010;375(9726):1624 Schoen. *N Engl J Med.* 2012; 366:2345
Colonoscopy (Cohort, case-control)	↓54-70%	↓68-70%	↓70-82% mortality	↓0-53% mortality	Baxter. *Ann Intern Med.* 2009;150:1 Brenner. *J Natl Cancer Inst.* 2010;102:89 Nishihara. N *Engl J Med.* 2013;369:1095

Accuracy of New CRC Screening Tests

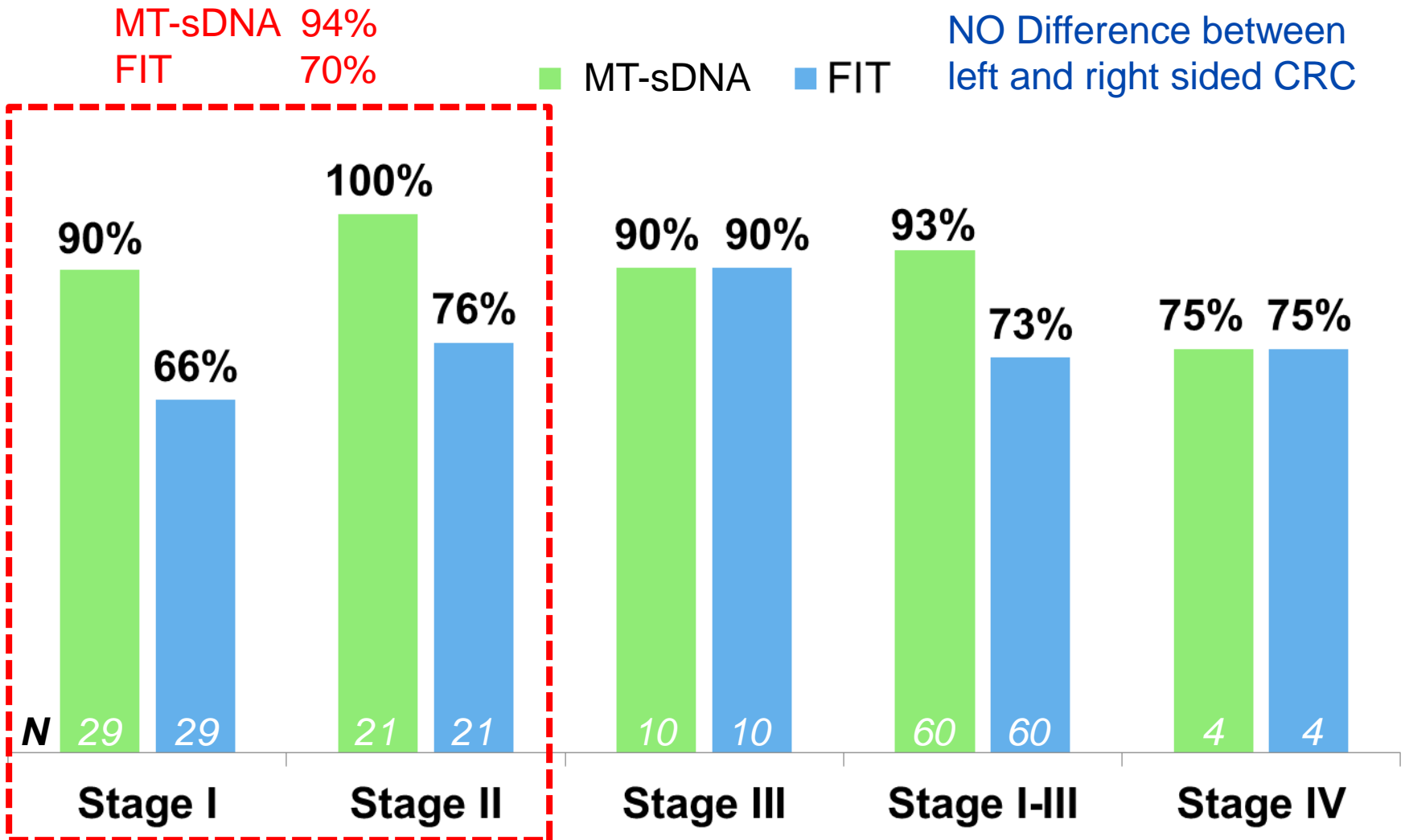| Test	CRC Sensitivity*	Adv Adenoma Sensitivity*	Specificity *	L>R CRC Bias	Reference
CT colonography	96%	83%	95%	NO	Pickhardt. *Radiology*. 2011;259:393 deHaan. Eur Radiol. 2011;21:1747

*vs colonoscopy

Why is CT colonography not in wider use?
- Availability
- Coverage
- Bowel prep
- ? Cost-effectiveness
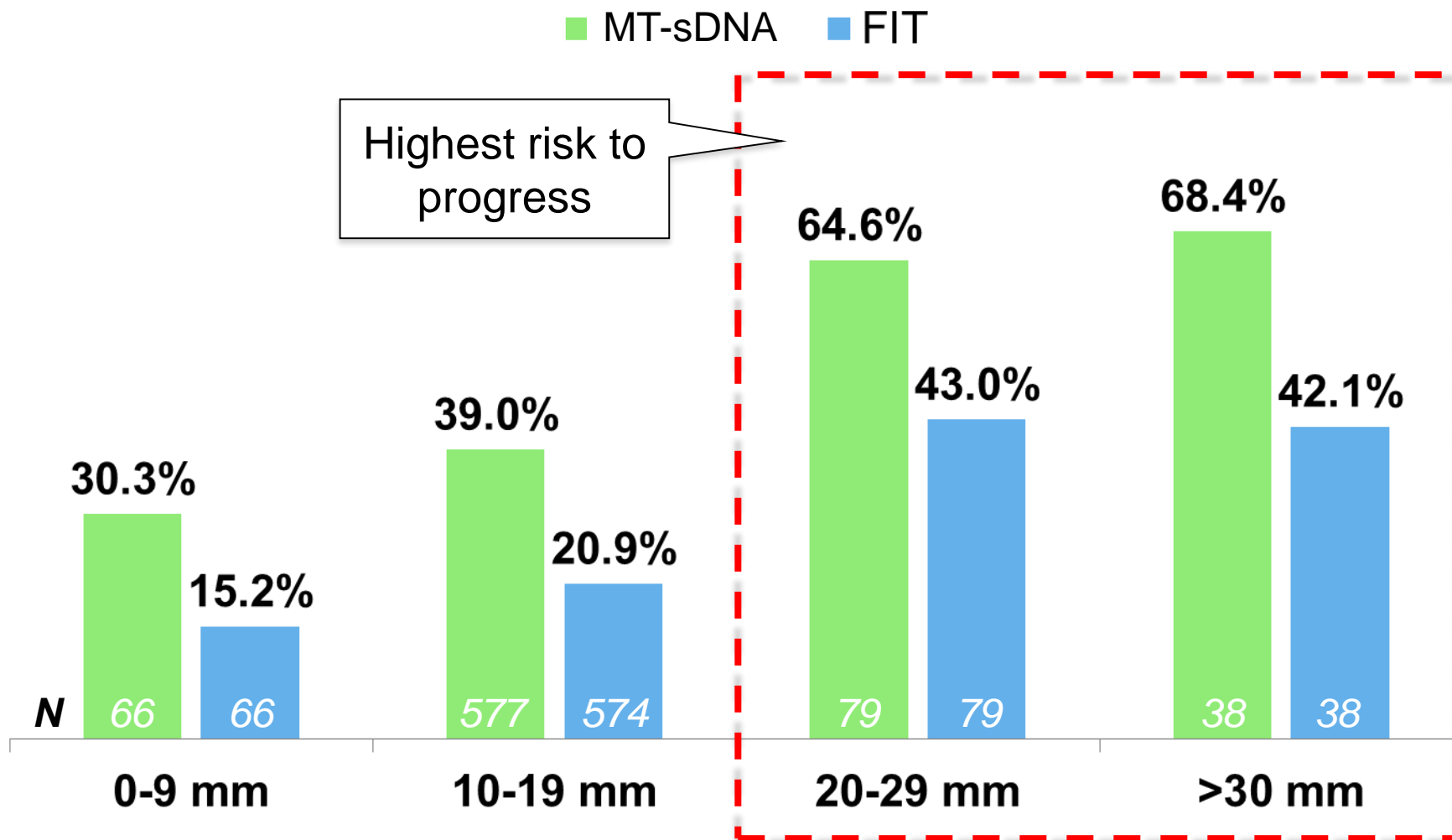- ? Diagnostic radiation exposure

Accuracy of Commercialized Multi-target Stool DNA Test vs FIT

- MT-sDNA test
  - Methylated *BMP3* & *NDRG4*
  - Mutant *KRAS*
  - *β-actin* (human DNA)
  - Hemoglobin (FIT)

- 10,000 average risk patients

- MT-sDNA and FIT

- Prior to blinded colonoscopy

Imperiale et al. *N Engl J Med* 2014; 370:1287

CRC Sensitivity by Stage

MT-sDNA 94%
FIT 70%

NO Difference between left and right sided CRC

Legend: ■ MT-sDNA ■ FIT

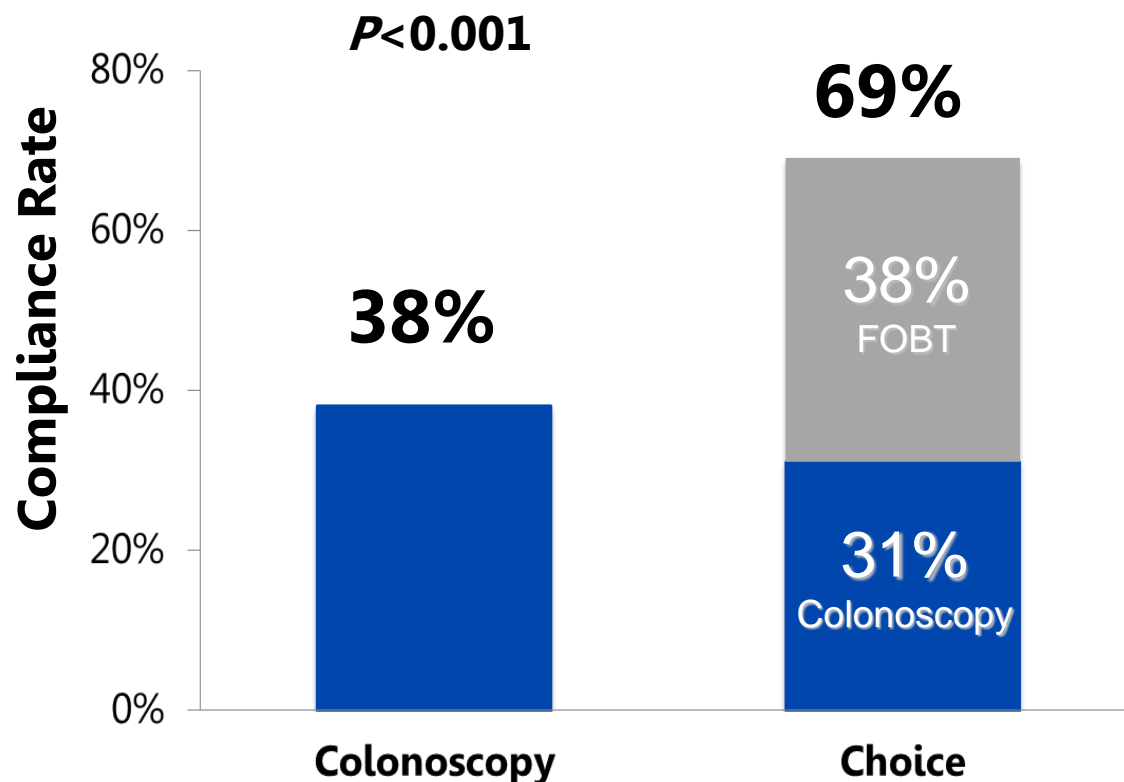|	Stage I	Stage II	Stage III	Stage I-III	Stage IV
MT-sDNA	90%	100%	90%	93%	75%
FIT	66%	76%	90%	73%	75%
N (MT-sDNA)	29	21	10	60	4
N (FIT)	29	21	10	60	4

The Future: Improve Compliance

- 2012 CRC screen rate 65%

- "80% by 2018 Initiative"
    - Educate clinicians
    - Reach newly insured
    - Target low socio-economic status populations
    - Communicate to unworried well
    - Engage payers
    - Medical neighborhoods/ partner organizations
    - Increase screening access

http://nccrt.org/tools/80-percent-by-2018/

Providing Non-invasive Screening Option Increases Program Screening Rates

Impact of sDNA?
- Mailed
- Acceptable
- No prep
- No work time
- May improve access
- May improve compliance

P<0.001

80%
60%
40%
20%
0%

Compliance Rate

69%

38%
FOBT

31%
Colonoscopy

38%

Colonoscopy   Choice

Patient Compliance Within 1 Year

Inadomi et al. *Arch Intern Med.* 2012;172:575
Schroy et al. Am J Prev Med. 2005;28:208

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The Future: Stop Single Organ Screening

- Screen multiple cancers in a single test

- Aggregate incidence outweighs organ incidence

- The PERSON as the new unit of analysis

- Stool test: cancers of the GI tract, lung, ENT

- Blood test: all cancers

MAYO
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The Pan-GI Cancer Detection Concept

- Discovery:
  - Genome-wide
  - Each major cancer

- Integration & filtration of results:
  - Best overall cancer markers
  - Most site-specific for each cancer

- Validation:
  - Multiple assay platforms
  - Independent tissue sets
  - Local biological media
  - Distant biological media

Cornerstone Project

Anatomic Site	Lesion Category	RRBS/ qMSP	Validation	Clinical pilot
Oropharynx, lung	Tonsil, tongue Tracheal, bronchial	In progress	Partial	
Esophagus	Normal Barrett's (+/- dysplasia Adenocarcinoma, Squamous carcinoma	**Complete**	**Complete**	**Complete**
Stomach	Normal Adenoma Adenocarcinoma	**Complete**	**Complete**	In progress
Pancreas	Normal colon, WBC, Benign pancreas Ductal adenocarcinoma	**Complete**	**Complete**	**Complete**
Pancreas precursors	Main, branch duct IPMN PanIN I-III	**Complete**	In progress	
Bile duct	Normal bile duct, liver Intra-hepatic CCA, Peri-hilar CCA	**Complete**	**iCCA complete** eCCA in-progress	In progress
Liver	Hepatoma Cirrhotic, NASH controls	In progress		
Small bowel	Normal Adenocarcinoma	In progress		
Colon	Normal SSA > 1cm, Adenoma > 1 cm, CRC	**Complete**	**Complete**	↓
IBD	Colitis LGD, HGD, CRC	In progress		**Complete**
Stool	Normal stools	**Complete**		
Peripheral blood	Buffy coat, plasma, cellular compartments	In progress		

Overall Model

Tissue source	Predicted by model			
	CTRLs	Colorectal neoplasia	Pancreatico-biliary cancer	Gastro-esophageal neoplasia
CTRLs	116	9	10	2
Colorectal neoplasia	1	86	1	7
Pancreatico-biliary cancer	1	0	65	4
Gastro-esophageal neoplasia	1	2	8	72
Overall accuracy			0.88, P<0.0001, chi-square	

Can this work non-invasively?

- 2 markers
  - *BMP3*
  - *QKI*

- 2ml plasma

Tissue source	Predicted by model			
	Controls	Colorectal neoplasia	Pancreatic cancer	Error
Controls (n=14)	**12**	0	2	0.14
Colorectal neoplasia (n=14)	4	**8**	2	0.43
Pancreatic cancer (n=14)	3	0	**11**	0.21
Overall accuracy Fisher Exact			**0.74 p<0.0001,**	

Kisiel, et al. *AACR* 2015

Conclusions

The present

- Current CRC screening reduces mortality

The Future

- Goal: eradicate CRC

- Improve performance & compliance & access

- Shift paradigm to multi-organ screening

Acknowledgements

GI Cancer Molecular Diagnostics Lab