Stool DNA Testing
A Closer Look at Specificity

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Disclosures

Relationship with Exact Sciences

- *Mayo Clinic*
  - Equity investor
  - Licensed technologies
- *Dr. Ahlquist*
  - Scientific Advisor
  - Inventor of licensed technology
  - Research collaborator

Multi-target Stool DNA Test

- FDA Approved (*Cologuard*, Exact Sciences)
- Endorsed in screening guidelines (ACS, USPSTF, NCCN)
- Included in Quality Measures (HEDIS, STARS)
- Covered by Medicare (CMS) and 3rd party payors
- Exponential growth in adoption
  - 42% of users report no prior CRC screening

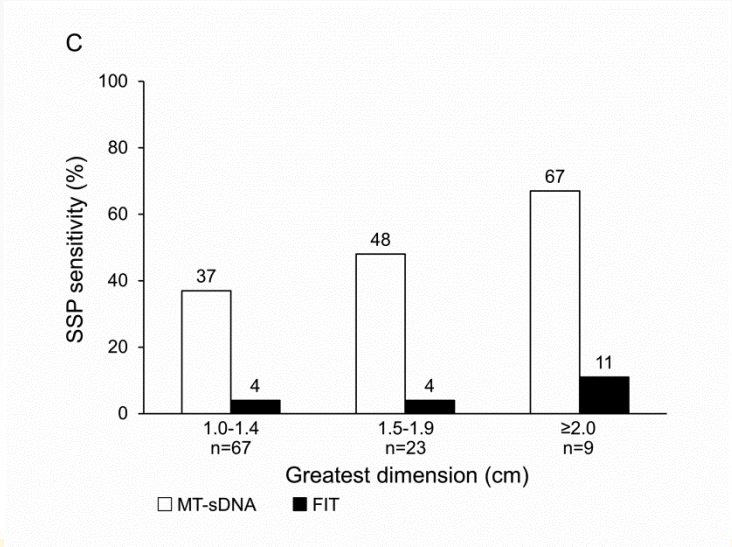
Point Sensitivity

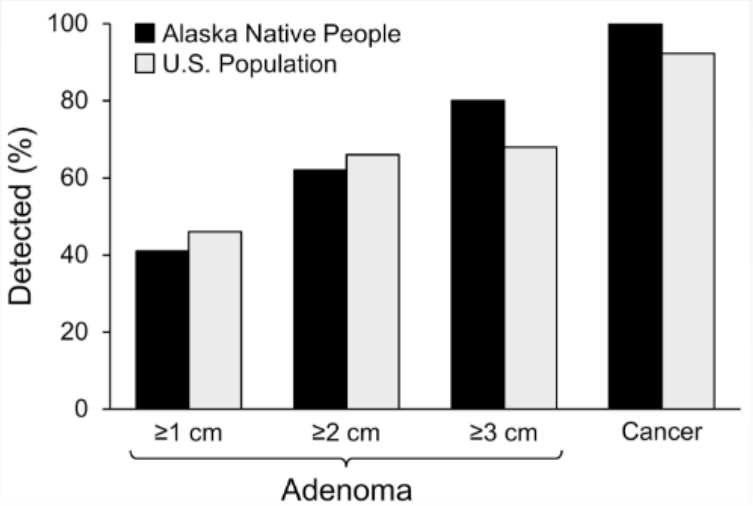
Cancer **92-100%**

Stage I-II 94-100%

Adenoma

SSP





Imperiale et al. NEJM 2014
Redwood et al. MCP 2016
Berger et al. DDW 2014

Program Sensitivity

Modeled Estimate (q3yr testing)

Cumulative Sensitivity **%**

For Lesion Cohort

	Large Precancer*		**CRC (I-II)**
	1-2 cm	***HGD***	
Screen 1	42-66	69	94
Screen 2	71-91	93	--
Screen 3	88-98	(99)	--

*Assumptions

1. Size doubling time: 6 yrs
2. Independent measurements

Ahlquist. DDS 2015; 60:623

Point Specificity

From screening studies (using blinded colonoscopy as criterion standard)

US study — Imperiale et al. NEJM 2014

- **Overall** **90%**
- **Ages 50-65** **94%**

Alaska study — Redwood et al. MCP 2016

- **Overall** **93%**

Real-world specificity may be higher when endoscopists aware of positive MT-sDNA

Knowledge of Positive MT-sDNA Improves Yield & Quality of Colonoscopy

	Un-blinded (172)	Blinded (72)	p-value
Any polyp	**78%**	**60%**	**0.0047**
Any adenoma or SSP	**70%**	**53%**	**0.013**
Advanced CRN	28%	21%	0.27
Flat R-sided polyp	**40%**	**9%**	**0.0017**
Med # polyps/patient	**2**	**1**	**0.0007**
Med withdrawal time	**19 min**	**13 min**	**0.0001**

Johnson et al. Gastrointest Endosc 2017; 85:657

Program Specificity

Critical metric: average false positives/year

- **FIT** q1yr
  - With point false pos rate of 3-5%, average false-positives would be ~ **3-5%/yr**
- **MT-sDNA** q3yr
  - With point false pos rate of 7-10%, average false-positives would be ~ **2-3%/yr**
  - Compared to conventional CRC screening approaches*
    - Highest benefit/harm ratio
    - Fewest lifetime colonoscopies

*2016 USPSTF Guidelines (JAMA 2016)

CRC Screening by MT-sDNA

Do false-positives warrant further evaluation?

MT-sDNA Screening (from US multicenter study)

F/U on False-positives

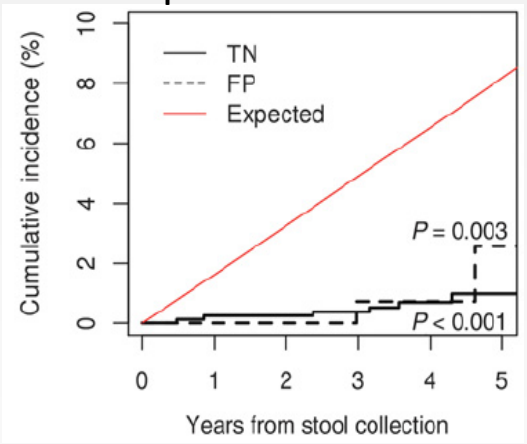
- Hilsden et al. DDW 2016 (Calgary)
  - Total studied (772)
    - CRC (7), 100% MT-sDNA pos; Adv ad (49), 53% MT-sDNA pos
  - MT-sDNA pos & Colonoscopy neg or non-adv polyps (118)
    - One metastatic pancreatic cancer after 6 mos F/U
- Geenen et al. DDW 2017 (WI, IN)
  - Colonoscopy neg or non-adv polyps (187); med 4 yr F/U
    - MT-sDNA neg (150) No cancers
    - MT-sDNA pos (37) One parotid tumor

Mayo Clinic "Long-Haul" Study

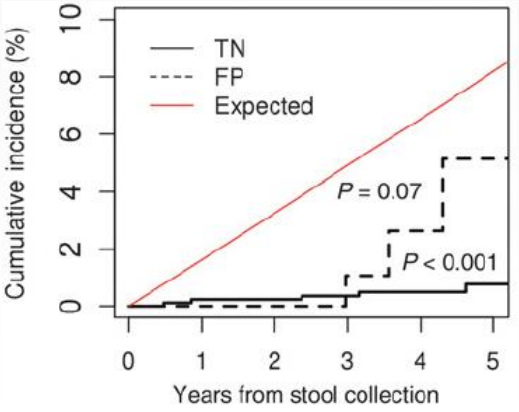
F/U of false-positive stool DNA

- N=1050 (3 pre-approval studies)
- Median F/U 4 yrs (range 3.5-5.3)
- Only BMP3 + NDRG4 markers eval'd
  - By per protocol & calibrated 90% cutoffs
- HRs for subsequent AD cancers (n=8)
  - Per protocol cutoff 1.3 (0.3–6.7)
  - Calibrated cutoff 4.1 (1.0–17.6)
- Observed incident AD cancers in FP group < expected in gen pop (SEER)

Per protocol cutoff



Calibrated cutoff



Cotter et al. CEBP 2017;26:614

MT-sDNA Summary

- High program sensitivity and specificity for CRC and advanced polyps
- Program false-positive rate at q3y estimated to be lower than that of FIT at q1yr
- Very low rate of incident AD cancers among false-positives over medium F/U duration

Based on findings to date, clinical workup of MT-sDNA false-positives <u>not</u> warranted.