STANFORD
SCHOOL OF MEDICINE

Colorectal Cancer Screening

36th EDRN Steering Committee Meeting
October 27, 2020

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Division of Gastroenterology and Hepatology
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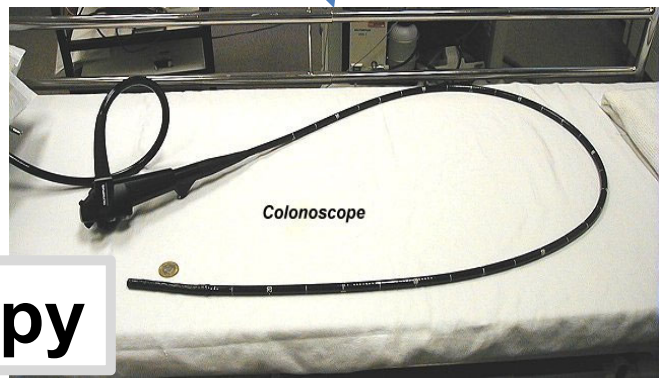
Disclosures – Advisor / consultant

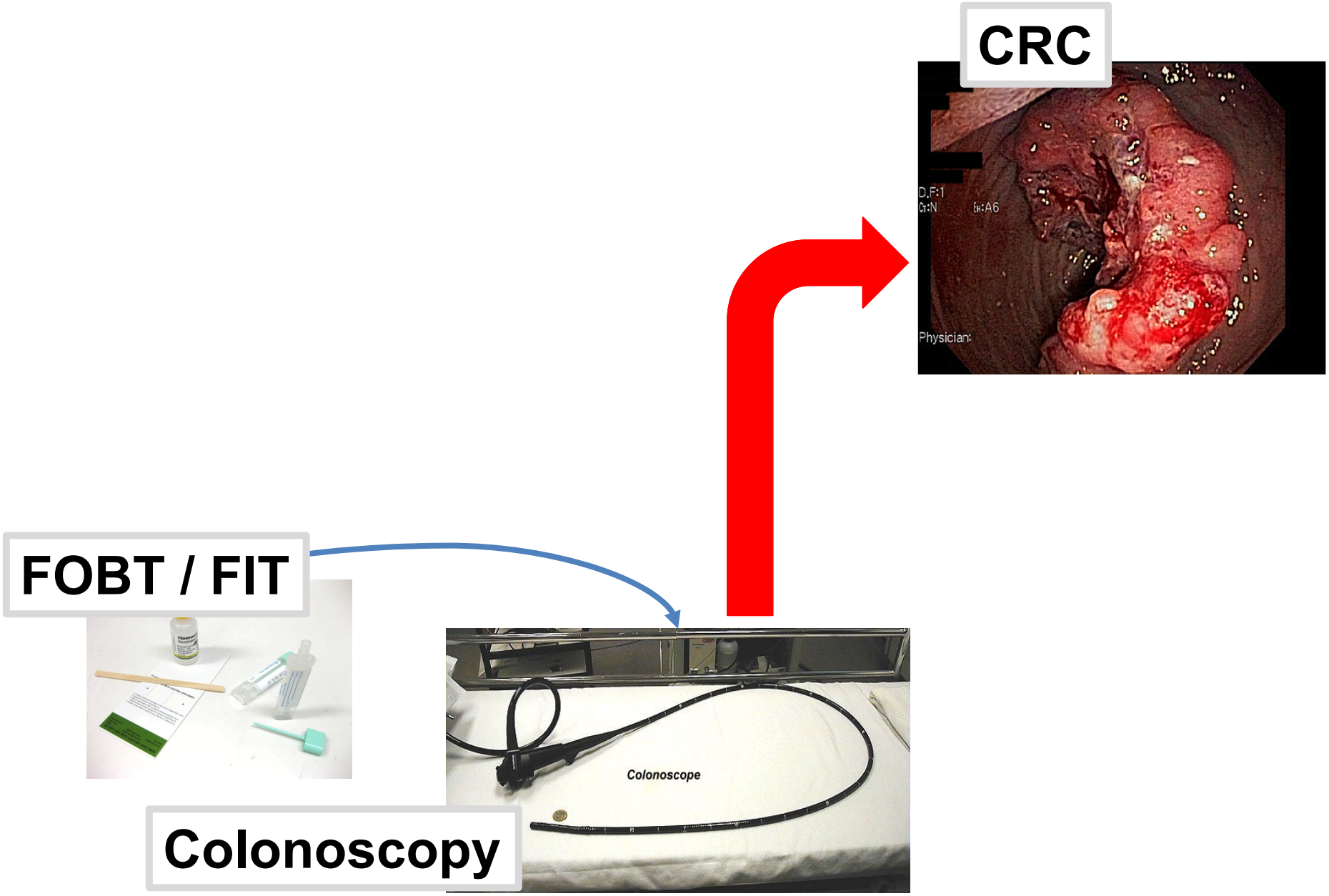
- Universal Dx
- Clinical Genomics
- Guardant Health
- Covidien / Medtronic
- Freenome
- Leerink
- ChekCap

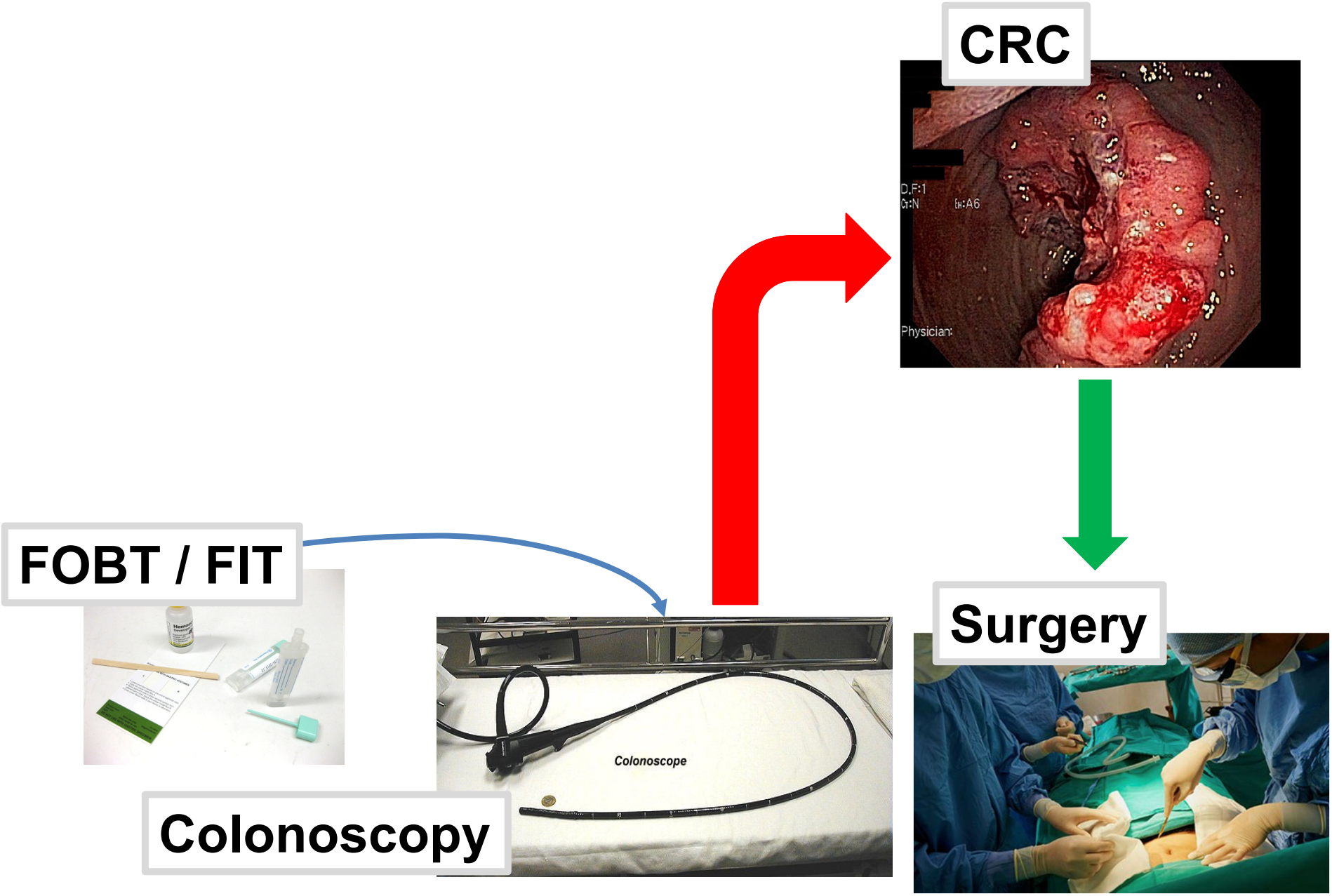
FOBT / FIT

FOBT / FIT



Colonoscopy


CRC
D.F:1
G:N
Physician:
FOBT / FIT
Colonoscopy
Colonoscope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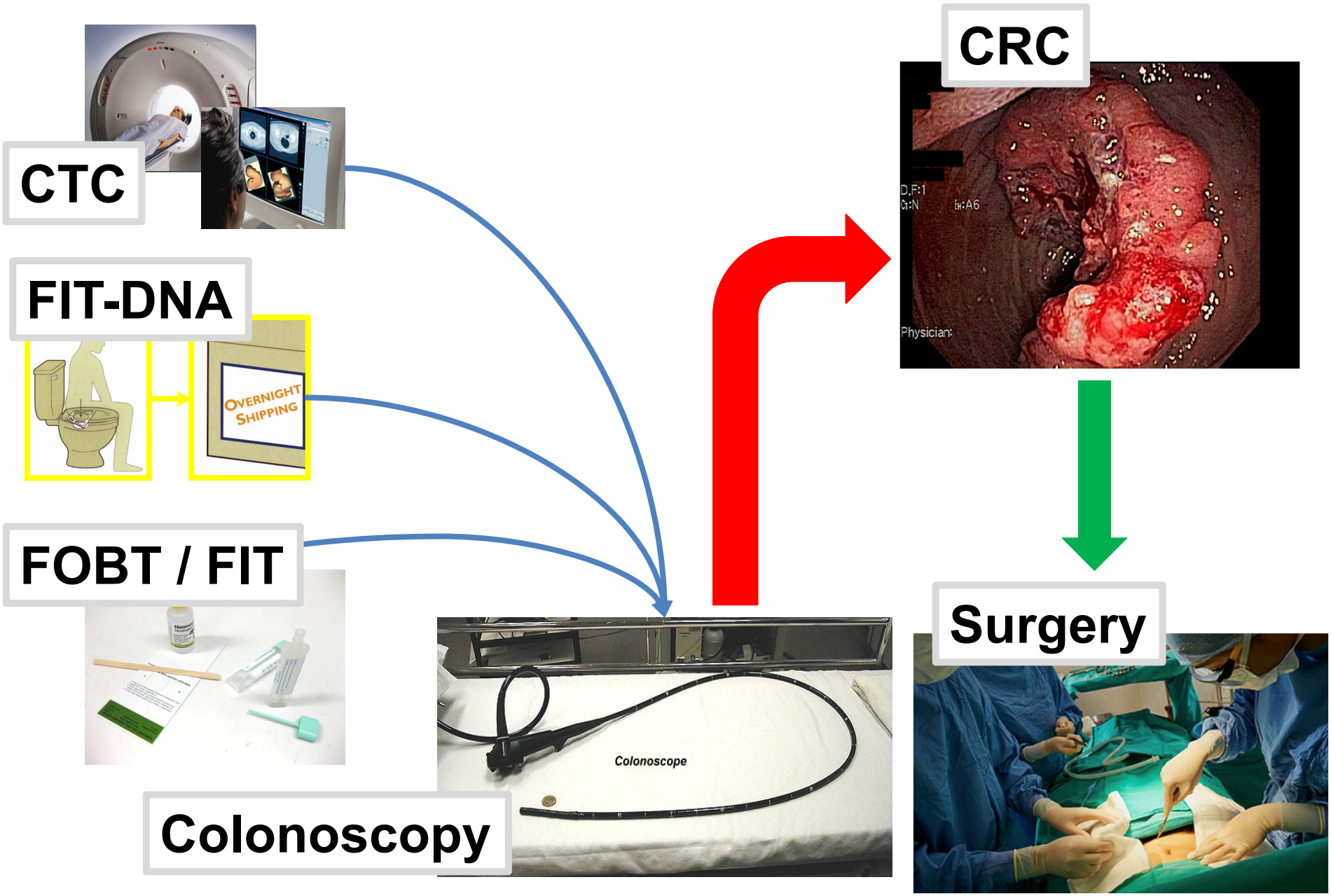
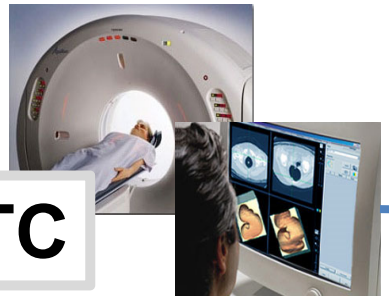
Colonoscope
Surgery

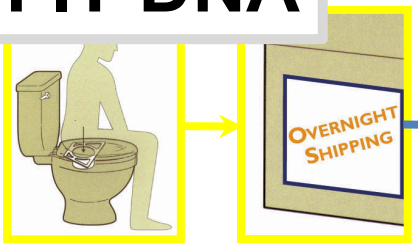

CTC
FIT-DNA
OVERNIGHT SHIPPING
FOBT / FIT
Colonoscopy
Colonoscope
CRC
Surgery

CRC Screening 3.0

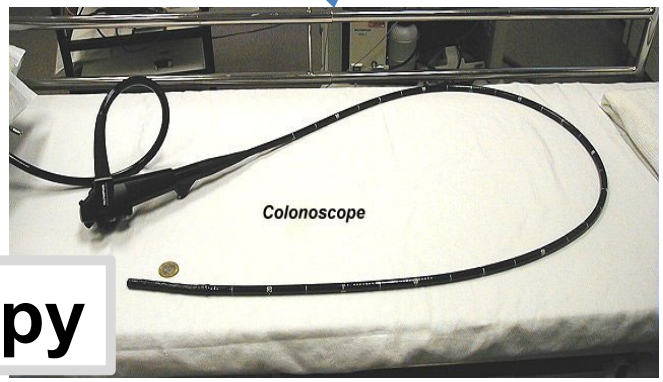


CTC

FIT-DNA

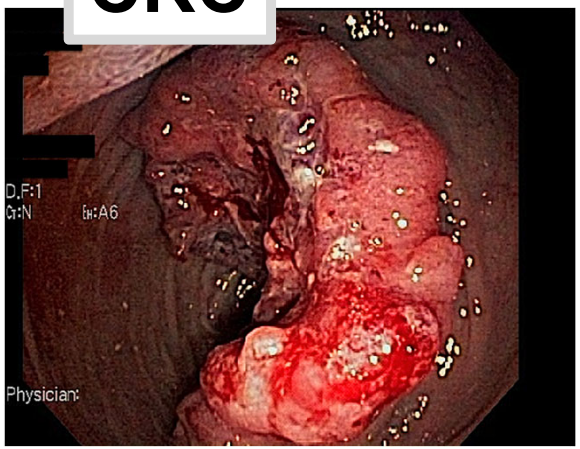


FOBT / FIT



Colonoscopy

CRC



Surgery

All roads lead to….

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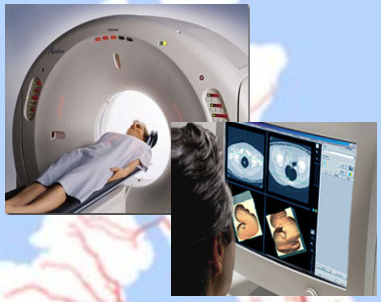
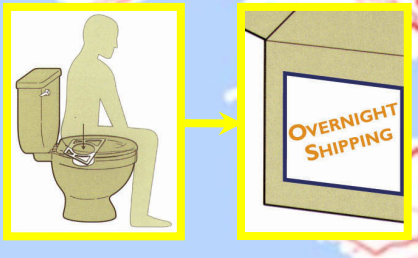
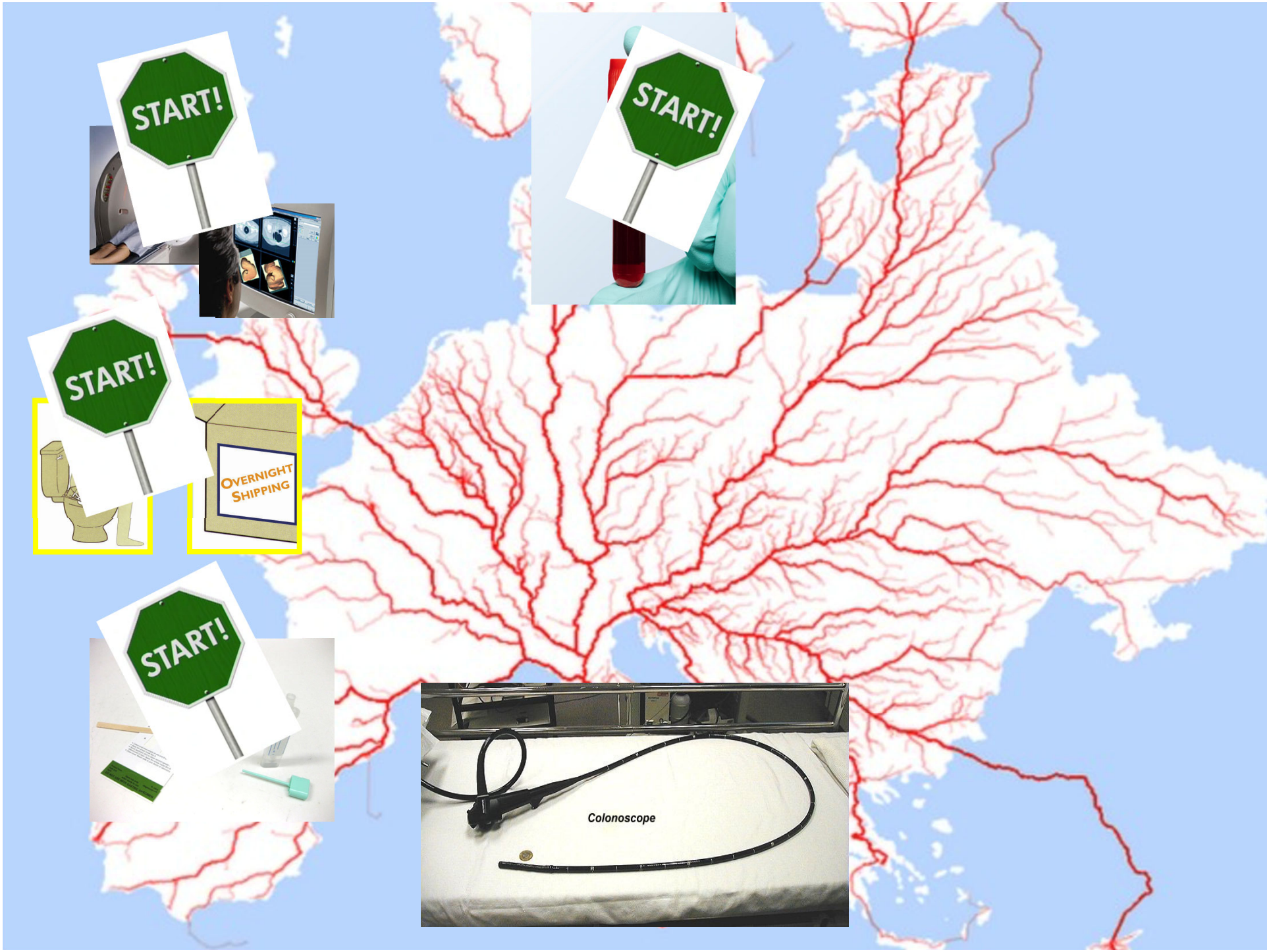
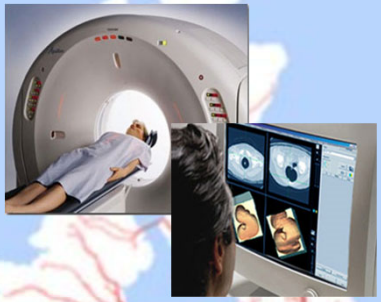
Colonoscopy

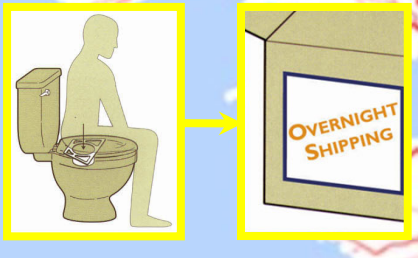



OVERNIGHT
SHIPPING

Colonoscope


START!
START!
START!
START!
OVERNIGHT SHIPPING
Colonoscope

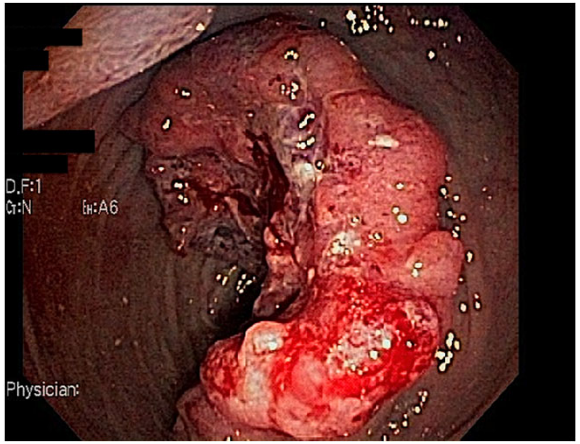


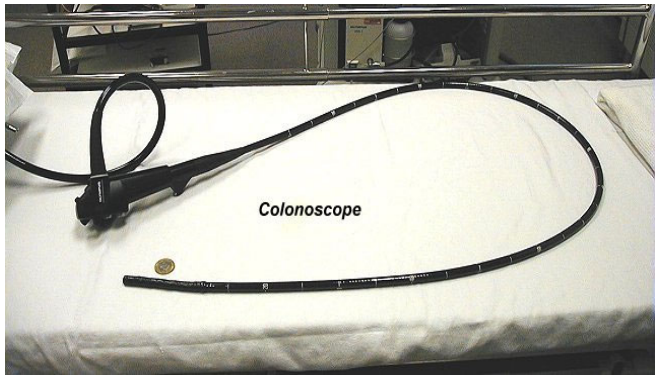

OVERNIGHT
SHIPPING

START!

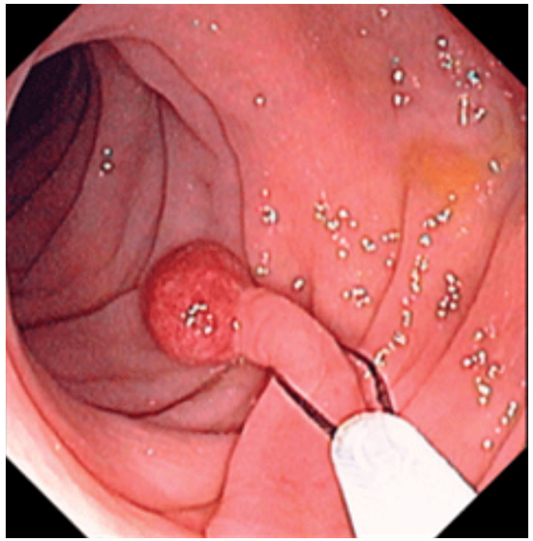
Colonoscope

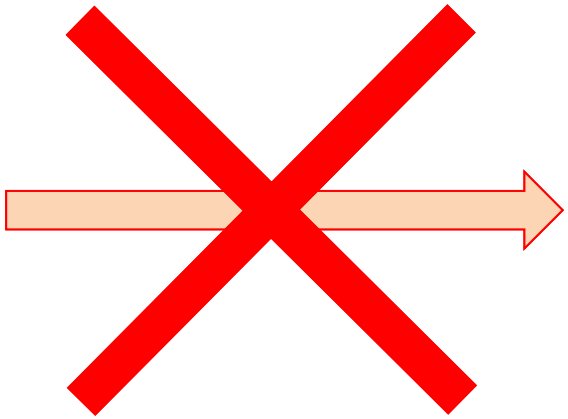
Colonoscopy is not only diagnostic

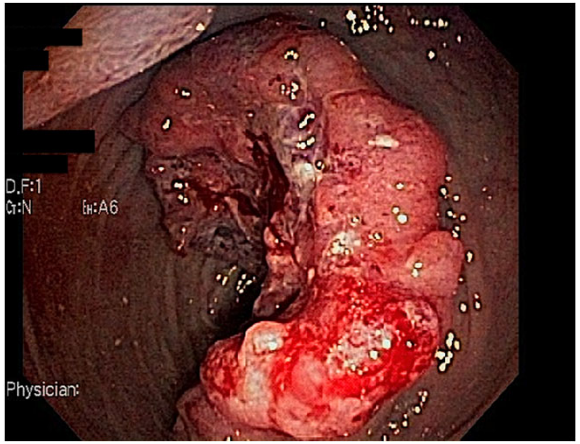


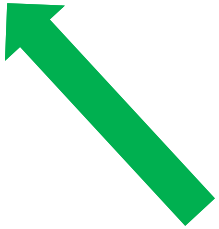


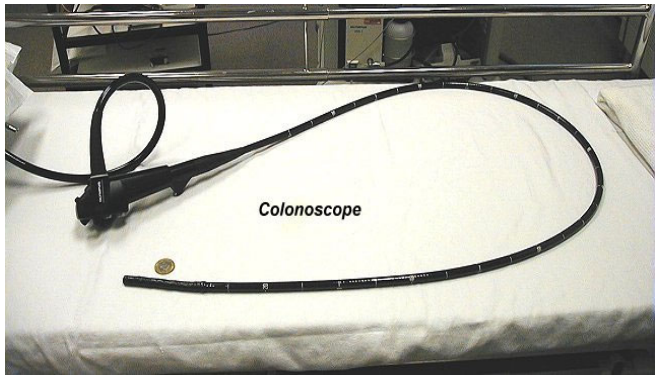
Colonoscopy is not only diagnostic











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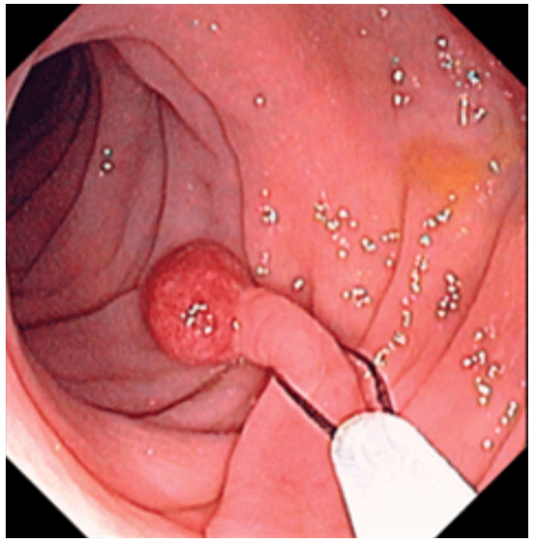
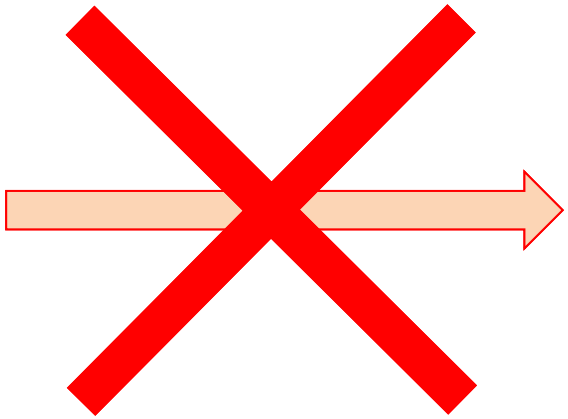
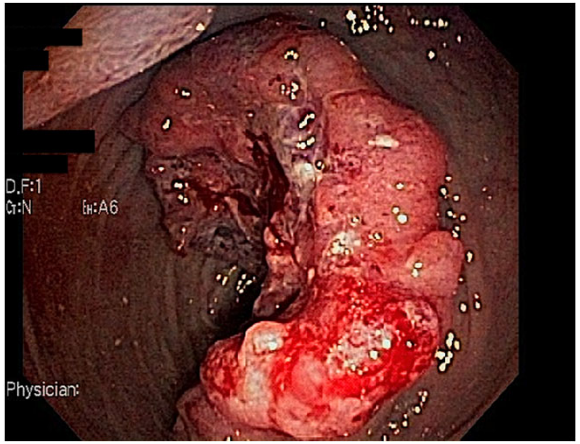
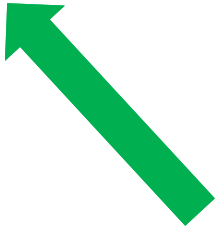
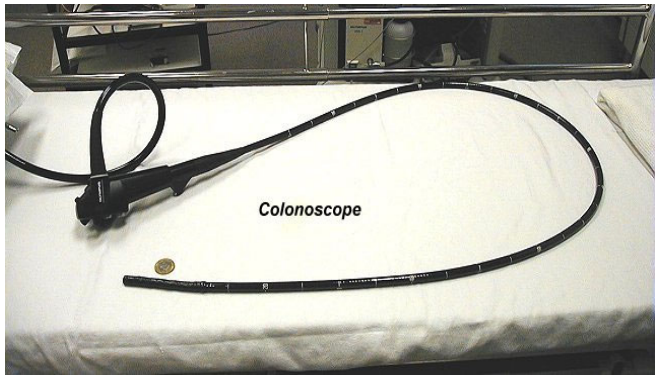


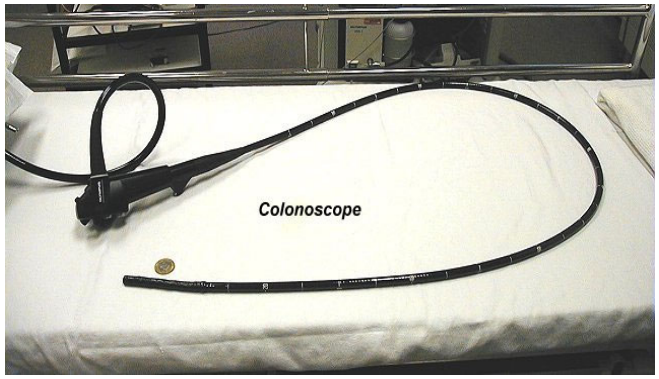




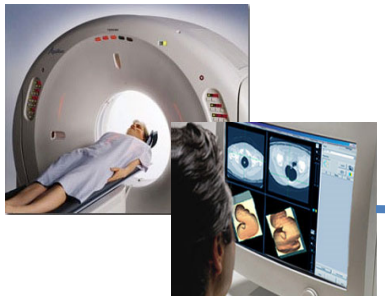


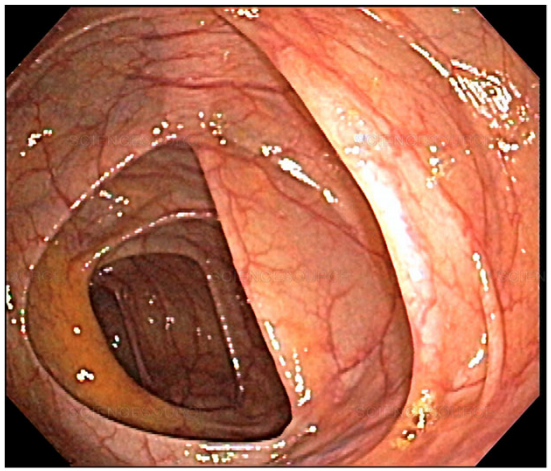


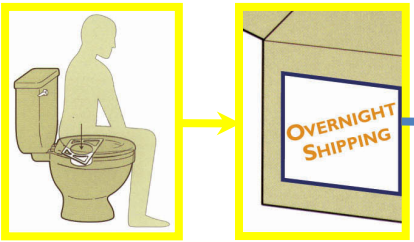
If colonoscopy is normal?

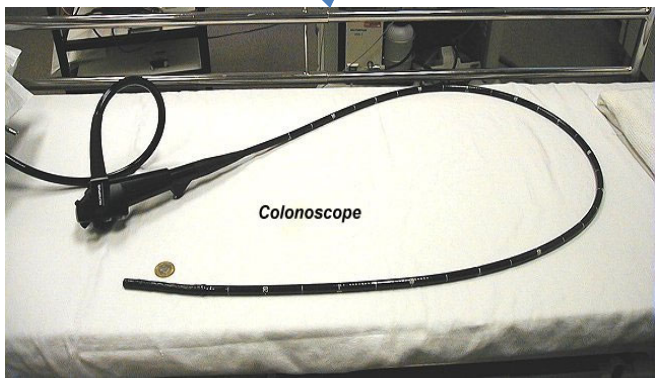


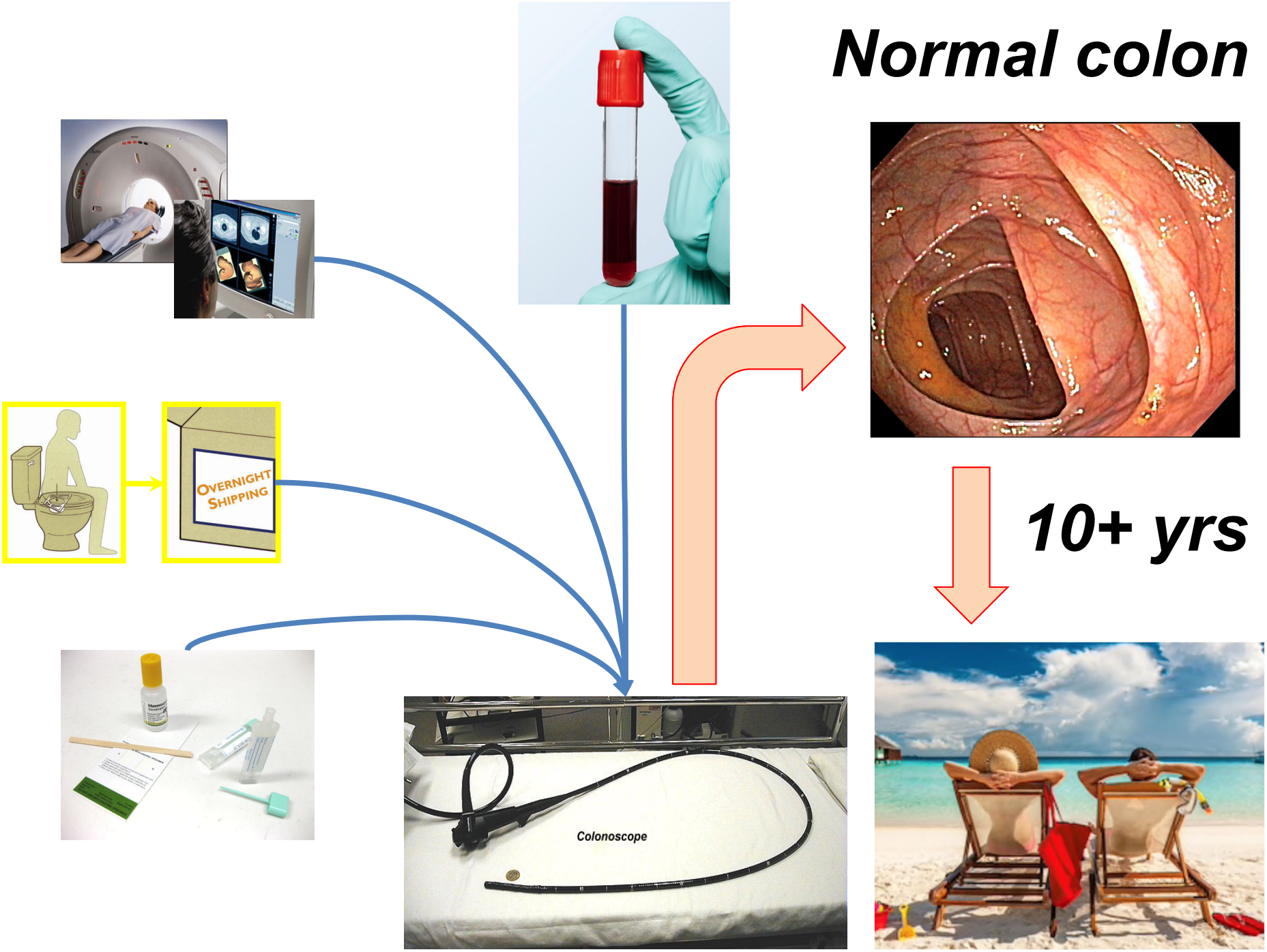
Normal colon









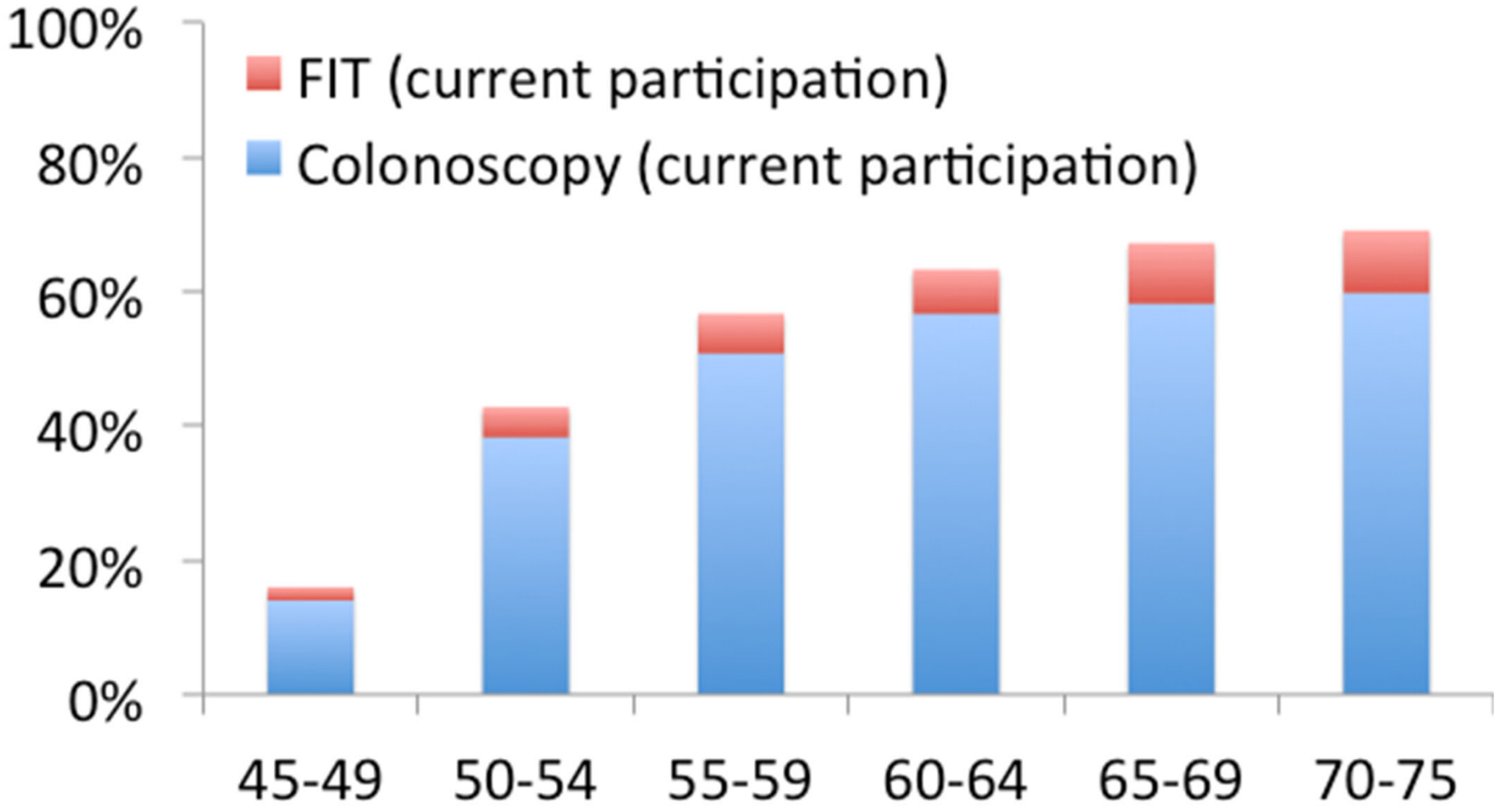

Normal colon
OVERNIGHT SHIPPING
10+ yrs
Colonoscope

CRC Screening: Current State

- RCTs show that screening decreases:
  - CRC mortality
  - CRC incidence
- We have multiple minimally invasive options
- All roads LEAD TO colonoscopy…
- …and a major road STARTS WITH colonoscopy
- Colonoscopy affects natural history
- Normal colonoscopy predicts low risk for >10 yrs
- The bar is high for “CRC Screening 3.0”

Effectiveness =
Participation x Efficacy

Current screening participation in U.S.



Sauer et al., Prev Med 2018;106:94 [NHIS data]

Screening test attributes

Accuracy	Interval	Safety	Ease and feasibility	Cost
Sensitivity **Specificity**				

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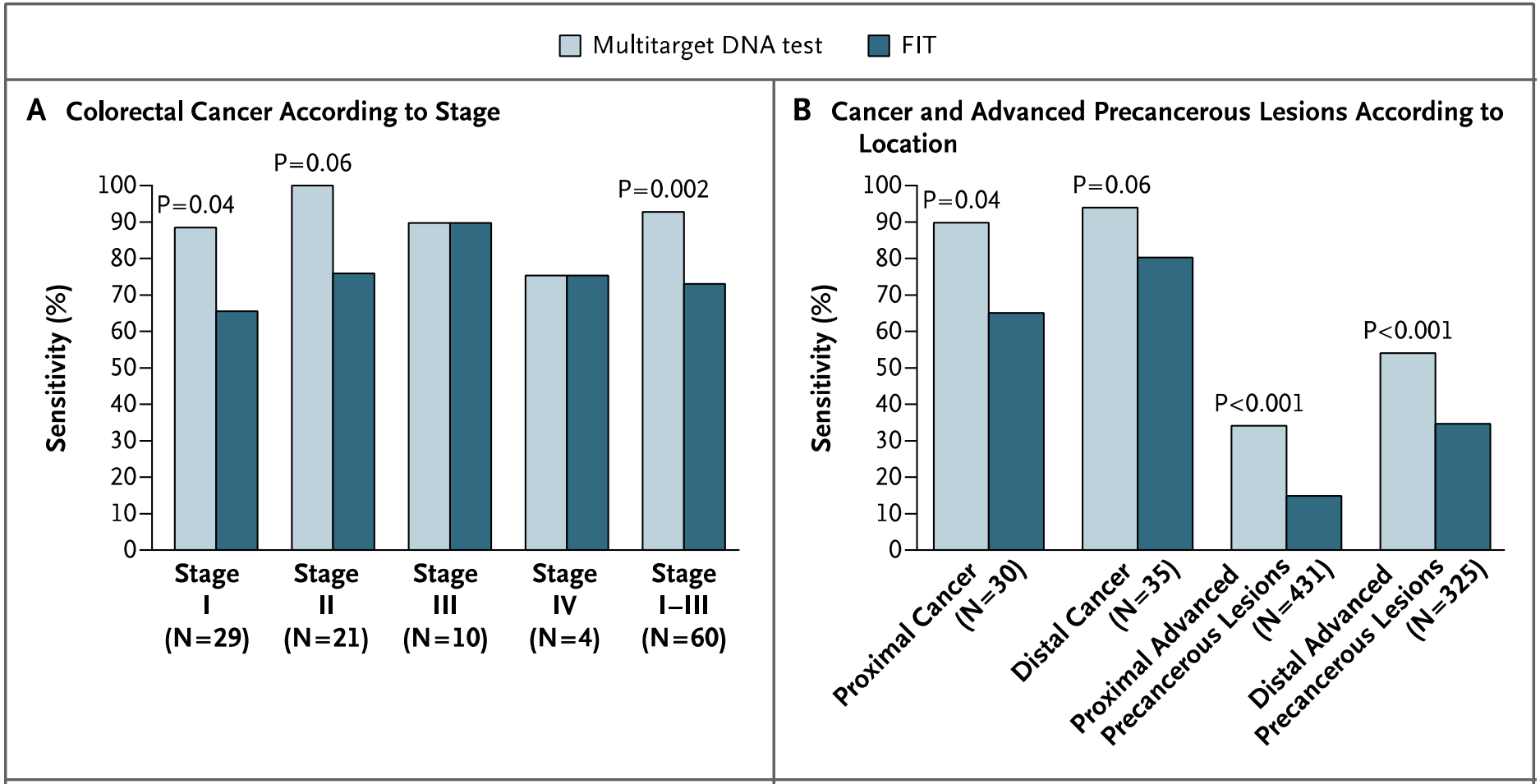
Sensitivity **Specificity**	A ***program*** vs. a ***test***	Complications Overdiagnosis	Participation	Cost-effectiveness
• High sensitivity for CRC and advanced polyps • Specificity has leeway (“go to colonoscopy”)	More accurate test = longer interval	• Colonoscopy has low risk overall • Overtreating polyps?	**Big opportunity**	• FIT is cheap • Outreach and navigation are not free

FIT and FIT-DNA (MT-sDNA): CRC detection



- Specificity: 89.8% (FIT-DNA, MT-sDNA) vs. 96.4% (FIT)
- Specificity: more relevant in colonoscopy-constrained setting

Imperiale *et al*, NEJM 2014; 370:1287

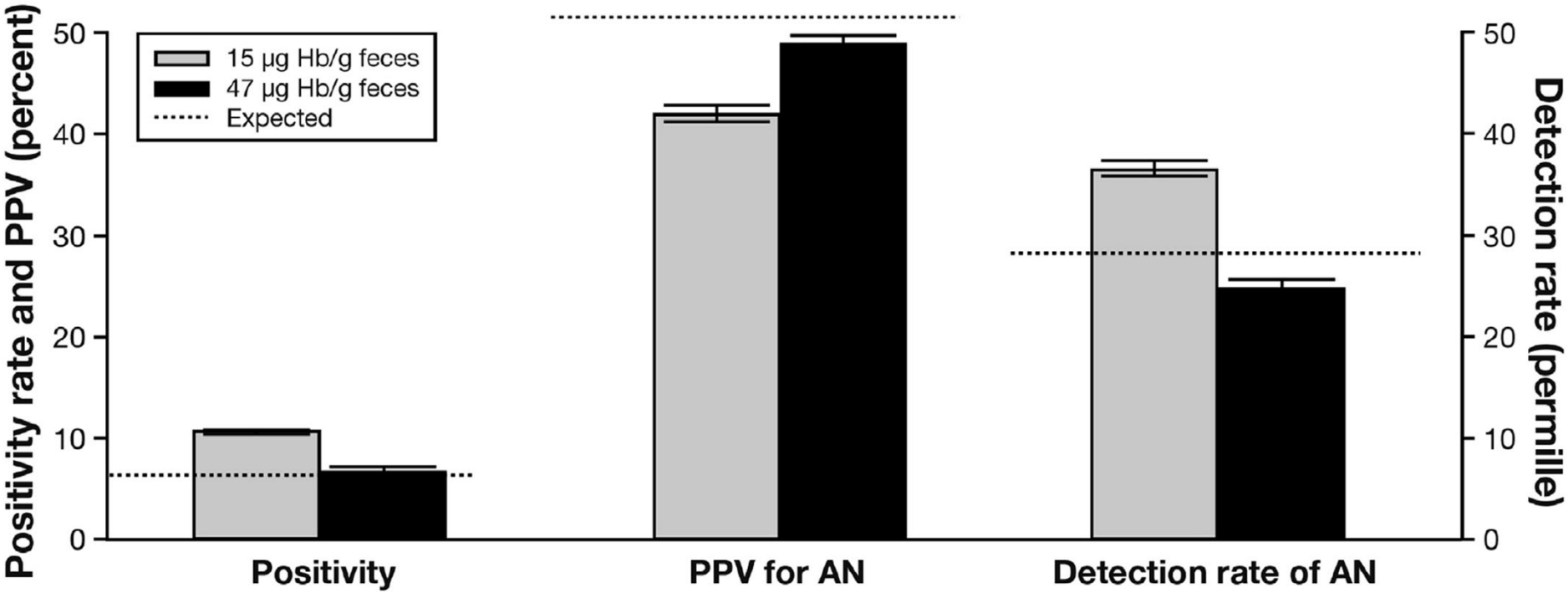
Multitarget DNA test FIT

Trading off sensitivity and specificity

- Real time monitoring of Dutch FIT program
- Participation and positive tests higher than anticipated
- "*To reduce the burden of unnecessary colonoscopies and alleviate colonoscopy capacity*…"
- FIT threshold: 15 → 47 mcg Hb/g feces

Toes-Zoutendijk et al, Gastro 2017;152:767

Trading off sensitivity and specificity



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Test performance characteristics

Test, Interval	Sensitivity for early stage CRC	Sensitivity for advanced polyps	Specificity
FIT *100 mcg/g*, 1-2y	65-70%	20-40% (5% serrated)	96%
FIT *8-10 mcg/g*, 1-2y			
FIT-DNA (MT-sDNA), 3y	85-95%	35-65%	90%
Plasma m-Sep9 DNA, ?			
Colonoscopy, 10y			
<u>CRC Screening 3.0</u>			

Imperiale *et al*, NEJM 2014; 370:1287

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Imperiale *et al*, AnnIntMed 2019; 170:319
Brenner *et al,* ClinEpi 2017; 9:377

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Colonoscopy, 10y	>95%	>85-90%	near 100%
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Brenner *et al,* ClinEpi 2017; 9:377

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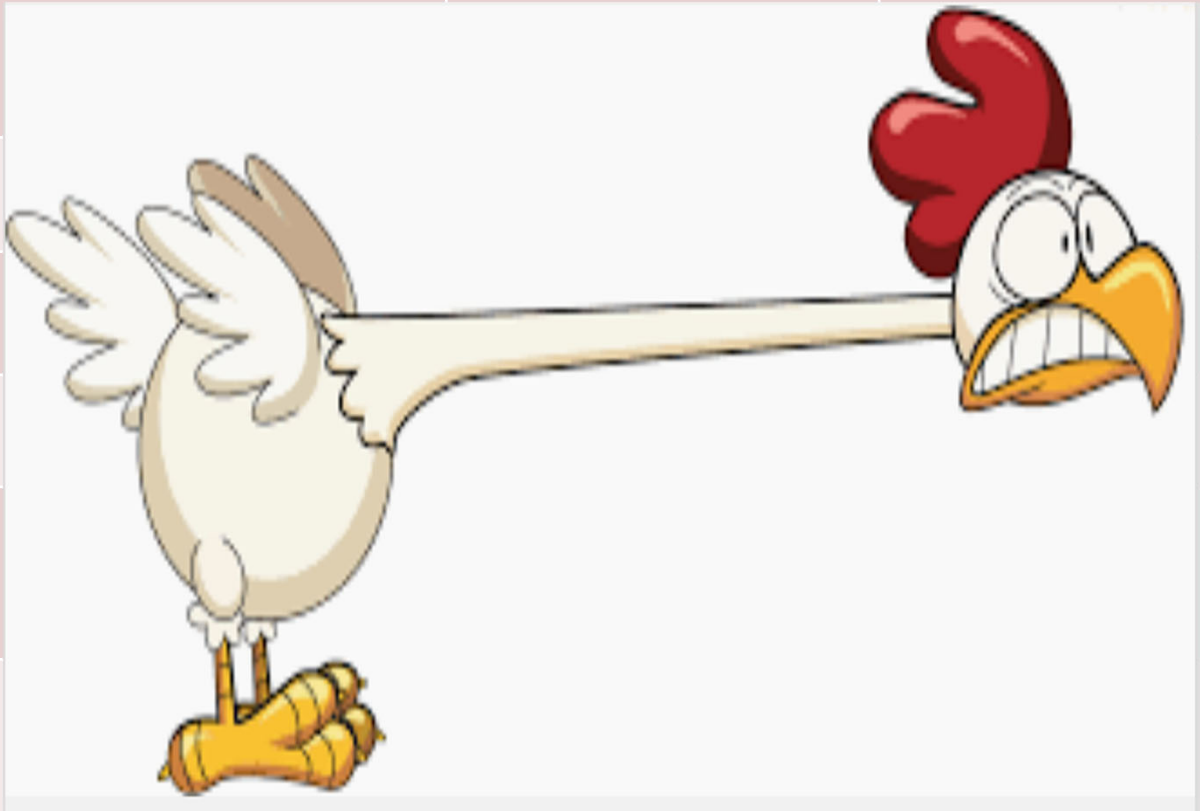

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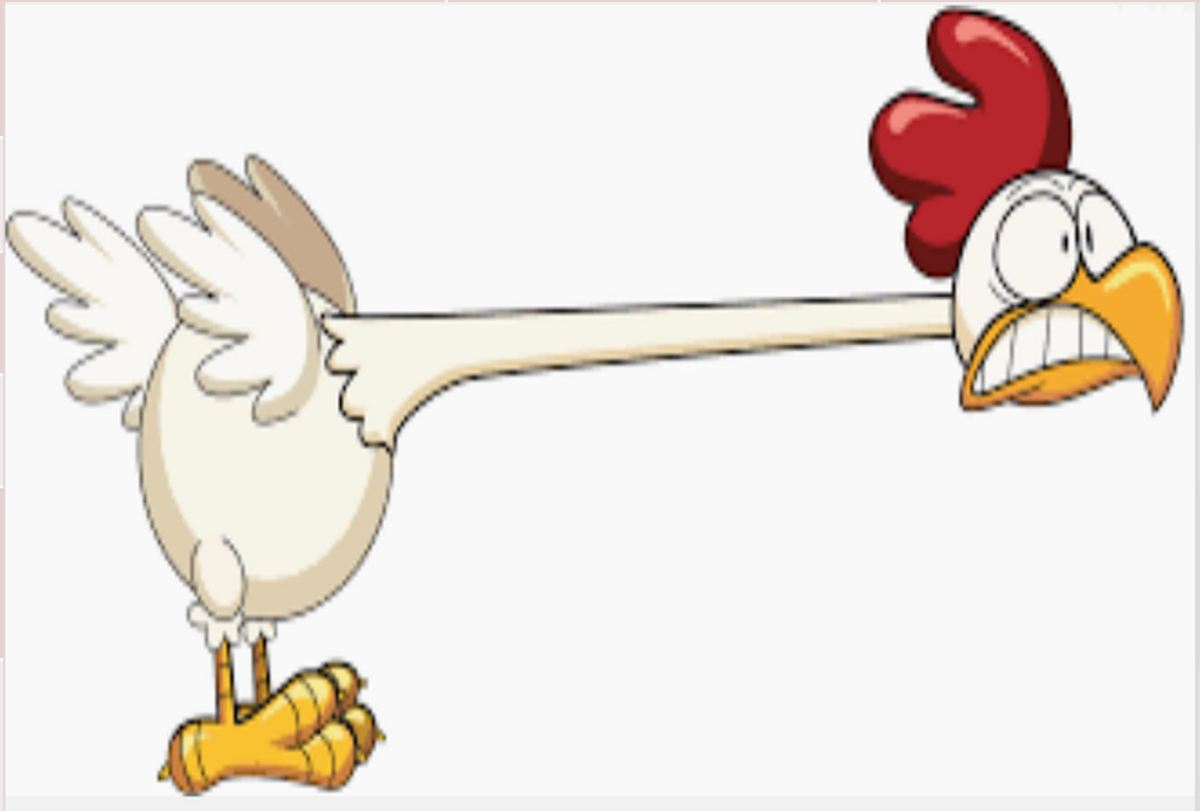

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Coverage: What does CMS think?

Table 5. Point Sensitivities and Specificities of Non-invasive CRC screening tests (compared to colonoscopy)		
	Sensitivity (%)	Specificity (%)
FIT	74	96
Stool DNA test	92	90
Epi proColon® test	72	81
Proposed blood-based biomarker (use lower number from among covered tests, Table 4)	*74*	*90*

Proposed Decision Memo for Screening for Colorectal Cancer - Blood-Based Biomarker Tests (CAG-00454N), October 16, 2020, **30-day comment period**

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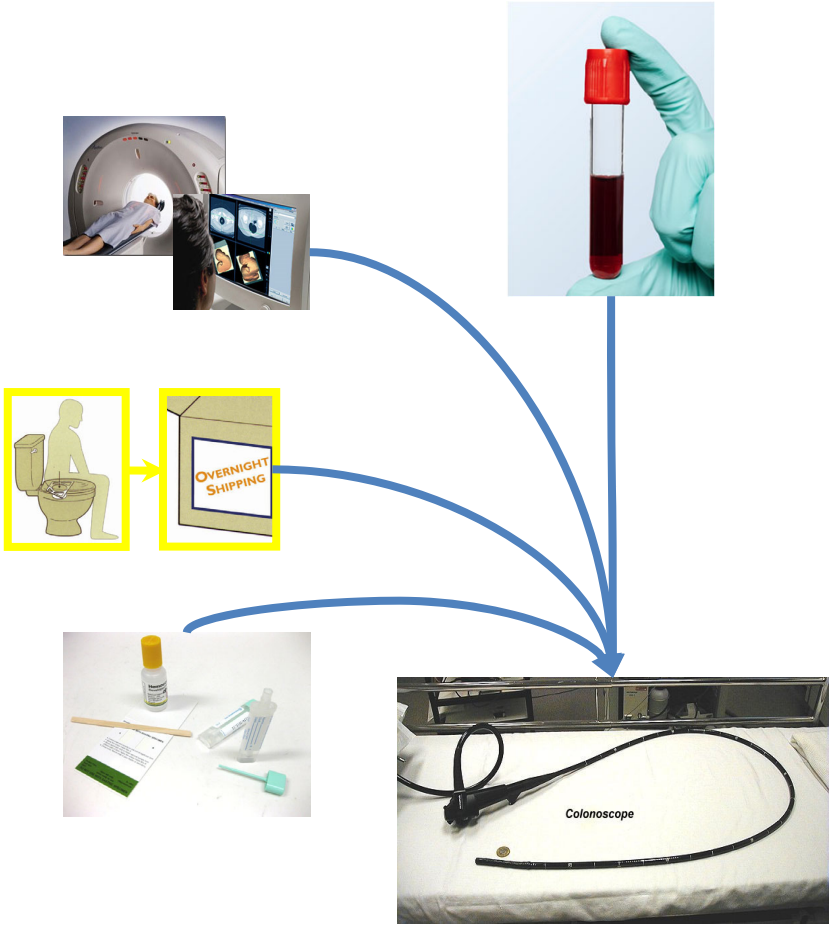
Proposed Decision Memo for Screening for Colorectal Cancer - Blood-Based Biomarker Tests (CAG-00454N), October 16, 2020, **30-day comment period**

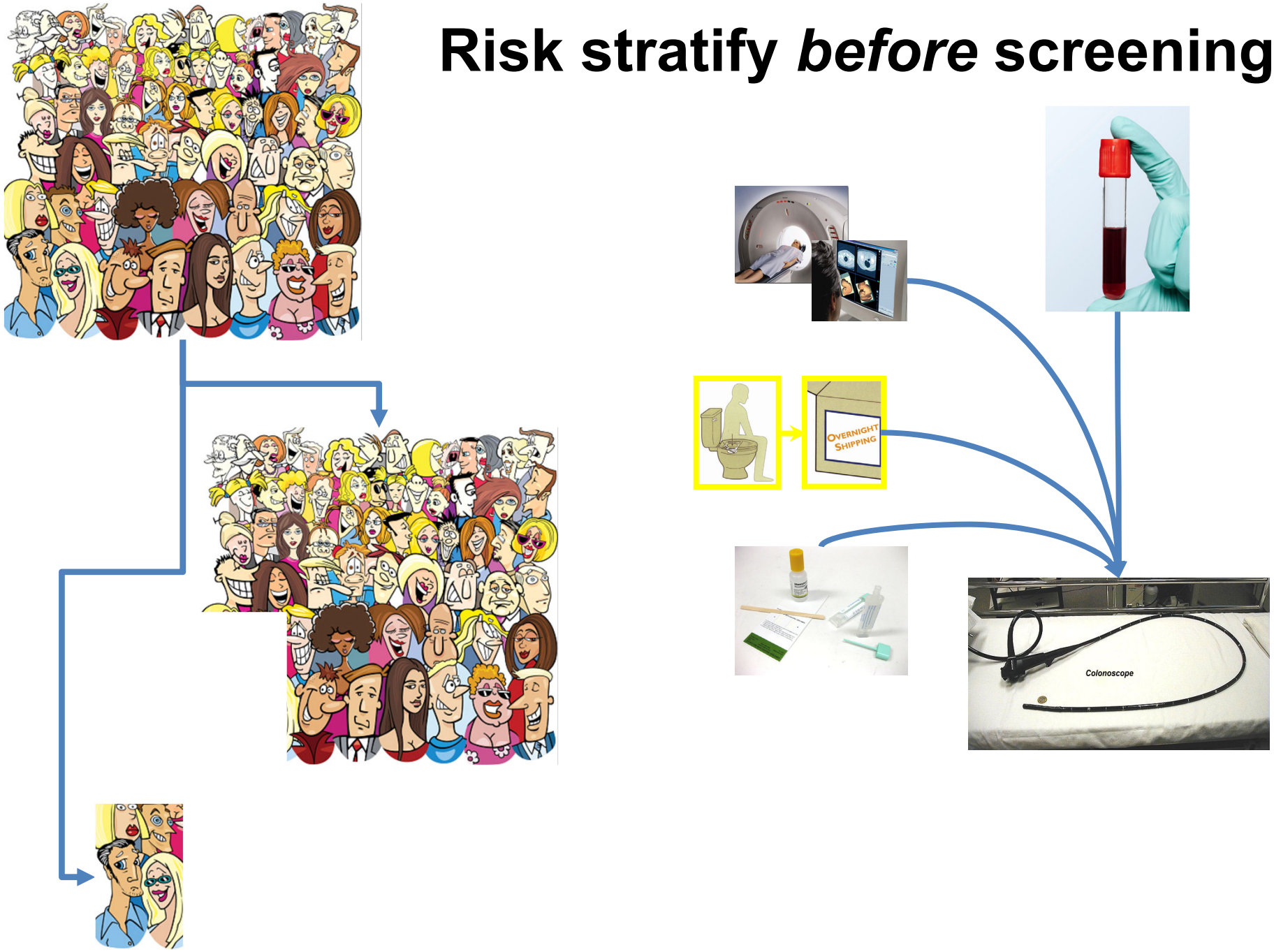
Opportunities beyond CRC screening tests

- Risk stratification *before* primary screening test:
  - Lower risk → non-invasive test
  - Higher risk → colonoscopy
- Testing intervals (beyond number and type of polyps found at colonoscopy; e.g. Lynch)

“Average risk” screening



Risk stratify *before* screening



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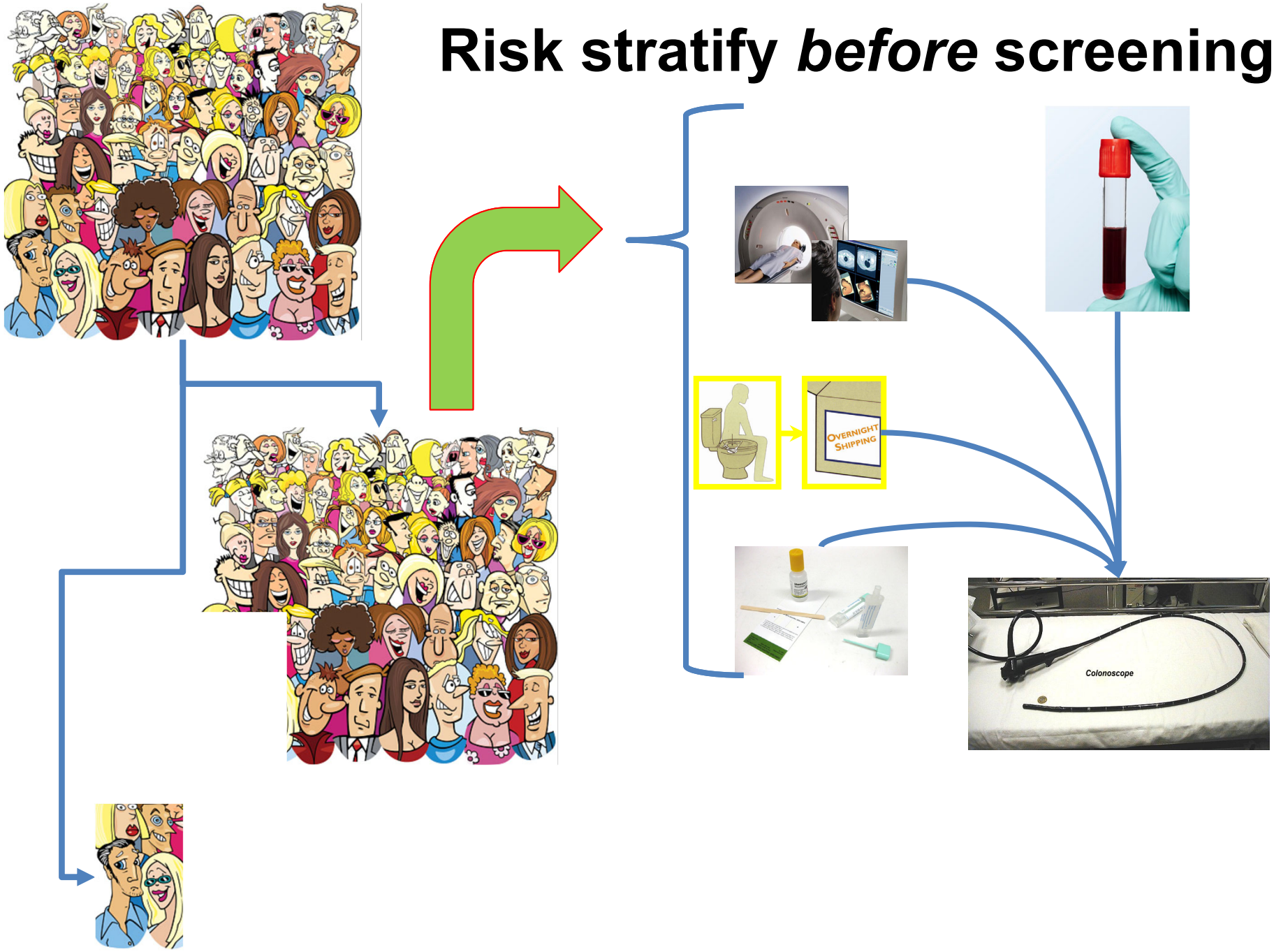
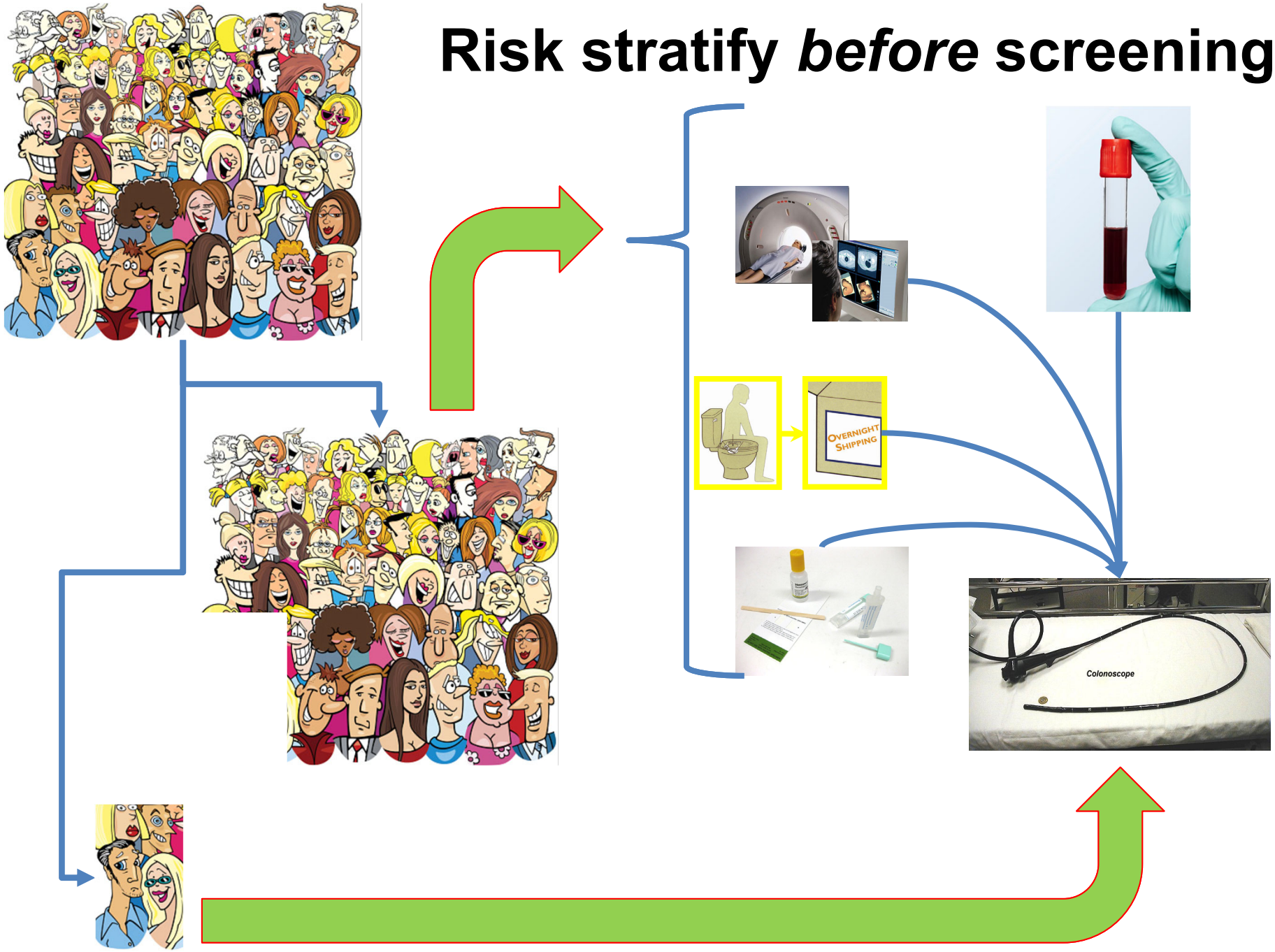
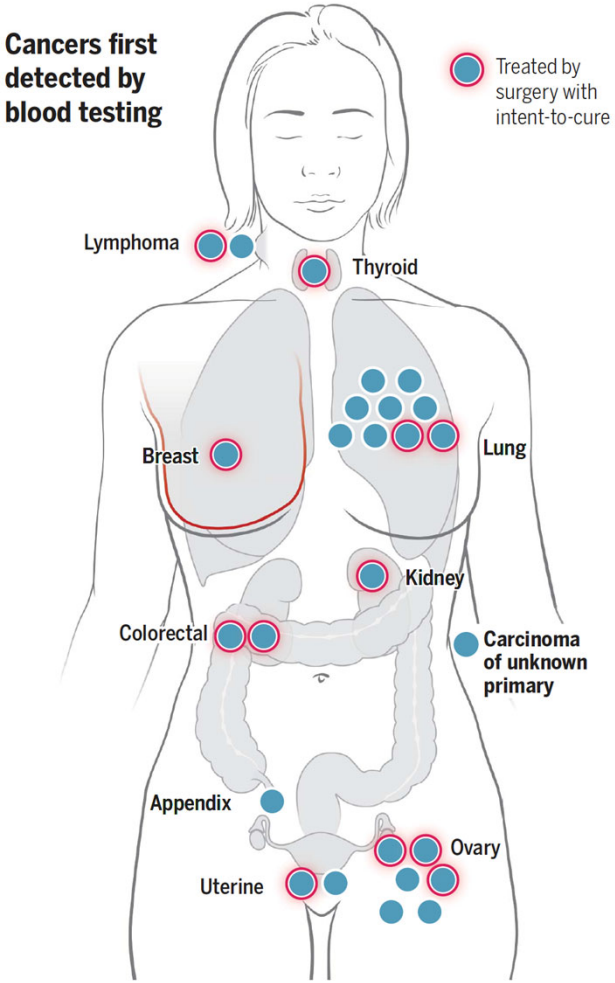


Risk stratify *before* screening



What about "pan-cancer" screening?

- "Pan-cancer" tests being developed
  - Less tissue-specific → Imaging
  - Tissue of origin specificity
- My opinion:
  - The "CRC / polyp" component of such a test faces a high bar
  - Otherwise, only "covers CRC" in people who WILL NOT take up a CRC screening alternative



Lennon *et al*, Science 2020; 369(6499)
Liu *et al*, AnnOnc 2020; 31:1266

CRC Screening: Summary

- CRC screening is a mature field
- High bar for “CRC Screening 3.0”
- Need high sensitivity for early CRC and advanced polyps
- Specificity: more forgiving
- Participation: Big opportunity
- Risk stratification?
- High bar for the CRC / polyp component of a pan-cancer test if it is to *substitute* for alternatives
- ***Should EDRN comment on CMS proposal?***