Colorectal Cancer: Early Detection and Prevention

Robert E. Schoen, MD, MPH
Professor of Medicine & Epidemiology
University of Pittsburgh, Pittsburgh, PA

U.S. Colorectal Cancer - Epidemiology

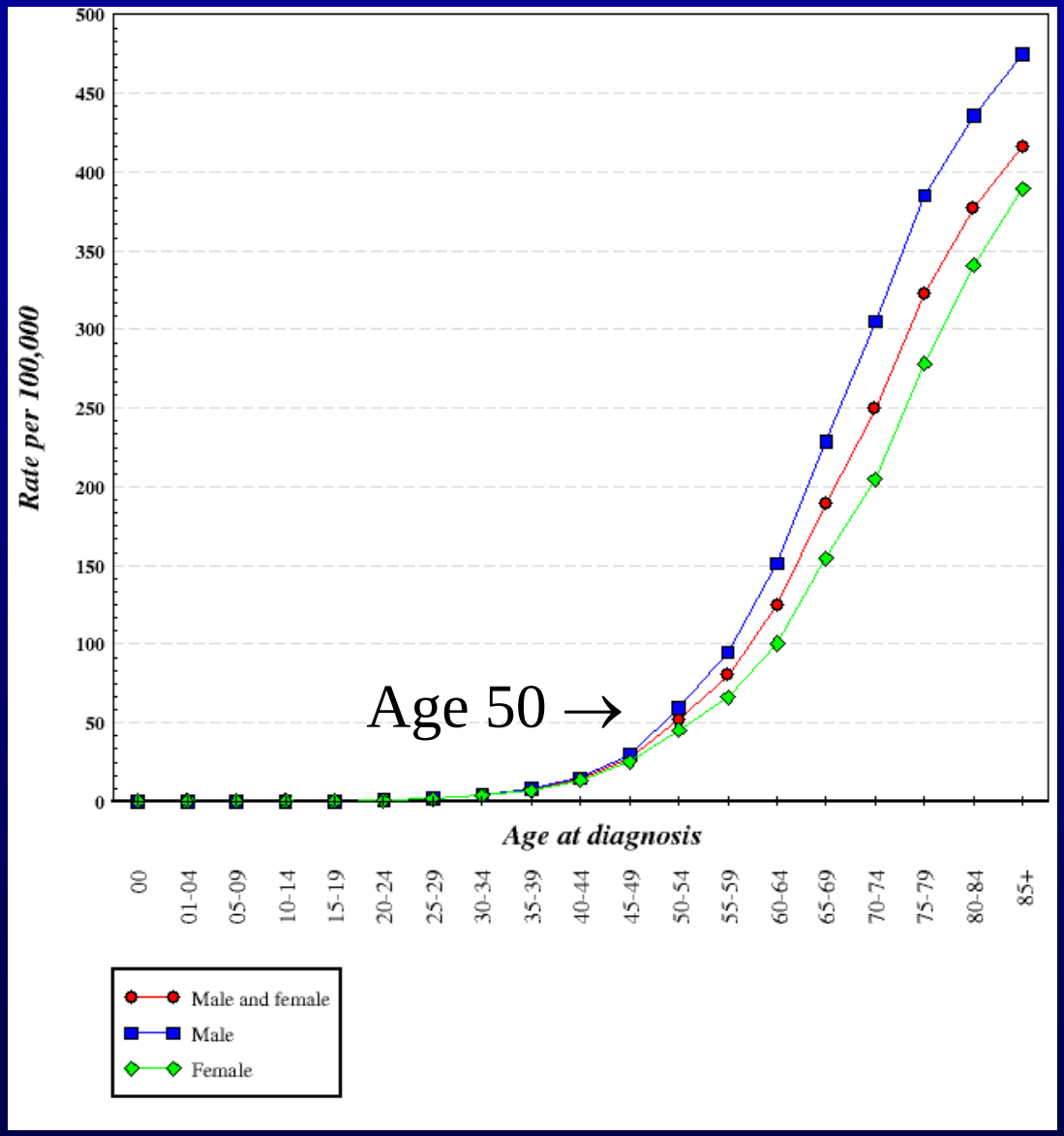
- 2nd leading cause of CA mortality in U.S.
- 3rd most common cancer
- > 136,000 new cases in 2014
- > 50,000 deaths in 2014

Lifetime Risk of CRC (%)

	LR Diagnosis	LR Death
Men	5.0	1.9
Women	4.7	1.7

Siegel R. CA Cancer J Clin 2014:64:104

Colorectal Cancer Incidence by Age



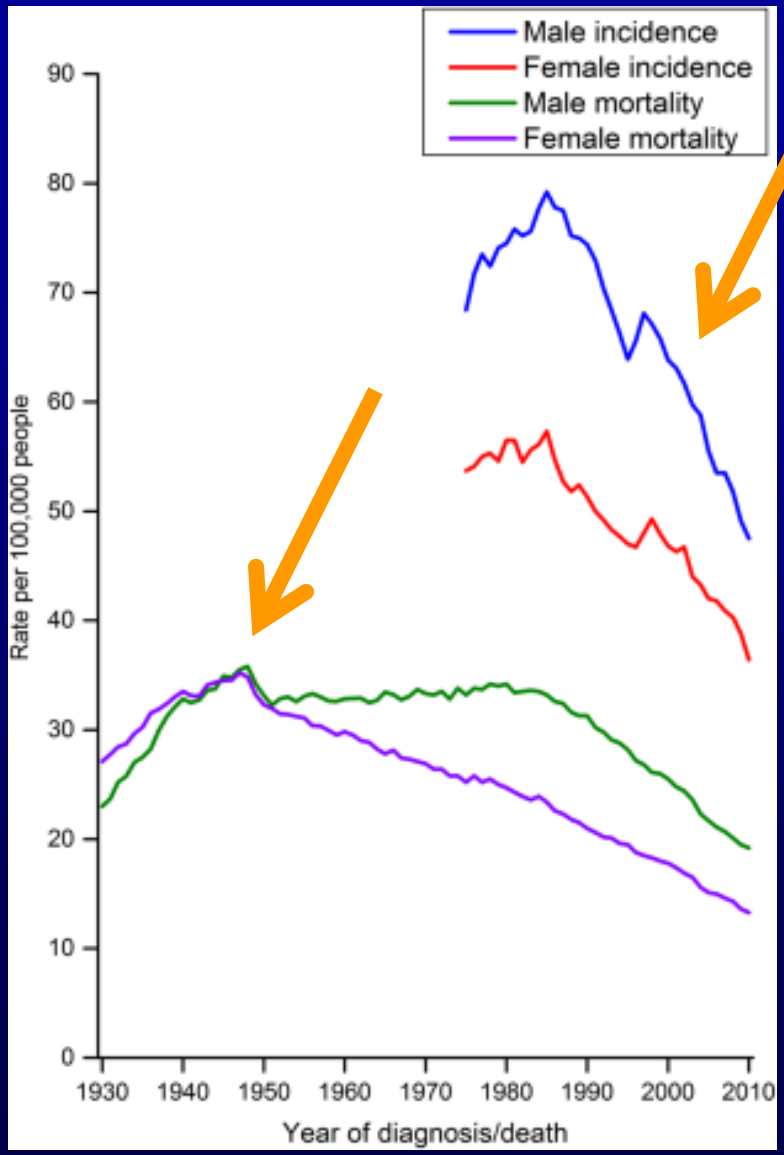
U.S. CRC Annual % Change

Mortality	Male	Female
’84 - ’02	-1.9	-1.8
’01 – ‘10	-3.0	-3.0

Incidence		
’95 - ’98	1.1	1.9
’98 - ’04	-2.8	-2.4
’01 – ‘10	-3.8	-3.2

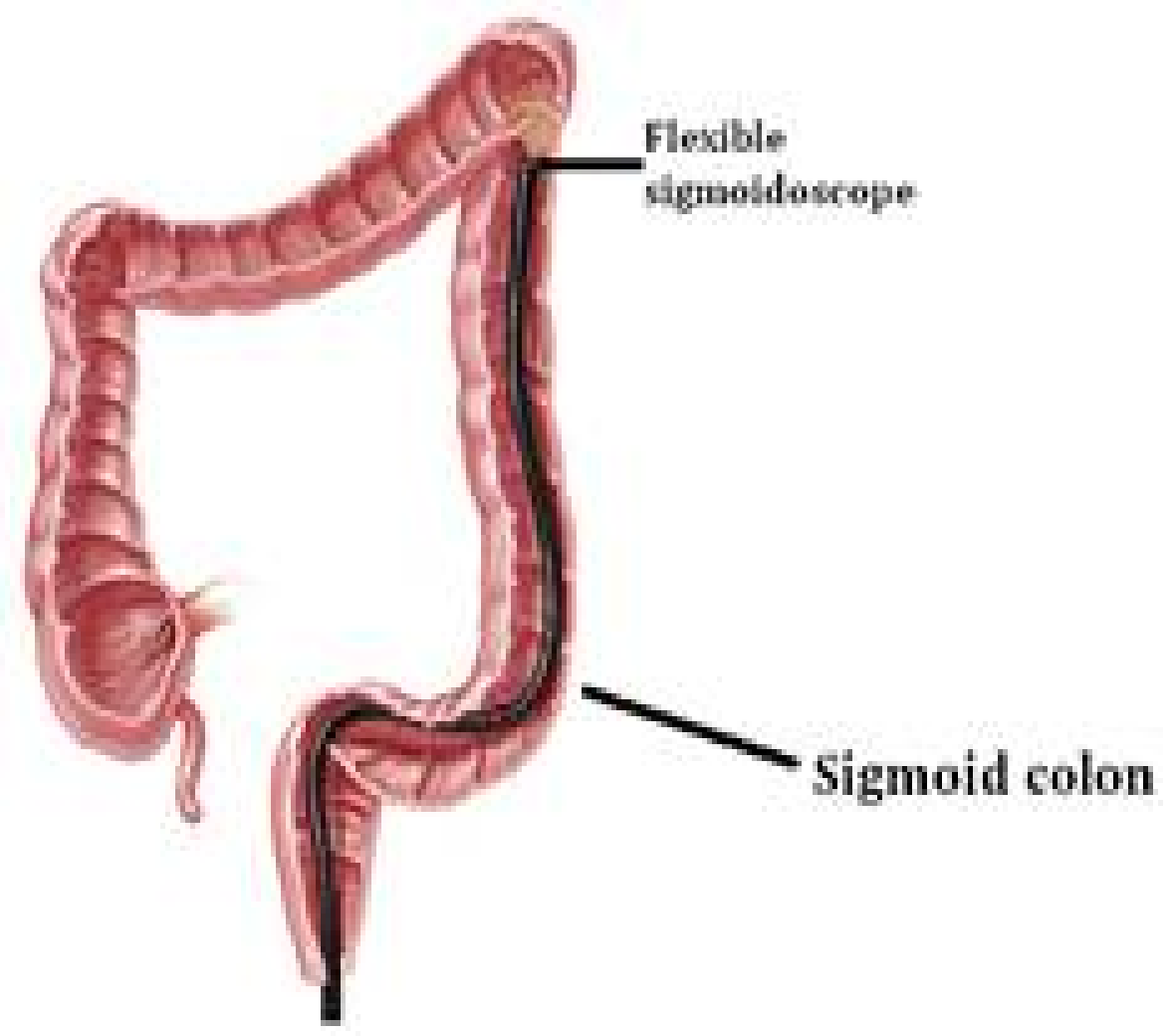
Espey, Cancer 2007;Oct 15
Siegel R. CA Cancer J Clin 2014:64:104

U.S. CRC Incidence and Mortality Trends



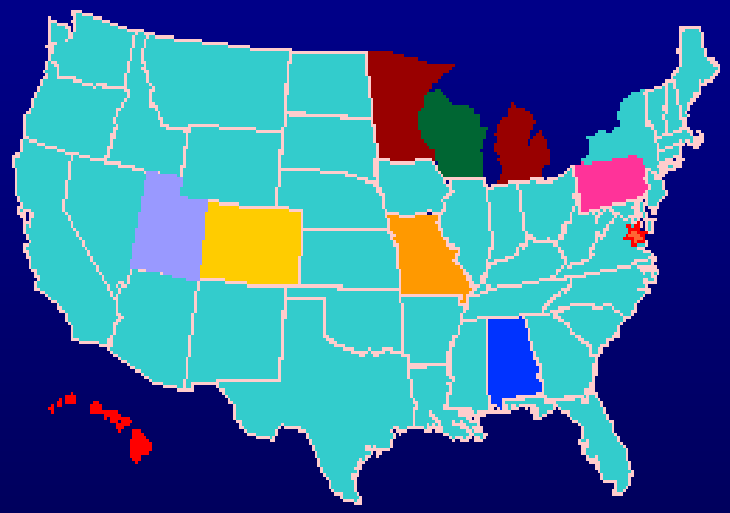
Siegel R. CA Cancer J Clin 2014:64:104

Endoscopic Screening



The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

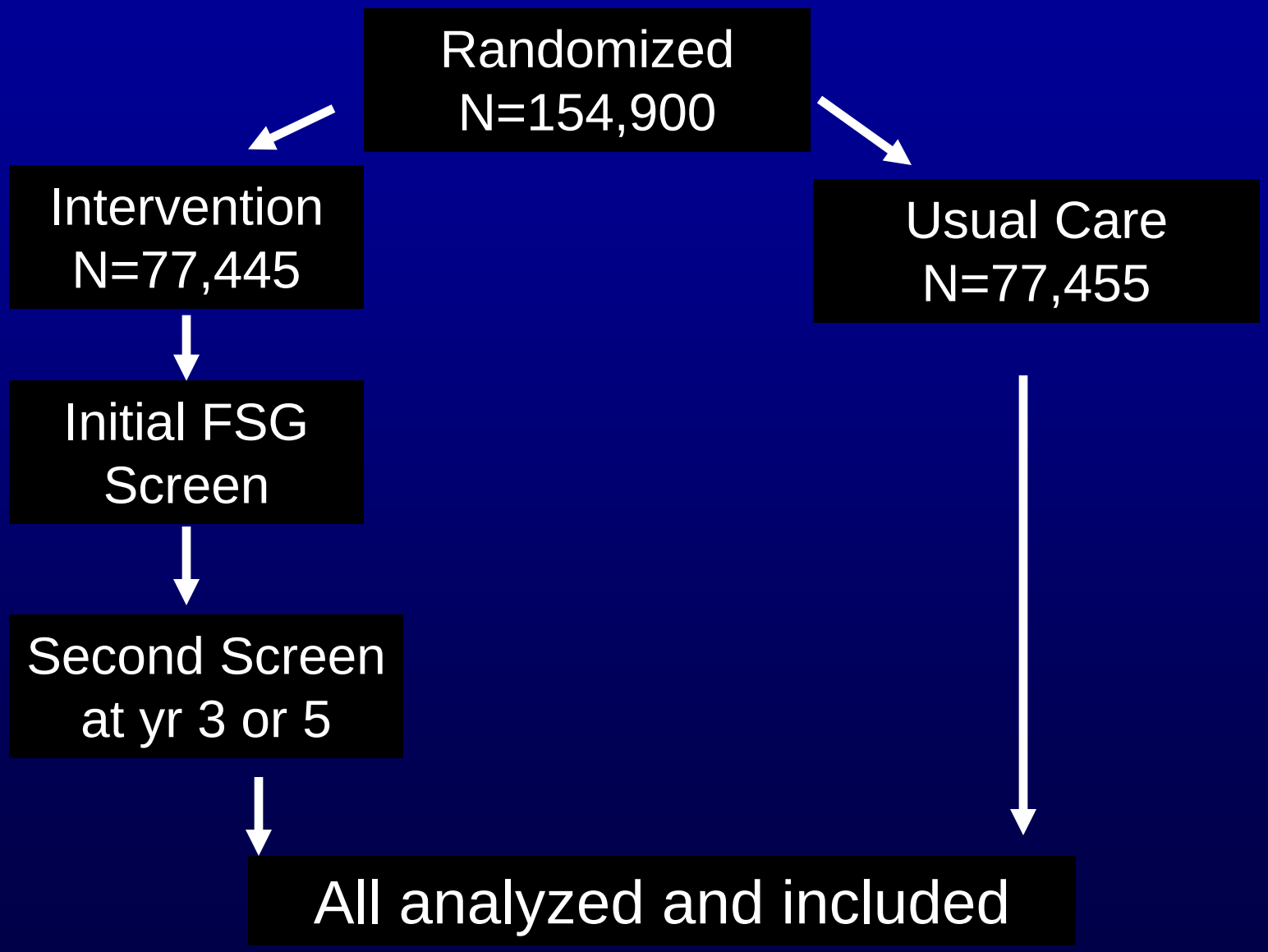
Screening Flexible Sigmoidoscopy



- Sponsored by NCI
- 10 U.S. clinical centers
- Randomized: Screening vs. Usual Care
- Screening began in 1993, concluded in 2001
- Followed mean 11 yr

Schoen, NEJM 2012;366:2345

Protocol


Randomized
N=154,900
Intervention
N=77,445
Usual Care
N=77,455
Initial FSG
Screen
Second Screen
at yr 3 or 5
All analyzed and included

Overall CRC Incidence

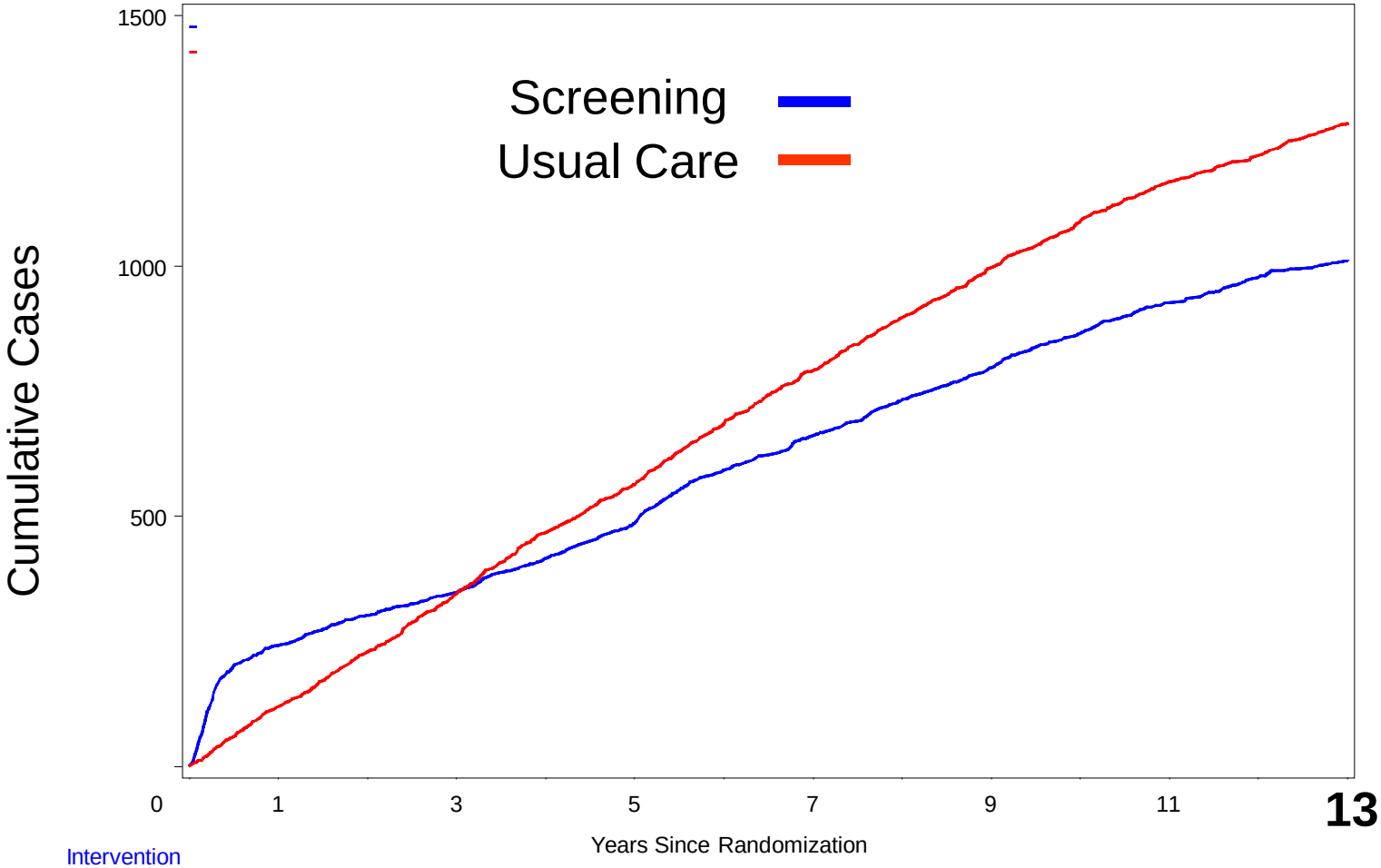
Mean F/U 11.2 yr; Median 11.9 yr

Usual Care		Intervention			
# Cases	Rate/ 10K PY	# Cases	Rate/ 10K PY	RR	P
1287	15.2	1012	11.9	.79 (.72-.85)	<.001

21% decrease in incidence

275 fewer cases

Overall Colorectal Cancer Incidence by Year



Intervention							
Cancers	242	347	487	659	797	927	1012
Person-years	76520	227007	373895	516773	654740	772625	848403
Usual Care							
Cancers	119	344	564	790	998	1169	1287
Person-years	76592	227438	374467	517055	654447	771744	847103

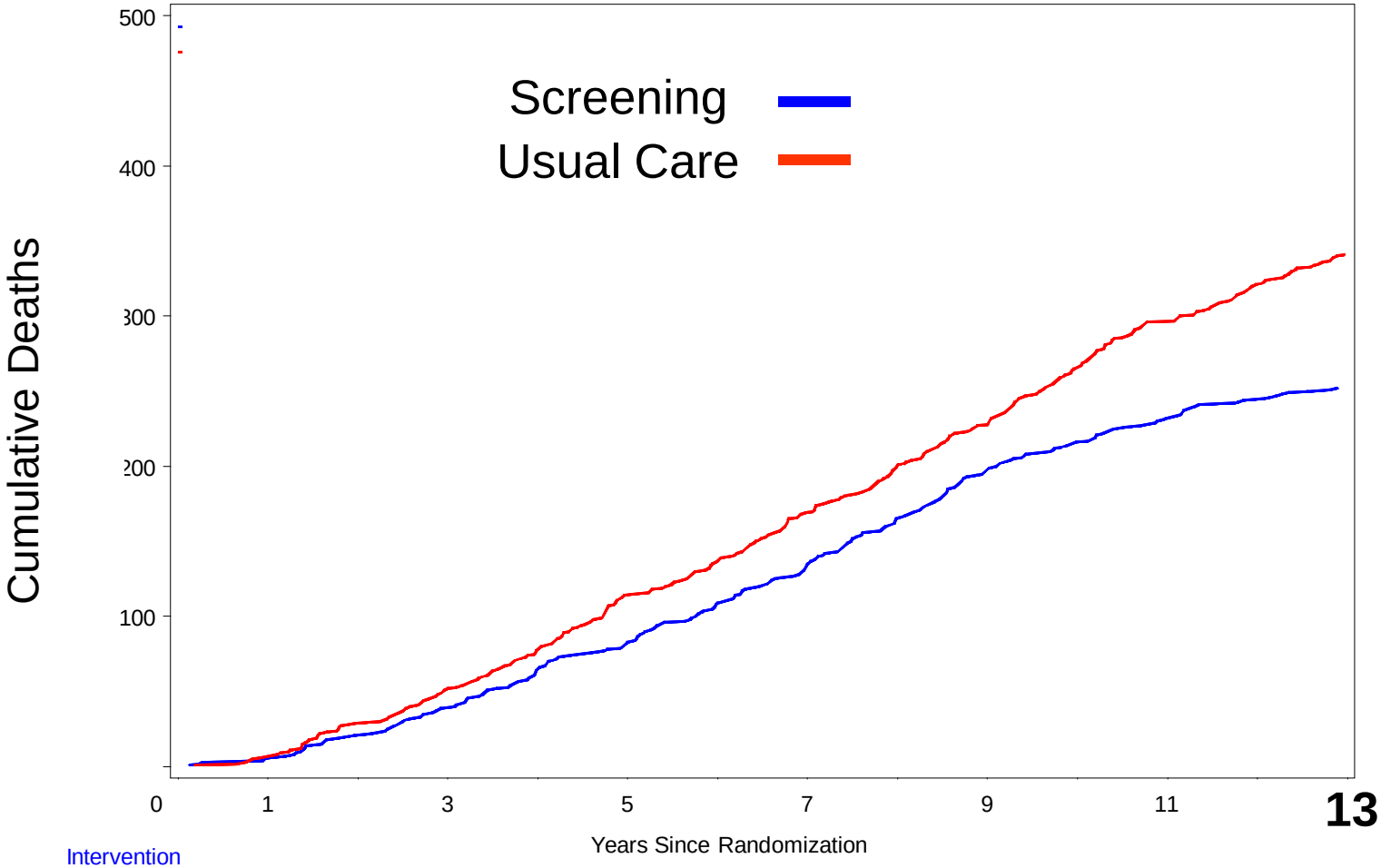
Overall: Mortality to CRC

Usual Care		Intervention			
# Deaths	Rate/ 10K PY	# Deaths	Rate/ 10K PY	RR	P
341	3.9	252	2.9	.74 (.63-.87)	<.001

26% decrease in mortality

89 fewer deaths

Overall Colorectal Cancer Mortality by Year

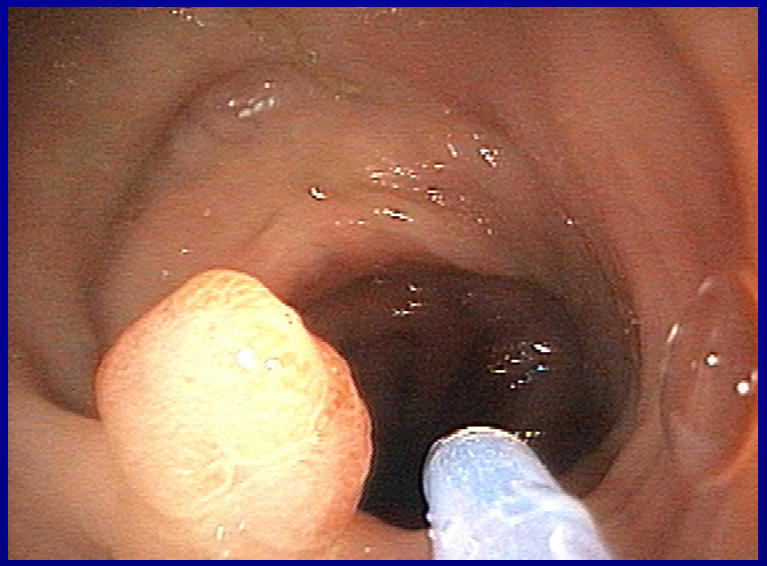


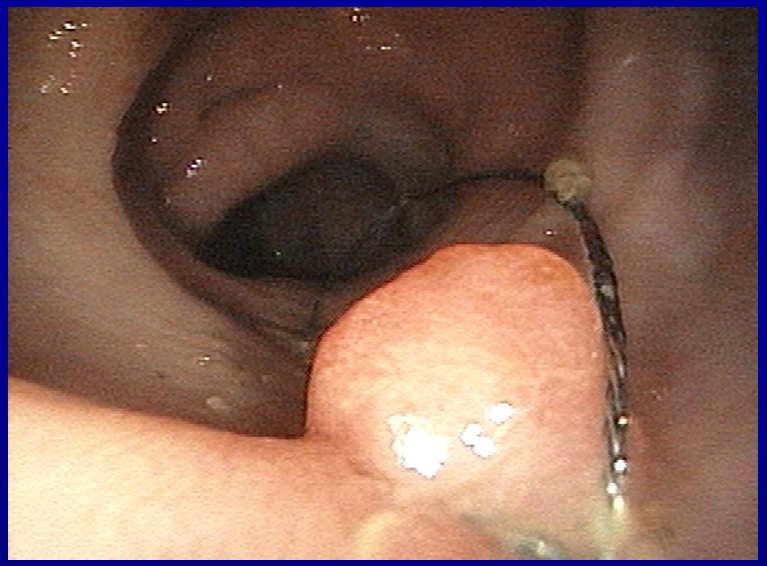
Intervention							
Deaths	6	39	83	135	198	232	252
Person-years	77276	230295	380730	528006	670832	793203	871930
Usual Care							
Deaths	6	51	114	169	228	296	341
Person-years	77288	230354	380731	527828	670526	792674	871275

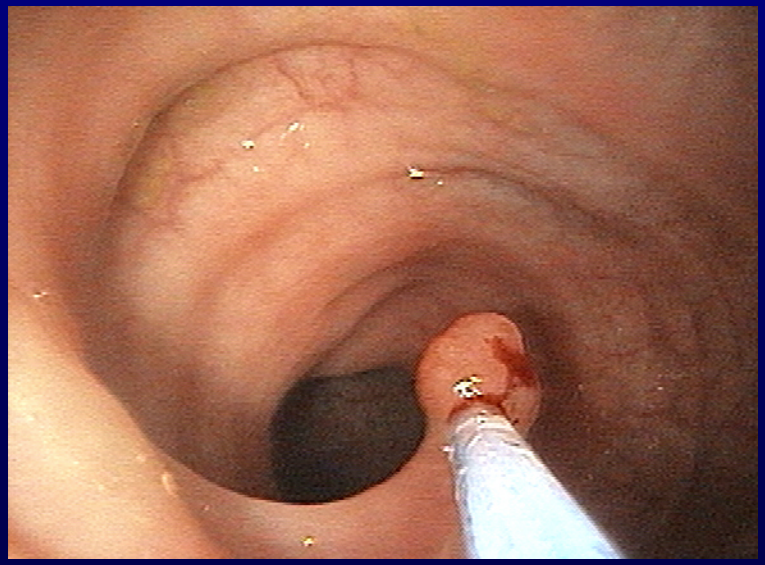
Randomized Trials of Flexible Sigmoidoscopy: Effect on Incidence and Mortality

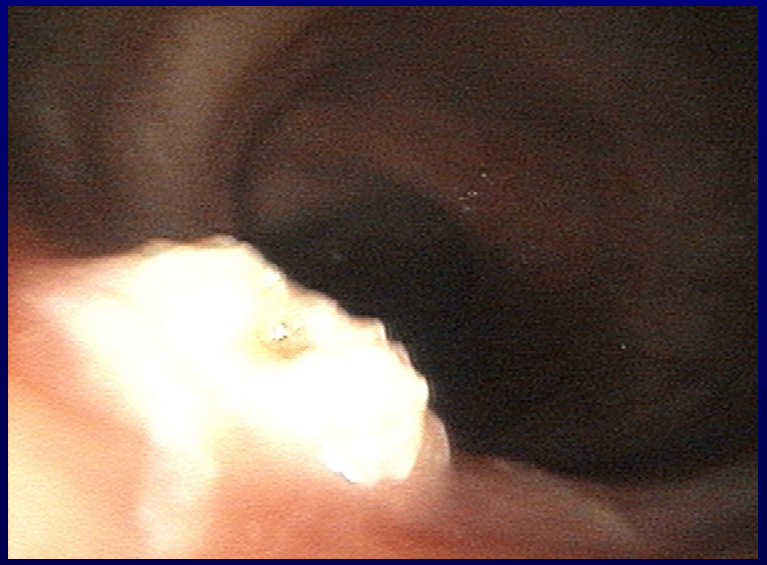
Pink = Not significant

ITT Overall Reduction	Incidence	Mortality
UK	23	31
Italy	18	22
PLCO (U.S.)	21	26
Norway	20	27
Distal Colon		
UK	36	50
Italy	24	27
PLCO (U.S.)	29	50
Norway	24	31

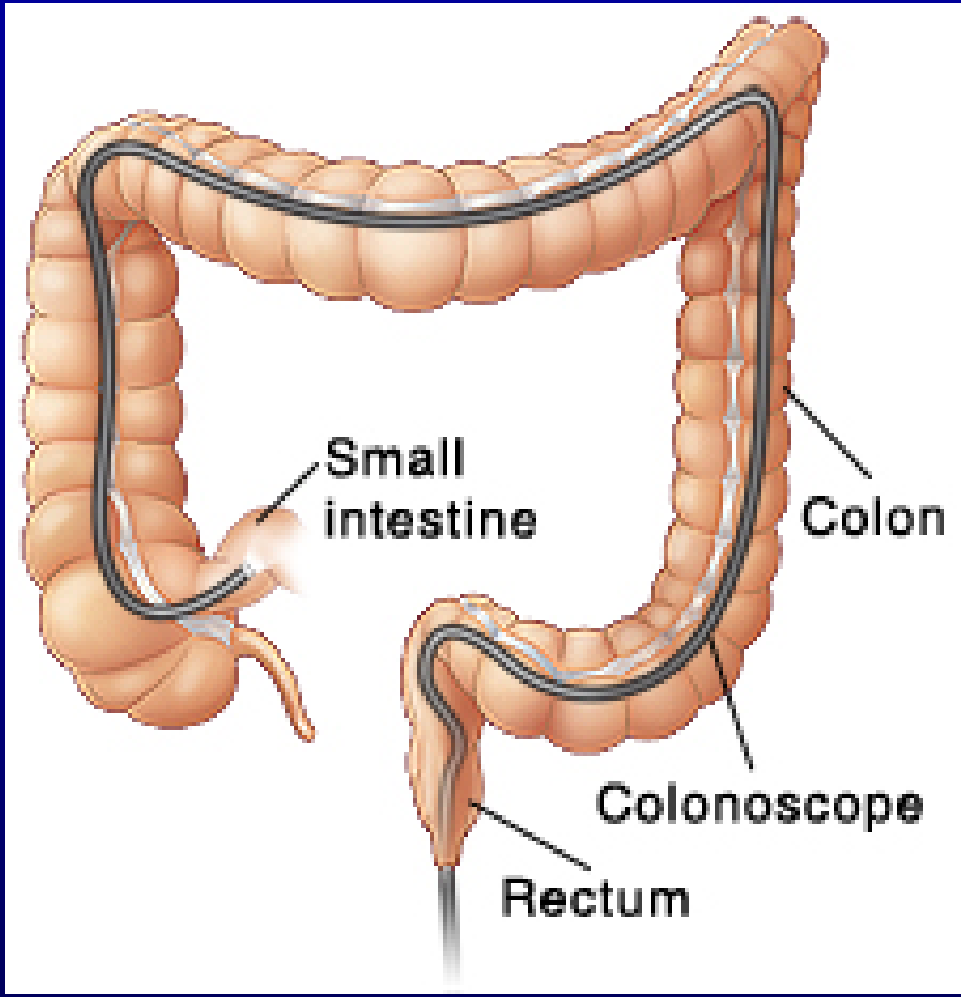








If half is good, whole must be….



Colonoscopy: Is it Effective in the Proximal Colon?

Observational Studies of Colonoscopy

- Uncertain effectiveness in reducing proximal CRC mortality
- Less protection against proximal than distal cancer

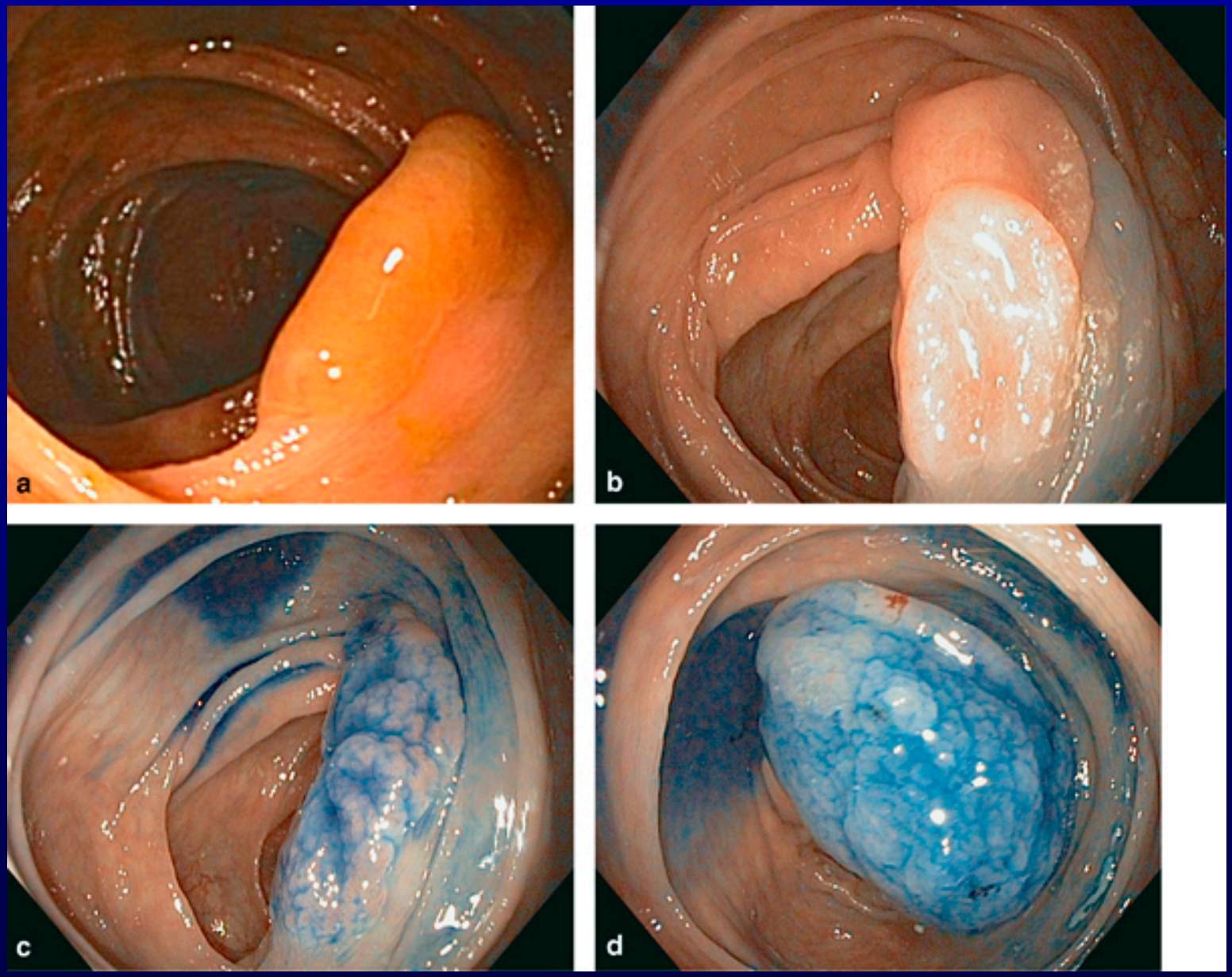
Baxter N, Annals 2009;150:1

Singh, Gastro 2010;139:1128

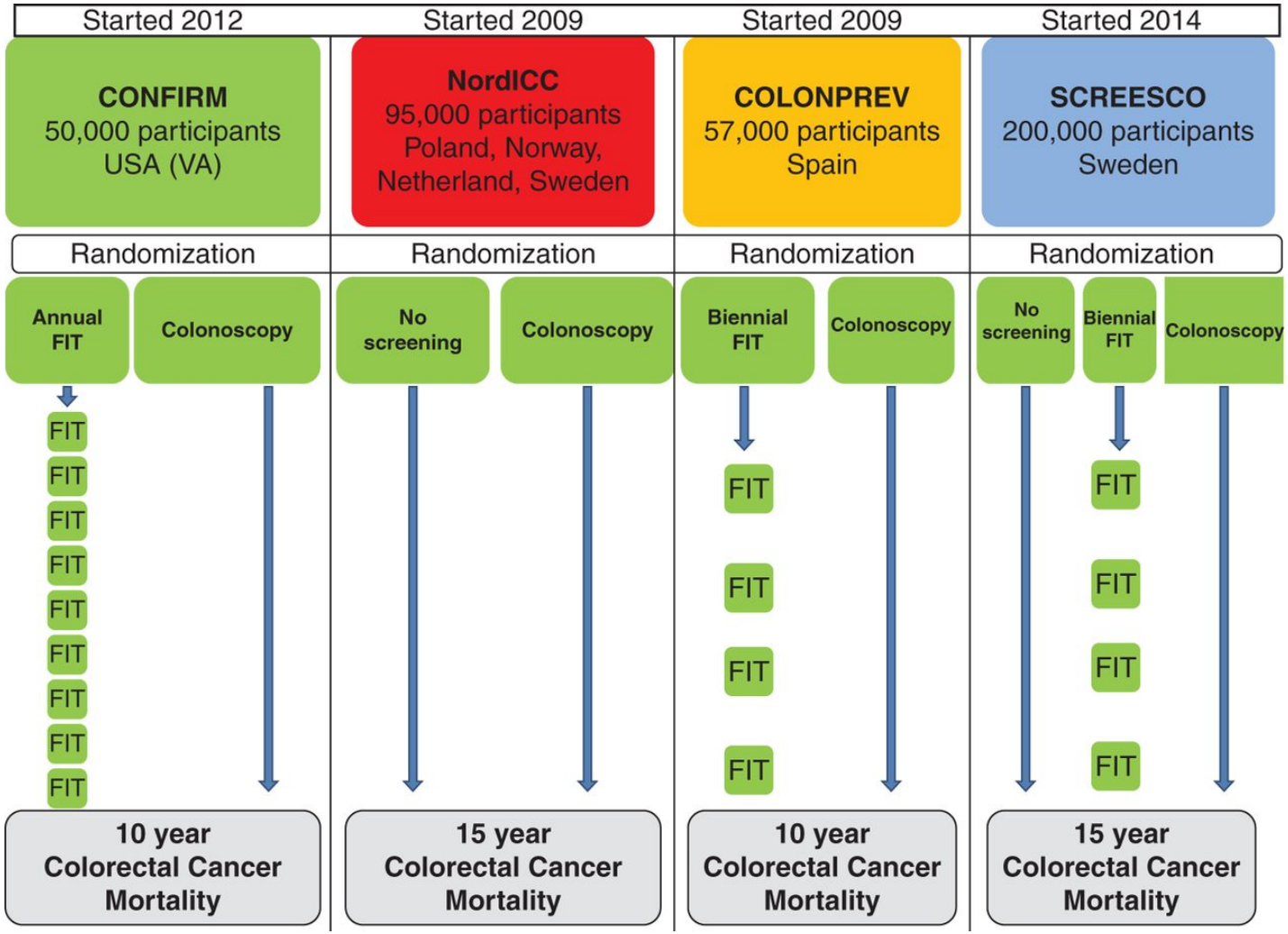
What About The Proximal Colon – Why is It More Difficult To Protect?

Why Right ≠ Left?

1. Biology
   - Molecular (CIMP, MSI)
   - Progression – Polyp recurrence more common in right colon
2. Operator
   - Missed Lesions: Flat
   - Serrated Adenomas: Mucin Covered
   - Bowel Prep
   - Incomplete CS


a
b
c
d

Ongoing Randomized Colonoscopy Screening Effectiveness Trials



GUT

Robertson DJ et al. Gut 2015;64:982-990

If We Have Such Good Screening Tests, Do We Need A Biomarker?

- Even if you have a great test, still have to get subjects to comply. A biomarker than can stimulate evaluation of the population at risk is worthwhile
- In colon, testing is effective, but trying: stool tests, endoscopic testing.
- BLOOD TEST is next frontier

U.S. CRC Screening Test Use

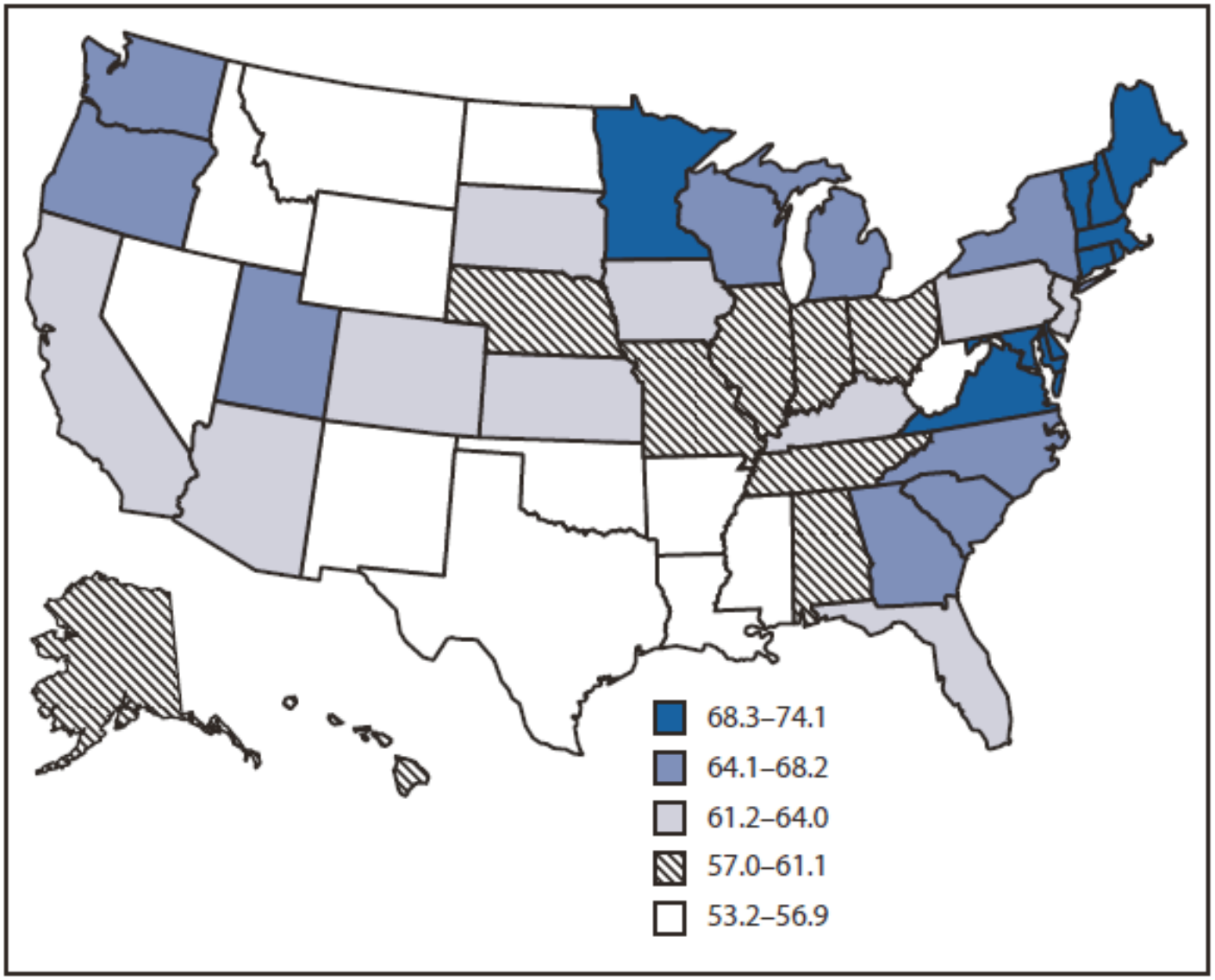
- Up to date with recommended screening:

  54% in 2002 → 65% in 2010

- Disparities in utilization

MMWR 2012;62:881

FOBT (past 1 yr) or Endoscopy (previous 10 yr): BRFSS



2008

OK: 53%

MA: 74%

2010

AK: 56%

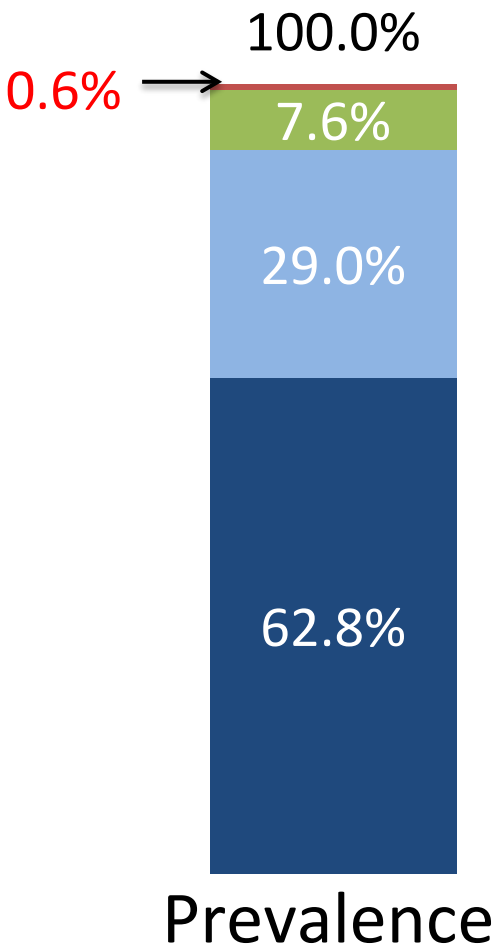
MA: 76%

Disparity in Screening for CRC

% Up to Date	
Ethnicity	
Hispanic	53.1
Non-Hispanic	66.4
Education	
< HS	48.3
College Grad	73.5
Annual Income	
< 15k	49.5
> 75k	74.0
Insurance	
No	36.9
Yes	68.9

MMWR 2012;62:881

Distribution of Colonoscopy Findings (N=9,989)



Finding	Valid Cases
CRC	65
Advanced Adenoma	757
Non-advanced adenoma	2,893
Negative	6,274

Imperiale TF. N Engl J Med 2014;370(14):1287

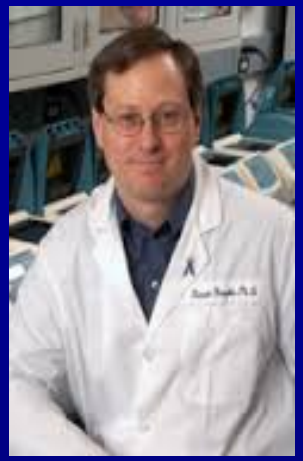
Do We Need A Biomarker?

- A biomarker could increase utilization
- Testing we have, though effective, is inefficient and expensive

EDRN: The Search for Biomarkers for CRC

Great Lakes-New England (GLNE) Clinical and Epidemiology Center (CEC)

- Conducting a 6 - 12,000 patient study evaluating stool markers, serum markers in relation to colonoscopy outcomes



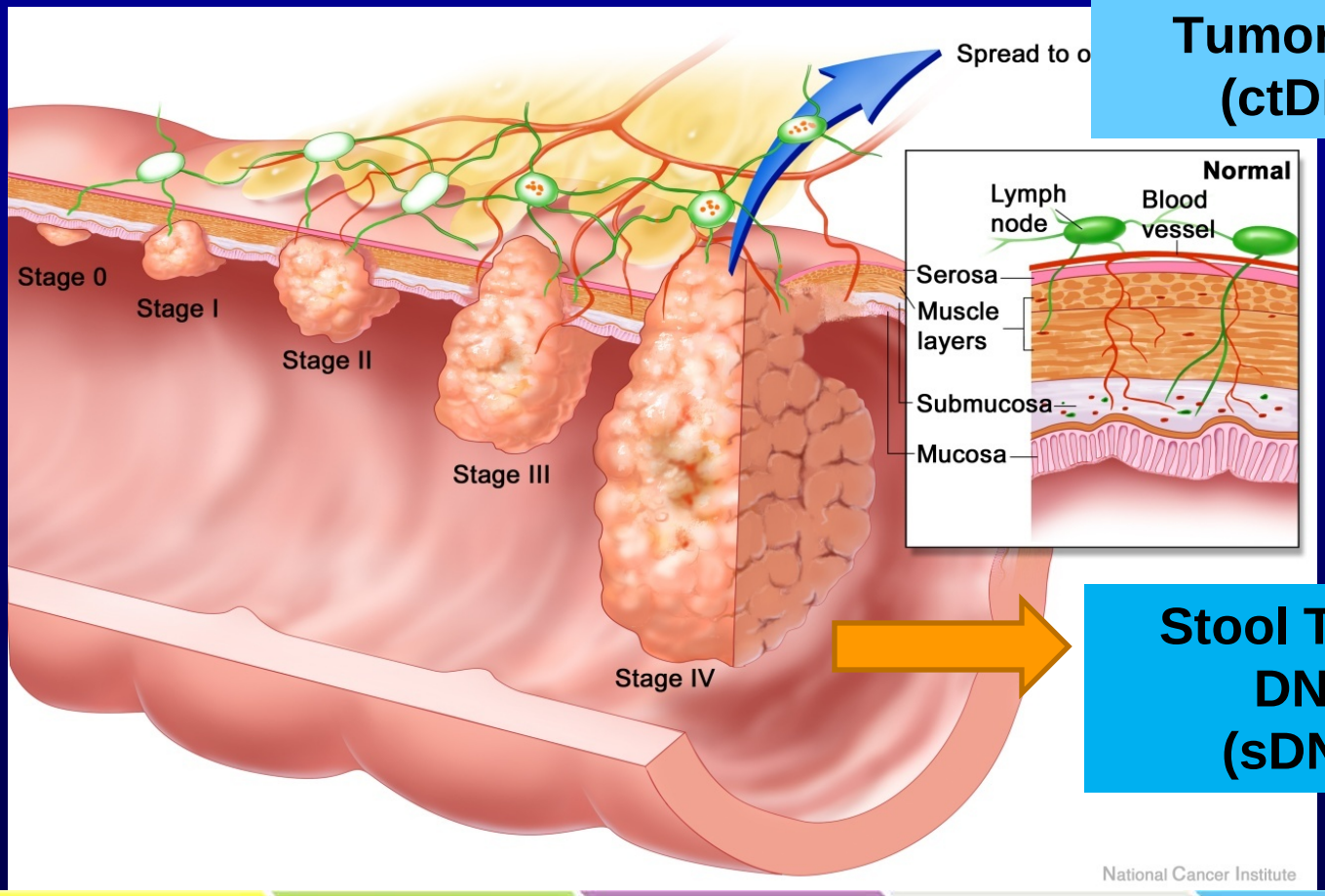
Ken Kinzler

ct-DNA for Early Detection and Monitoring of CRC

ct-DNA: Circulating Tumor DNA

- Small fragments of nucleic acid (160-180bp) that originate from apoptotic cell turnover
- Mutational profile corresponds to that in tumor tissue
- Half life <1.5 hours

Released DNA as a Cancer Biomarker

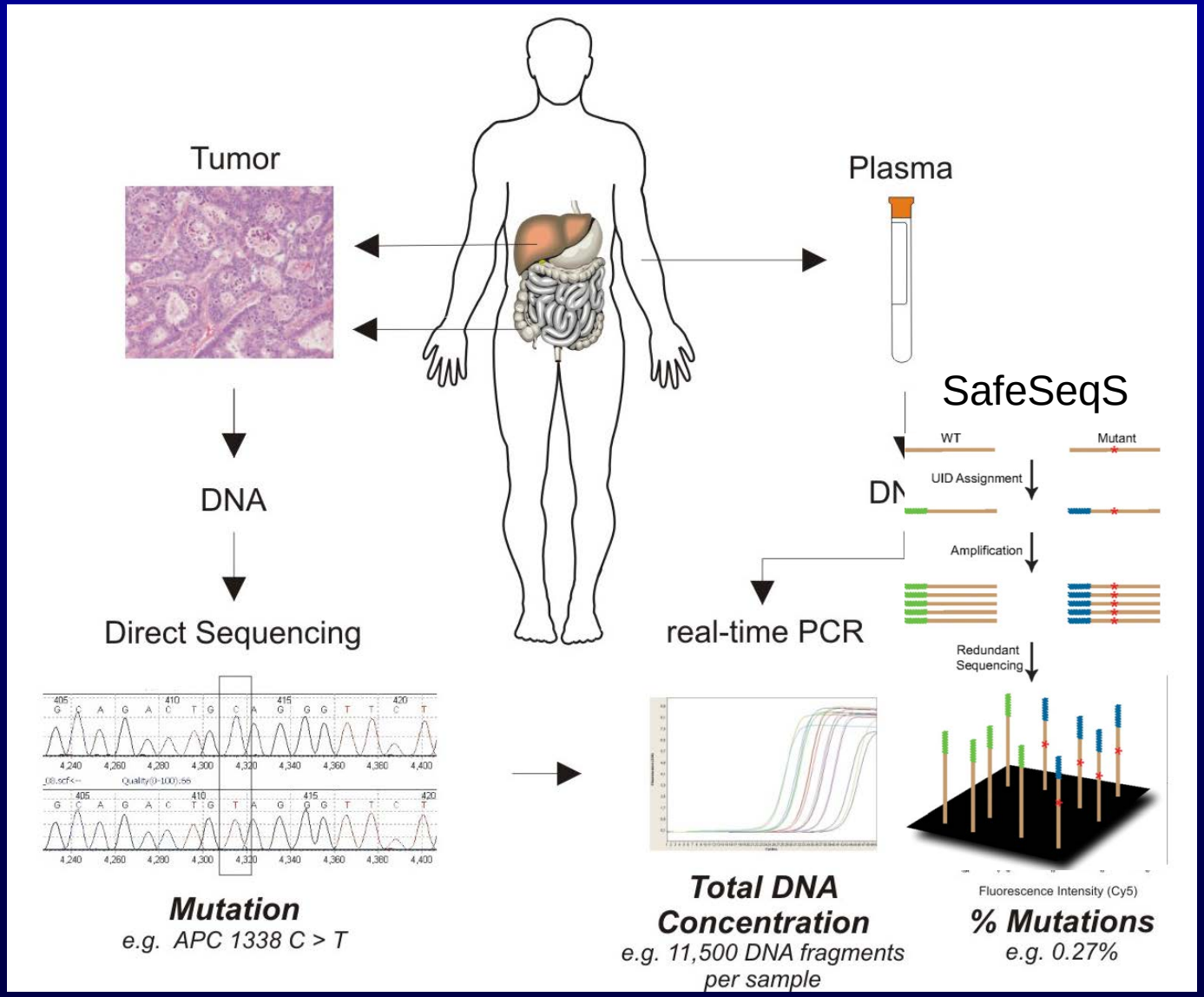


Circulating Tumor DNA (ctDNA)

Stool Tumor DNA (sDNA)

Risk Assessment → **Screening** → **Diagnosis/ Prognosis** → **Monitoring** → **Response Prediction** → **Monitoring Resistance**

Experimental Design



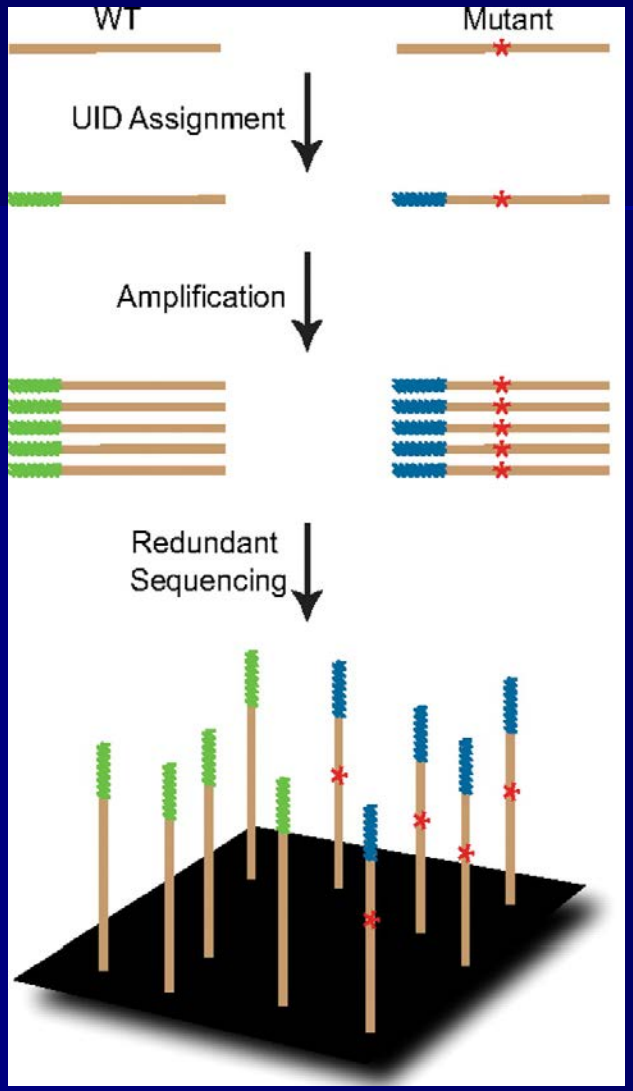
Safe-SeqS

Safe

Sequencing

System

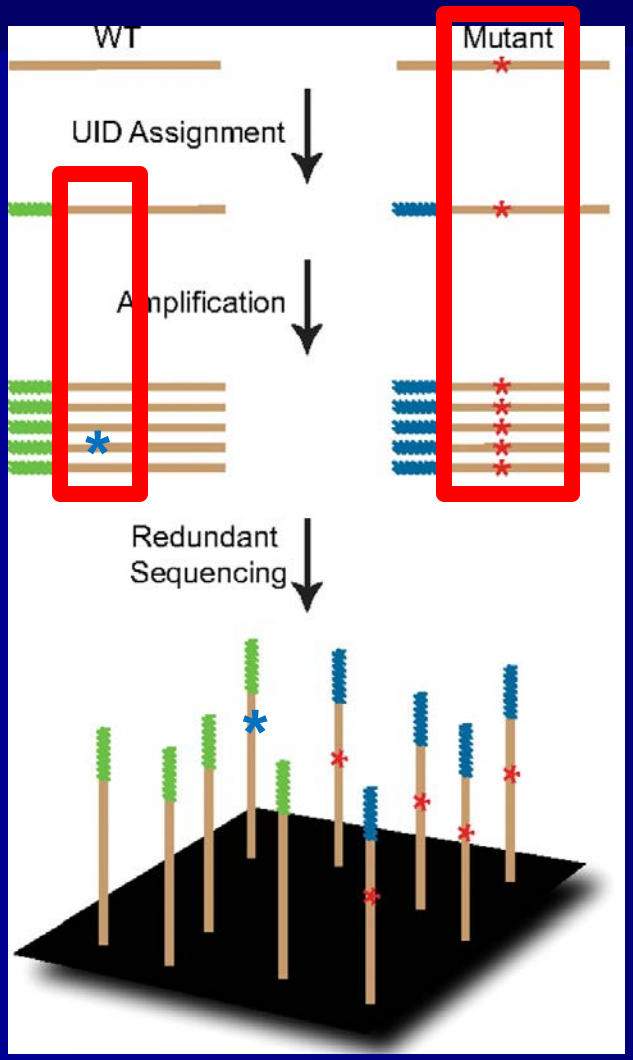
Method for detection and quantification of rare mutations



Kinde I et al. PNAS 108:9530-9535, 201

Essential elements of Safe-SeqS

Sequencing or Replication Error

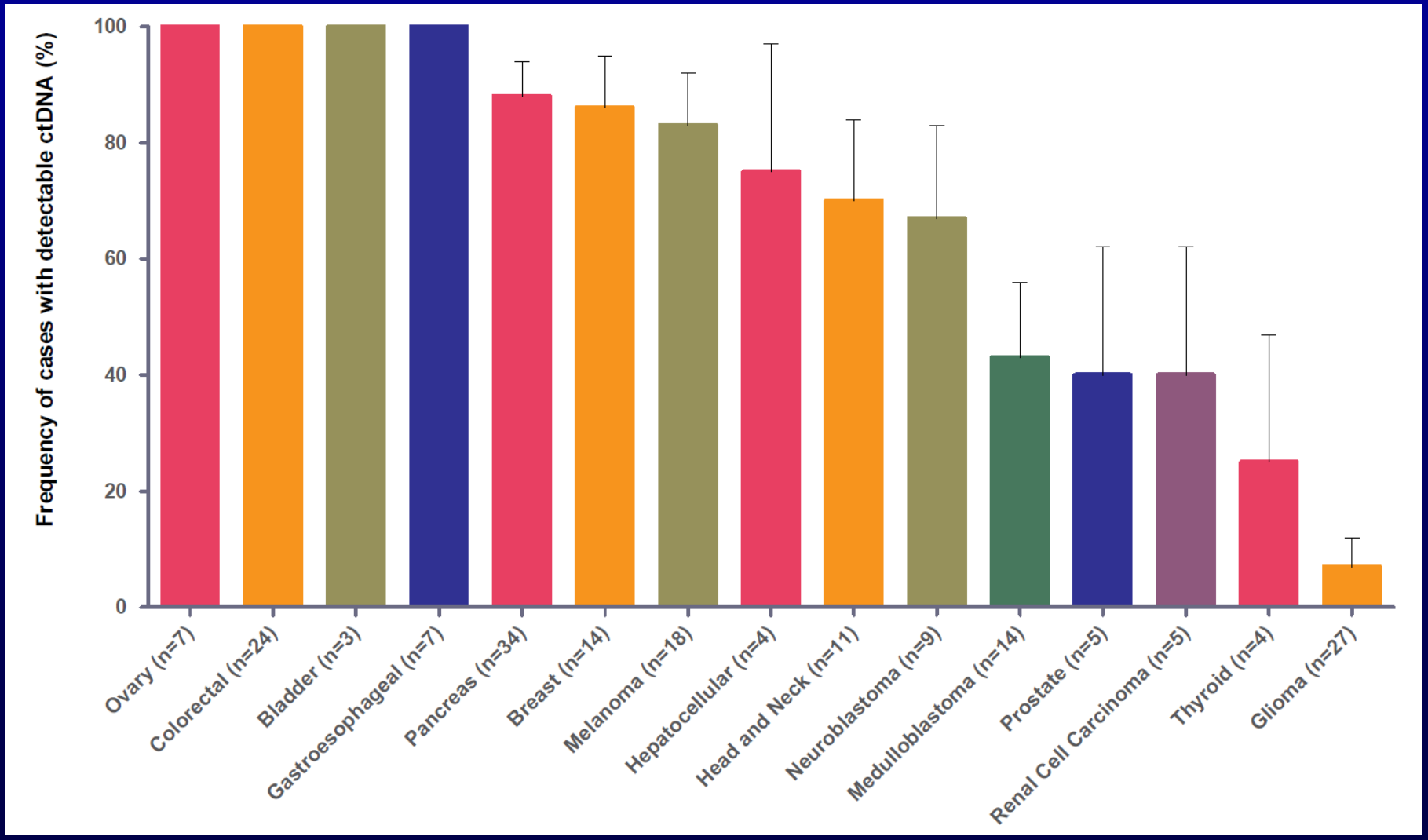


vs. Legitimate Change

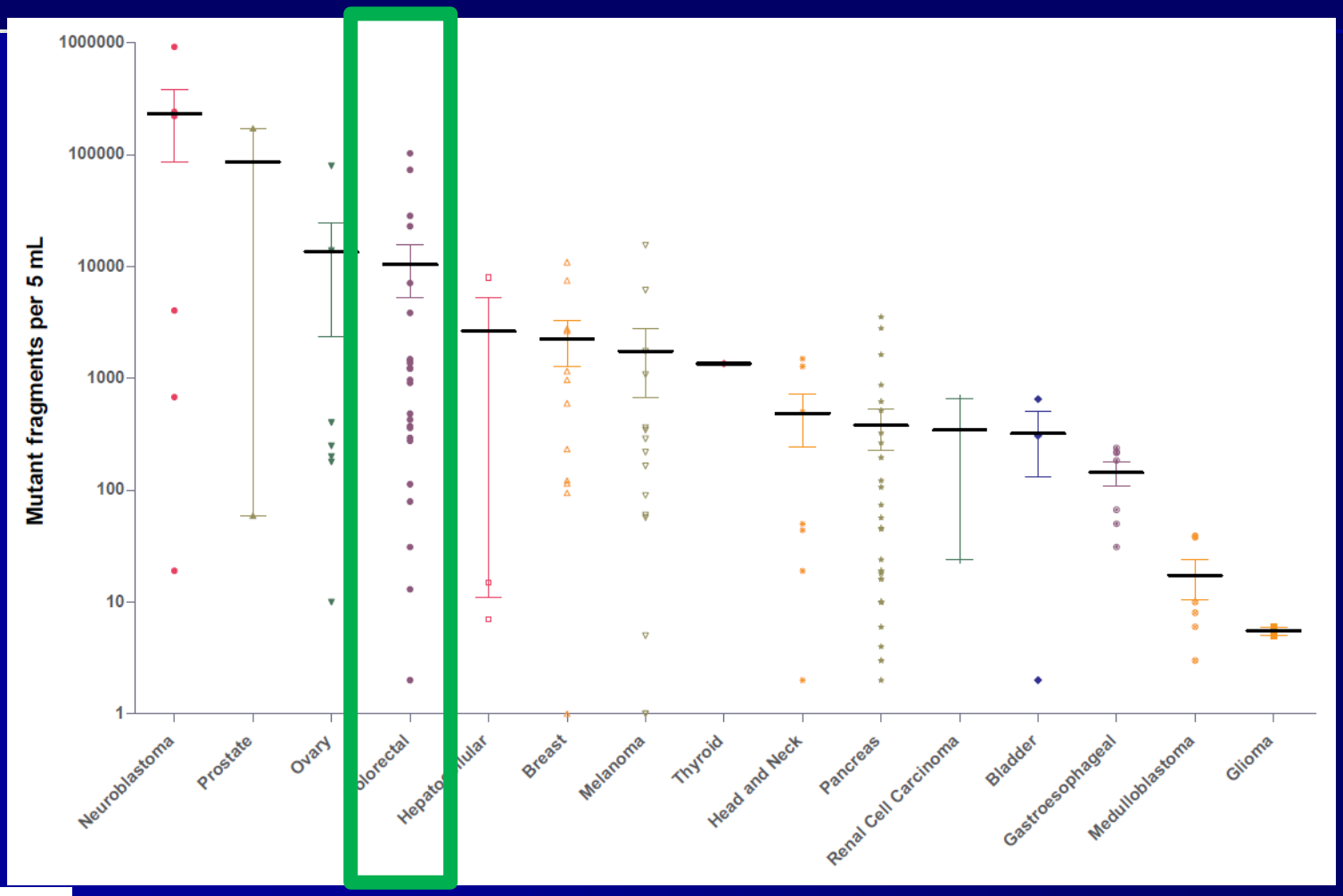
This strategy can decrease error rates by 70-fold

Kinde I et al. PNAS 2011;108:9530-9535

ctDNA in Advanced Cancers

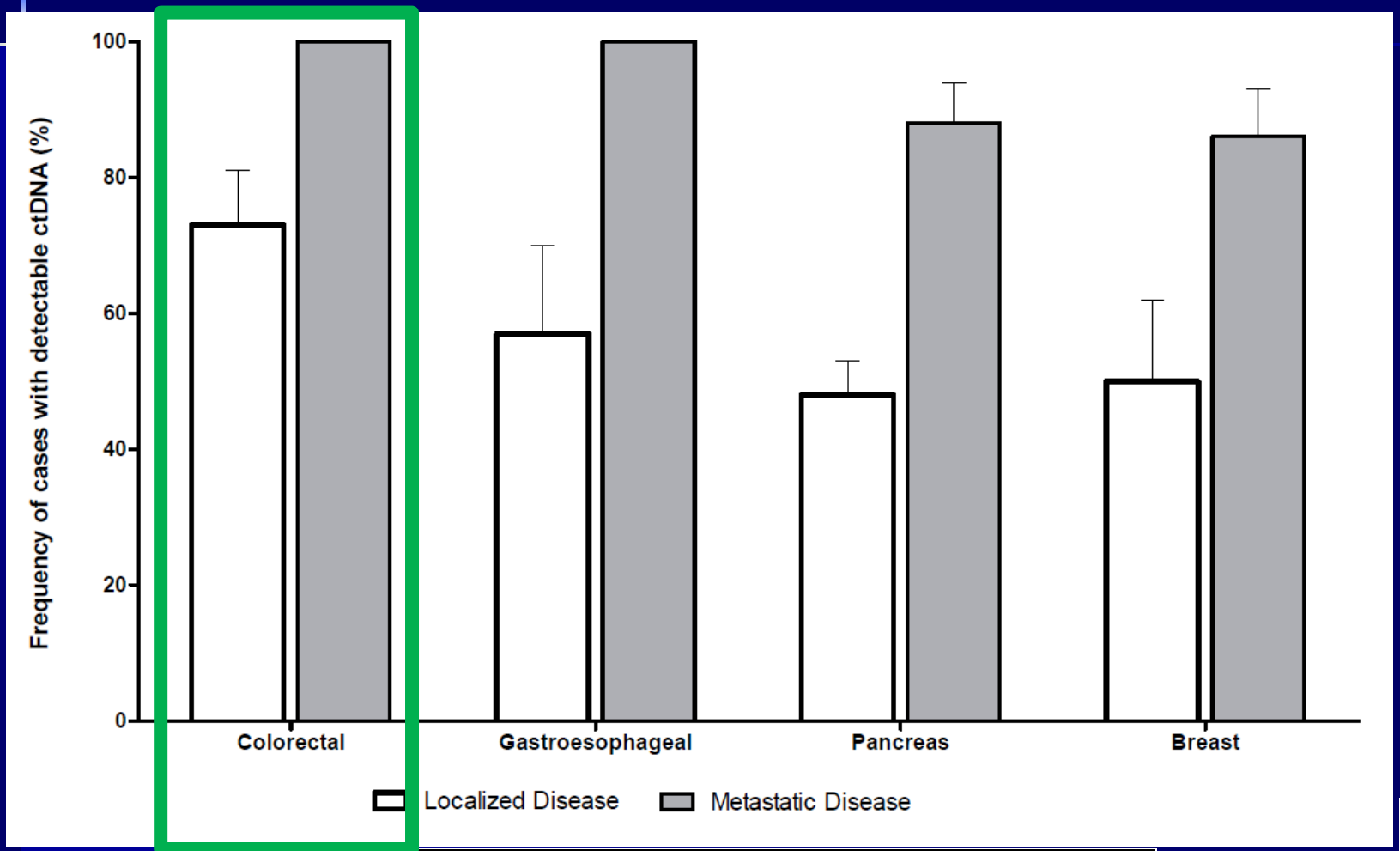


ctDNA in Advanced CRC



LUDWIG CENTER | JOHNS HOPKINS

ctDNA: Localized vs. Advanced Cancer



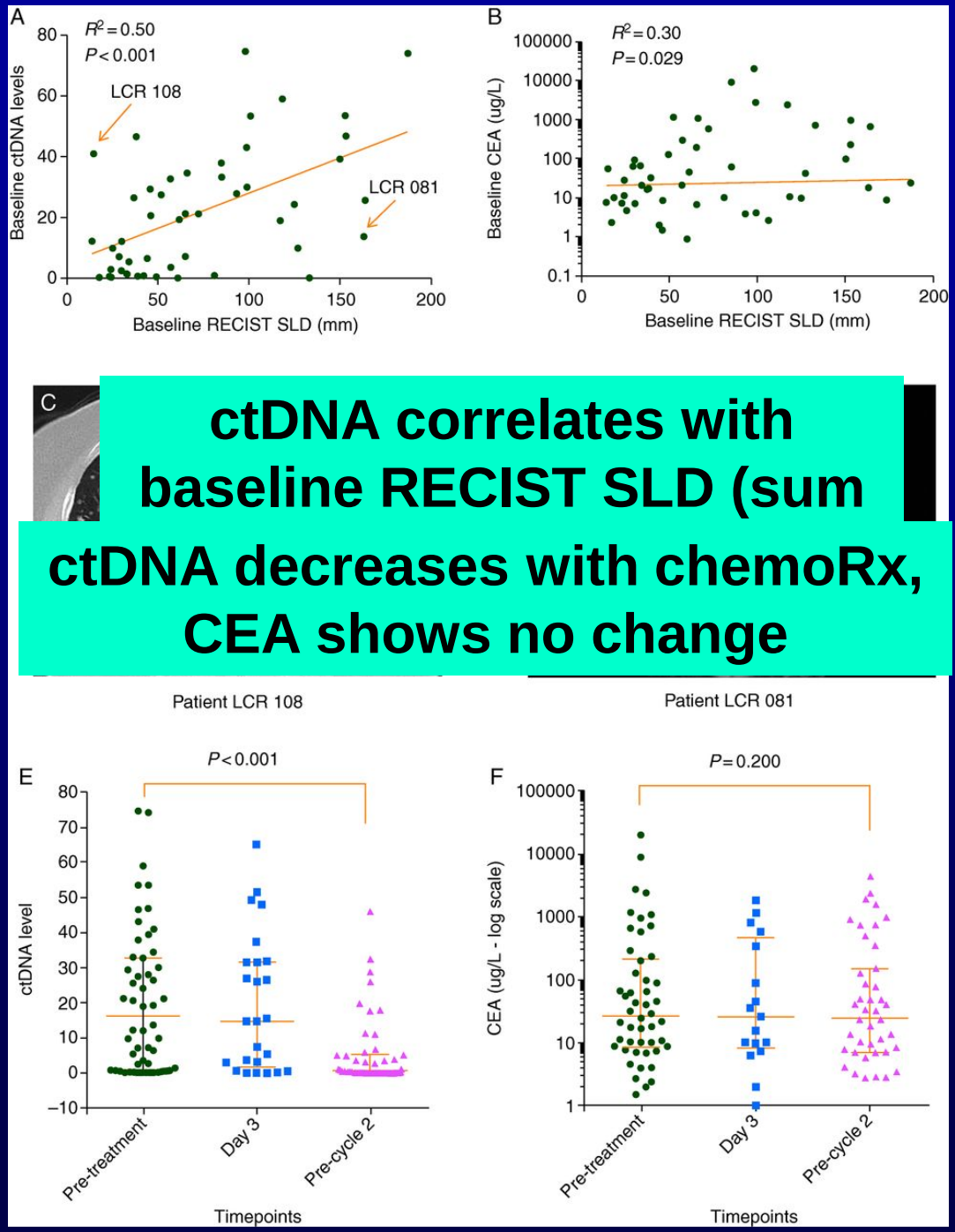
Localized disease 73%

LUDWIG CENTER | JOHNS HOPKINS

ctDNA as a Marker of Therapeutic Response in Stage IV CRC

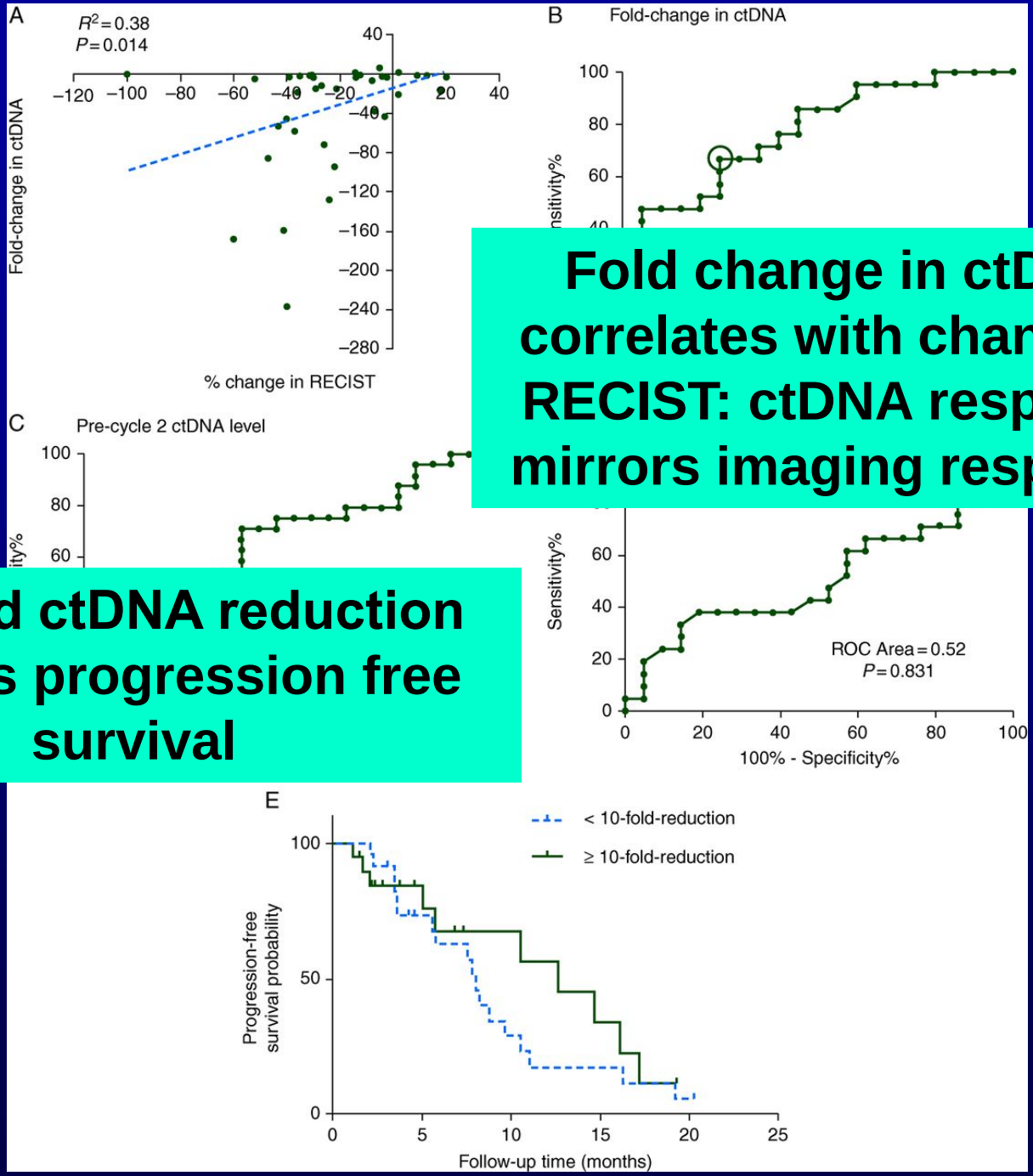
- N=53, serial blood collection, CT week 8-10
- RECIST: image-based Response Evaluation Criteria in Solid Tumors
- Explore ctDNA as a marker of treatment response

J. Tie et al. Ann Oncol 2015



ctDNA correlates with baseline RECIST SLD (sum

ctDNA decreases with chemoRx, CEA shows no change



Fold change in ctDNA correlates with change in RECIST: ctDNA response mirrors imaging response

≥ 10 fold ctDNA reduction predicts progression free survival

Conclusions

- ≥10 fold ctDNA reduction pre-cyle 2 (@14-21days) predicts progression free survival (14.7 vs. 8.1 months)

Application

- Could use ct-DNA to prognosticate
- Could use ct-DNA to try a different chemoRx

ctDNA After Surgery in Stage II CRC: Predicts Disease Recurrence

	Recurrence	No recurrence	Total
Post-op ctDNA - positive	7	2	9
Post-op ctDNA - negative	7	96	103
Total	14	97	112

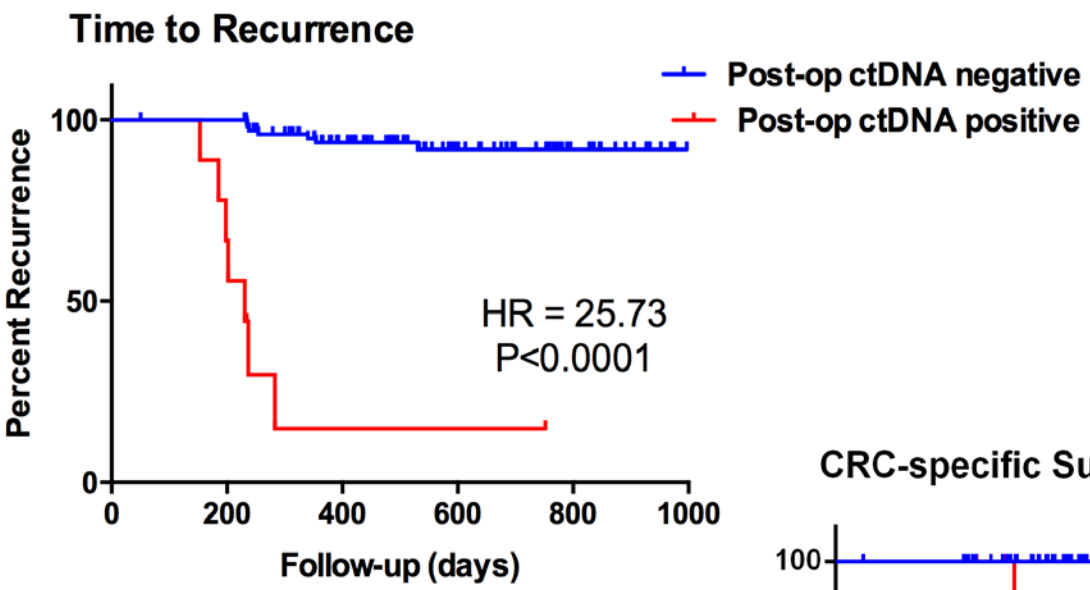
Fisher's Exact P < 0.0001

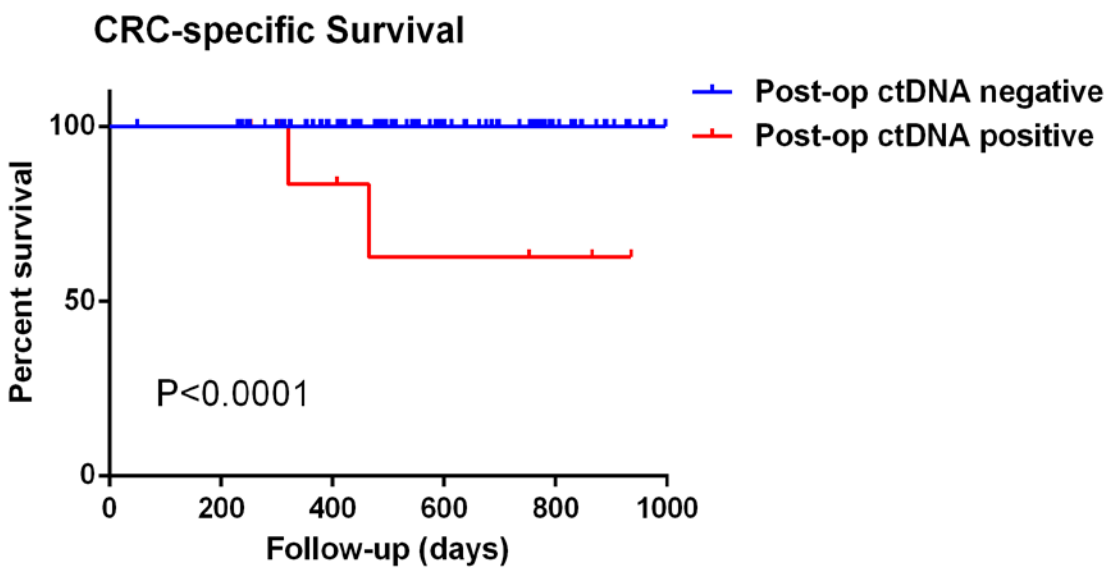
RR = 11.44
(95% CI 5.16 – 25.37)

Positive predictive value = 77.8%

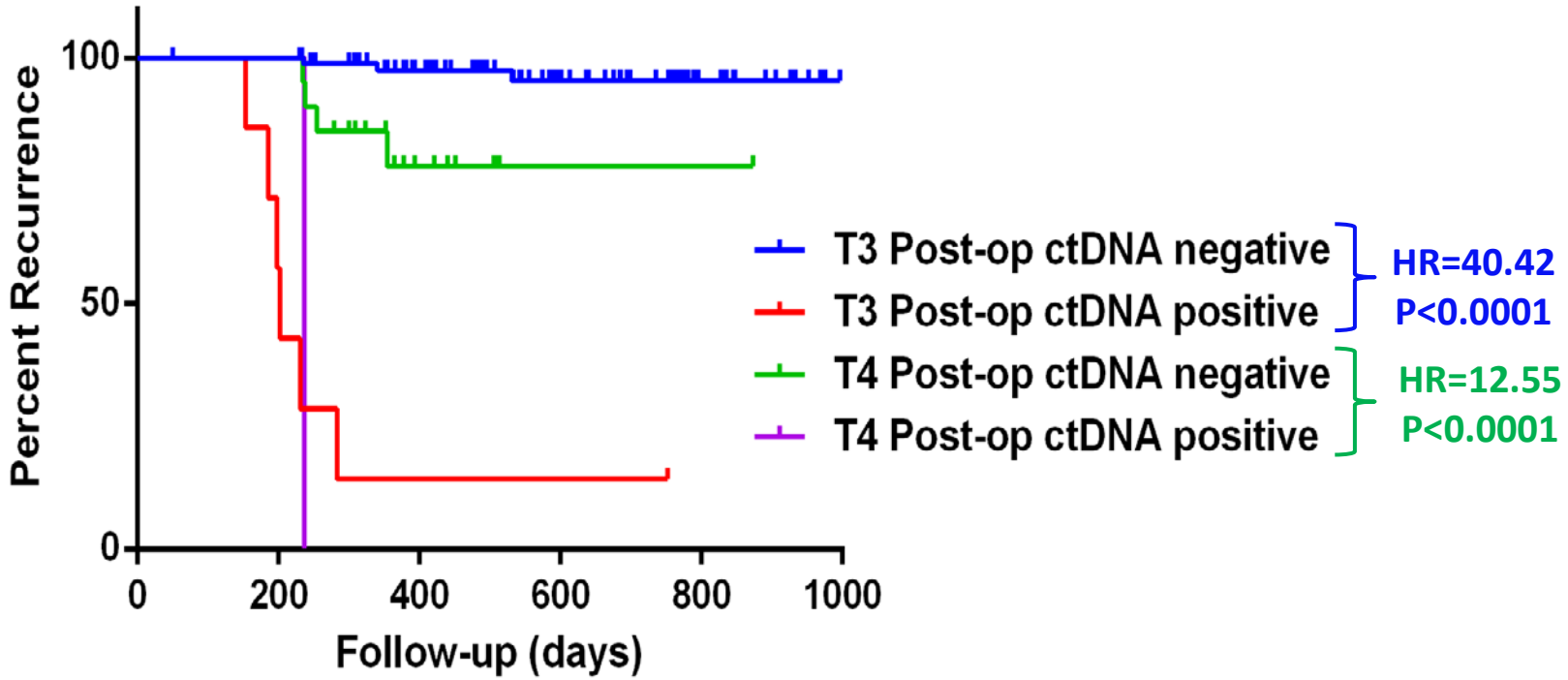
Negative predictive value = 93.2%

Post-op ctDNA, time-to-recurrence and CRC-specific survival





Time-to-recurrence according to post-op ctDNA results for patients with T3 and T4 tumor



Conclusions

- ctDNA is a marker for recurrence in patients with stage II CRC
- ctDNA findings discriminate within clinicopathologic subgroups

Application

- Could use ct-DNA to aid in decision of who should get chemoRx in stage II CRC

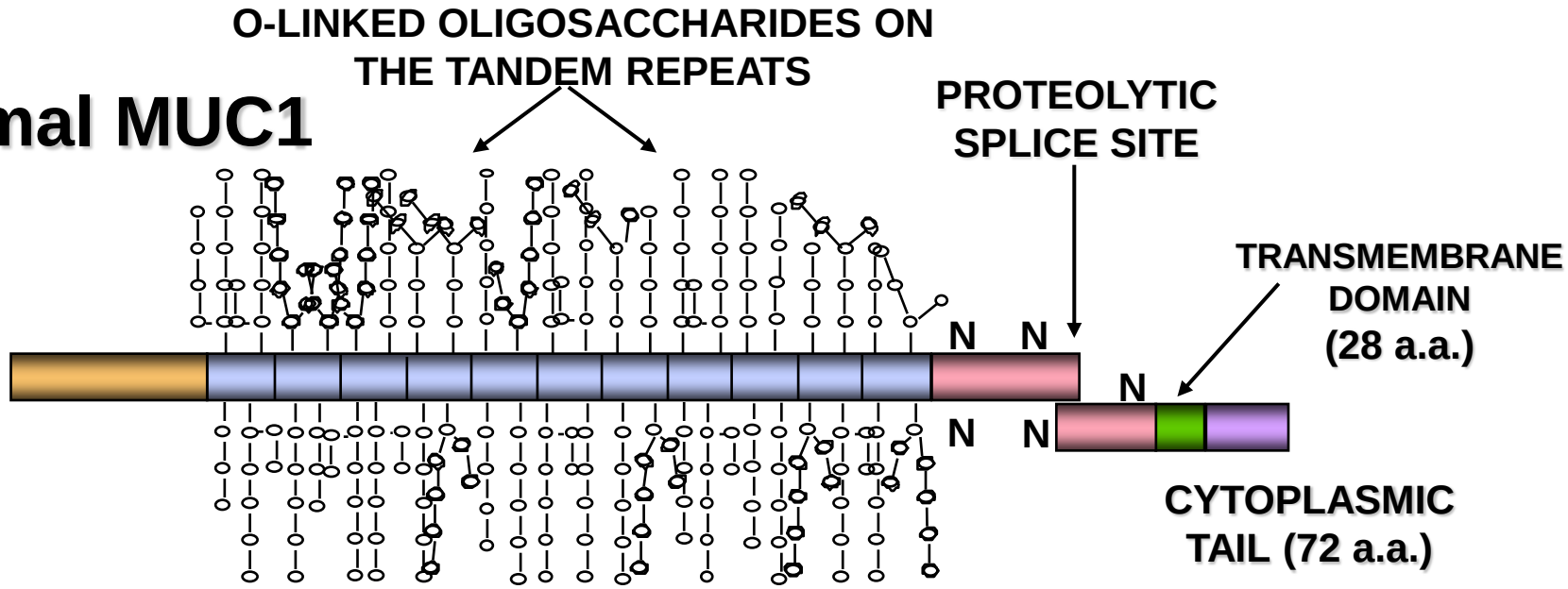
Immuno-Prevention

Immunize people at high risk for cancer when the immune system is still powerful and effective

Immunotherapy in a Preventive Mode: Immune Interception

Kimura. Ca Prev Resch 2013;6:18
Dhodapkar. Ca Prev Resch 2013;6

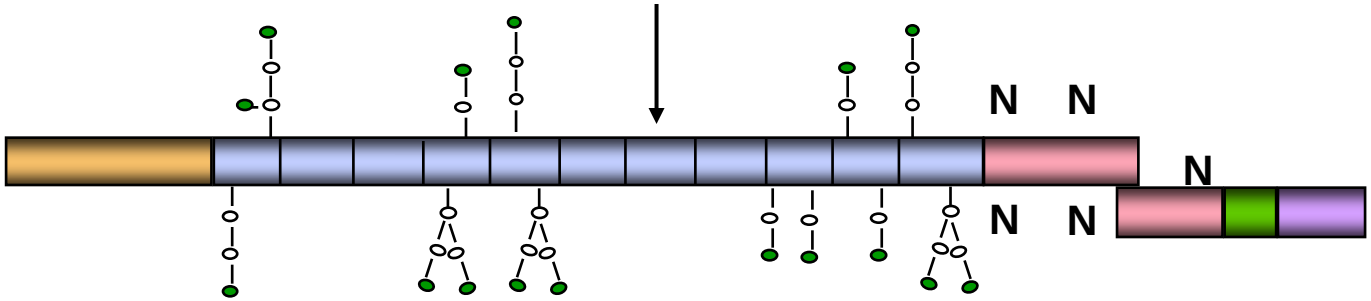
Normal MUC1



Abnormal MUC1

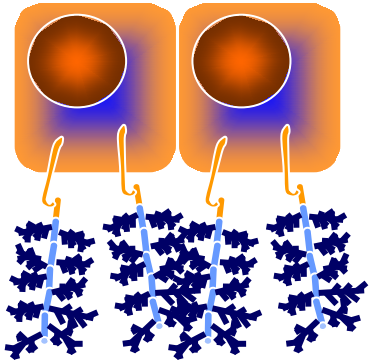
1 repeat = 20 a.a.

HGVTSAPDTRPAPGSTAPPA

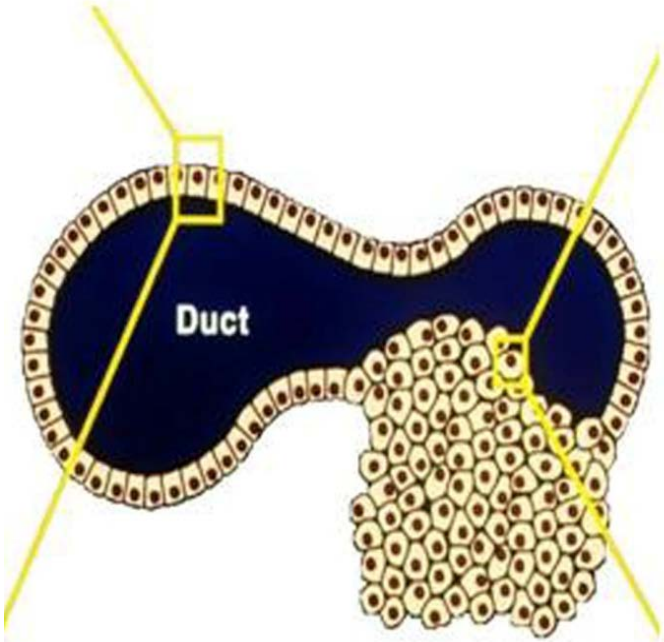


Normal

Basolateral side

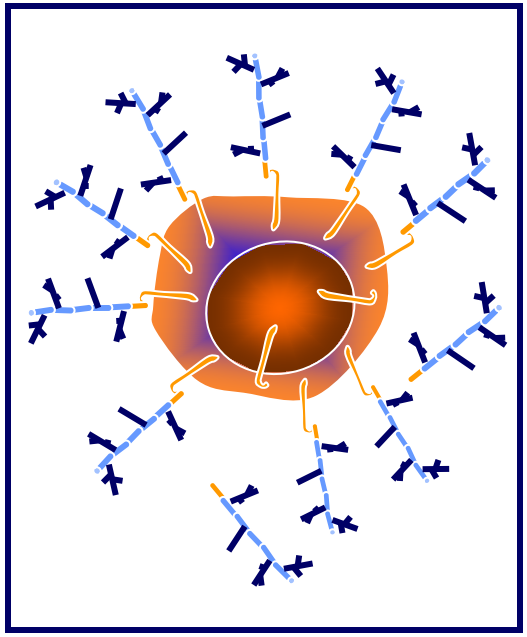


Apical (luminal) side



Polyp or Tumor

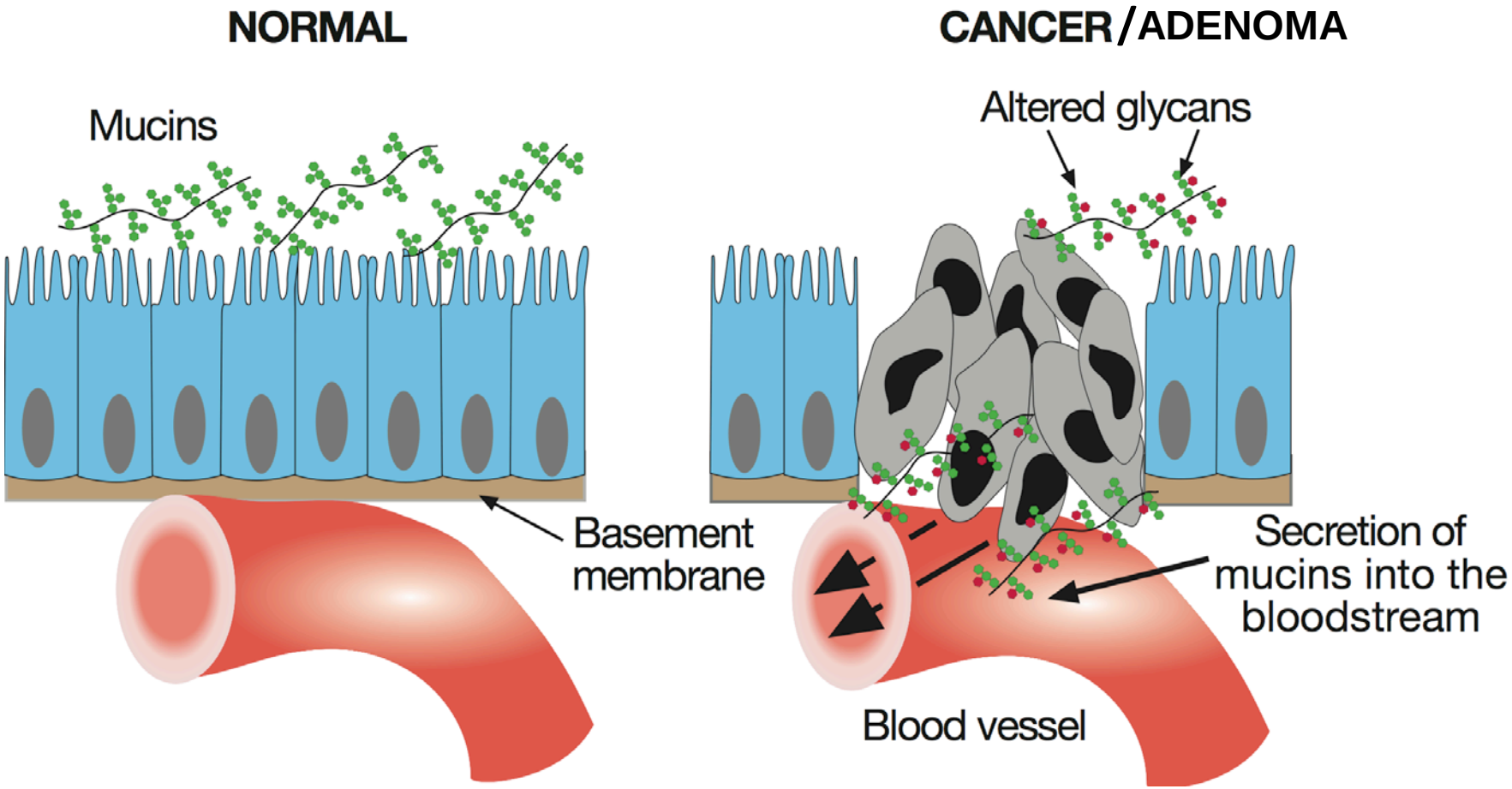
Abnormal: Polyp or Tumor



Hypoglycosylated MUC1 on entire surface

Protein backbones, which on normal tissue are concealed by glycosylation are exposed to immune system.

Abnormal Mucins Exposed to Systemic Circulation

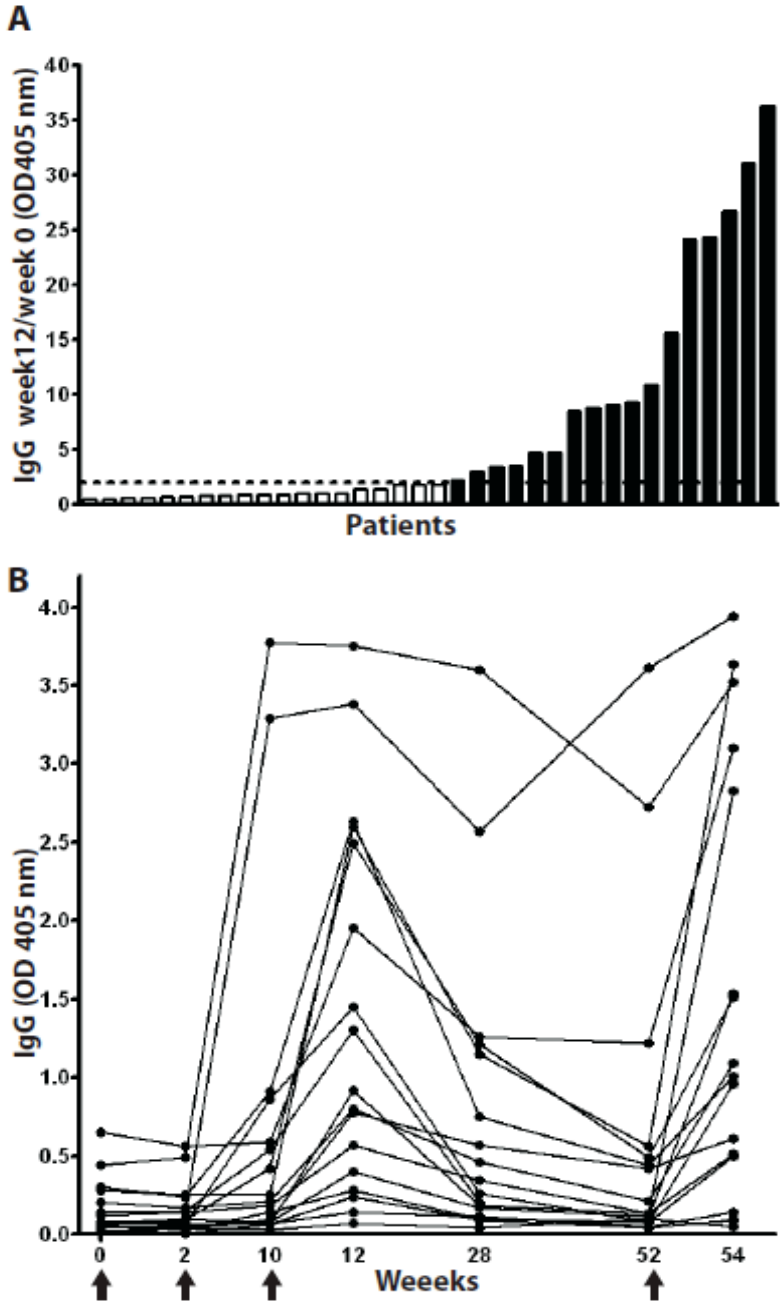


Vaccine Prevention Trial Against Tumor Associated Antigen

Strategy

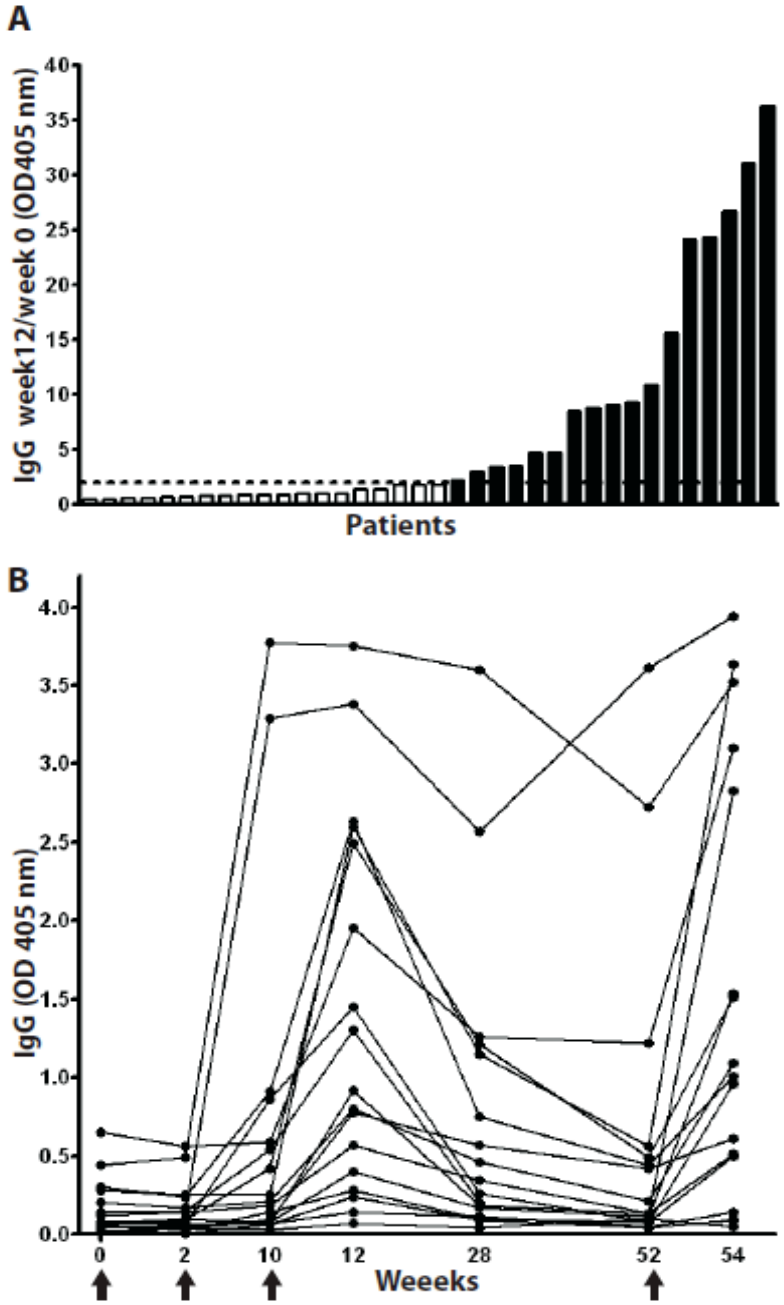
Subjects with advanced adenomas who are at higher risk to develop colorectal cancer: Vaccinate them against tumor associated MUC1 antigen

Kimura, CA Prev Res 2013;6:18-26



Ratio range among Responders: 2.2 – 36.3

Peak response week 12, post 3rd injection



Booster response at week 54

Randomized, Double-Blind, Placebo-Controlled Trial of MUC1 Vaccine in Patients with Newly Diagnosed Advanced Adenomas

- In Conjunction with the Mayo Cancer Prevention Network (CPN) and the NCI Division of Cancer Prevention
- 7 centers

Trial Progress

Date: June 10, 2015

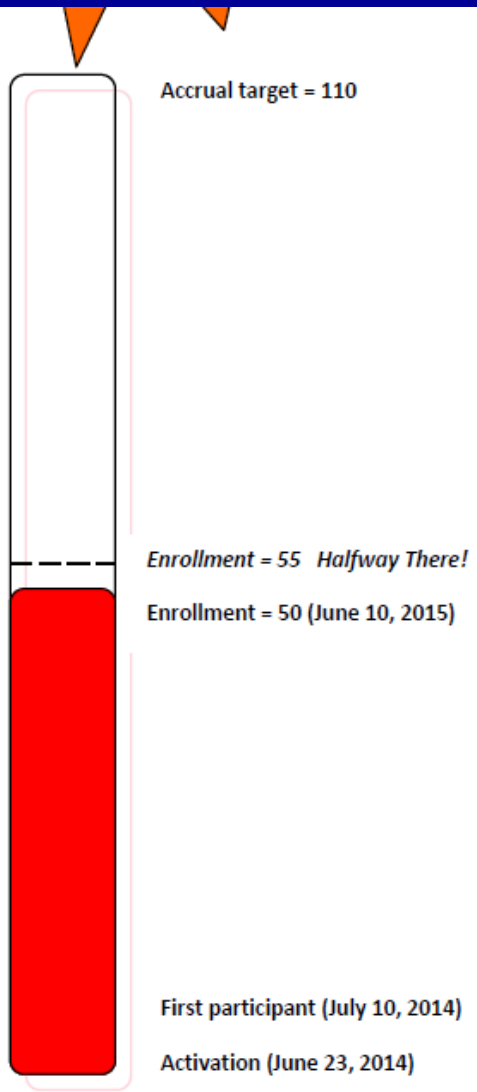
Accrual Update for MAY2013-01-01, " Randomized, Double-Blind, Placebo-Controlled Trial of MUC1 Vaccine in Patients with Newly Diagnosed Advanced Adenomas"

Site	Pre-Registered	Randomized	"Next Tasks"
Mayo Clinic in Rochester	12	10	Identifying potential participants using pathology report.
University of Pittsburgh	21	20	Randomized 4 participants the month of May by reviewing pathology reports.
University of Puerto Rico	12	11	Jessica is actively screening potential participants in clinic.
Massachusetts General Hospital	2	1	One appointment scheduled for consent/screening.
Thomas Jefferson University	8	4	No report provided.
Kansas City VA Medical Center	4	4	Welcome Andrew Price – he randomized a patient his first week! Way to go!
Fox Chase Cancer Center			Eileen is reviewing path reports daily to identify potential participants. One potential participant identified and will be contacted after repeat colonoscopy in July.
Totals	**59**	**50**	

Current Status: All sites are actively recruiting study participants.

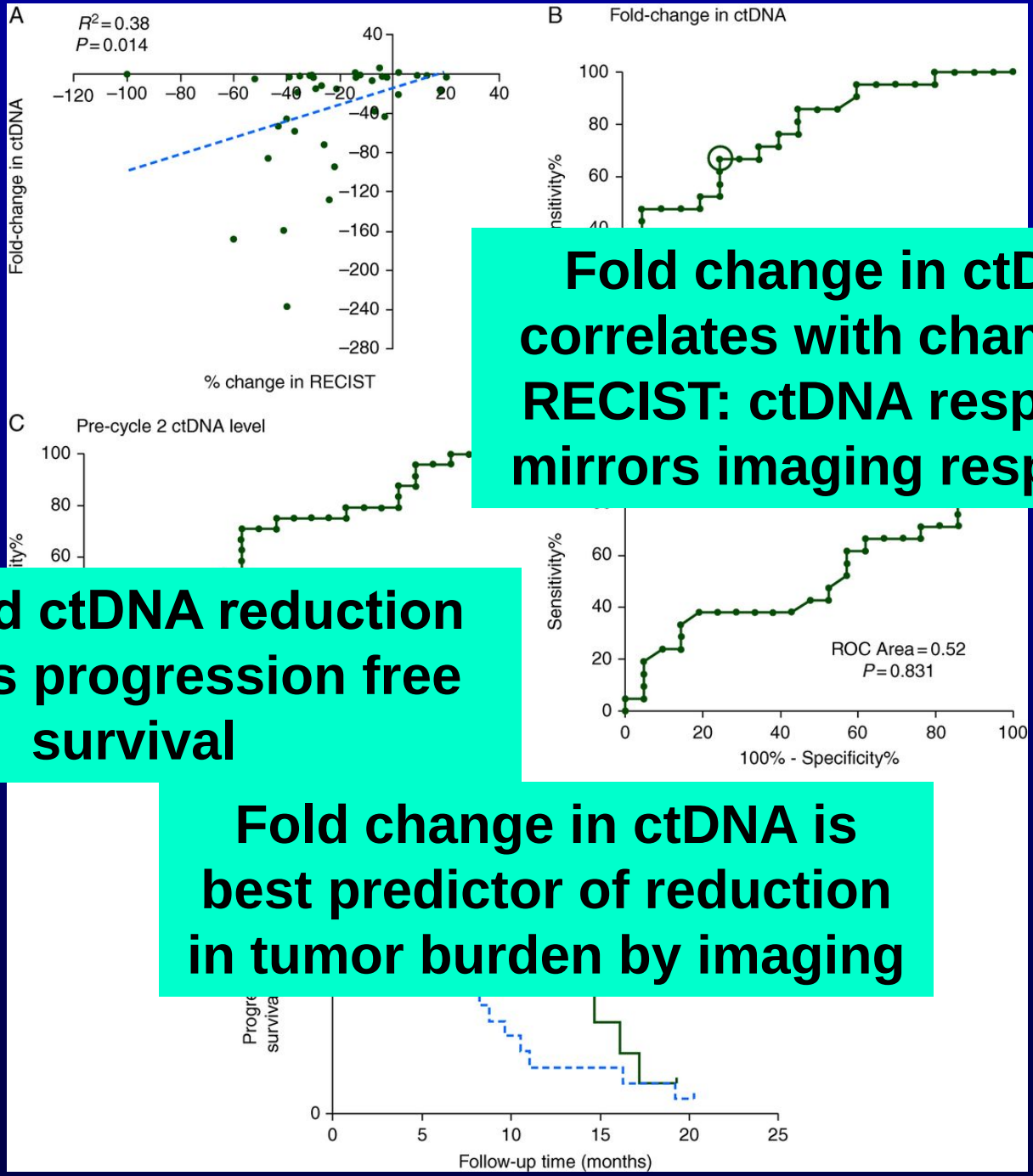
Reminder: Please submit V5A4 of the protocol to your local IRBs as soon as possible and forward your approval to the CPN Operations office. Submissions should take place within 30 days of receipt of the amendment documents.

Next Study Coordinator Call is Thursday June 18th at 10 a.m. EDT; 9 a.m. CDT. Please let us know if you have any discussion items for the agenda.



Optimizing CRC Screening

- Access for all at risk
- Develop new more accessible means to increase screening utilization
- Develop new methods for prevention such as vaccines or personalized medicine



Fold change in ctDNA correlates with change in RECIST: ctDNA response mirrors imaging response

≥ 10 fold ctDNA reduction predicts progression free survival

Fold change in ctDNA is best predictor of reduction in tumor burden by imaging