GI01
06/27/2020
11:40am

Robert Schoen, M.D., M.P.H., University of Pittsburgh

GI01
06/26/2020
5:49am

ctDNA as a Biomarker for Monitoring of CRC

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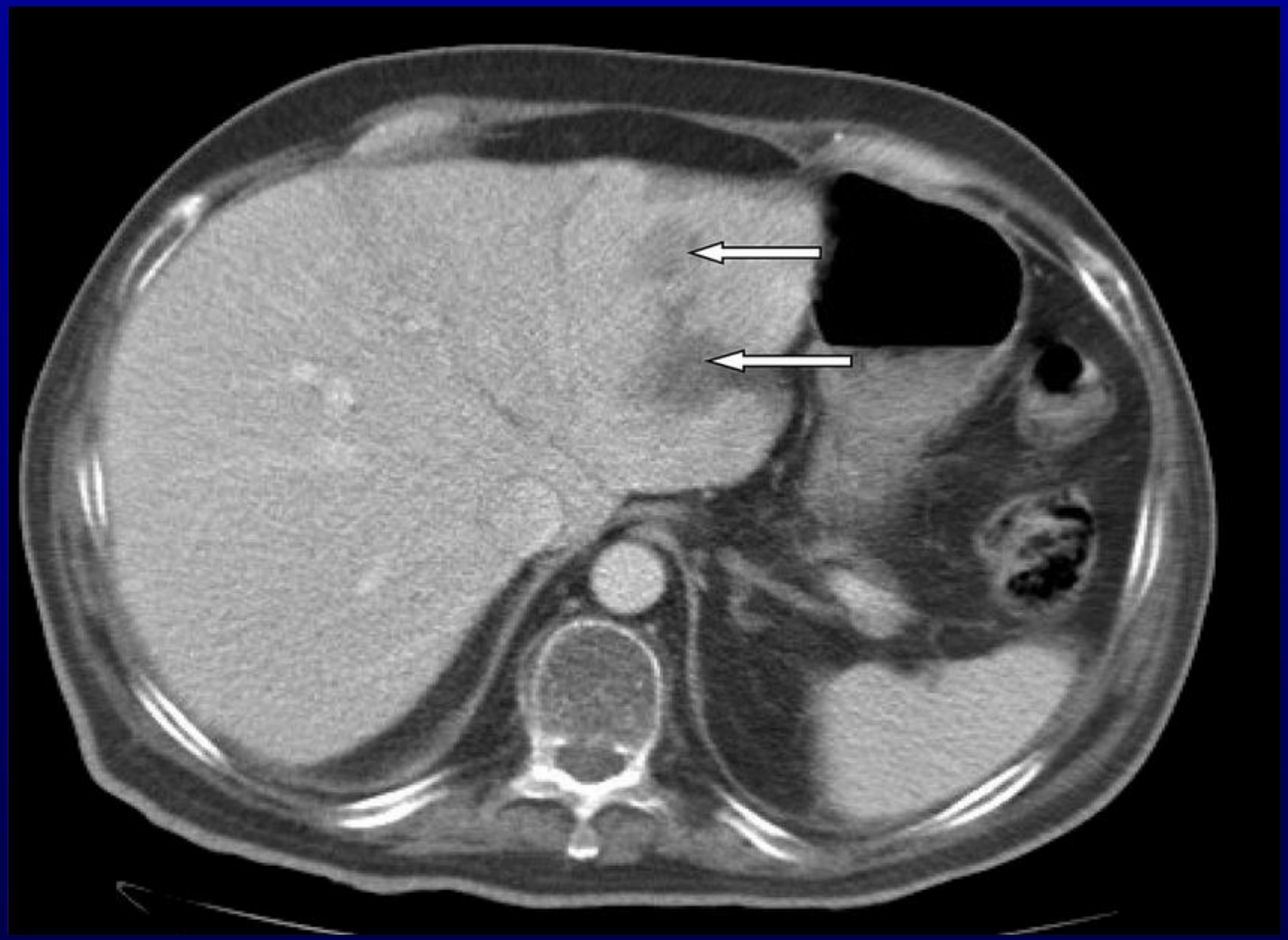
ctDNA for Monitoring of Recurrent CRC



Tumor Directed?

- Agnostic panel
- Guided by mutational analysis of tumor
- Genomic: SNV/indels
- Epigenetic/Protein Markers

MRD: Minimal Residual Disease

- Leukemia/lymphoma – residual cancer cells post treatment
- Solid tumors: prognostic marker - likelihood of recurrence
- ctDNA+ sign of MRD

Science Translational Medicine AAAS

RESEARCH ARTICLE

CANCER

Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer

Jeanne Tie,[1,2,3,4*†] Yuxuan Wang,[5†] Cristian Tomasetti,[6,7] Lu Li,[6] Simeon Springer,[5] Isaac Kinde,[8] Natalie Silliman,[5] Mark Tacey,[9] Hui-Li Wong,[1,3,4] Michael Christie,[1,3,10] Suzanne Kosmider,[2] Iain Skinner,[2] Rachel Wong,[1,11,12] Malcolm Steel,[11] Ben Tran,[1,2,3,4] Jayesh Desai,[1,3,4] Ian Jones,[4,13] Andrew Haydon,[14] Theresa Hayes,[15] Tim J. Price,[16] Robert L. Strausberg,[17] Luis A. Diaz Jr.,[5] Nickolas Papadopoulos,[5] Kenneth W. Kinzler,[5] Bert Vogelstein,[5*†] Peter Gibbs[1,2,3,4,17*†]

Sci Transl Med. 2016 Jul 6;8(346):346ra92
ASCO Annual Meeting, 2016, Abstract 3511

ctDNA in Stage II CRC

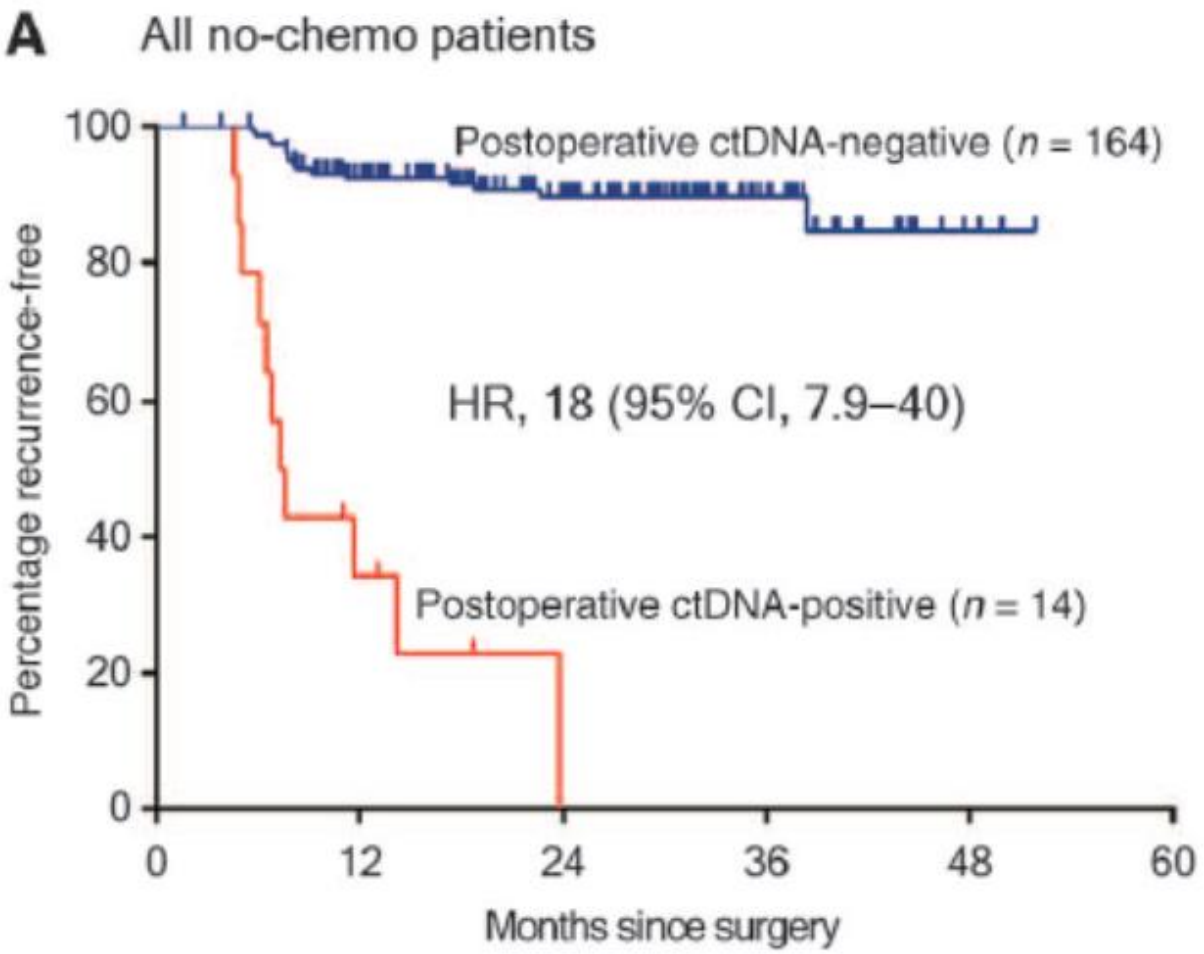
N=250, post-op and serial plasma
23% adj chemo Rx at clinician direction

- Targeted 15 genes using safe-SeqS
- 20/231 +ctDNA post op (9 p53, 8 APC, 3 KRAS)
- Median f/u 27 mo
- 34 (14.8%) radiologic recurrence

27/178 (15%) no chemo Rx
7/52 (13%) with chemo Rx

Tie, Science Trans Med 2016

Recurrence Free Survival (RFS) in Stage II CRC Patients not treated with adjuvant chemotherapy



Jeanne Tie et al., Sci Transl Med 2016;8:346ra92

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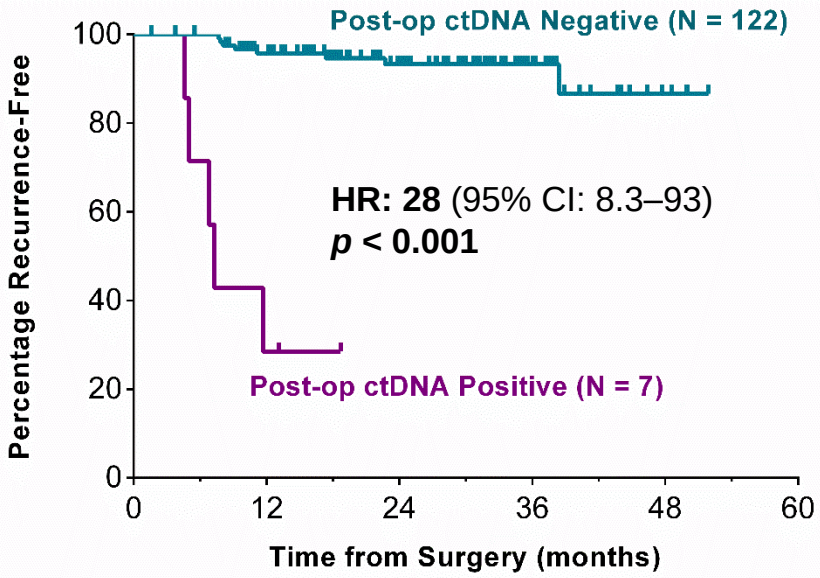
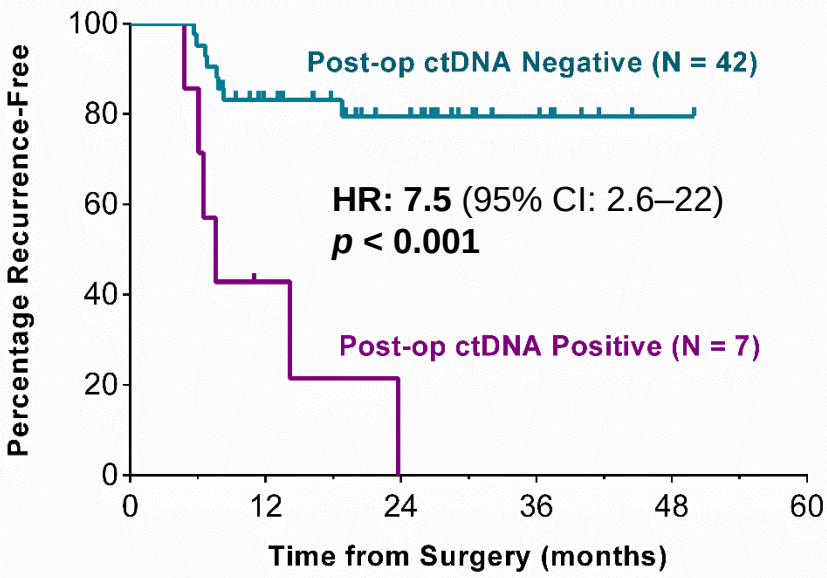
Recurrence-Free Survival: Stage II CRC

Clinical Low-Risk
(dMMR *or* pMMR + no poor prognostic features)

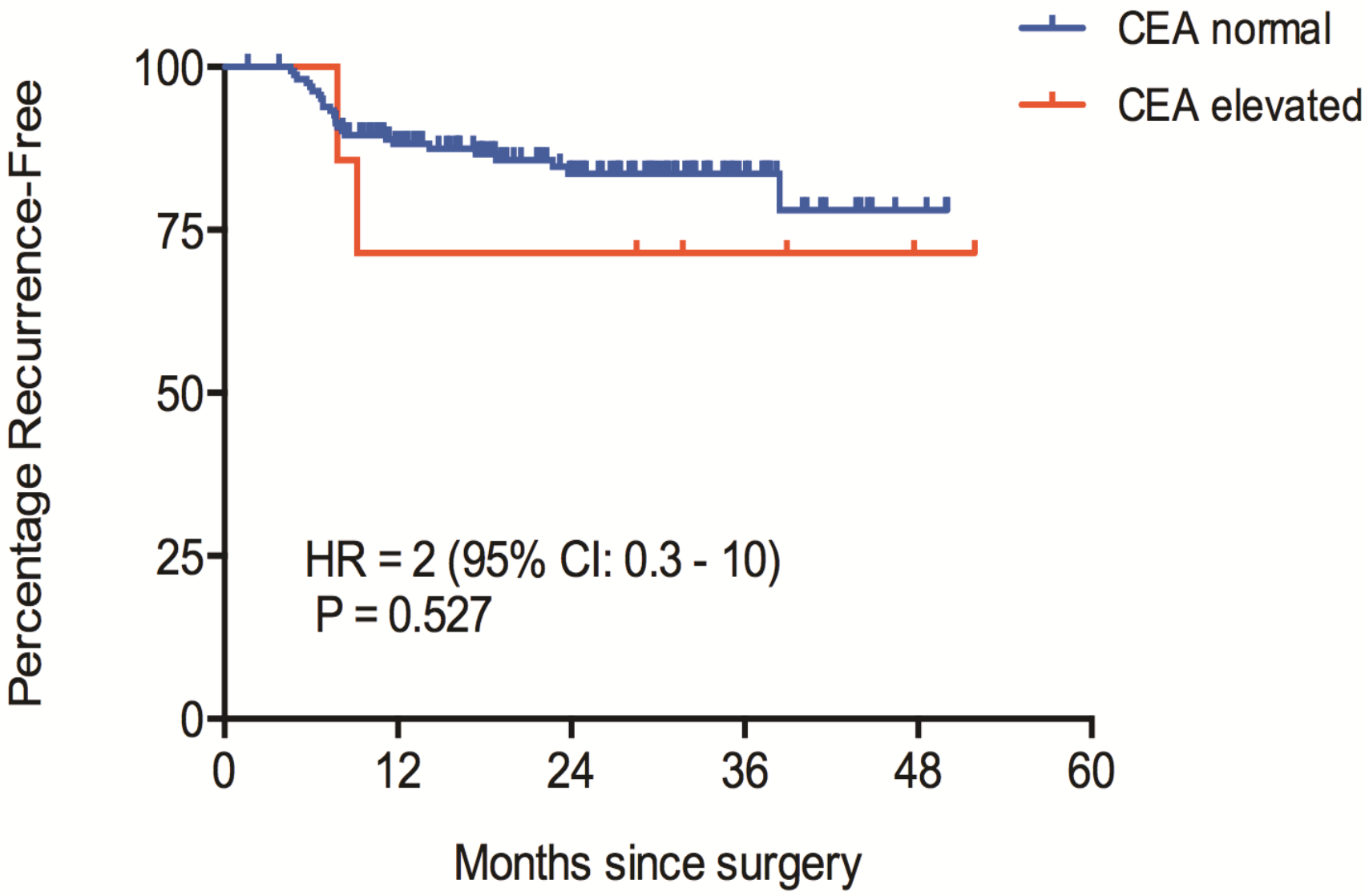


Clinical High-Risk
(pMMR + at least one poor prognostic features)

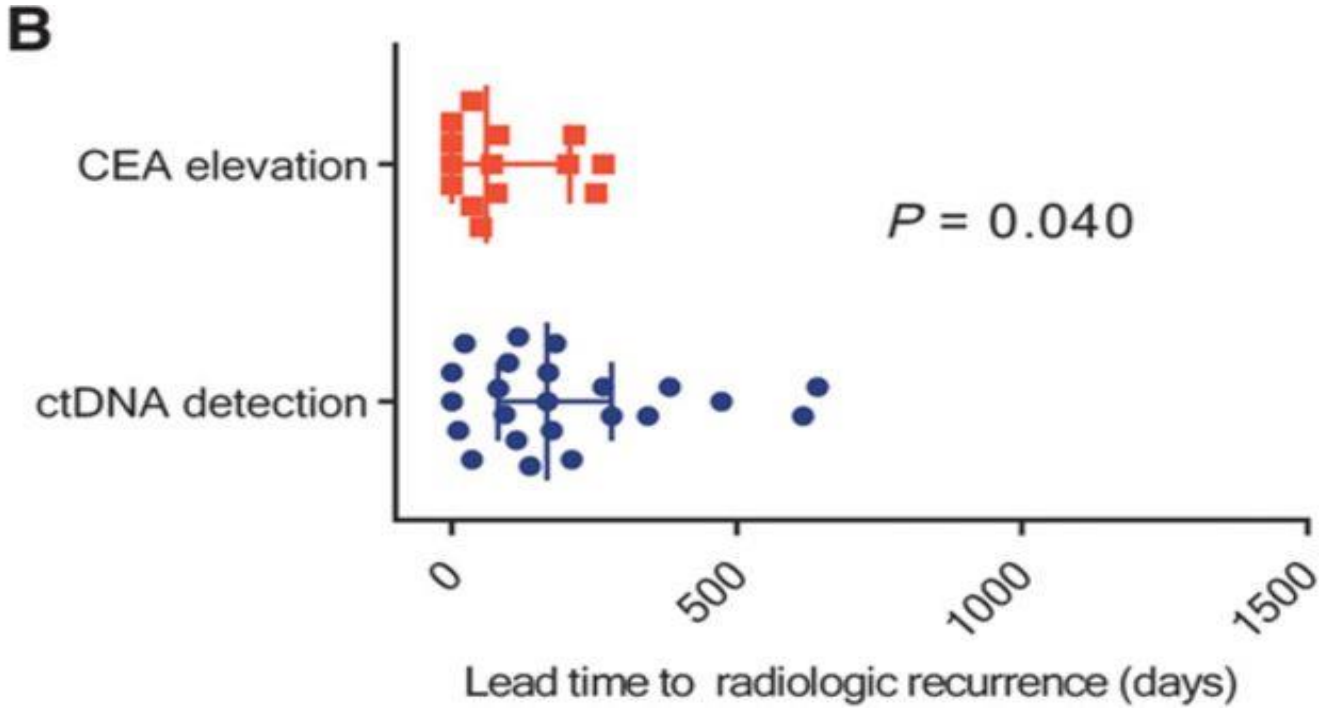


Sci Transl Med. 2016 Jul 6;8(346):346ra92

Recurrence Free Survival (RFS) in patients not treated with adjuvant chemotherapy by CEA level



Lead Time to Radiological Recurrence: ctDNA vs. CEA



Time from detection to recurrence: ctDNA 167 days vs. CEA 61 days, p=.04

Conclusions

- ctDNA is an excellent marker for recurrence in patients with stage II CRC
- ctDNA findings discriminate within clinicopathologic subgroups
- But: Does it make a therapeutic difference to know prognosis?

“DYNAMIC” Study

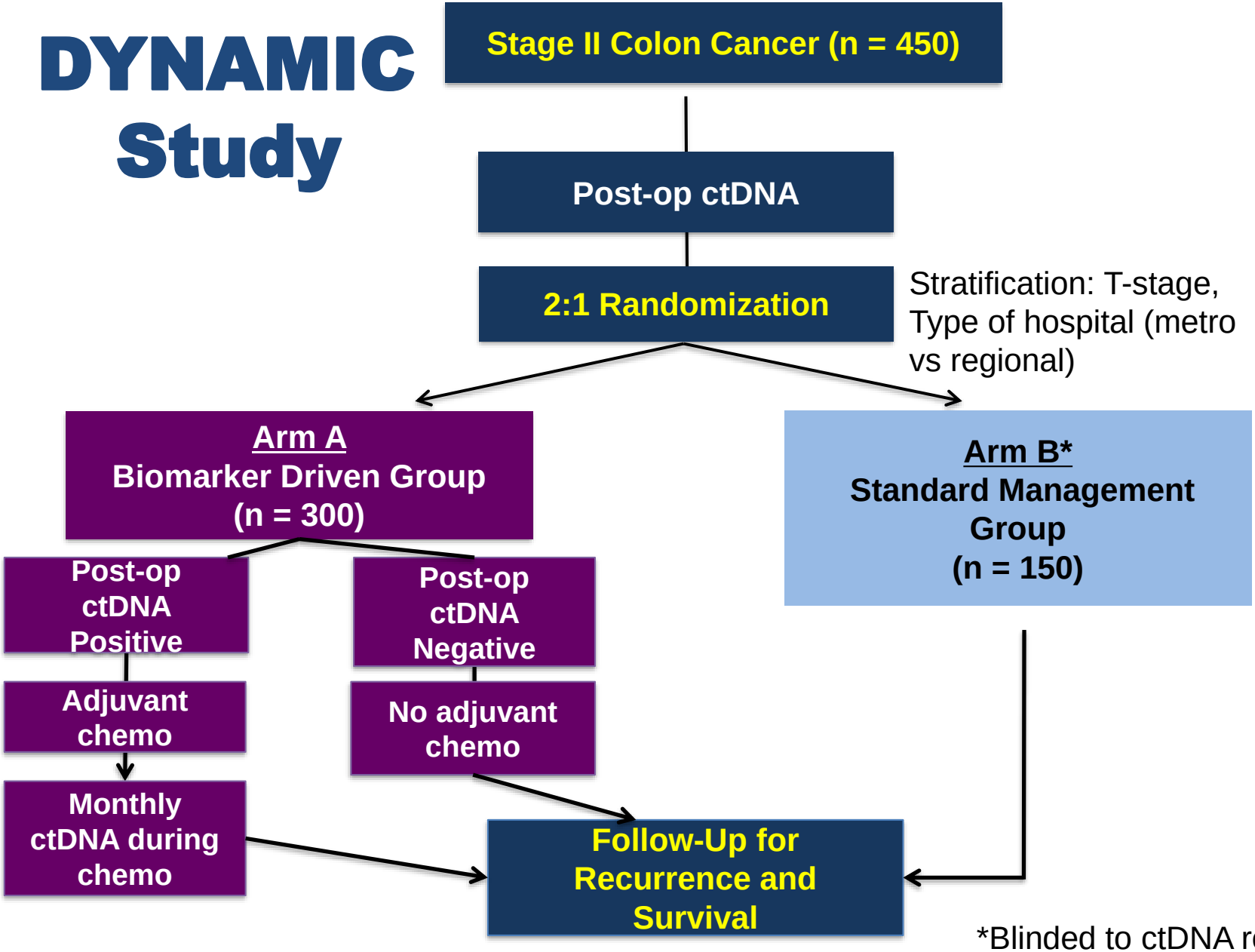
Circulating Tumour DNA Analysis Informing Adjuvant Chemotherapy in Stage II Colon Cancer

“DYNAMIC” Study

- **Study Design**
  - Randomised multi-centre biomarker-driven adjuvant treatment study

- **Primary end-points**
  - Number of patients treated with adjuvant chemotherapy
  - Recurrence-free survival

DYNAMIC Study



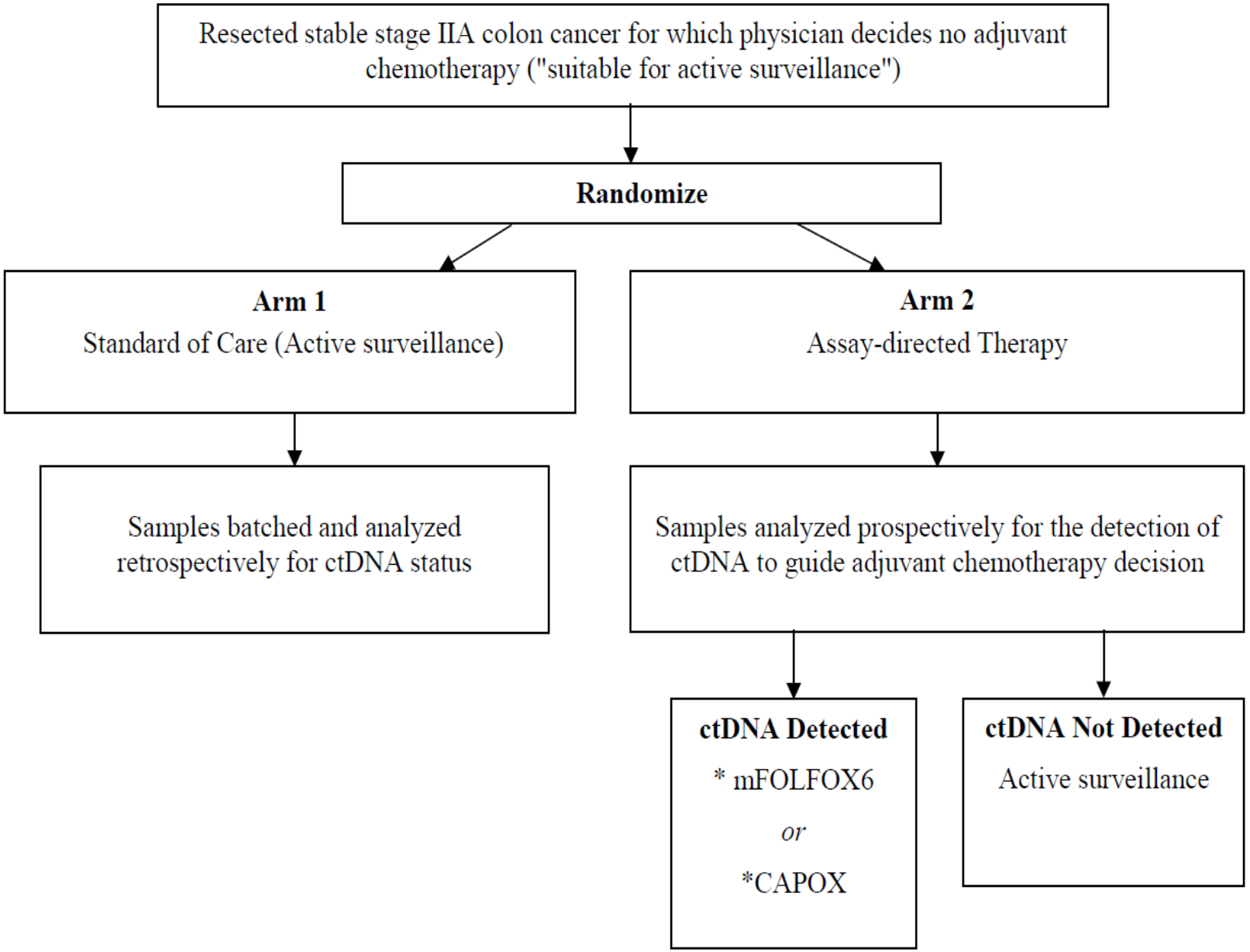
NRG GI005 - COBRA Trial: Guardant LUNAR Assay

- N=1400, resected stage II CRC
- No adj chemoRx planned
- Randomized to SOC vs ctDNA directed
- +ctDNA → FOLFOX or CAPOX x 6 mos
- LUNAR: genetic and epigenetic

Endpoints

- (phase II) - clearance of ctDNA
- (phase III) – RFS for +ctDNA treated with adj chemoRX

COBRA Trial


Resected stable stage IIA colon cancer for which physician decides no adjuvant chemotherapy ("suitable for active surveillance")
Randomize
Arm 1
Standard of Care (Active surveillance)
Arm 2
Assay-directed Therapy
Samples batched and analyzed retrospectively for ctDNA status
Samples analyzed prospectively for the detection of ctDNA to guide adjuvant chemotherapy decision
ctDNA Detected
* mFOLFOX6
or
*CAPOX
ctDNA Not Detected
Active surveillance

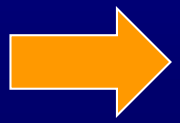
“Signatera” ctDNA Assay

- Assay targeting 16 clonal, somatic mutations known to be present in tumor
- Selecting clonal, tumor-specific variants enables deeper sequencing and a higher probability of ctDNA detection
- Quantitative sampling: copies/ml plasma informative mutation and average for all informative mutations

Signatera: ctDNA in Stage I-III CRC

Denmark: N=130 (5 stage I, 39 II, 81 III) – blood q 3 mos, 16 SNP or Indels

Stage	% Pre-op positive
I	40
II	92
III	90



10/94 (10.6%) positive on post-op day 30

Recurrence:

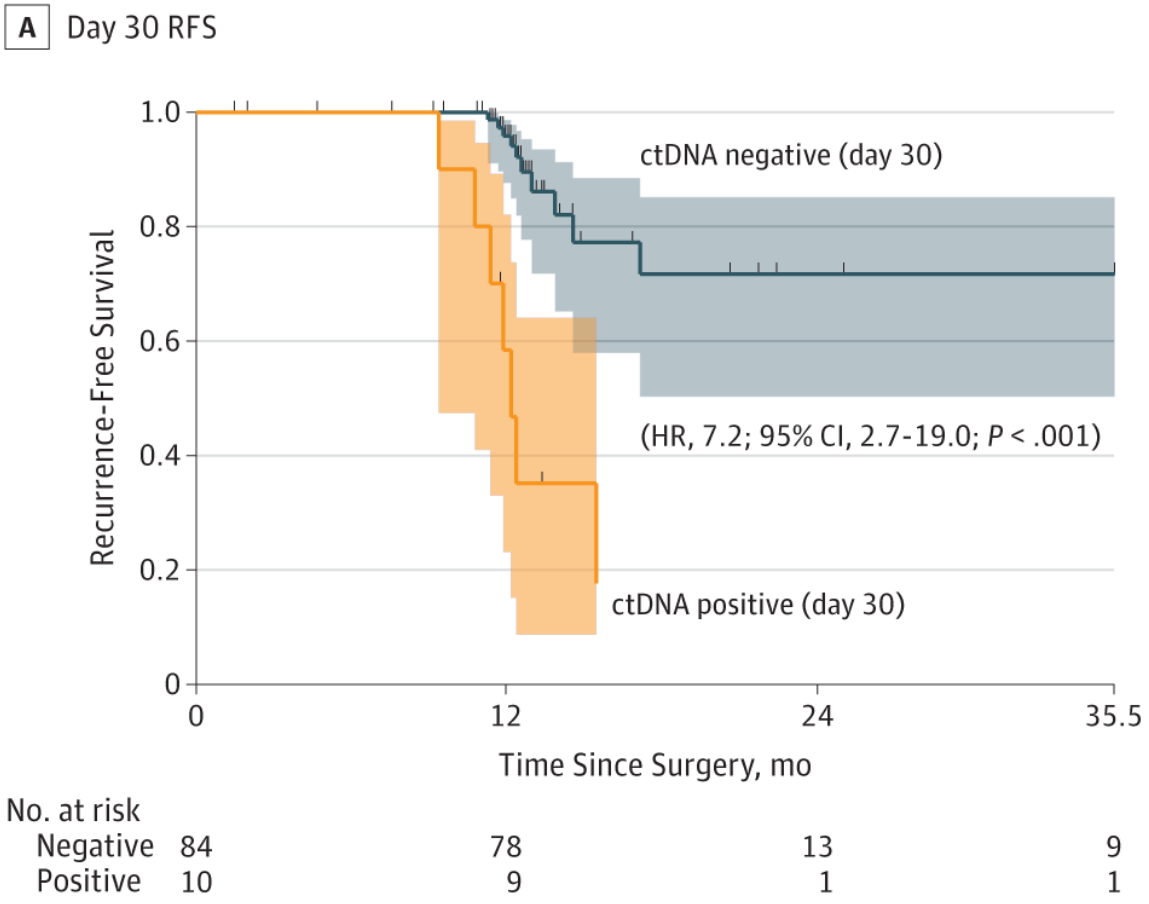
7/10 ctDNA+ (70%)

10/84 ctDNA- (12%)

HR=7.2 (2.7-19)

Reinert, JAMA Oncology 2019

Recurrence Free Survival by ctDNA+ at Day 30



Denmark: ct DNA+ - Post-chemo rx

Post-chemo ctDNA status as predictor of relapse (n=58)

Relapse

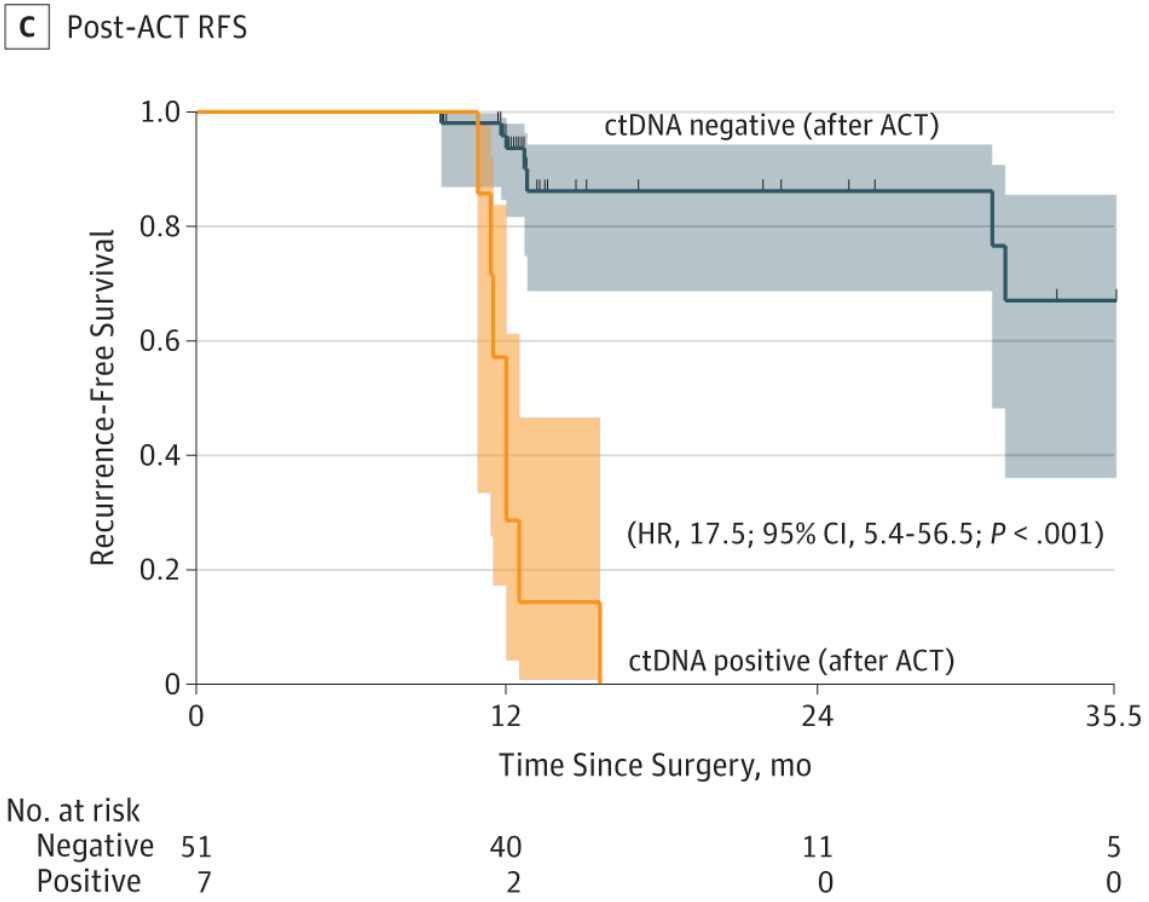
ct DNA+: 7/7 (100%)

ct DNA-: 7/51 (14%)

HR=17.5 (5.4-56.5)

Reinert, JAMA Oncology 2019

Post-adjuvant ChemoRx ctDNA Status as Predictor of Relapse



ctDNA: Lead time to CT Detected Radiologic Recurrence

Mean Time to Recurrence:

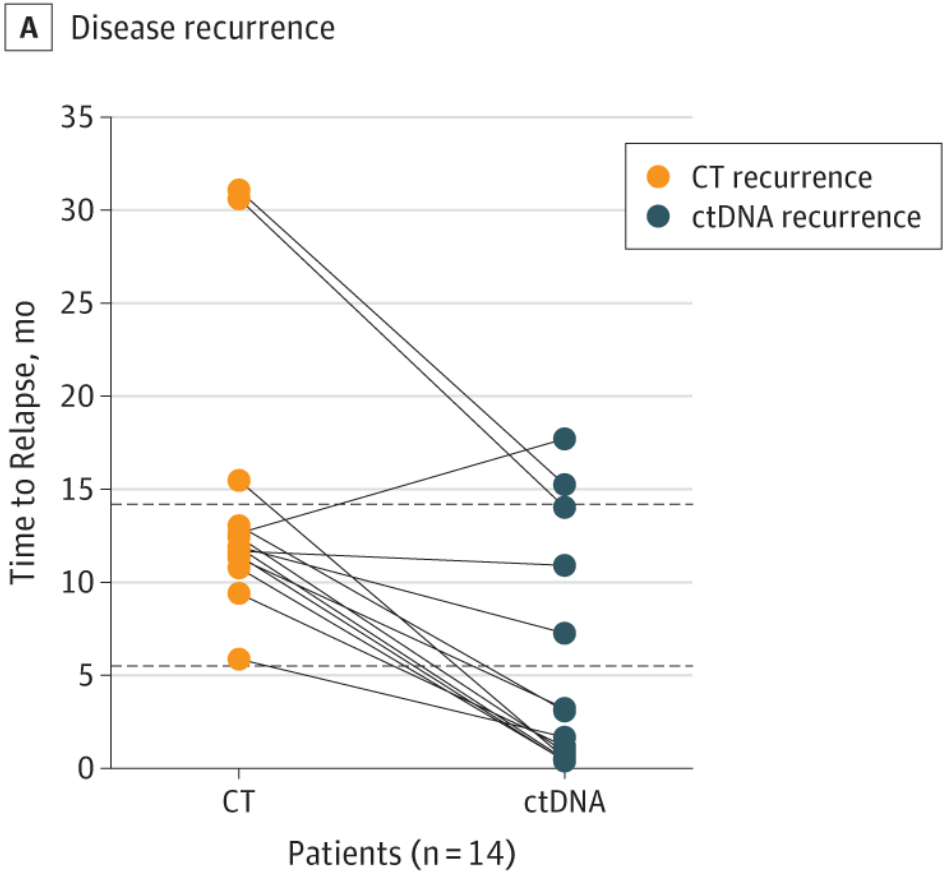
ctDNA - 8.7 mo.

CEA - None

Mean Time from Surgery to CT Relapse:

ctDNA – 5.5 mo.

CT – 14.2 mo



Denmark: ctDNA vs CEA

CEA:	Sensitivity	69%
	Specificity	64%

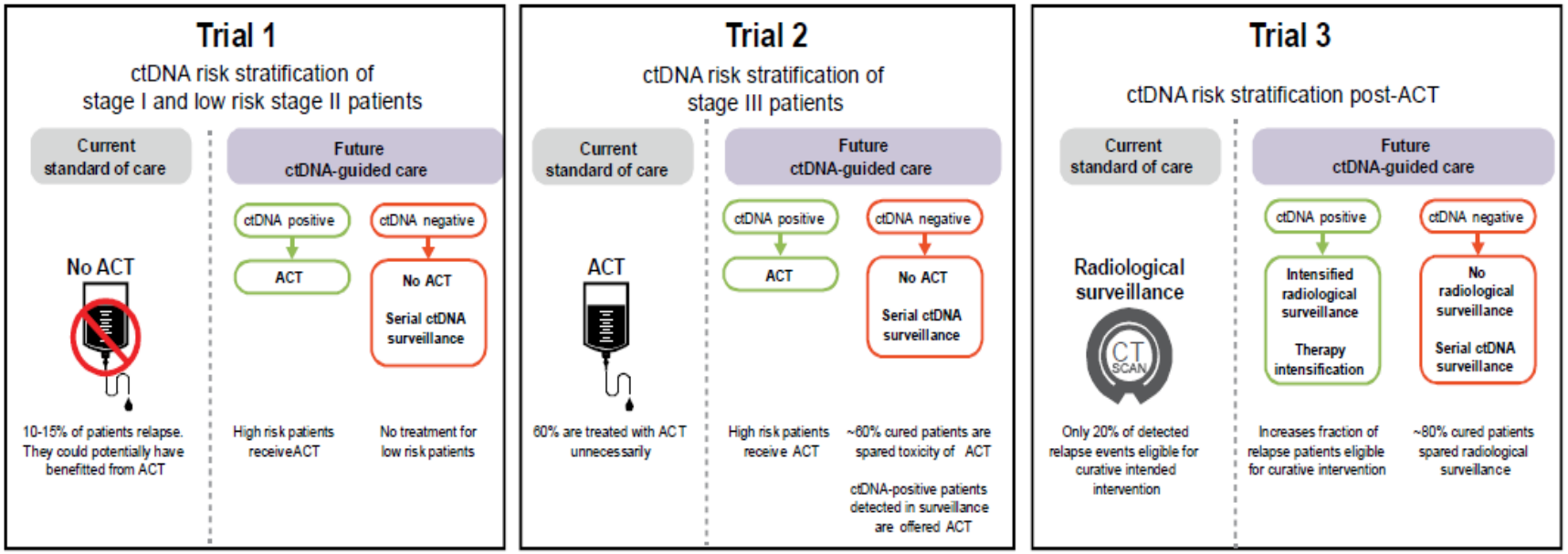
In multivariable analysis including age, stage, histology, CEA:

Only ctDNA associated with RFS

HR=39.9 (7.5-211)

Reinert, JAMA Oncology 2019

Clinical Trial Proposals for Integrating ctDNA into CRC Treatment



ctDNA and Stage III CRC

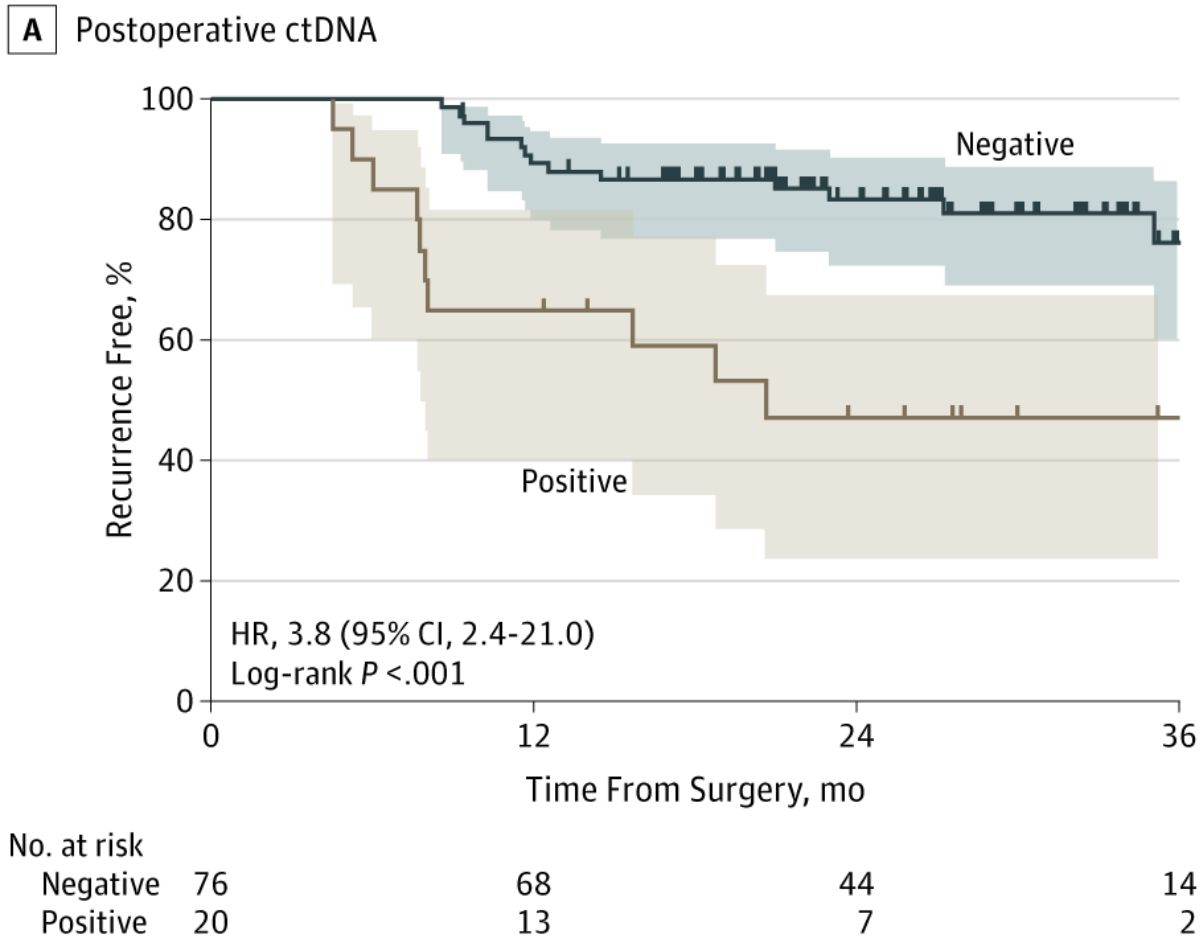
- Evaluate prognostic significance of ctDNA post-op and post chemoRx
- N=96, Australia
- 15 gene panel for somatic mutations on tumor specimen to select 1 mutation for plasma ctDNA measurement
- Median f/u 28.9 mo

Tie. JAMA Onc 2019

ctDNA and Outcome

- +ctDNA in 20/96 (21%) post-surgery
- No association of +ctDNA with demographic/pathologic characteristics
- +ctDNA post surgery - ⬆ HR recurrence 3.8 (2.4-21, p <.001)
- RFI: 47% +ctDNA vs 76% -ctDNA

+ctDNA and Post Op Recurrence Free Interval (RFI)

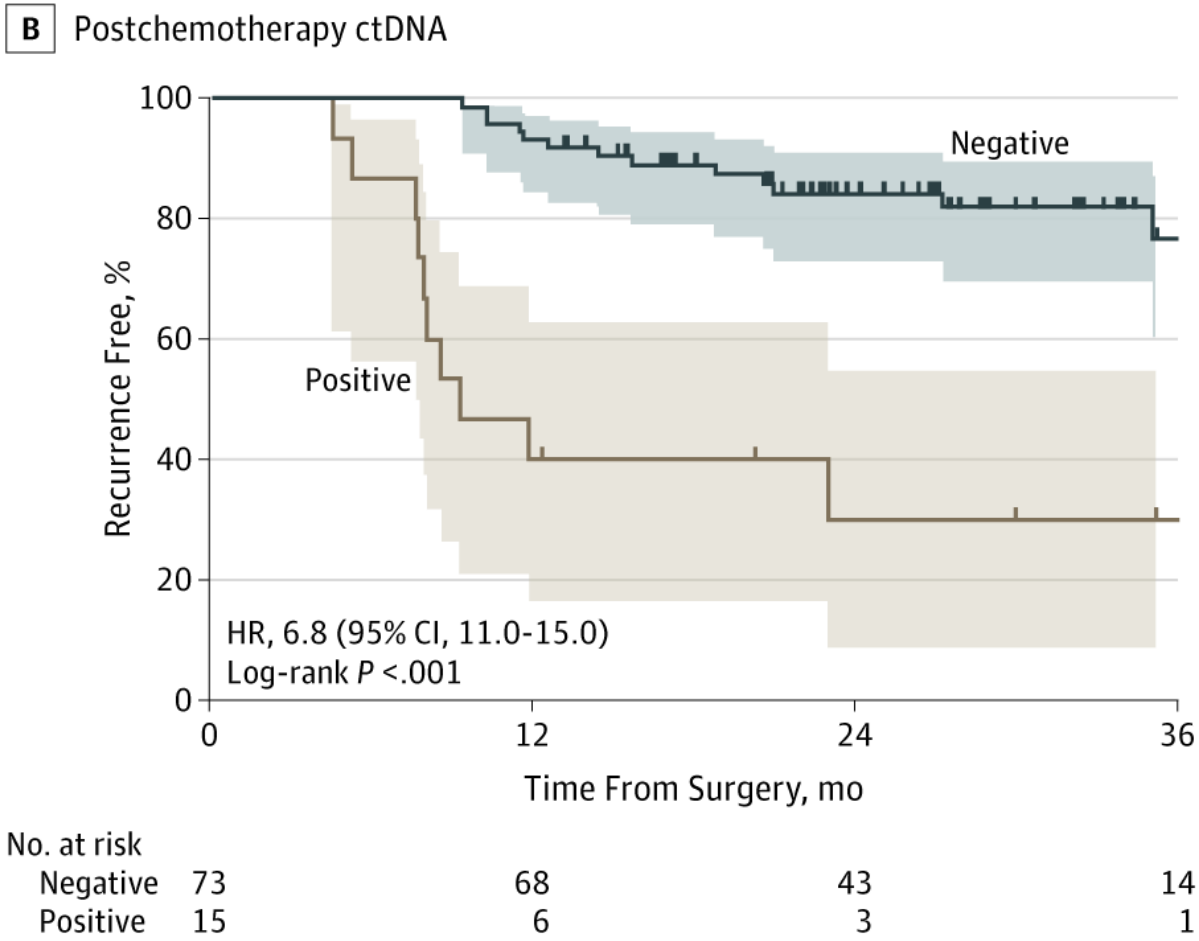


ctDNA and post-ChemoRx Outcome

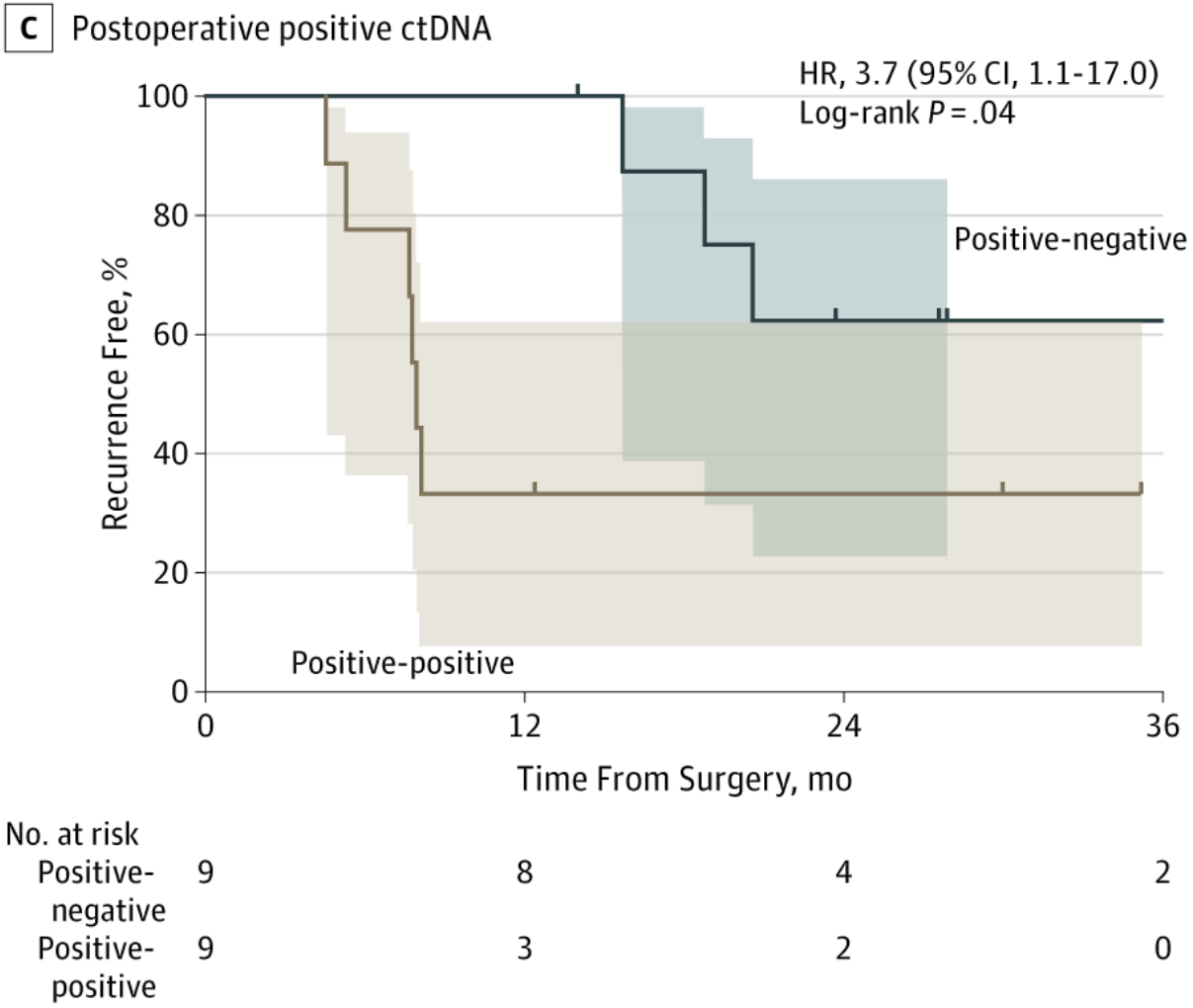
- +ctDNA in 15/88 (17%) post chemoRx
- +ctDNA post chemo - ⬆ HR for recurrence 6.8 (1.1-15.7, p <.001)
- 3 year RFI (Recurrence Free Interval):
  30% +ctDNA vs 77% -ctDNA

Tie. JAMA Onc 2019

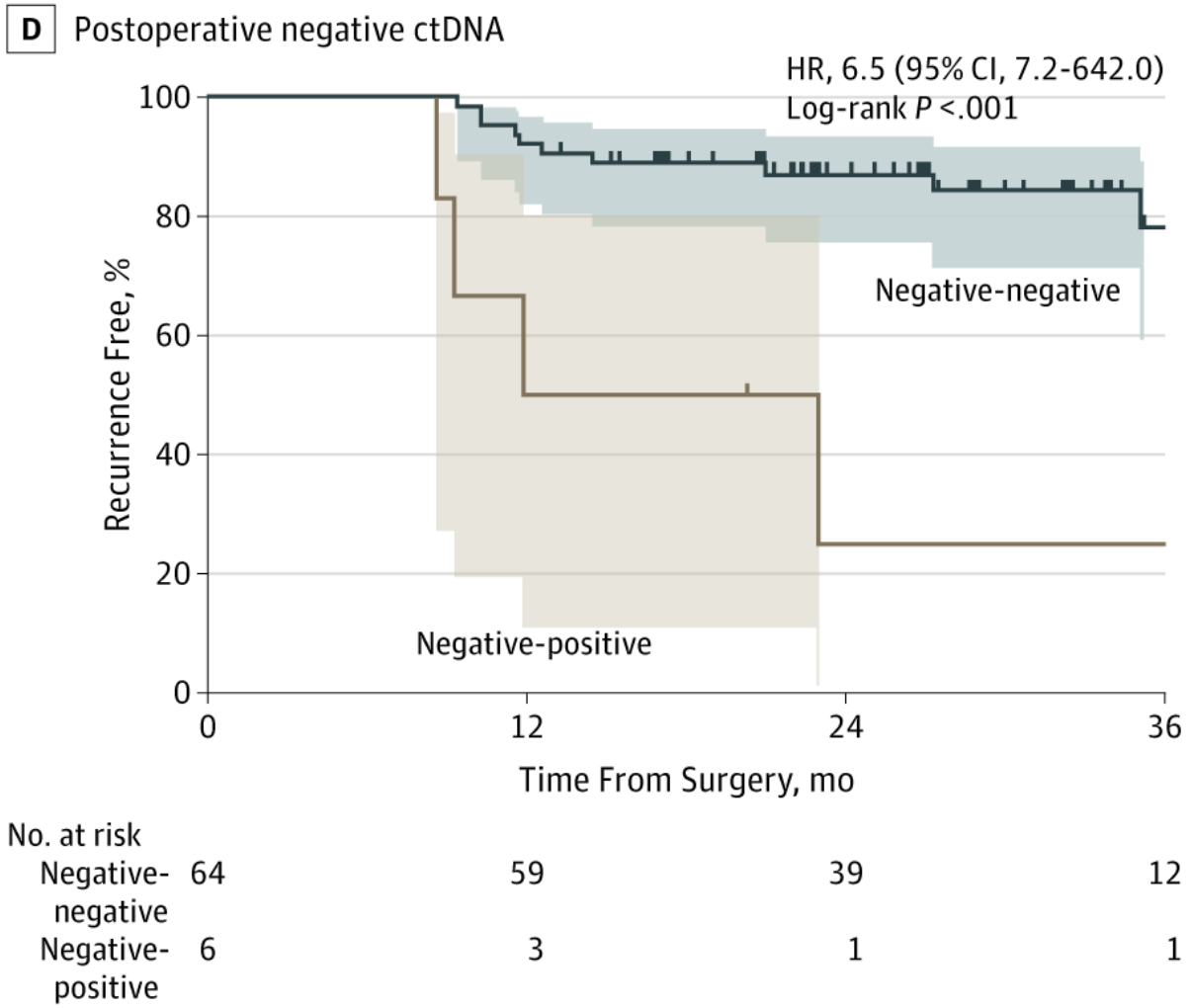
+ctDNA Post ChemoRx Stage III: Recurrence Free Interval (RFI)



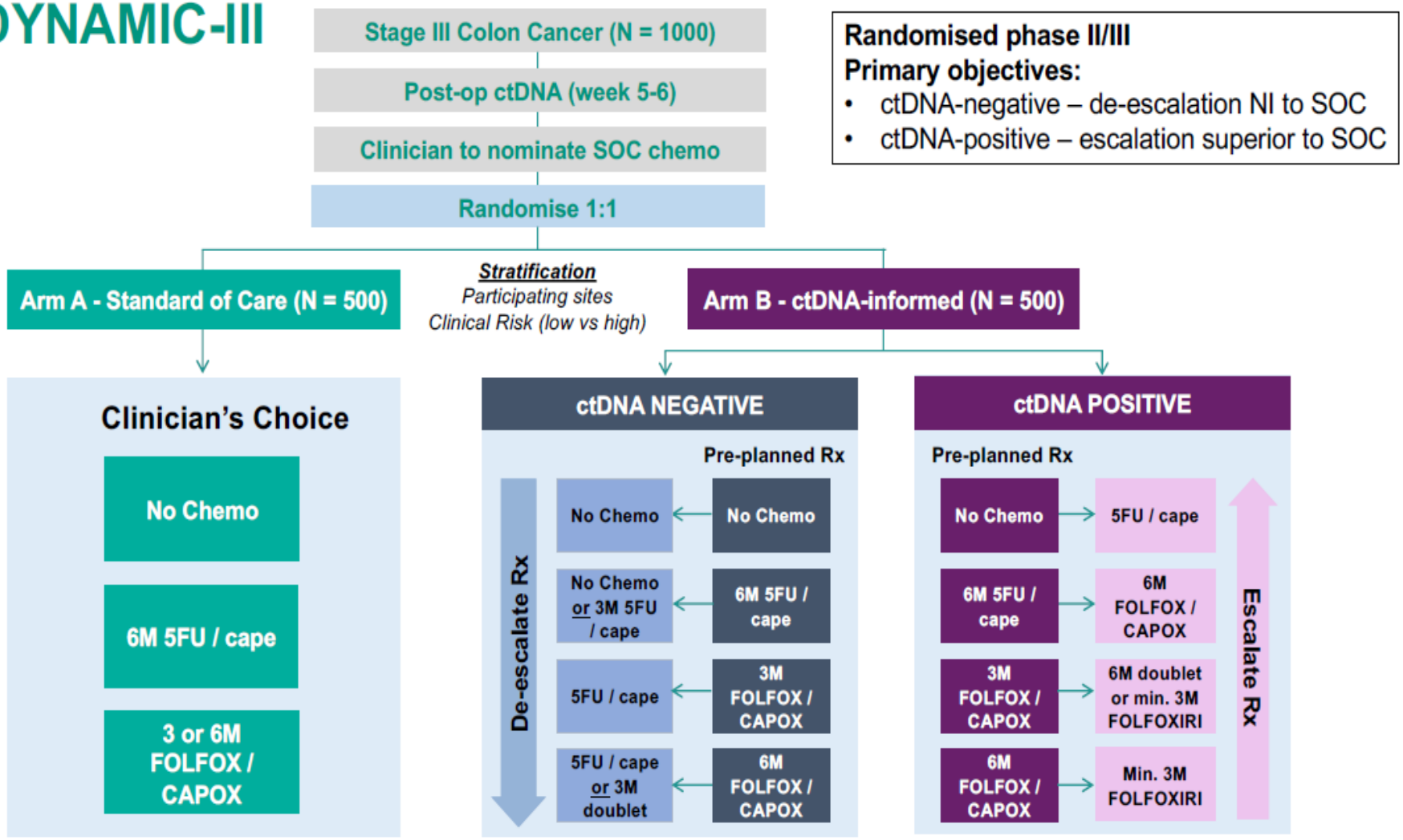
+ctDNA Post Op Stage III:
Δ to Negative vs. Remain Positive



Post Op ctDNA Stage III:
Δ to Positive vs. Remain Negative



DYNAMIC-III



Cape = capecitabine
Iri = irinotecan
F = 5FU
Ox = oxaliplatin
FOL = leucovorin

Our CRCIII Study: Aims

- To evaluate relationship between time course of ctDNA and progression free and overall survival in stage III CRC
- To compare ctDNA to CEA in stage III CRC

UPMC Clinical Trials Network

N=137 in 19 UPMC sites

Arnold Palmer - Mt View, Arnold Palmer - Mt Pleasant, Arnold Palmer – Norwin, Altoona – UPMC CC, Beaver - UPMC CC, Greenville- UPMC CC, Hillman – UPMC CC, Indiana - UPMC CC, McKeesport - UPMC CC, Monroeville - UPMC CC, Murtha - UPMC CC, New Castle - UPMC CC, Northwest - UPMC CC, Passavant (HOA) - UPMC CC, Passavant (OHA) - UPMC CC, St Margaret - UPMC CC, Uniontown - UPMC CC, Upper St Clair - UPMC CC, and Washington - UPMC CC.

Collection Protocol

- Identify Stage III CRC prior to onset of chemoRx
- Tumor block
- Large volume plasma prior to Rx and q3 months x 3 years, q 6 months yrs 4-5
- Streck tubes – stabilize WBC to prevent release of genomic DNA
- CEA (Quest) with each blood draw

Follow Up

- N=137, Mean f/u 1.5 yrs (range: 0.3-3.5)
- Mean age 64
- Of 128 with known recurrence status: 18/128 (14% recurred)

# Draws	# Patients	Post–Recurrence Draws
≥7	7	1-7 in 12 pts
4 - 6	6	
≤3	5	

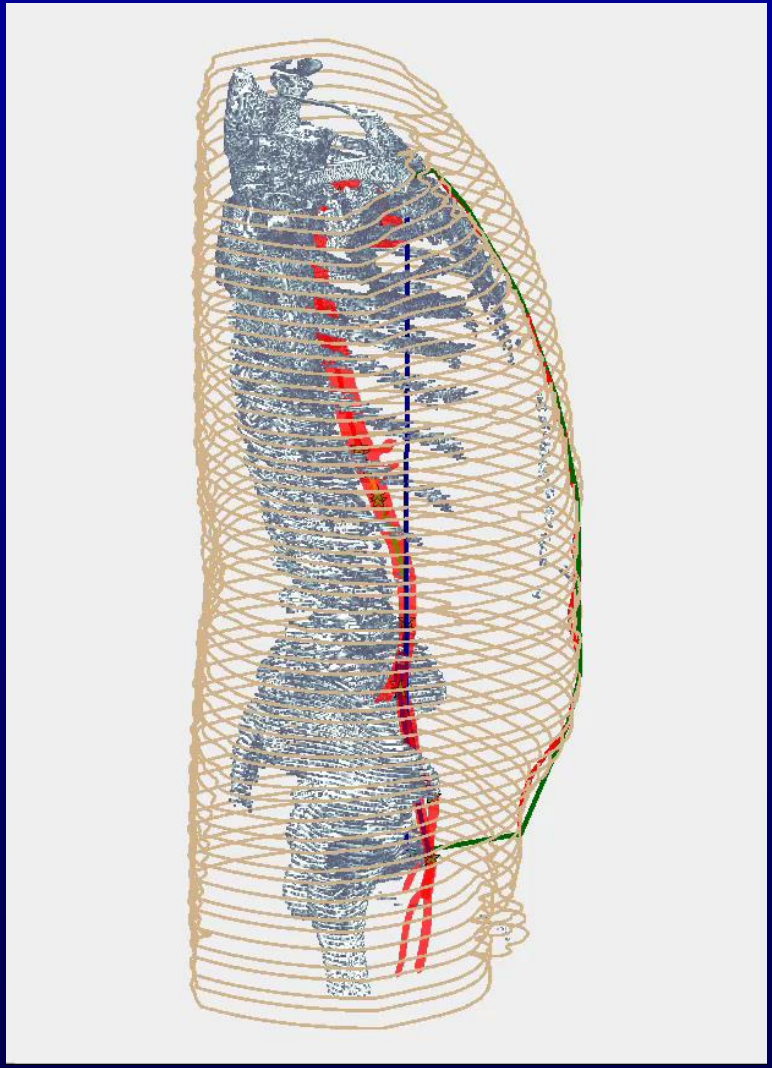
Image Guided Biomarkers for CRC Recurrence

CT-scan A/P: Parameters

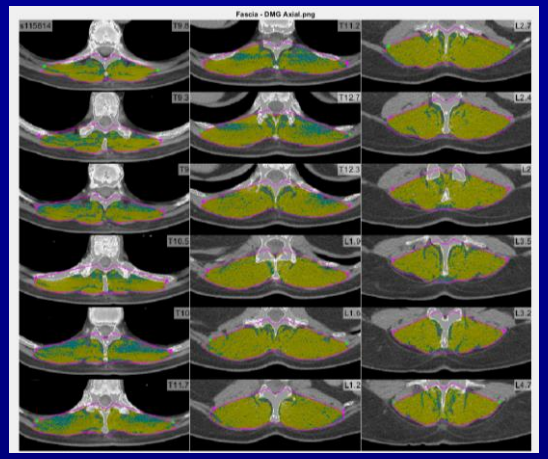
- Radiomic
- Morphomic

Analytic Morphomics

- Platform for image processing for high throughput data extraction which maintains geospatial information
- Morphomics platform: Nested cycles of artificial intelligence and supervised anatomic indexing/measurements



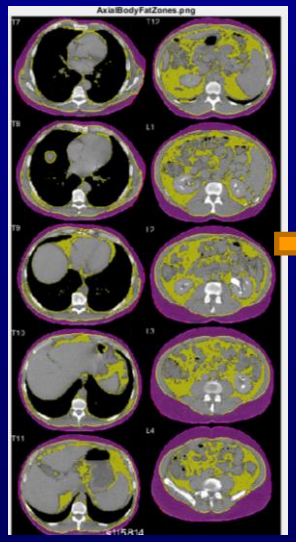
Morphomics Measurements

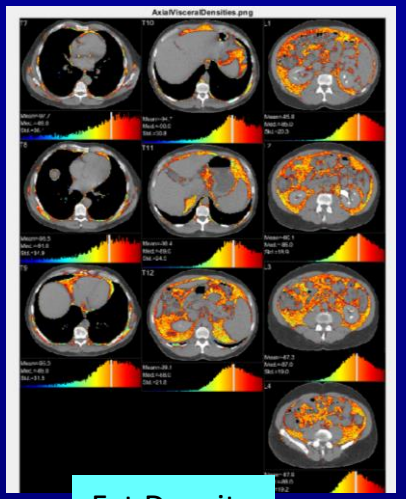


Muscle Features

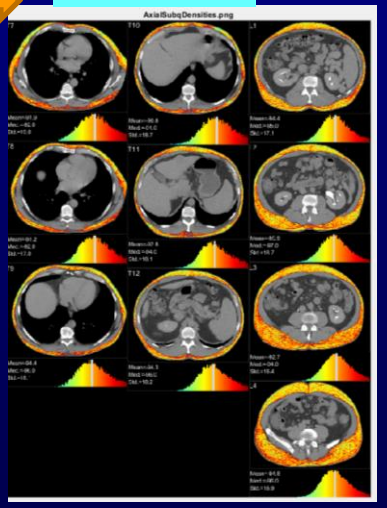
Anatomic Indexing

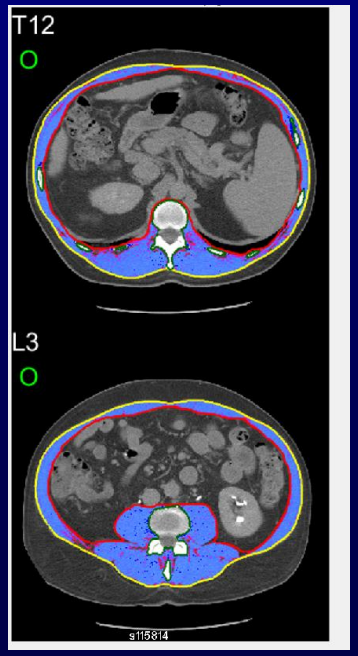
Fat features:
Visceral and SQ

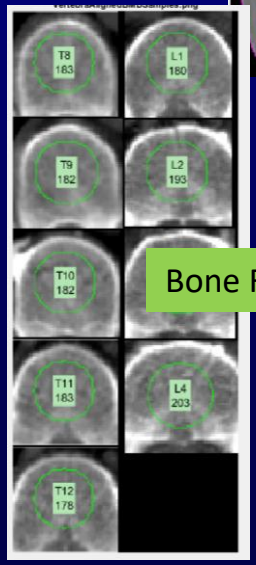




Fat Density







Bone Features

Building Comprehensive Dataset for Prediction of Recurrence

Machine Learning combining clinical, longitudinal biomarker ctDNA, CEA, & CT parameters

Conclusions

- Monitoring for cancer recurrence – ctDNA performs better than current testing, such as CEA
- Lead time to CT (but don’t always have simultaneous CT/ctDNA measurement
- Studies ongoing to assess impacts on treatment

Colleagues and Collaborators

U. of Pitt

- O. Finn
- B. Diergaarde
- M. Saul
- M. Morris
- L. Dzubinski
- A. Borhani

Johns Hopkins

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- B. Vogelstein
- N. Papdapoulous

U. of Mich

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UPCI

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- N. Bahary
- D. Normolle

NCI

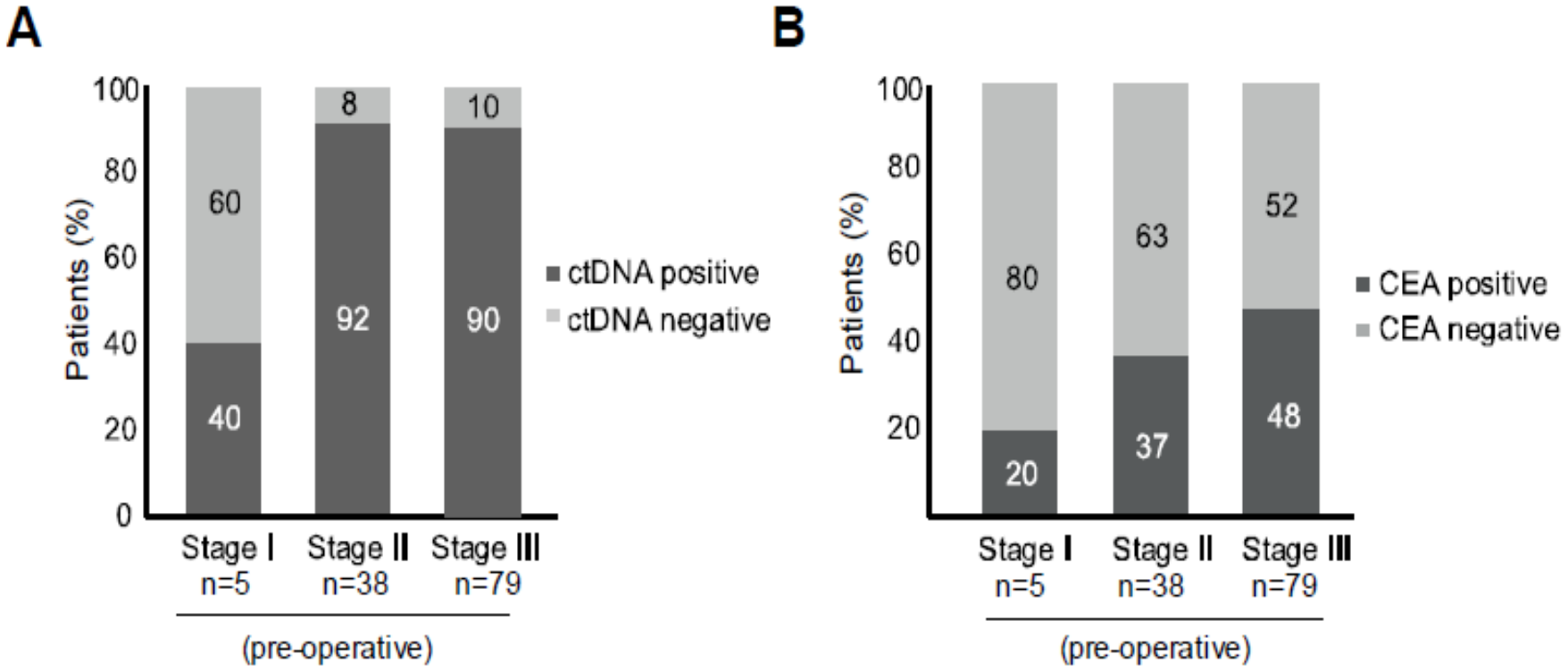
- P. Pinsky
- E. Szabo
- A. Umar
- L. Rodriguez

Mayo Clinic

- P. Limburg
- CPN staff
- CPN Collaborators

Pre-operative ctDNA and CEA

N=122



5 minute Q&A

Chair/Co-Chair/NCI
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and Track Time
NCI and Production Team
answer Chat questions not related to presentations
and use Slack