NCCN 2021 Virtual Congress:
Biomarkers in Solid Tumors

Friday, November 12, 2021
4:40 PM – 5:25 PM EST

What's on the Horizon?

Jennifer J.D. Morrissette, PhD
Abramson Cancer Center
at the University of Pennsylvania

Aparna R. Parikh, MD, MS
Massachusetts General Hospital Cancer Center

David T. Ting, MD
Massachusetts General Hospital Cancer Center

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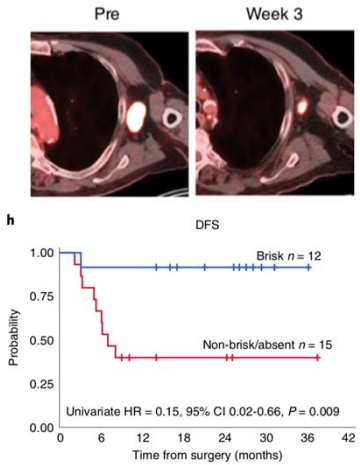
What's on the Horizon?

Biomarkers in Solid Tumors

Jennifer J.D. Morrissette, PhD
Abramson Cancer Center at the University of Pennsylvania

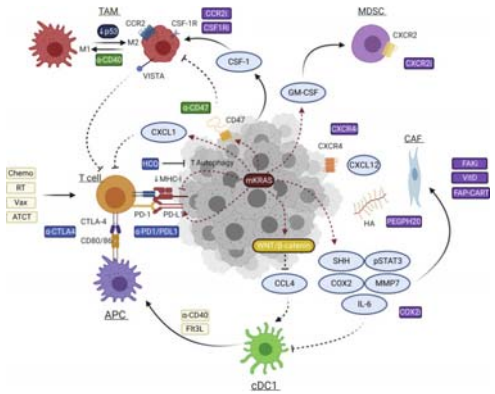
New applications of known technologies

- Immunotherapy
  - Currently using markers like microsatellite instability (MSI) and tumor mutational burden (TMB) with PDL1 IHC to assist in identifying patients likely to respond to IO
  - Future: capturing data from the TME
    - Immune system as a “sensory organ”: immune profiling to capture “brisk” responders to IO
    - Cellular therapy to target driver mutations in solid tumors



Melanoma patients:

- **Immune responses in blood to predict tumor responses**
- **Single dose of immunotherapy**
- **Key immune correlates**



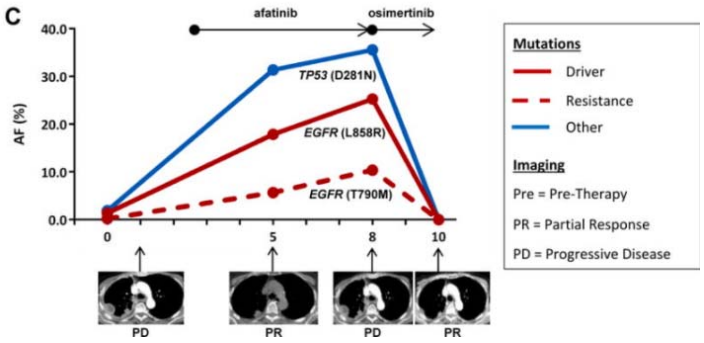
Bear et al Cancer Cell. 2020. 38:788-802.. PMID: 32946773

Bear et al Nat Commun. 2021 12:4365. PMID: 34272369;

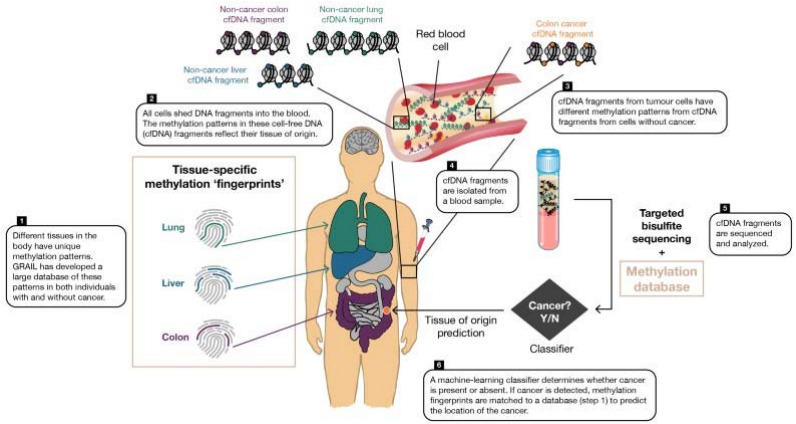
Byrne et al Clin Cancer Res. 2021. 27:4574-4586. PMID: 34112709.

New applications of known technologies

- Circulating tumor DNA (ctDNA)
  - Currently using to detect disease associated variants at diagnosis and through monitoring
  - Future:
    - Early detection of cancers (presymptomatic)
    - Definitive surgical resection [discussed next by Dr. Aparna Parikh)



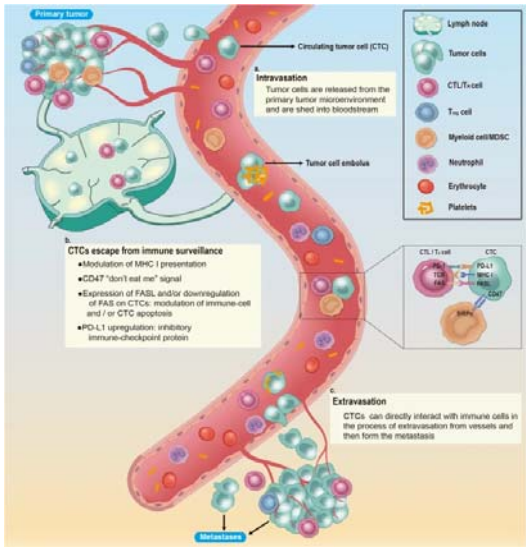
Thompson et al Clin Cancer Res. 2016. 22:5772-5782. PMID: 27601595



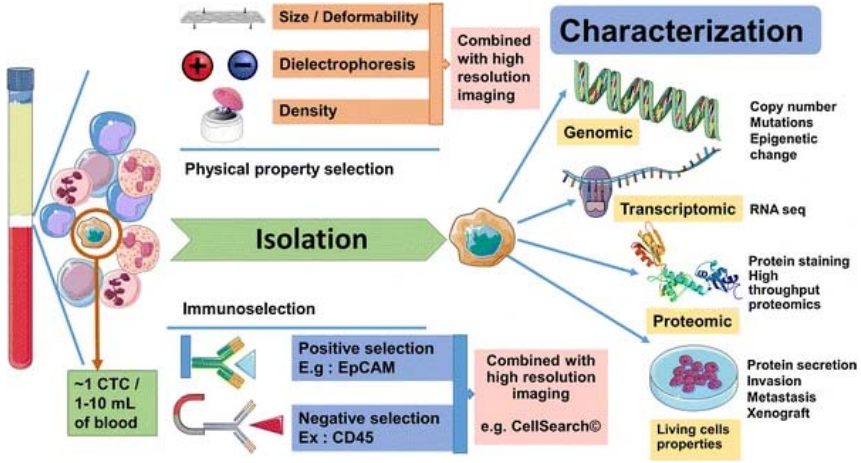
Ofman J et al. Nature Portolio. Sponsor Feature. 25 Mar 2020. https://www.nature.com/articles/d42473-020-00079-y.

New applications of known technologies

- Circulating tumor cells (CTCs)
  - Current: FDA-approved: CTCs counts associated with PFS and OS in metastatic prostate, colorectal and breast cancer
  - Future: identifying EMT transition associated with chemoresistance [discussed by Dr. David Ting]

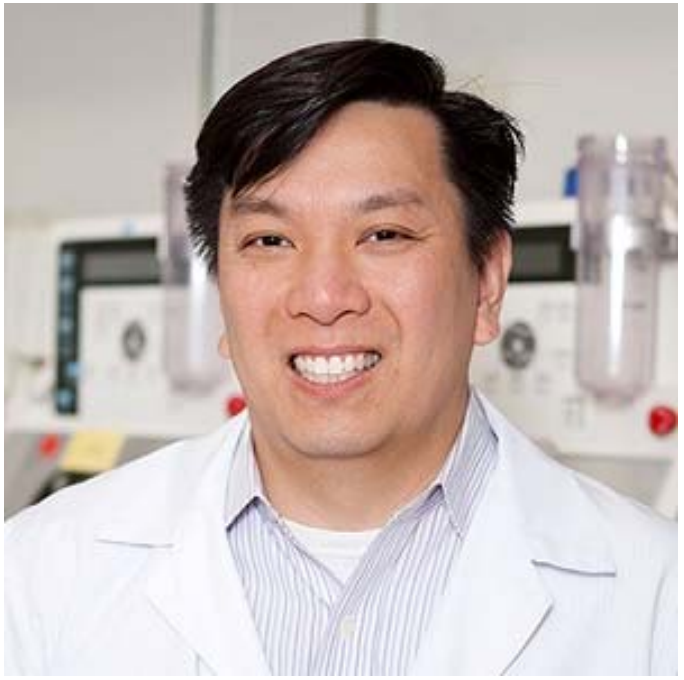


Zhong *et al. Mol Cancer* **19,** 15 (2020).



Cabel *et al. Int J Clin Oncol* **22,** 421–430 (2017).

Aparna R. Parikh, MD, MS



David T. Ting, MD

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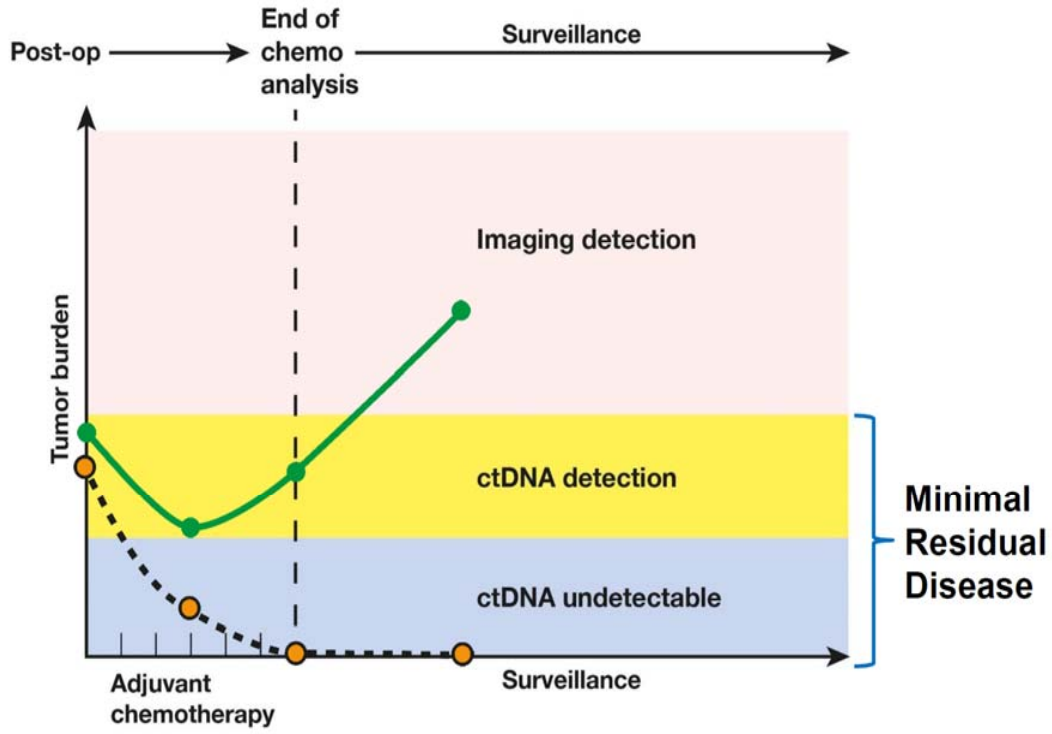
What's on the Horizon?

Liquid Biopsies in Colorectal Cancer

Aparna R. Parikh, MD, MS
Massachusetts General Hospital Cancer Center

Minimal Residual Disease in Colorectal Cancer

ctDNA Marker of Minimal Residual Disease:

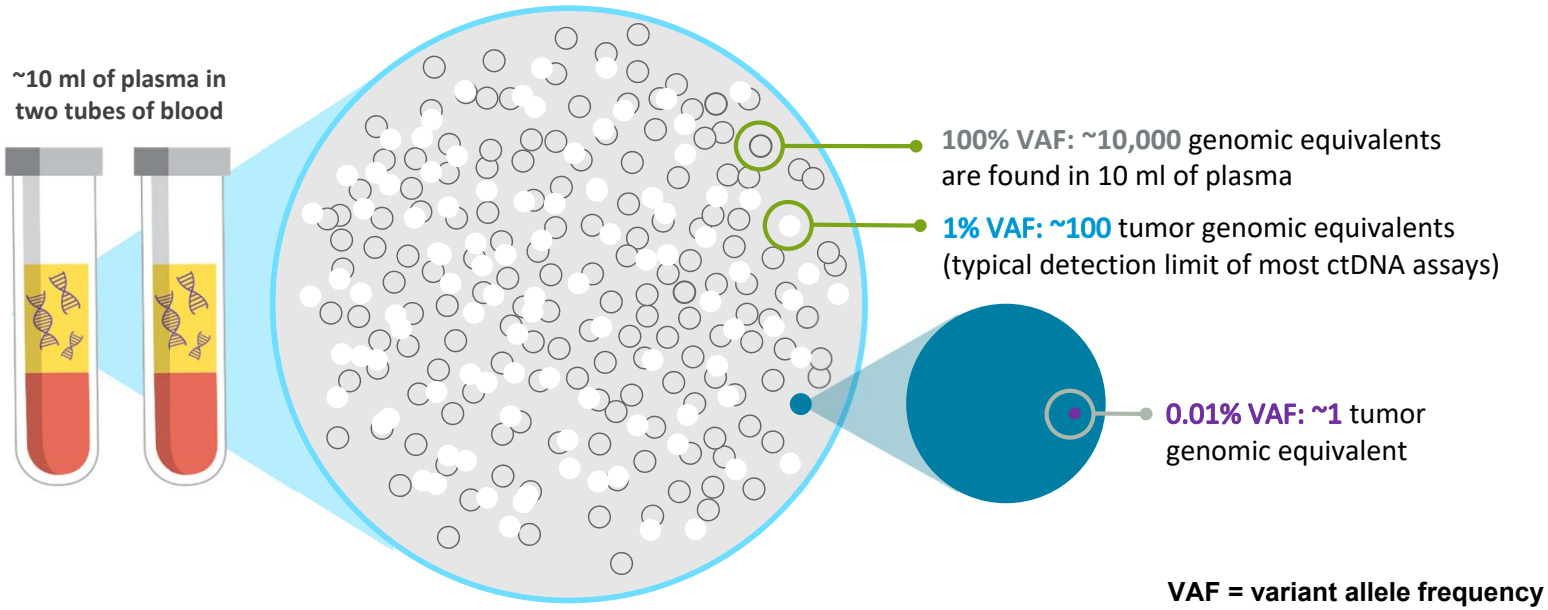


- MRD applications high positive predictive value (low false positives) for recurrent disease in patients with ctDNA detected in the "adjuvant" setting
- Defines molecular persistence of disease
  - Stage I-III patients with ctDNA+ after definitive interventions should be considered as a Stage IV minimal residual disease, or Stage IV MRD

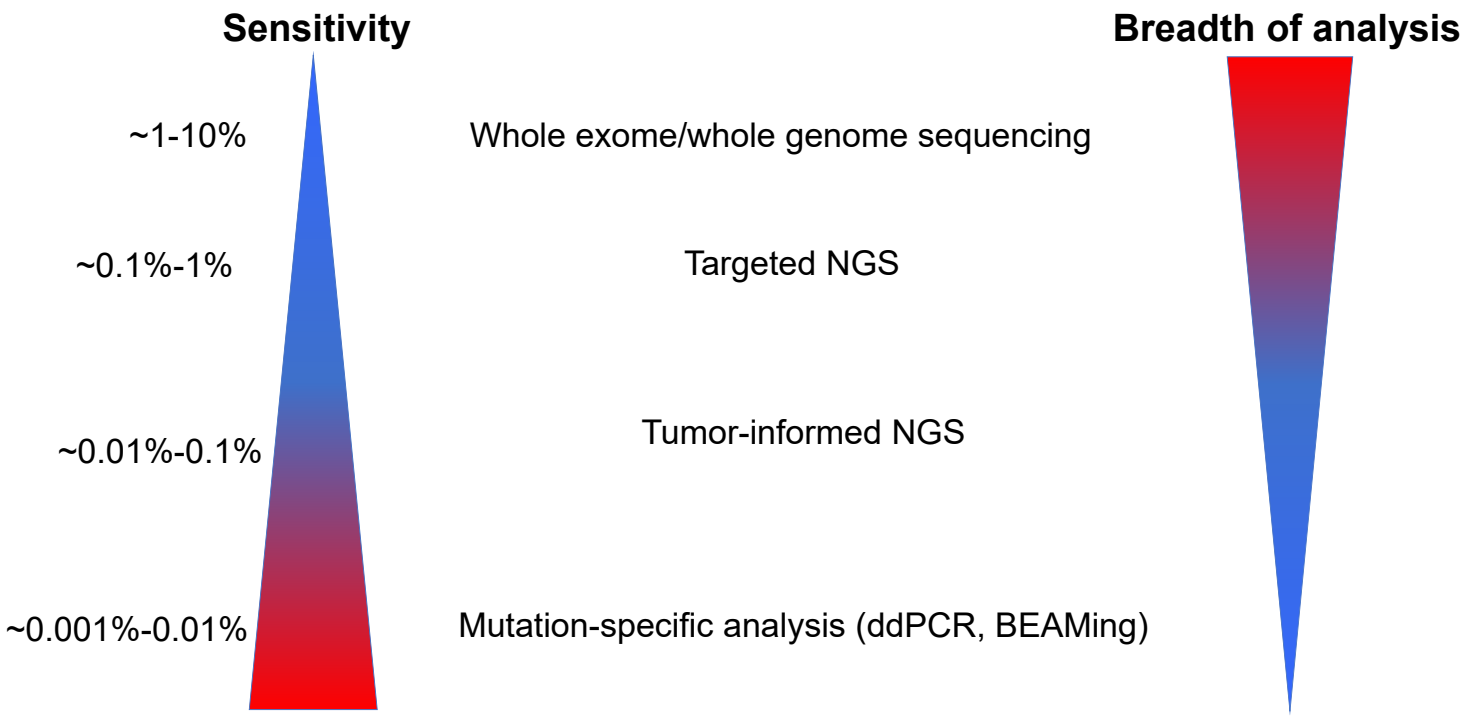
Dasari A, Grothey A, Kopetz S. J Clin Oncol. 2018.; Kasi P, The 2019 Gastrointestinal Oncology Conference. October 10-11, 2019. Arlington, VA.

Detection Down to as Few as One Genomic Equivalent in 10 ml of Plasma (VAF = 0.01%) Critical

Higher blood volumes may improve performance but requires prospective studies



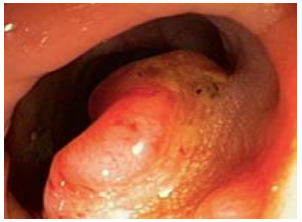
Methods for ctDNA Analysis



Case 1

29-year-old male musician no family history presents with rectal bleeding

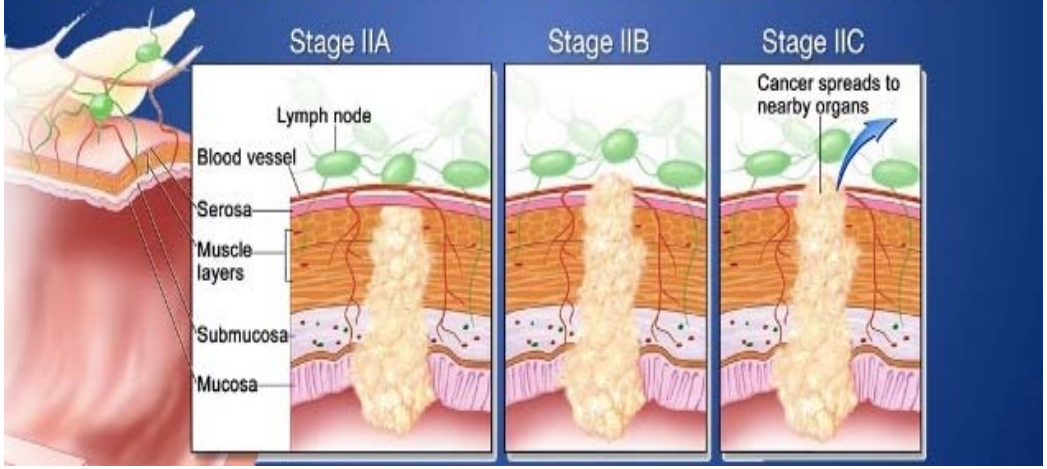
- **Colonoscopy**
  - Sigmoid Mass
  - MSS adenoCA
- **LAR**
  - Stage II CRC
  - Path T3N0
  - 0/26 nodes
  - Tumor Budding Score of 12
  - Poorly Differentiated



Stage II CRC

- Nearly 100K cases of CRC annually
- 25% of diagnosed cases are Stage II
- 20-30% of patients with Stage II CRC receive adjuvant chemotherapy
- Most cured by surgery alone
- Overall benefit of adjuvant chemotherapy in stage II colon cancer is marginal (~5%) in an unselected population
- Reduces risk of death 5FU 3-3.5 %
- Many patients “overtreated” with associated risk/toxicity of chemotherapy

- Invasion at least through muscularis propria (=stage IIA ⇔T3 tumors)
- Higher substages:
  - IIB for T4a tumors: invasion through the serosa
  - IIC for T4b tumors: direct invasion into adjacent organs
- No lymph node involvement (stage III) or distant metastasis (stage IV)



PDQ Adult Treatment Editorial Board. Colon Cancer Treatment (PDQ®): Health Professional Version. 2021 Aug 13. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. [Table], Table 4. Definitions of TNM Stages IIIA, IIIB, and IIICa. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65858/table/CDR0000062687__580/

Decisions in Stage II are Dizzying

6m of oxaliplatin-based treatment is option in high-risk Stage II

NCCN recommends consideration of adjuvant chemotherapy (5-FU or FOLFOX) for patients with "high-risk" colon cancer

T4, inadequate nodal harvest, poorly differentiated, obstruction, perforation, vascular/perineural invasion, tumor budding, margins

FOLFOX ok for Stage II w/ high-risk factors (not for good- or average-risk Stage II)

No survival benefit for addition of oxaliplatin to 5-FU/leucovorin in Stage II

Pooled analysis of high-risk Stage II patients in IDEA collaboration did not show non-inferiority of 3 months compared to 6 months of adjuvant treatment

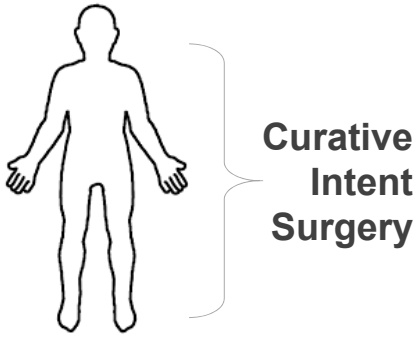
Duration associated with small (not statistically significant) difference in DFS between 3 and 6 months of CAPEOX

Less grade 3–5 toxicities with 3 months versus 6 months

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer (Version 3.2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

Minimal Residual Disease: The Problem

Stage III CRC:
All patients get adjuvant chemo
>50% cured by surgery alone



Stage II CRC:
SOC is NO adjuvant chemo
10-15% of patients recur

Minimal Residual Disease: The Problem

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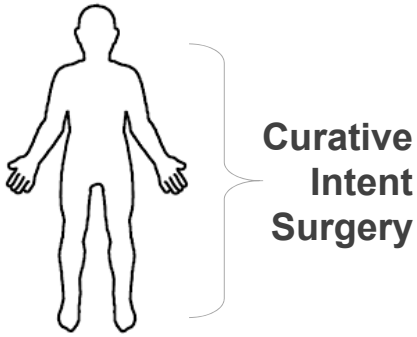

Curative Intent Surgery

Stage II CRC:
SOC is NO adjuvant chemo
10-15% of patients recur

Minimal Residual Disease: The Problem

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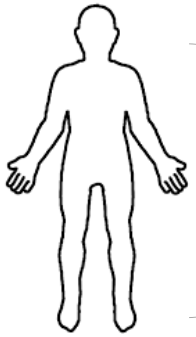

Curative Intent Surgery

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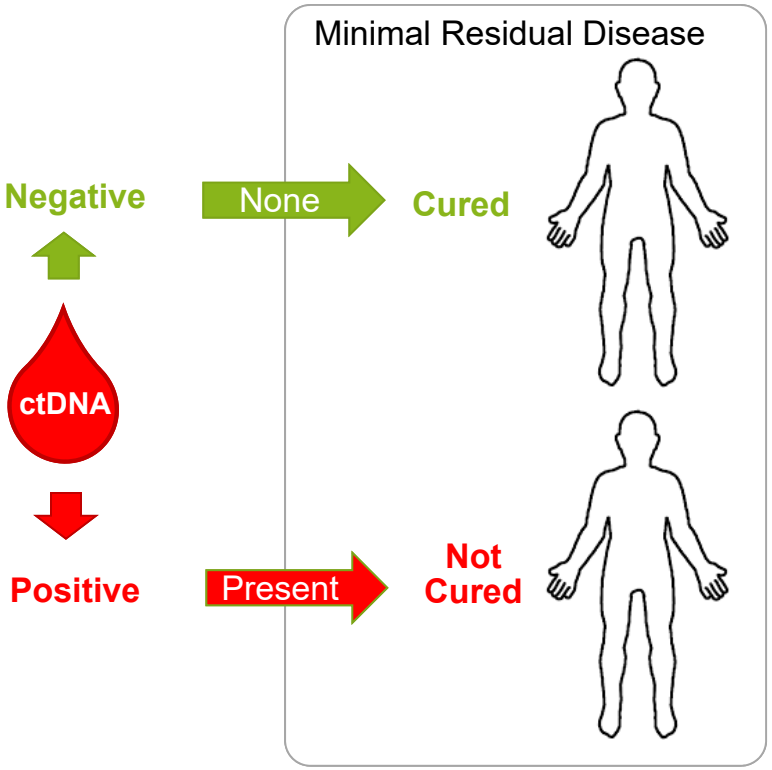


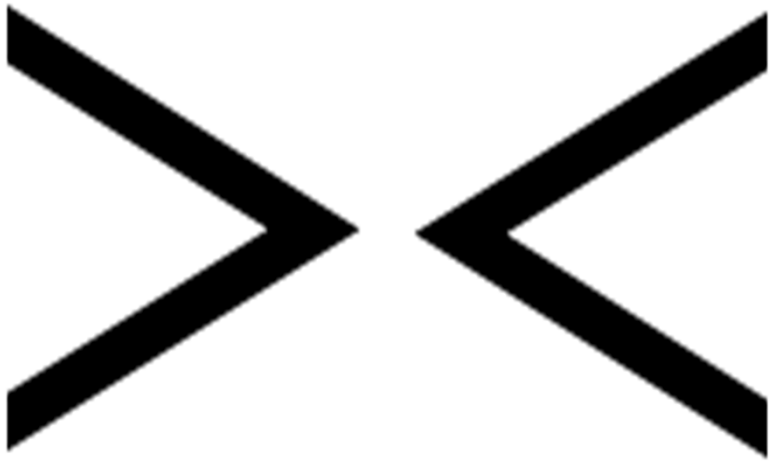
We have no way to determine who is cured and who will recur

Biomarker

There is a need for a PREDICTIVE BIOMARKER to identify:

Stage II/III colon cancer patients at **highest risk** for recurrence who may benefit from adjuvant chemotherapy

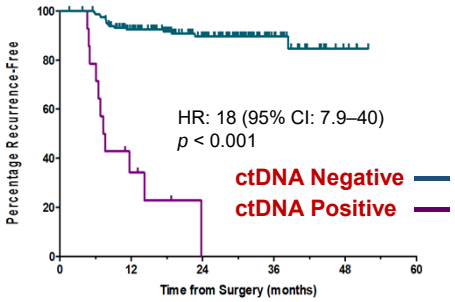
Those at **lowest risk** who may be exposed to unnecessary chemotherapy



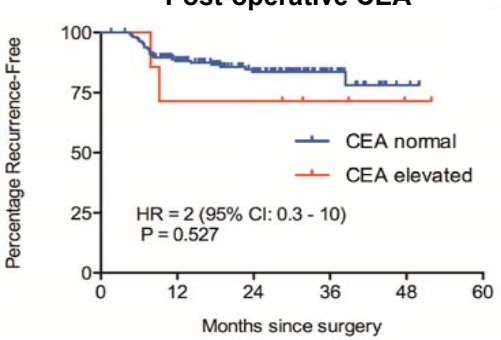
ctDNA is a Prognostic Biomarker in Resected CRC

Recurrence-free Survival (Stage II CRC post-resection)

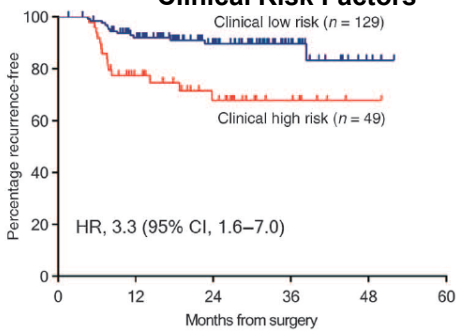
Post-operative ctDNA



Post-operative CEA



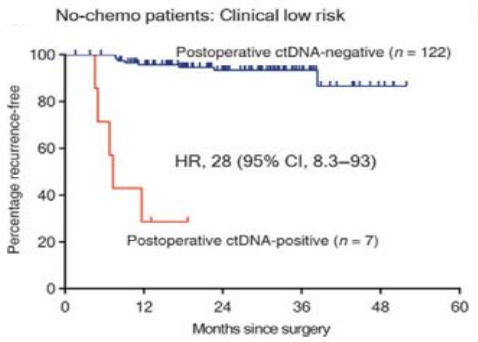
Clinical Risk Factors

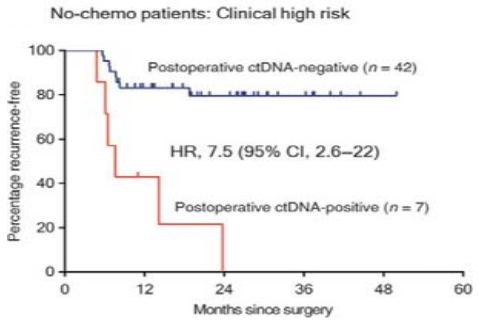


- No consensus for adjuvant chemotherapy for patients with resected stage II colon cancer based on a lack of a predictive biomarker
- Presence of (+) ctDNA postoperatively is associated recurrence
- Despite the prognostic relevance for (+) ctDNA in patients with resected colon cancer, use of ctDNA as a predictive biomarker is not employed currently, **due to the lack of validated prospective data**

Tie J et al, Sci Transl Med. 2016 Jul 6; 8(346): 346ra92

ctDNA is More Prognostic than Standard Risk Factors for Determining Likelihood for Recurrence in Resected Stage II Colon Cancer



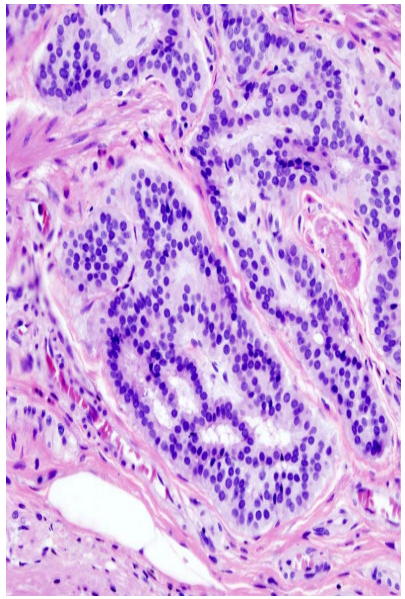


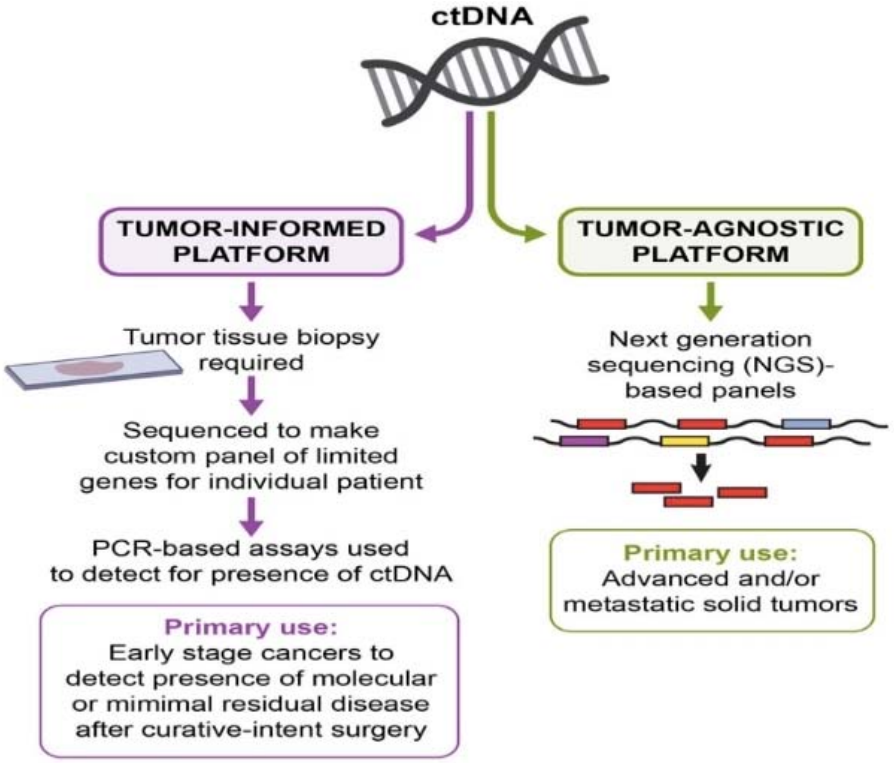
ctDNA(+) status may redefine a patient with stage II colon cancer at "high risk" for recurrence to justify further evaluation with a fluoropyrimidine/oxaliplatin combination

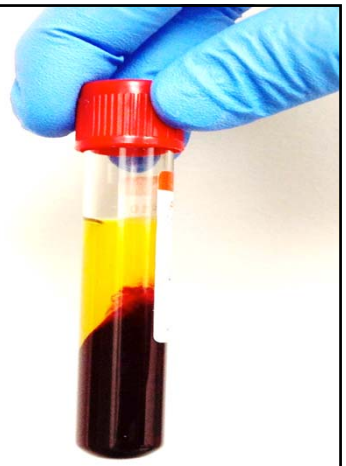
- In 230 patients with resected stage II colon cancer, the detection of postoperative ctDNA outperformed all traditional risk factors traditionally considered for adjuvant chemotherapy selection in identifying patients at high risk for recurrence
- The detection of ctDNA, a surrogate for persistent (microscopic) disease, associates with clinical recurrence within 24 months
- The prognostic implications of ctDNA status link to clinical outcomes, regardless of the traditional "low risk" or "high risk" stratifications

Tie J et al, Sci Transl Med. 2016 Jul 6; 8(346): 346ra92

Generalized Approaches





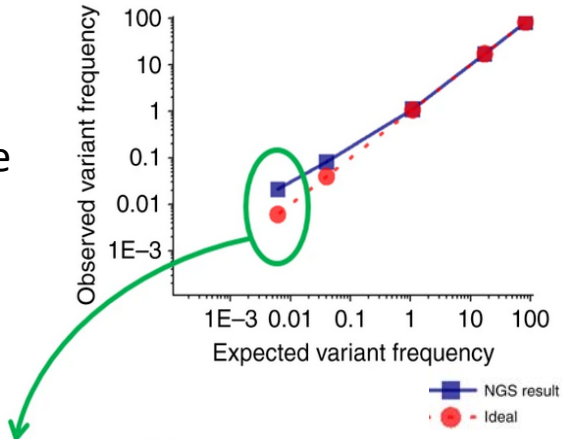


ctDNA: different assays for different purposes

	"Tumor naïve"	"Tumor informed"
Gene coverage	Large panel of commonly altered genes	Limited panel of genes personalized to the patient's tumor
Tissue sequencing required?	No	Yes
Key applications	• MRD • Assess heterogeneity • Detect actionable alterations • Identify drivers of resistance • Serial monitoring	• Detect MRD • Assess treatment response • Serial recurrence monitoring
Screens out germline, CHIP alterations?	No*	Yes
Turnaround time	1-2 wks	First test: 2-3 wks (includes tissue WES profiling) Subsequent tests: 1 wk

Tumor Informed Analyses Can Reduce Impact of Assay Error

- Reagents and sequencing error can result in false positive calls
  - A small panel can have a million possible false positive nucleotide variants
  - When panels are utilized, then bioinformatic efforts are utilized to reduce this error
  - As a result, lower limits of detection are impacted to ensure that this noise of the assay can be excluded



- Tumor informed pipelines substantially reduce the spectrum of alterations (i.e. 16 potential variants) allowing theoretically greater sensitivity and reduced risk of false positives

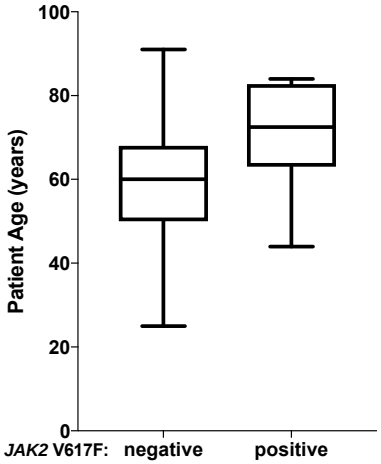
Slide courtesy of Scott Kopetz, MD, PhD

Clonal Hematopoiesis of Indeterminate Potential

JAK2 Mutations as a clear example

Frequency of *JAK2* V617F mutations

cfDNA	16/1397 (1.14%)
TCGA	0/228 (0%)
NHS/HPFS	0/619 (0%)
GENIE	0/1149 (0%)
All tissue cohorts	0/1996 (0%)



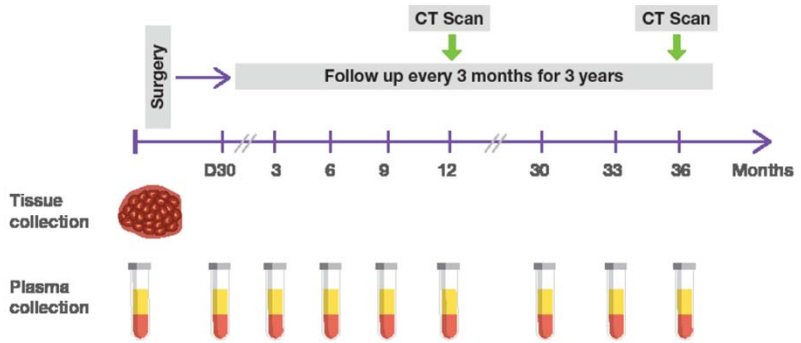
… but also TP53

Strickler JH, et al. Cancer Discov. 2018 Feb;8(2):164-173. Kunimoto H, Nakajima H. Int J Hematol. 2017 Jul;106(1):34-44.

Serial ctDNA monitoring: CRC study

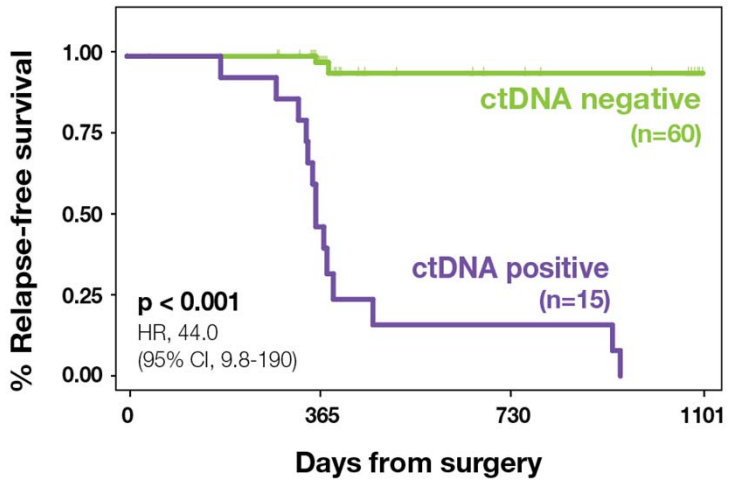
Denmark, May 1, 2014 to January 31, 2017

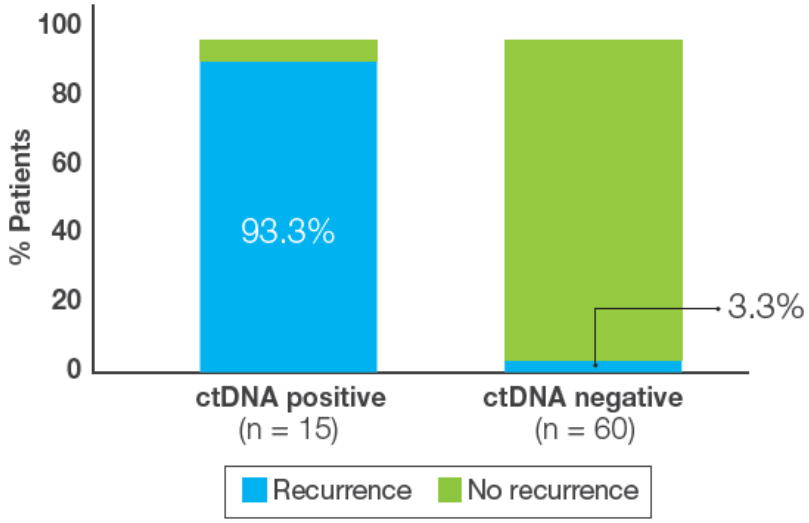
- 130 patients (125 eligible) with stages I-III colorectal cancer
- Treated with curative surgery and optional adjuvant chemotherapy
- 795 plasma samples were longitudinally collected:
  - at baseline, up to 14 days prior to surgery
  - on post-operative day 30
  - and every third month until death, study withdrawal, or month 36



Reinert et al JAMA Oncology, 2019 May 9;5(8):1124–31

Positive ctDNA Status after Adjuvant Therapy is Highly Predictive of Relapse on Serial Testing

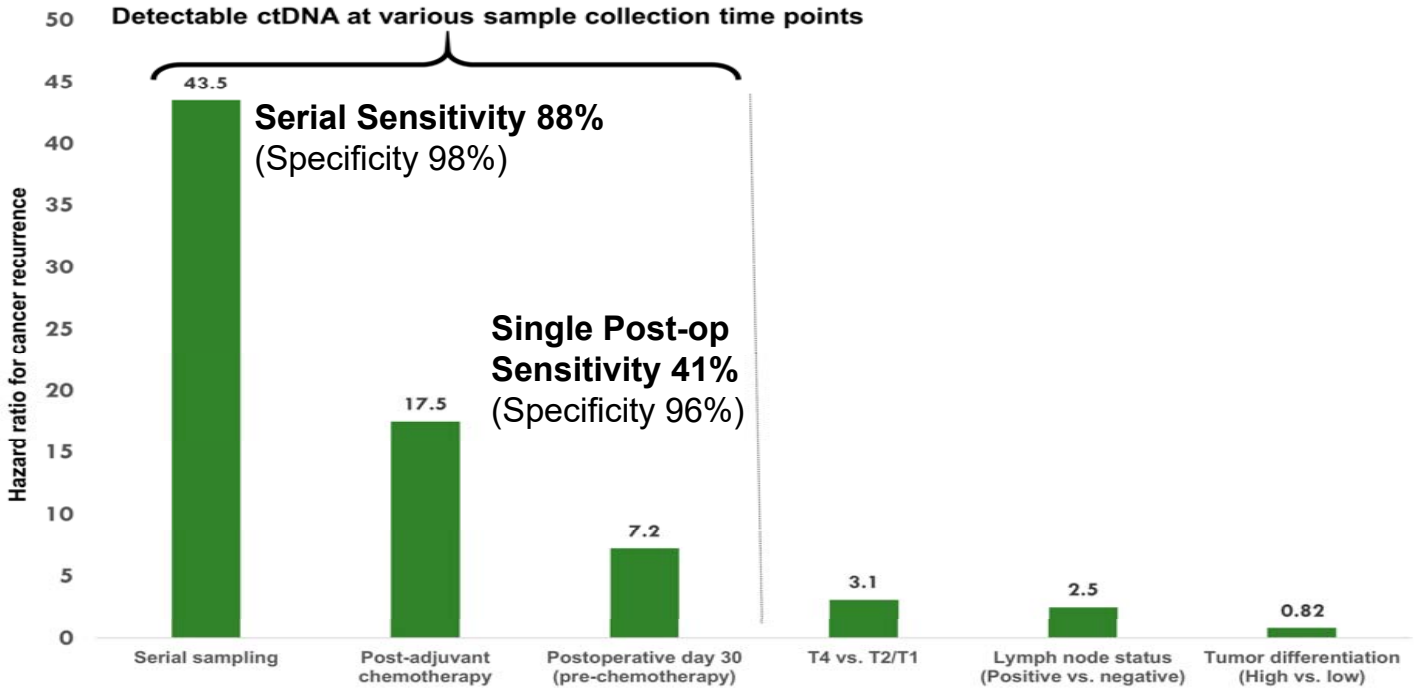




Reinert et al JAMA Oncology, 2019 May 9;5(8):1124–31

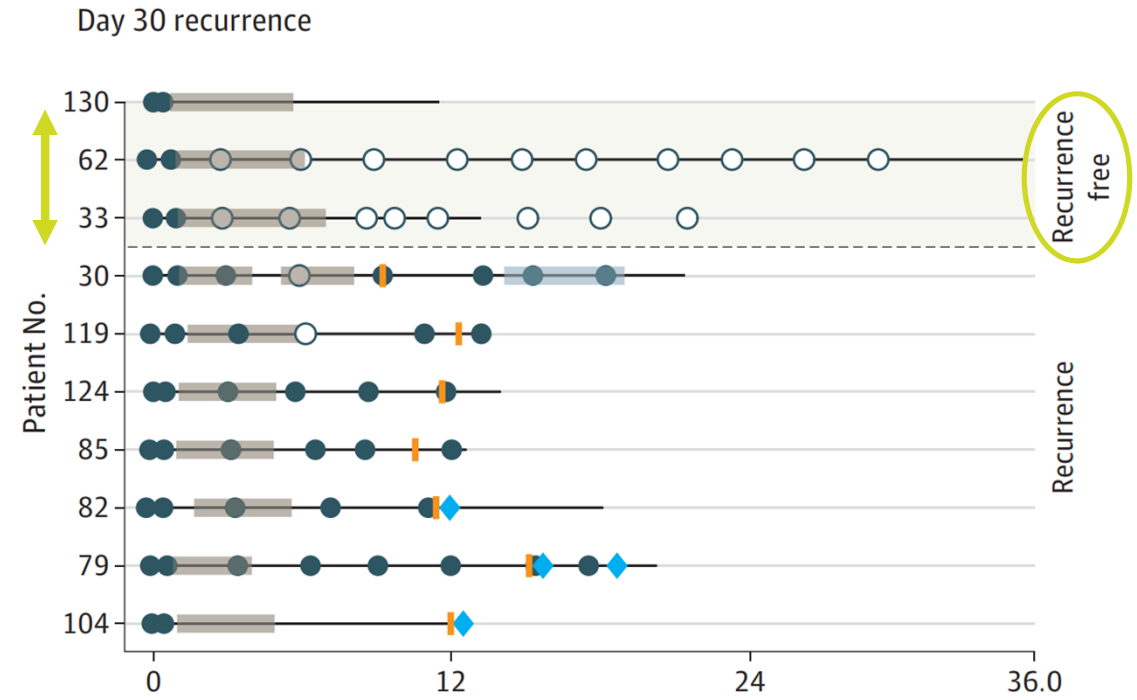
Detectable ctDNA across Various Time Points

ctDNA Outperforms Existing Clinicopathologic Risk Factors as a Prognostic Biomarker



Chakrabarti et al, Cancers (Basel). 2020 Sep 29;12(10):2808

Prognostic and possible predictive of therapeutic response?

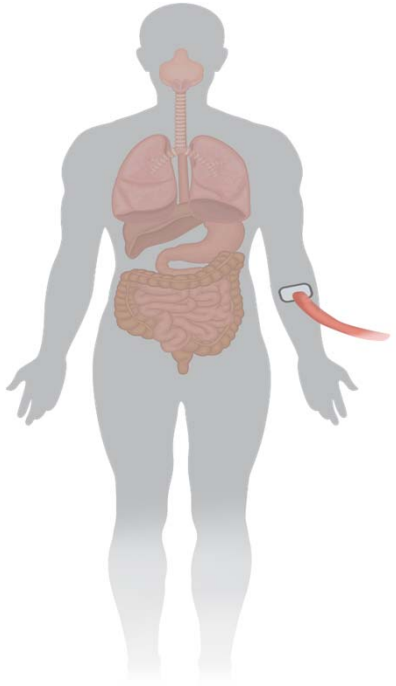


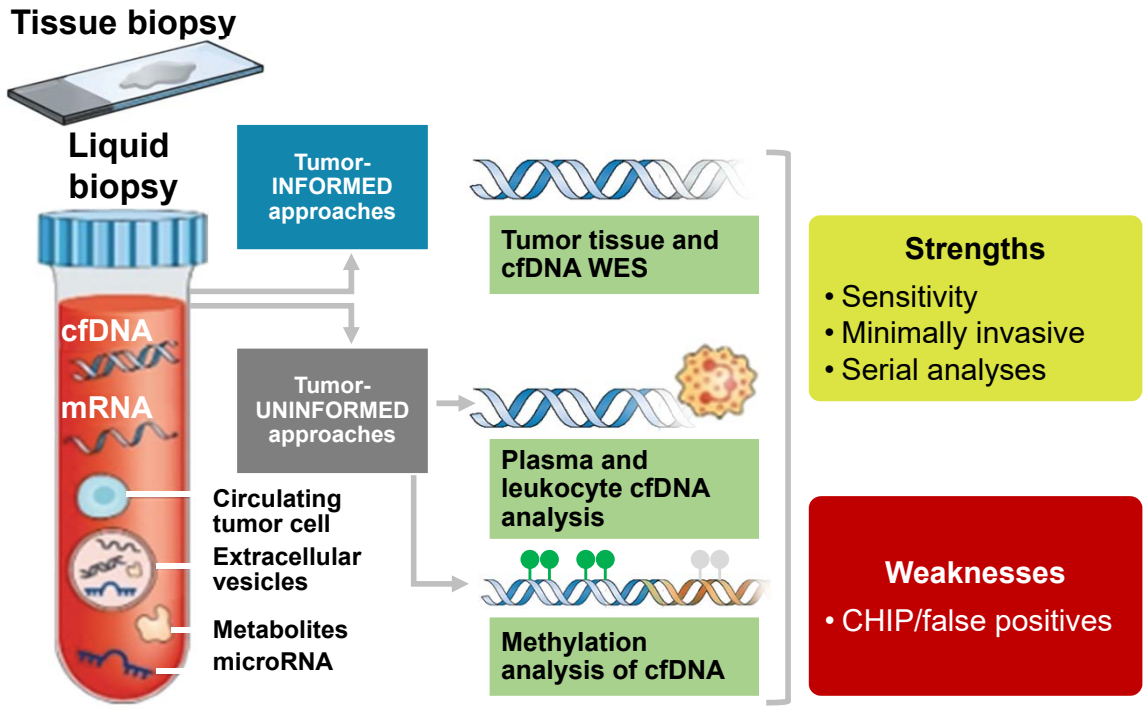
9 months lead time to radiographic recurrence

- ctDNA-negative blood sample
- ctDNA-positive blood sample
- Radiologic relapse
- ACT
- Chemotherapy
- Surgical intervention
- Clinical follow-up

Reinert et al JAMA Oncology, 2019 May 9;5(8):1124–31

Challenges

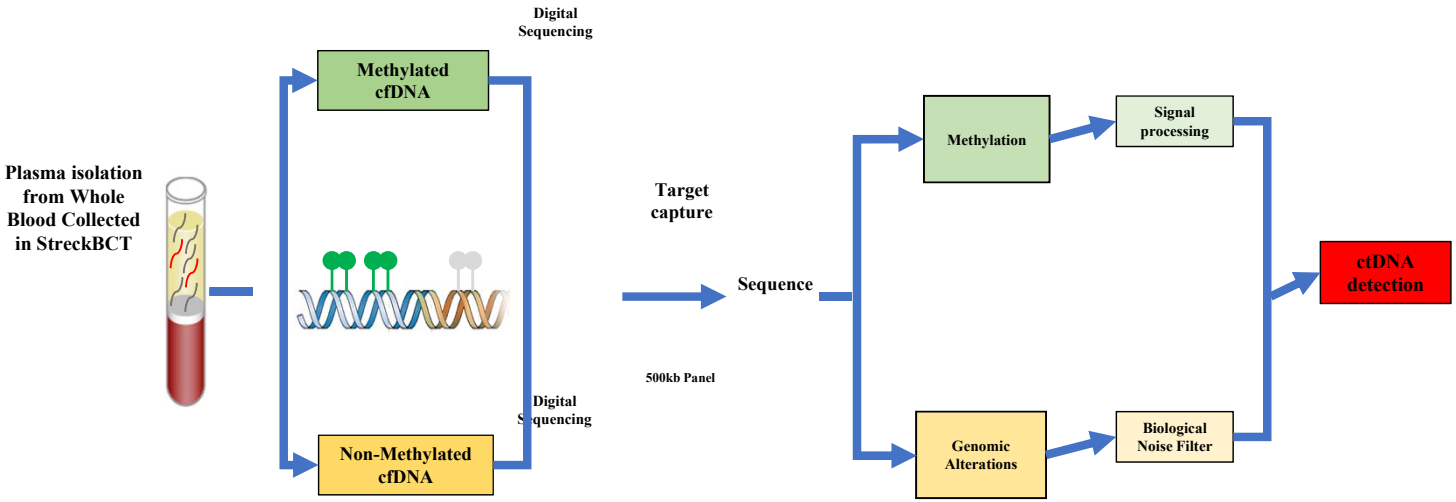




mRNA = messenger ribonucleic acid
WES = whole-exome sequencing
CHIP = clonal hematopoiesis of indeterminate potential

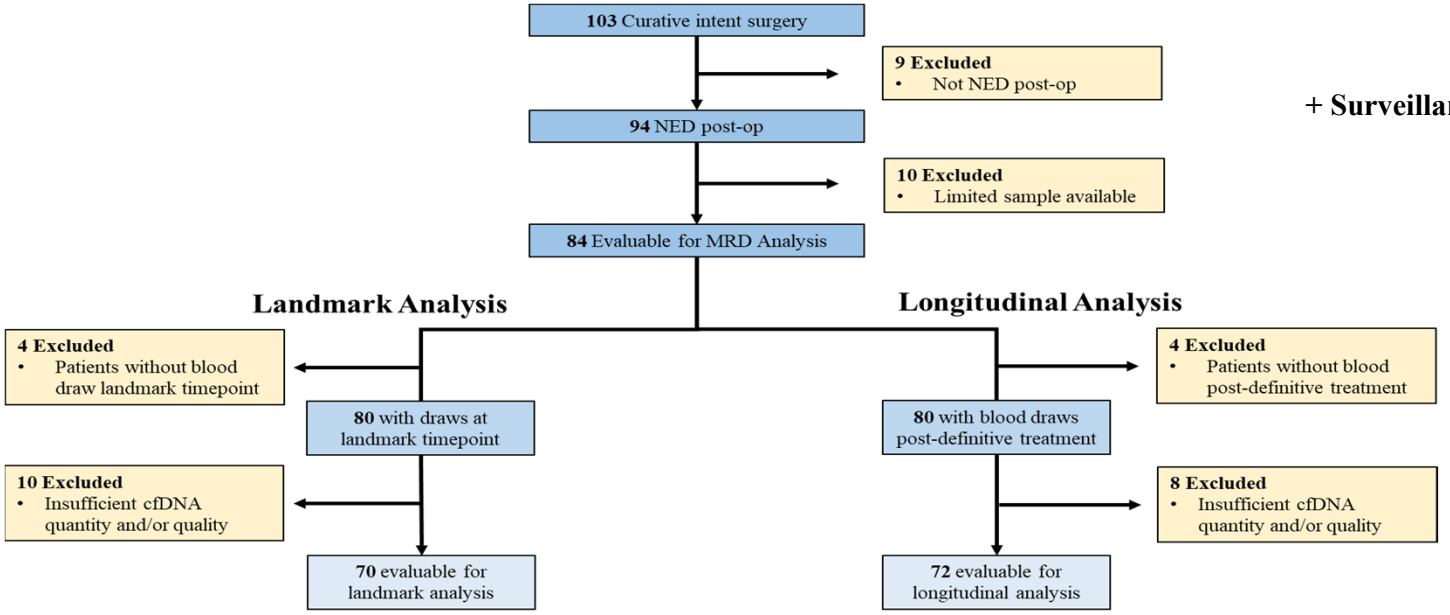
Slide from Dr Charu Aggarwal .

Tumor Uninformed (REVEAL)



MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Schema

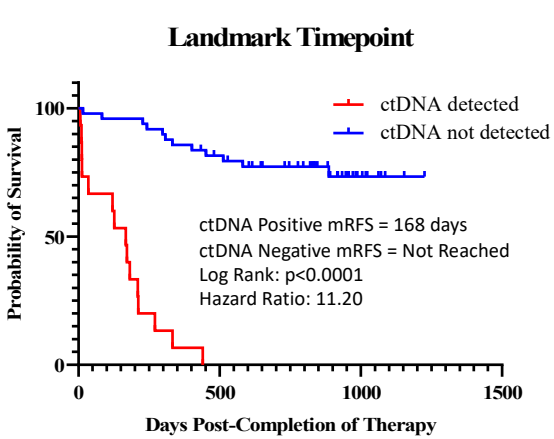


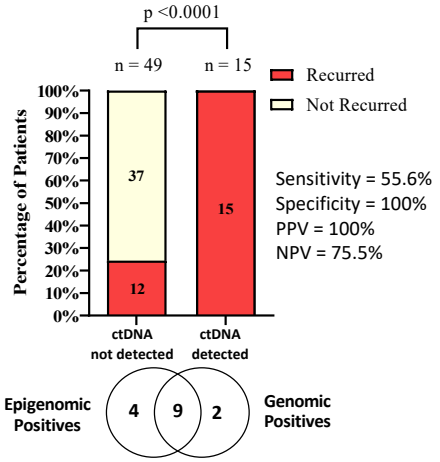
+ Surveillance Analysis

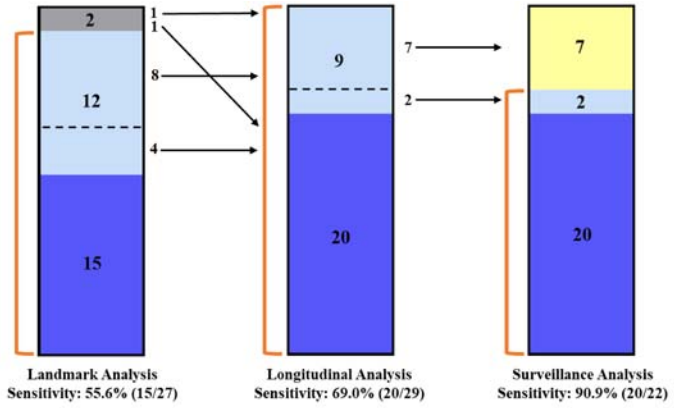
Parikh AR, et al. Clin Cancer Res. 2021 Apr 29:clincanres.0410.2021. doi: 10.1158/1078-0432.CCR-21-0410.

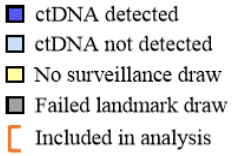
MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

A plasma-only Assay to Detect MRD After Surgery: Results

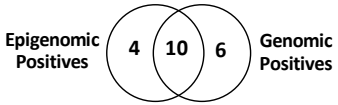








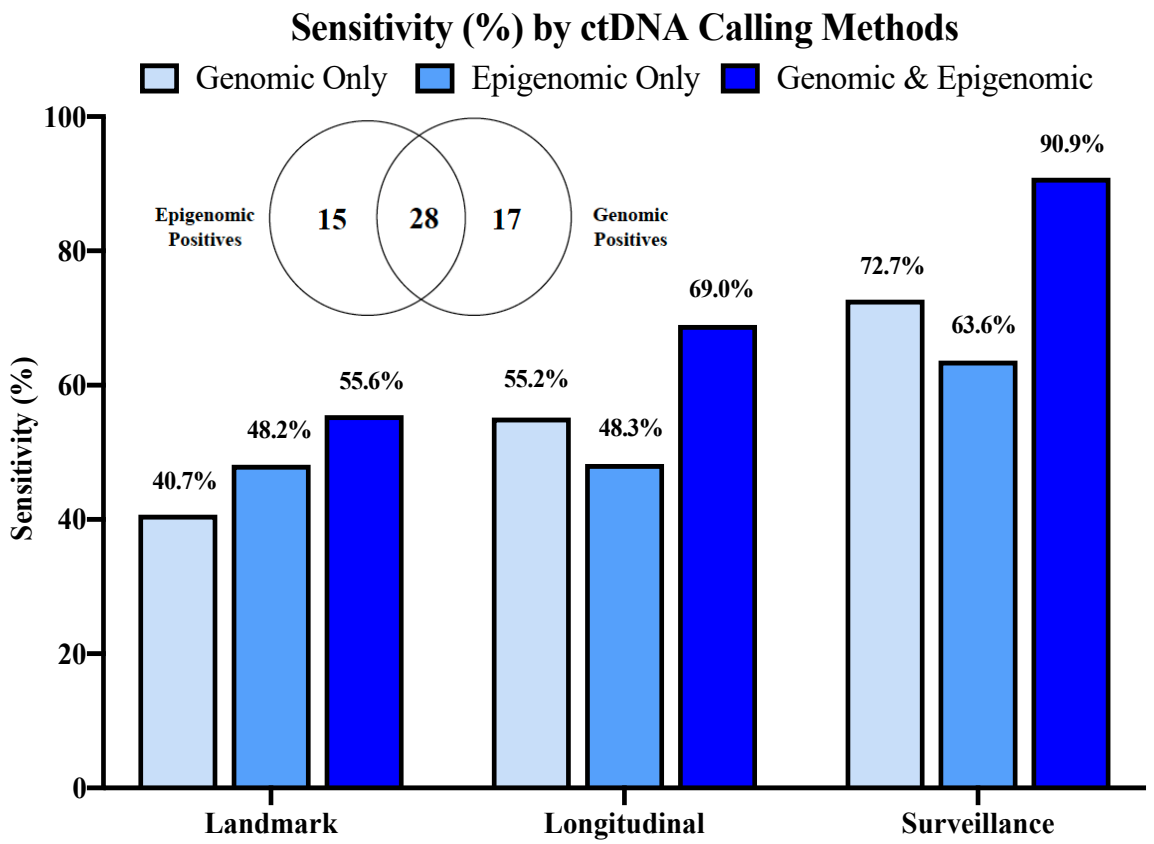
CEA at landmark timepoint failed to predict recurrence



Parikh AR, et al. Clin Cancer Res. 2021 Apr 29:clincanres.0410.2021. doi: 10.1158/1078-0432.CCR-21-0410.

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

The Combination of Genomic and Epigenomic Calls is Key to Improve ctDNA Detection



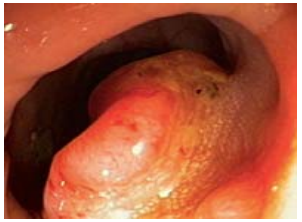
Parikh AR, et al. Clin Cancer Res. 2021 Apr 29:clincanres.0410.2021. doi: 10.1158/1078-0432.CCR-21-0410.

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Case 1

29-year-old male musician no family history presents with rectal bleeding

- **Colonoscopy**
  - Sigmoid Mass
  - MSS adenoCA
- **LAR**
  - Stage II CRC
  - Path T3N0
  - 0/26 nodes
  - Tumor Budding Score of 12
  - Poorly Differentiated



What do you do?

Signatera Positive

Date: 10/07/2020
MTM/mL: 0.28

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

COBRA Study NCT04068103

Primary Objective Phase II

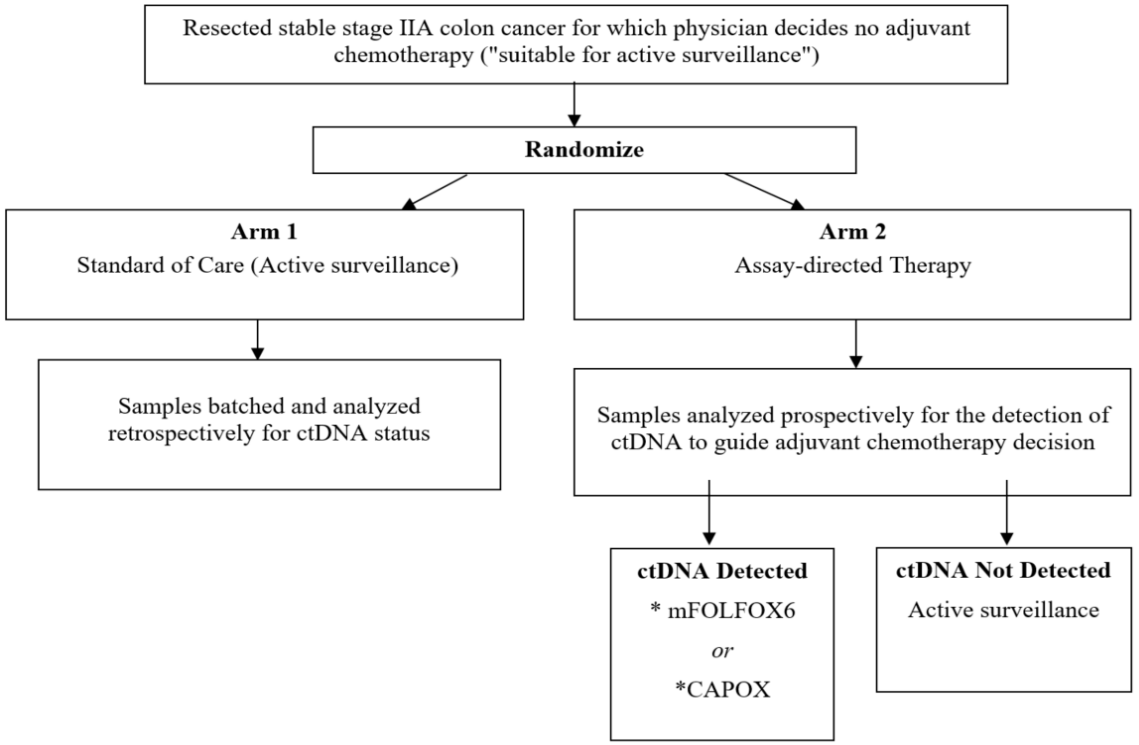
To compare the rate of ctDNA clearance in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of stage IIA colon cancer

Phase III

To compare recurrence-free survival (RFS) in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of state IIA colon cancer

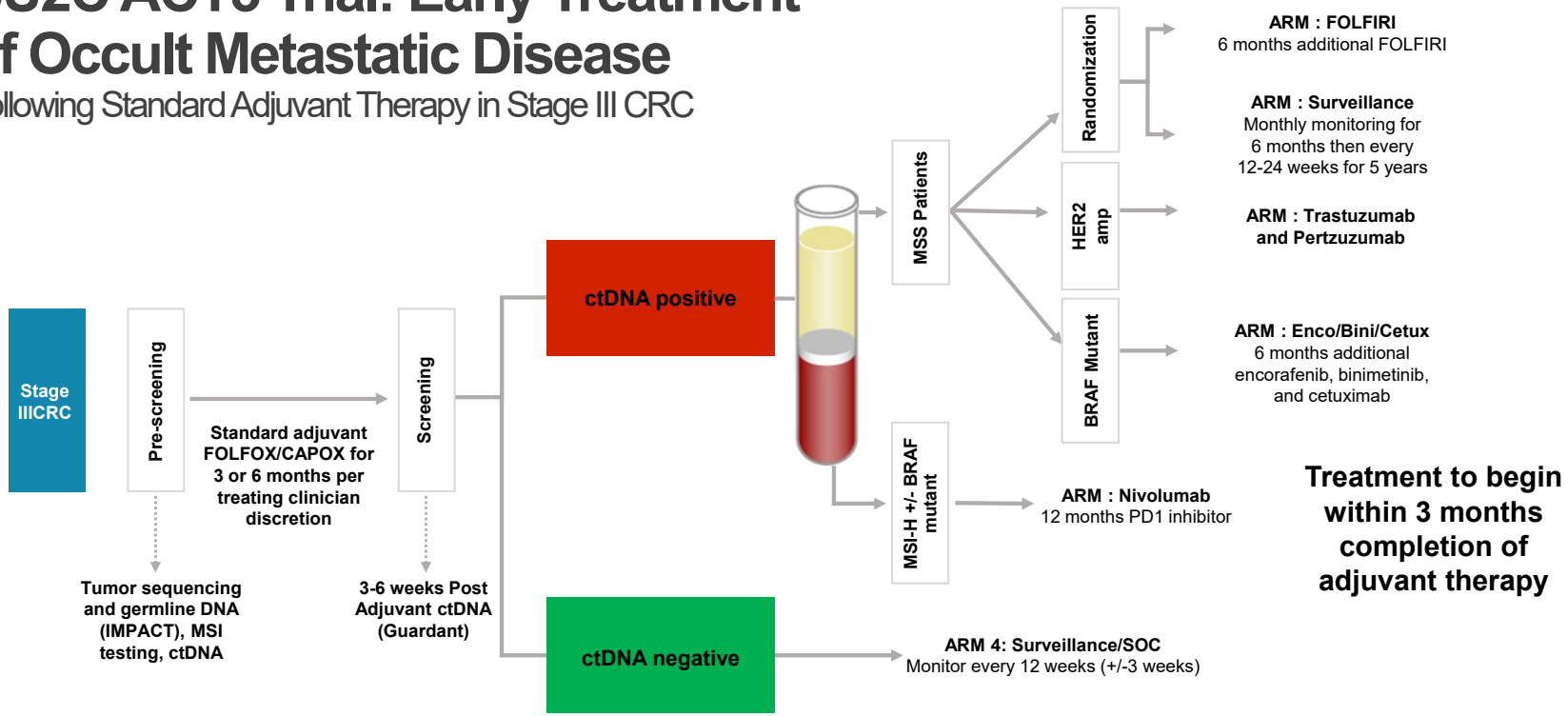
Van K. Morris, MD, Principal Investigator
Greg Yothers, PhD
Scott Kopetz, PhD
Thom George, MD

https://clinicaltrials.gov/ct2/show/NCT04068103



SU2C ACT3 Trial: Early Treatment of Occult Metastatic Disease

Following Standard Adjuvant Therapy in Stage III CRC



STAND UP TO CANCER

Assay Characteristics for Routine Testing for MRD

- For escalation applications
  - High specificity/PPV, even at the expense of lower sensitivity
  - PPV should be >90-95%; no more than 1 in 10 false positives
- Turnaround time will be critical to make real-time decisions and may require non-personalized approaches
- Having matched tumor available to minimize false positives (OR PBMCs)
- Multi-gene would be preferred to allow broad capturing of potential patients and high sensitivity

High sensitivity is needed for de-escalation. What are the limitations to sensitivity?

- Assay technology
- Tumor location
- Number of mutations
- Fragment size
- Methylation
- Amount of blood available for testing
- Number of times sampled: one time point or serial sampling
- Multi-Unique Molecular Identifiers to mitigate PCR errors

High Level Differences

	Tumor Informed	**Plasma Only**
Volume	2 tubes of blood	4 tubes of blood
Cost	$850	$5000
Tube Collection	same	Same
TAT	1st time 3-4 weeks	7-10 days
Tissue Needed	Yes	No
Technology	16 clonal, need 2	Fixed CRC panel (epigenomic/genomic)
Results	Molecules/ml	Qualitative + or – *
Tumor Type	Any	CRC

Minimal Residual Disease in 2021: Conclusions

ctDNA is prognostic and may be predictive of response to therapy

- Clearance is possible

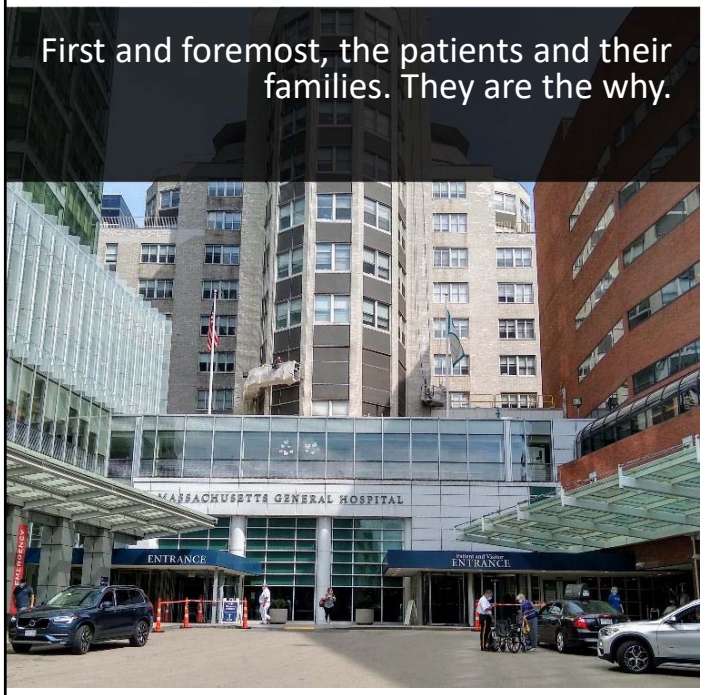
Minimal residual disease applications have tremendous opportunity

- Requires larger, prospective cohorts
- Trials underway
- Great opportunities for novel drug development following ***biology*** of MRD

Attention to false positives and improving sensitivities will be critical to ensure success of this effort

- Bioinformatically informed pipelines can address sources of false positives
- More data on Tumor Informed vs Uninformed approach to minimize false positives and ensure clinical relevance of the findings

Acknowledgements



MGH Center for GI Cancers

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Director, Gastrointestinal Cancer Center Program

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Hetal Desai, MD
Nicholas Jessop

MGH Rapid Autopsy Program

Dejan Juric, MD

MGH GI Research Asst Team

Islam Baiev
Emily VanSeventer
Joy Jaqnian
Yojan Shah

Other Mentors

Bruce Chabner, MD
Keith Flaherty, MD
Alan Venook, MD, UCSF

FUNDING: NIH/NCI DF/HCC GI SPORE

NCCN 2021 Virtual Congress:
Biomarkers in Solid Tumors

What's on the Horizon?

Pancreatic Cancer Heterogeneity: A Therapeutic Challenge and Opportunity

David T. Ting, MD

Associate Professor of Medicine, *Harvard Medical School*

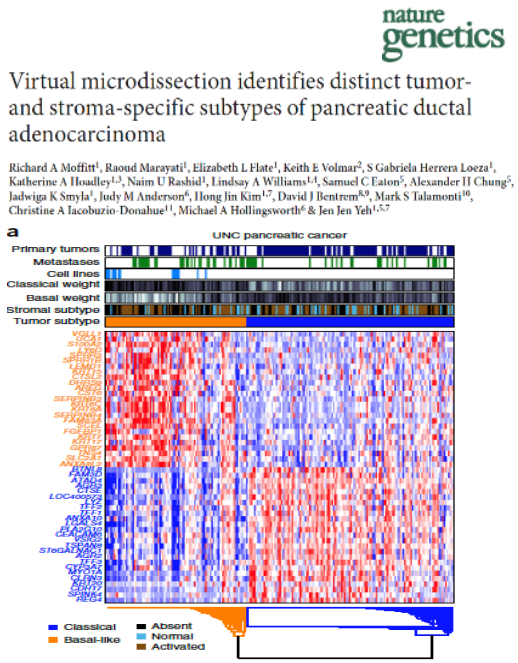
Associate Clinical Director for Innovation, *Massachusetts General Hospital Cancer Center*

National Comprehensive Cancer Network®

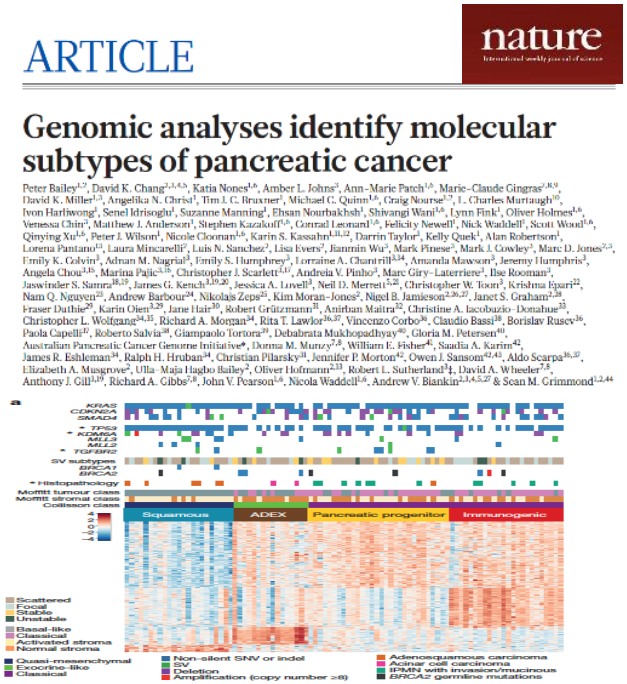
NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

Pancreatic Ductal Adenocarcinoma (PDAC)
Not a Single Cancer

Collisson EA et al. ***Nature Medicine*** 2011



Moffitt RA et al. ***Nature Genetics*** 2015



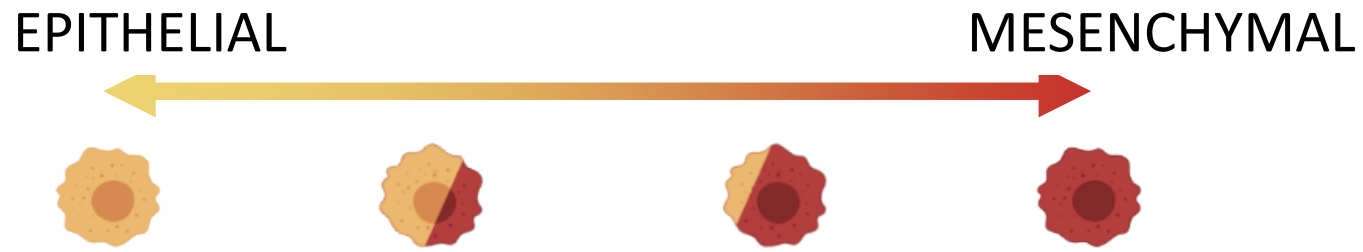
Bailey P et al. ***Nature*** 2016

Epithelial-Mesenchymal Plasticity Drives Tumor Cell Heterogeneity

EPITHELIAL

MESENCHYMAL

Epithelial-Mesenchymal Plasticity Drives Tumor Cell Heterogeneity



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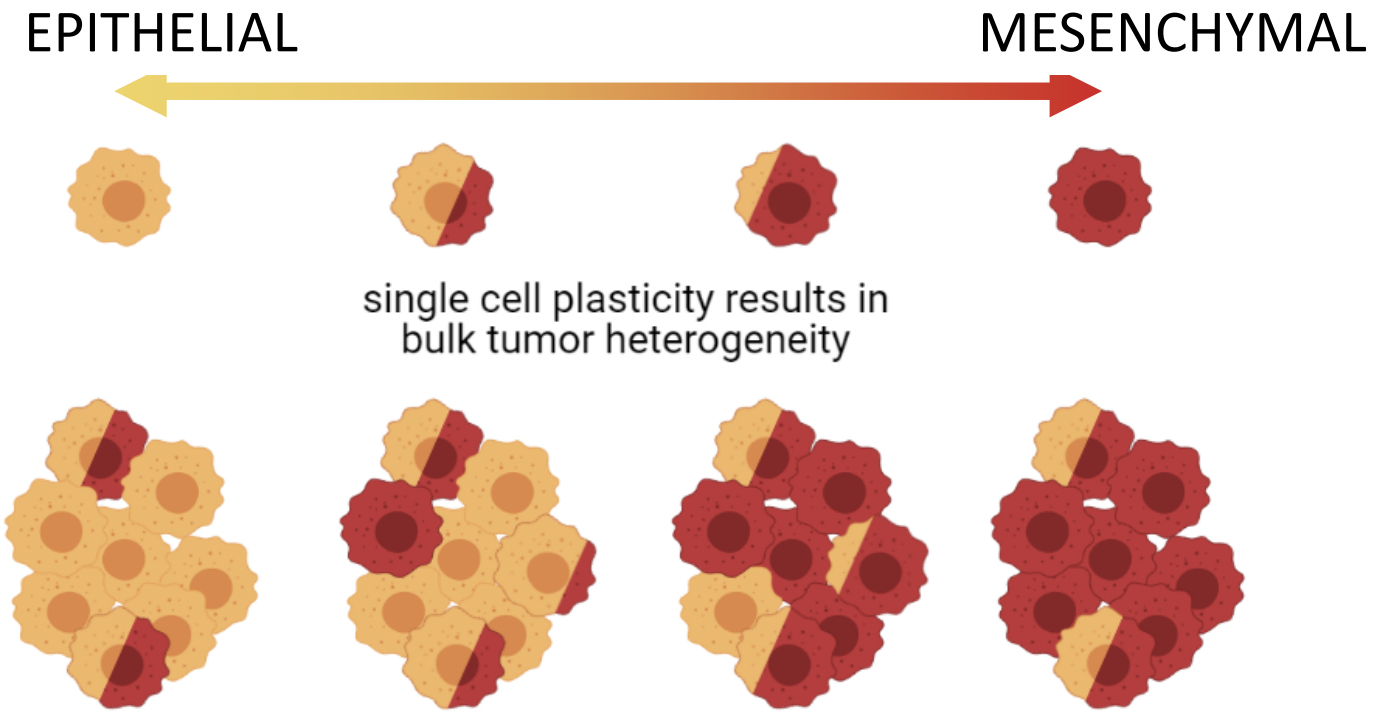
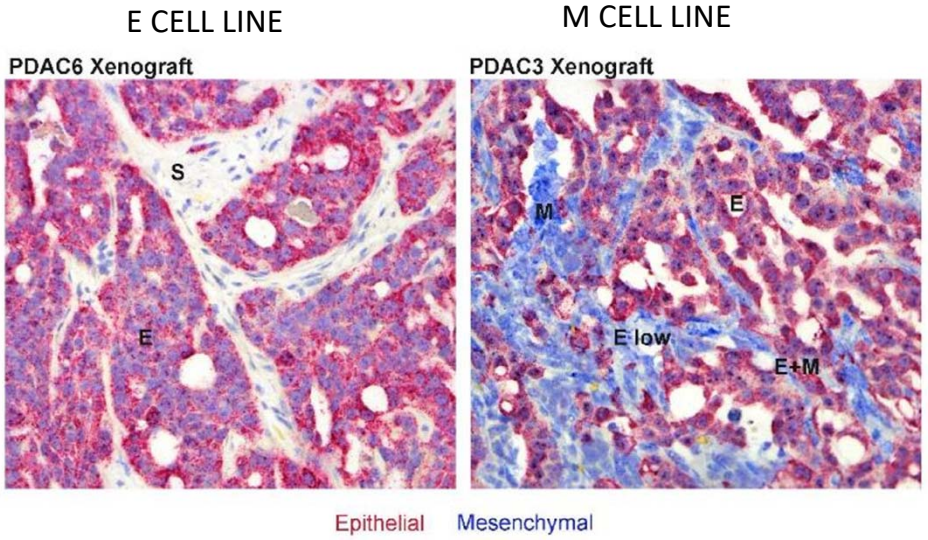


Human Cancers on a Spectrum of Epithelial-Mesenchymal States

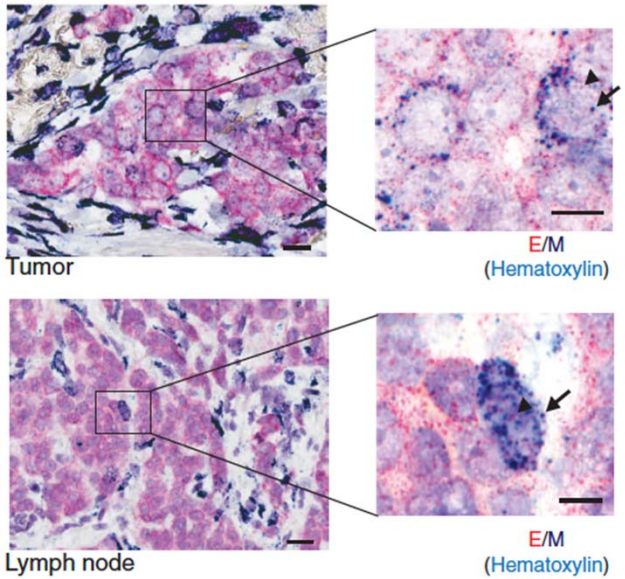
Pancreatic cancer (PDAC)



Epithelial – CDH1, EPCAM, KRT5, KRT7, KRT8, KRT18, KRT19
Mesenchymal – FN1, CDH2, SERPINE1

Porter, *PNAS,* 2019

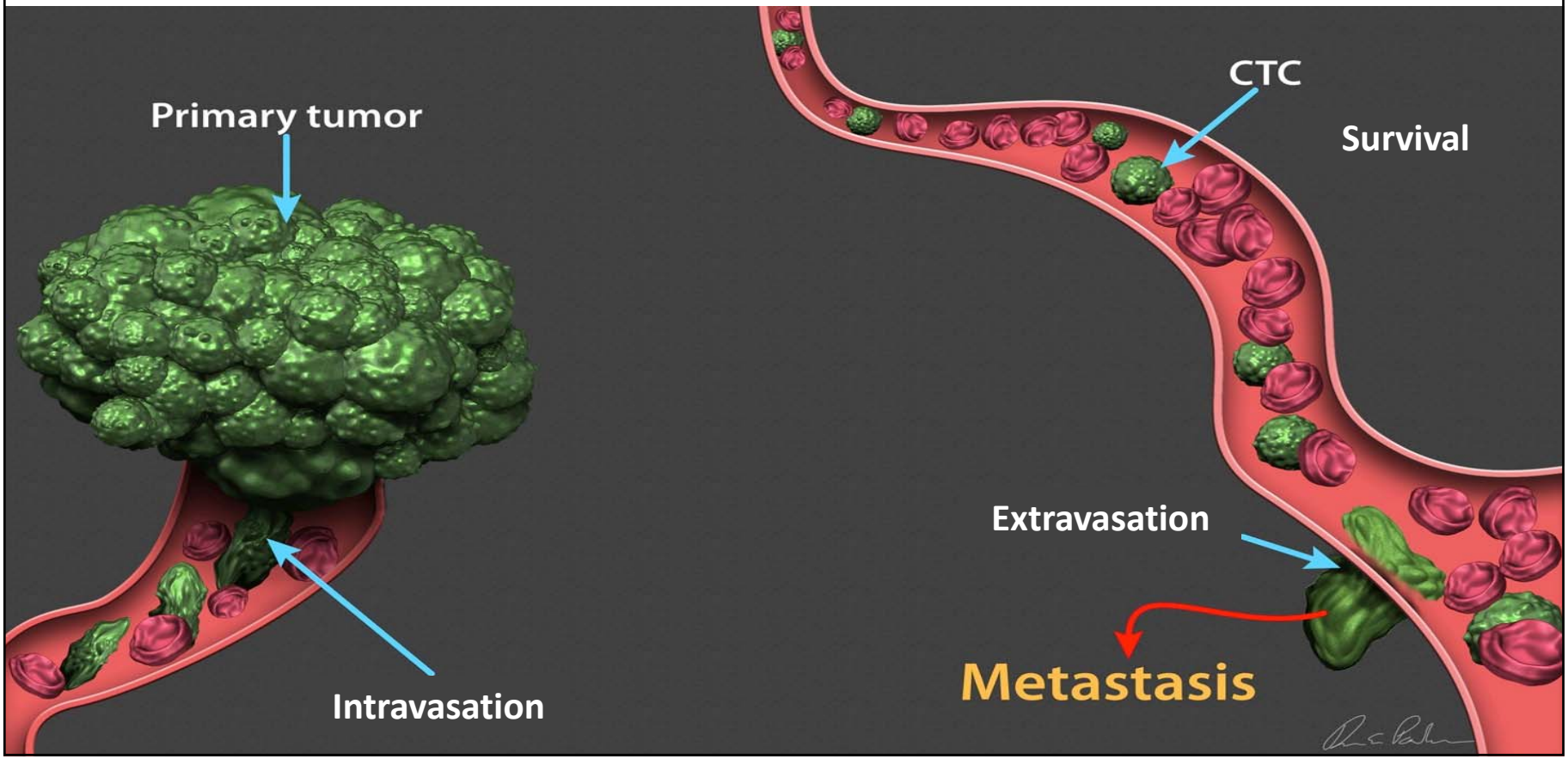
Breast cancer



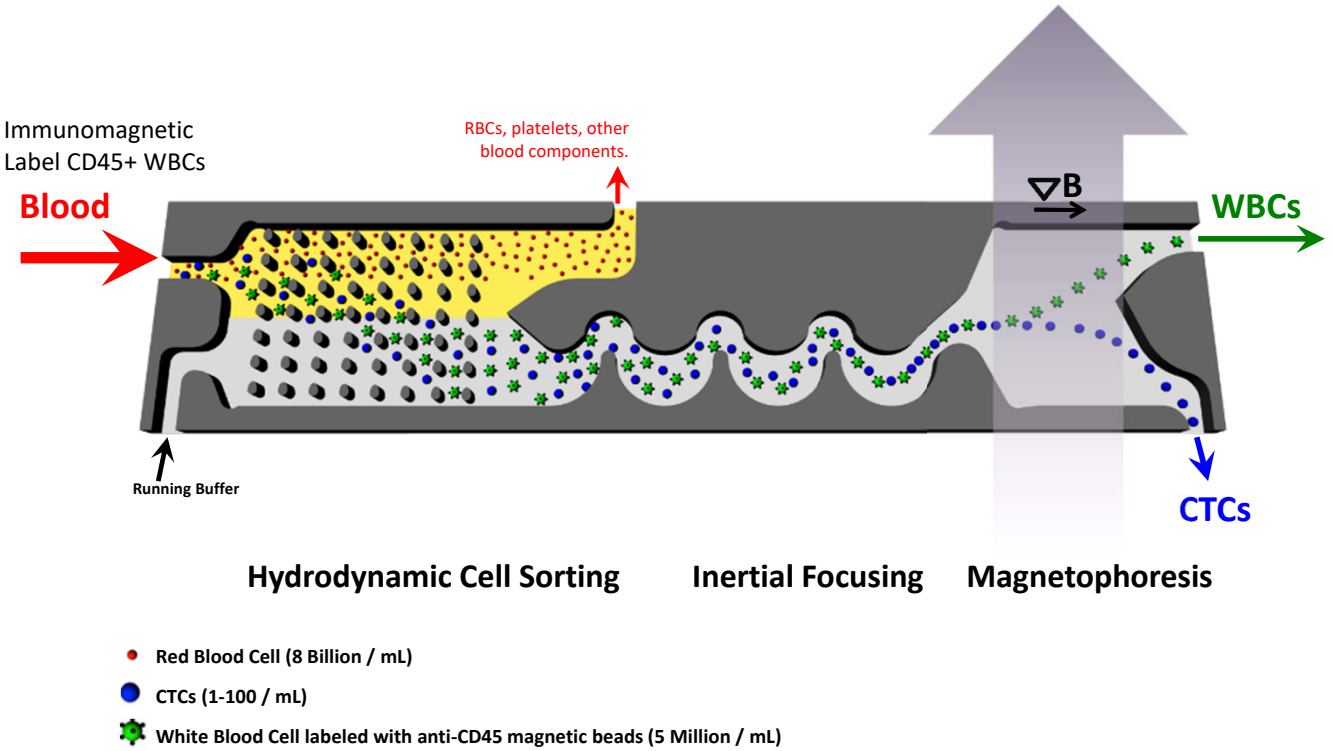
Yu, *Science,* 2013

Cell Autonomous
EMT Plasticity

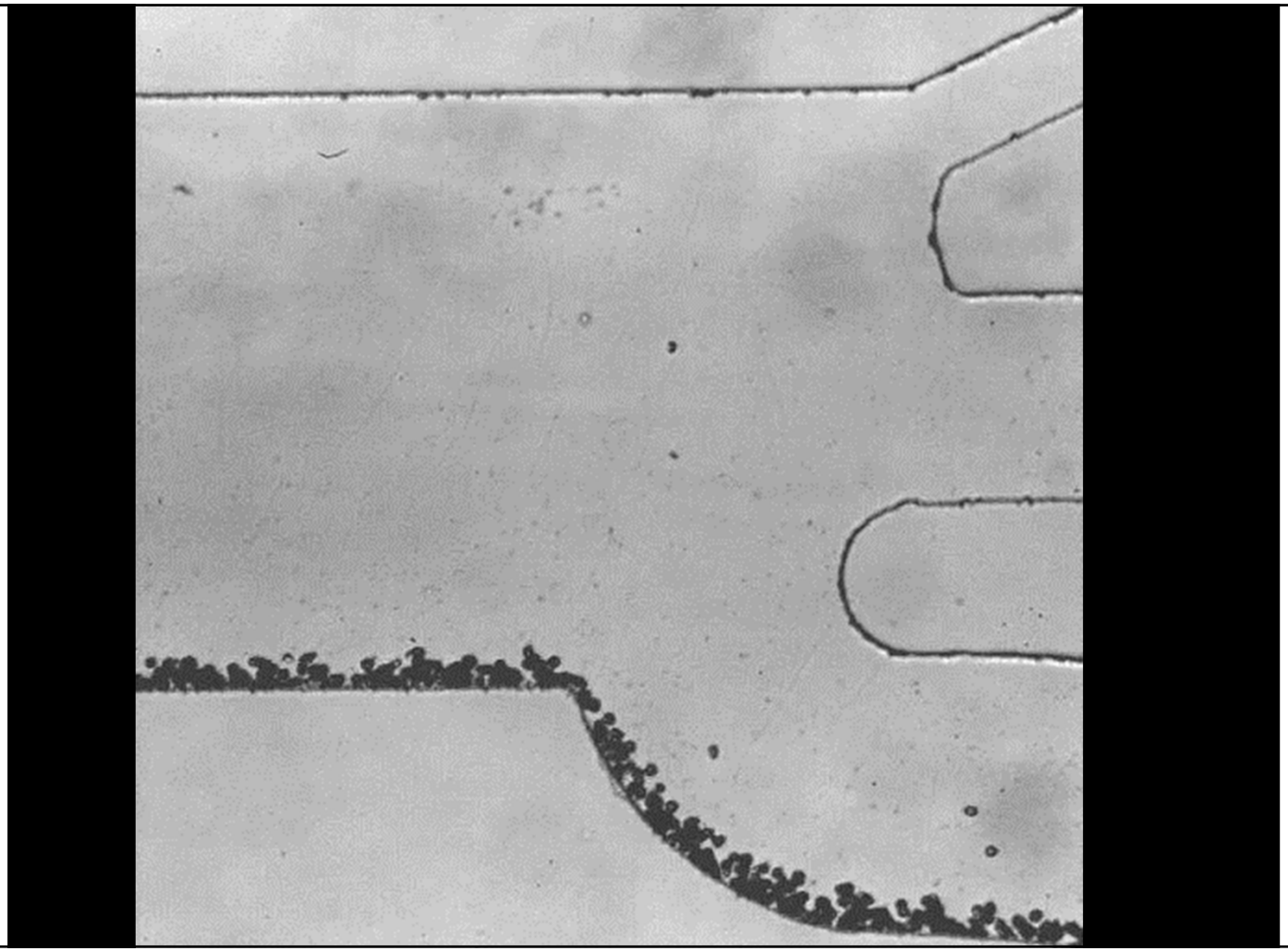
EMT Plasticity Important for Circulating Tumor Cells (CTCs)



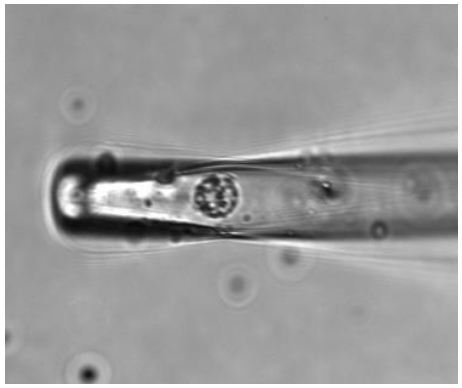
Negative Depletion CTC-iChip



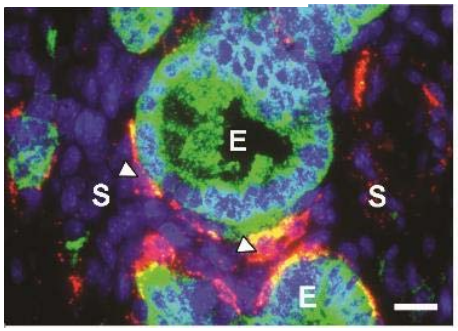
Ozkumur E*, Shah AM*, et al. ***Sci Transl Med***, 2013; 5(179): 179ra47.
* Equal contribution



Single CTC RNA-seq: Heterogeneous EMT and Stem Cell Gene States

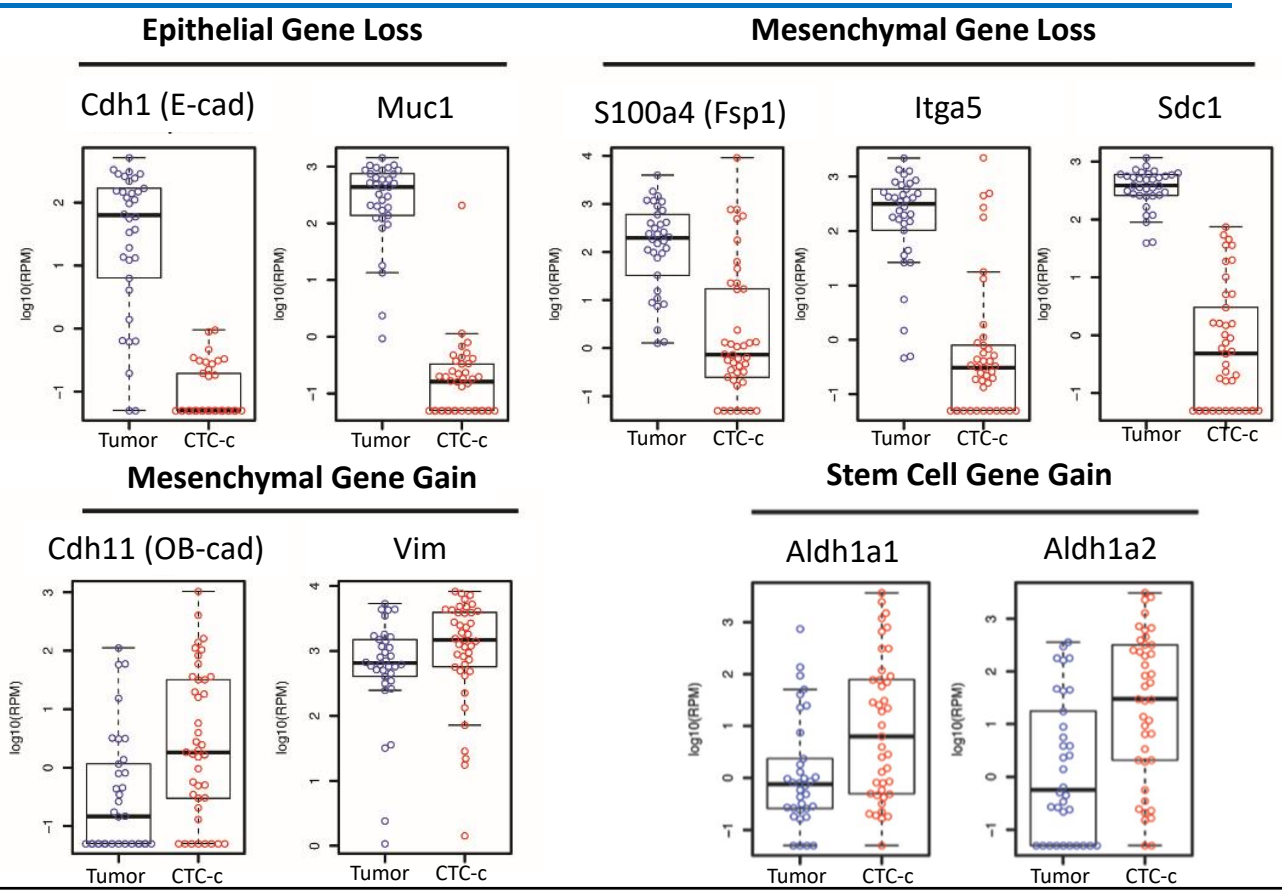


Mouse Primary Tumor



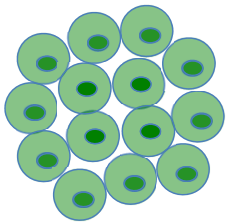
Igfbp5 (CTC gene) / CK / DAPI

Ting DT, et al. ***Cell Reports,*** 2014; 8:1-14.



Microenvironment Driven EMT Plasticity

Modeling PDAC:CAF Heterogeneous Interactions



Ligorio M*, Sil S*, et al. ***Cell*** 2019
* Equal contribution

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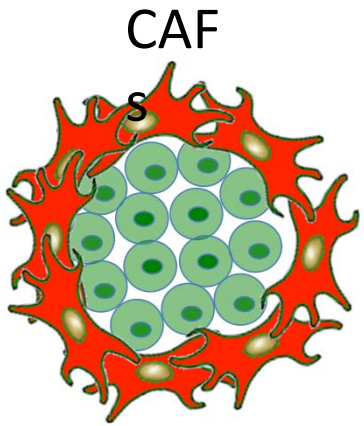

Ligorio M*, Sil S*, et al. ***Cell*** 2019
* Equal contribution

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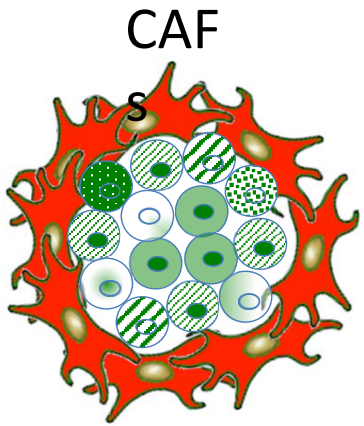

Ligorio M*, Sil S*, et al. ***Cell*** 2019
* Equal contribution

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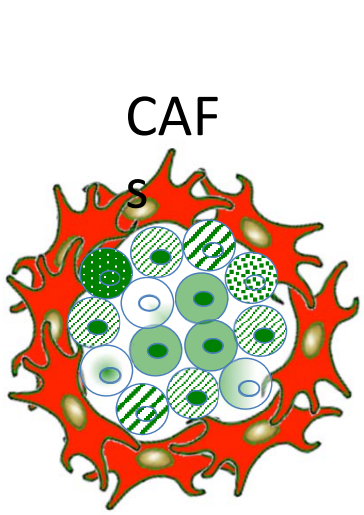
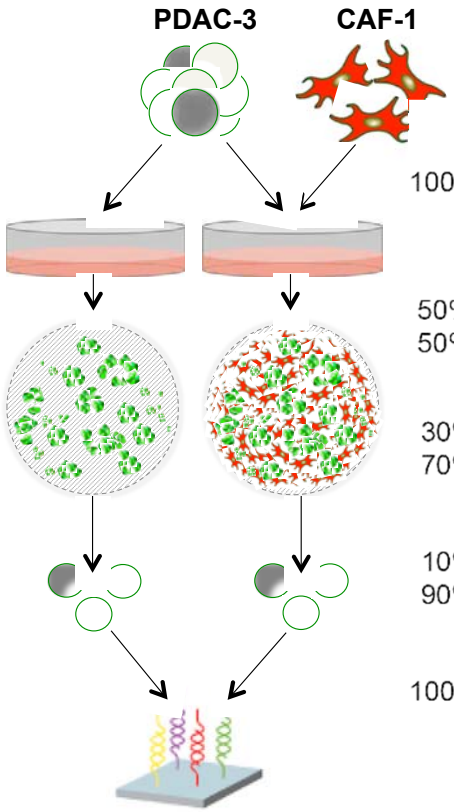
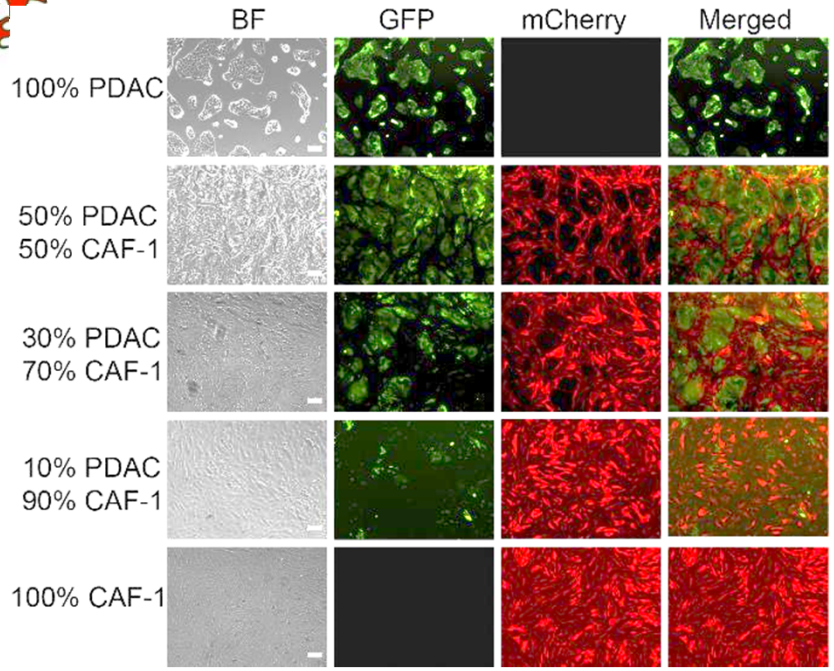


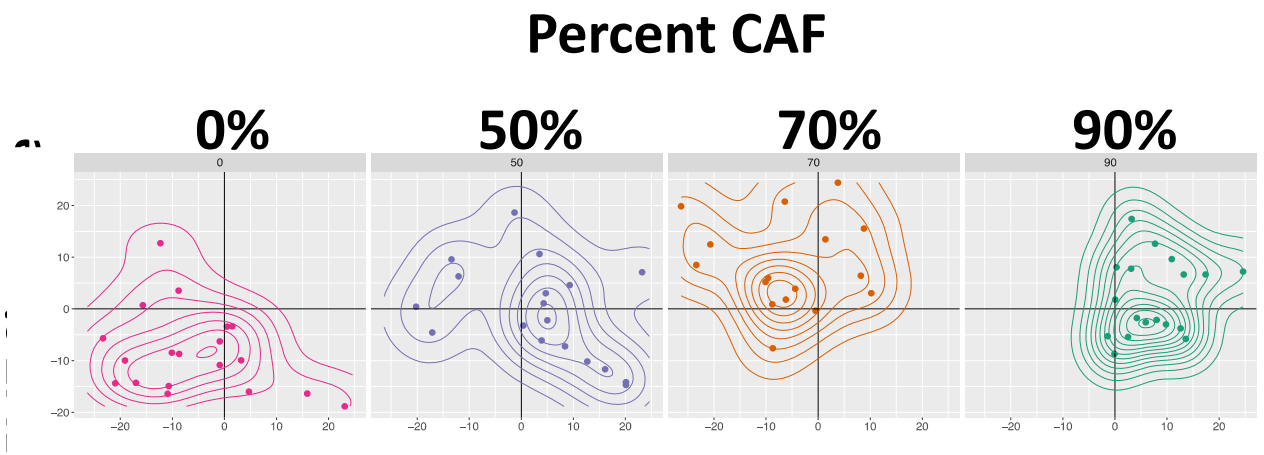


Varying CAF Co-Culture Ratios



Ligorio M*, Sil S*, et al. ***Cell*** 2019
* Equal contribution

Stromal CAFs Modulate Changes in Single Cell Phenotypes Observed in CTCs



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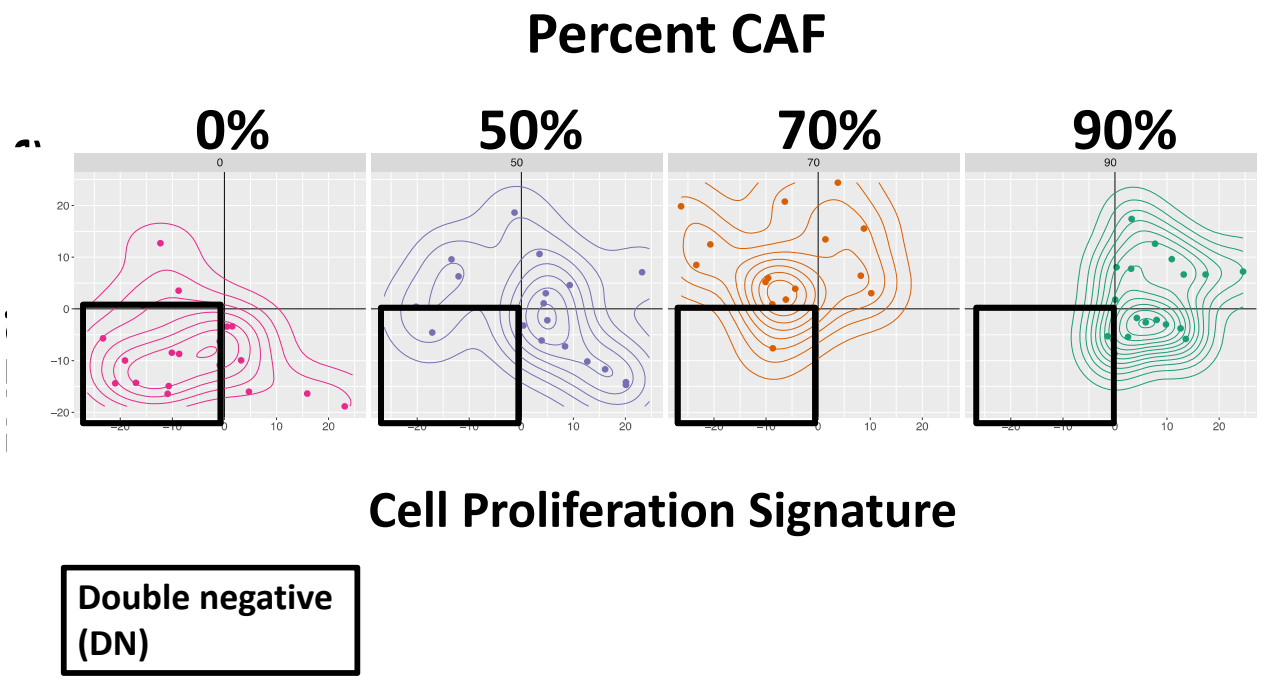

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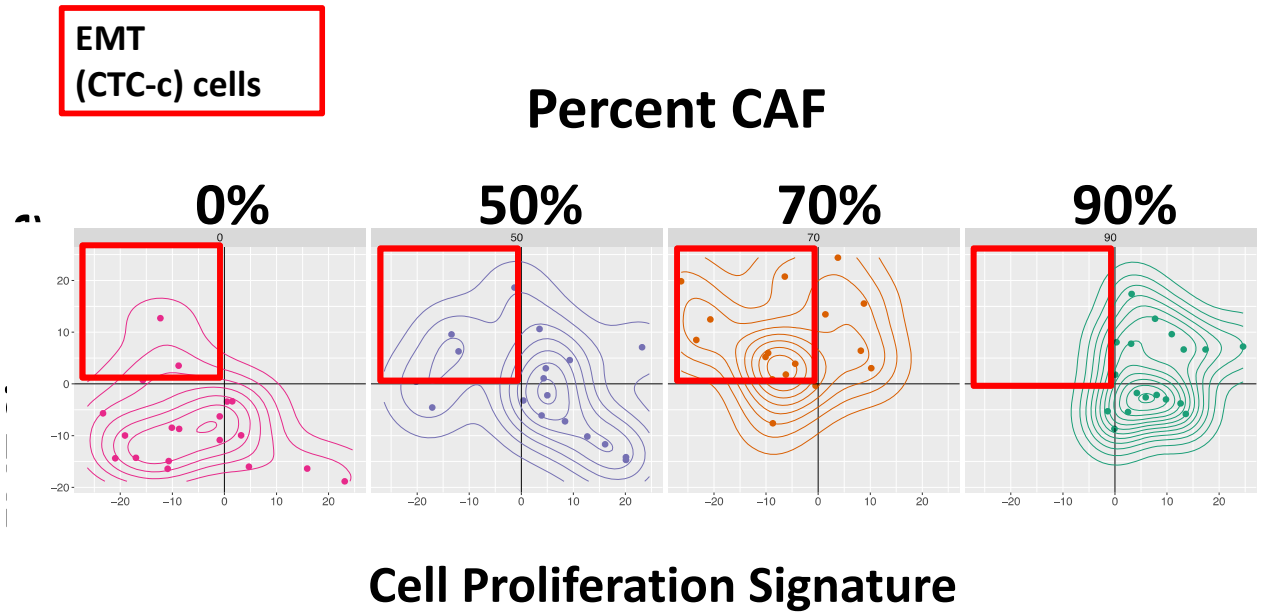

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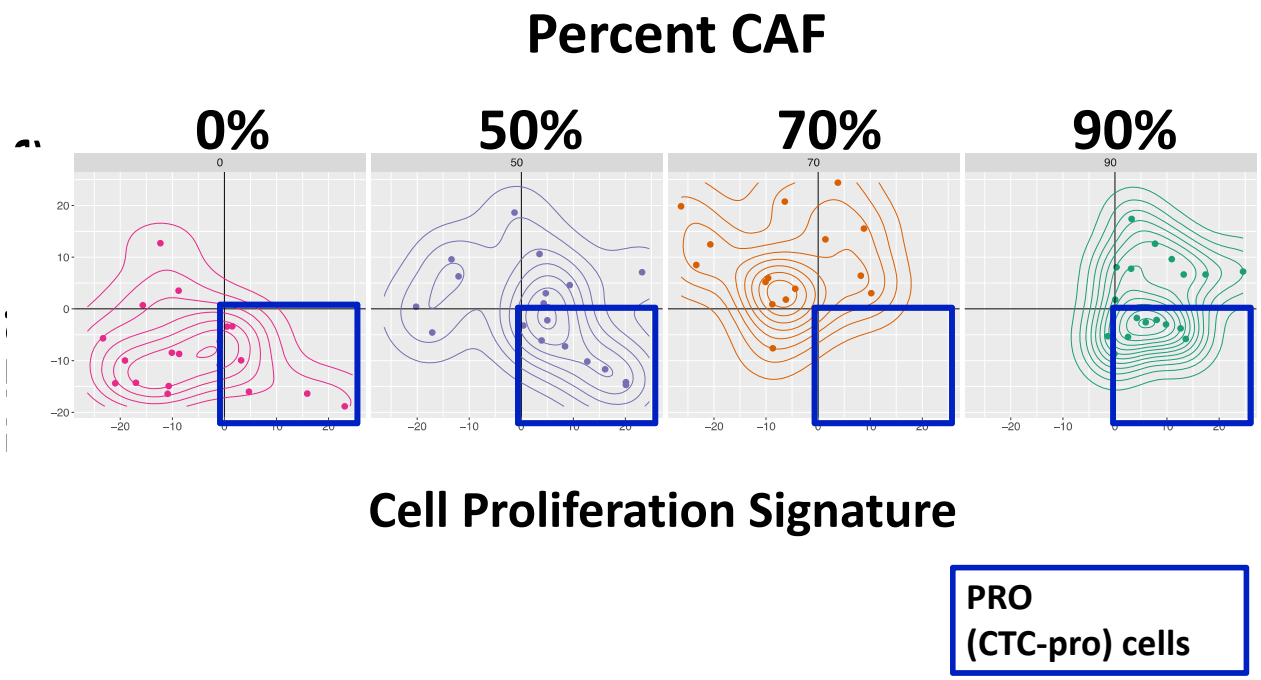

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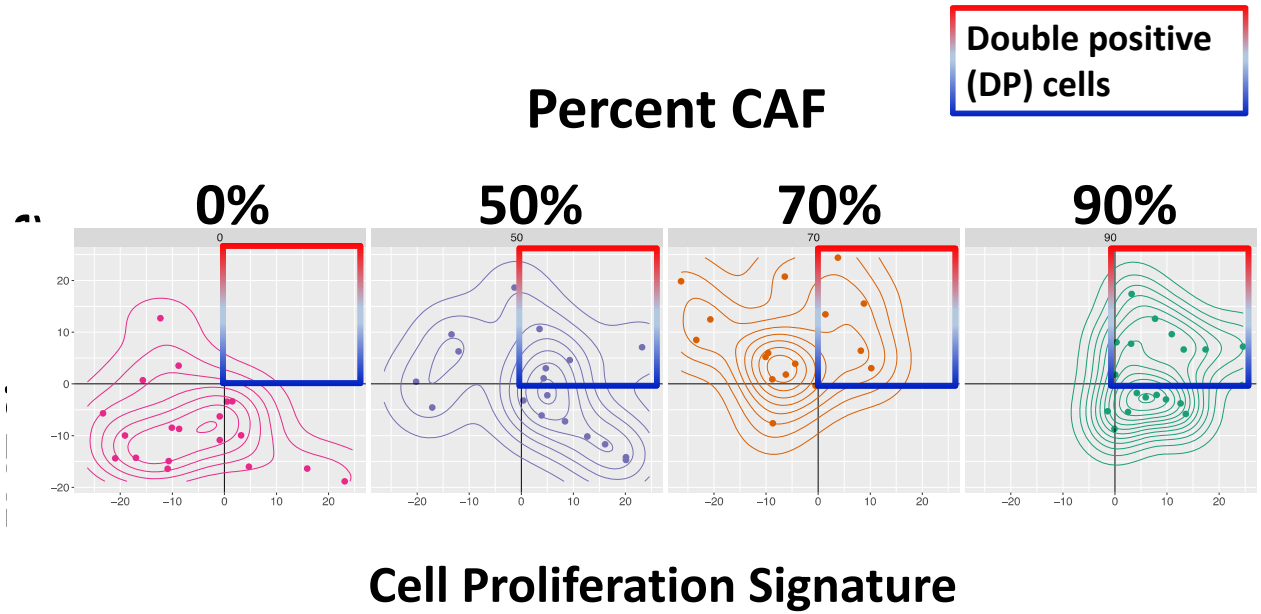
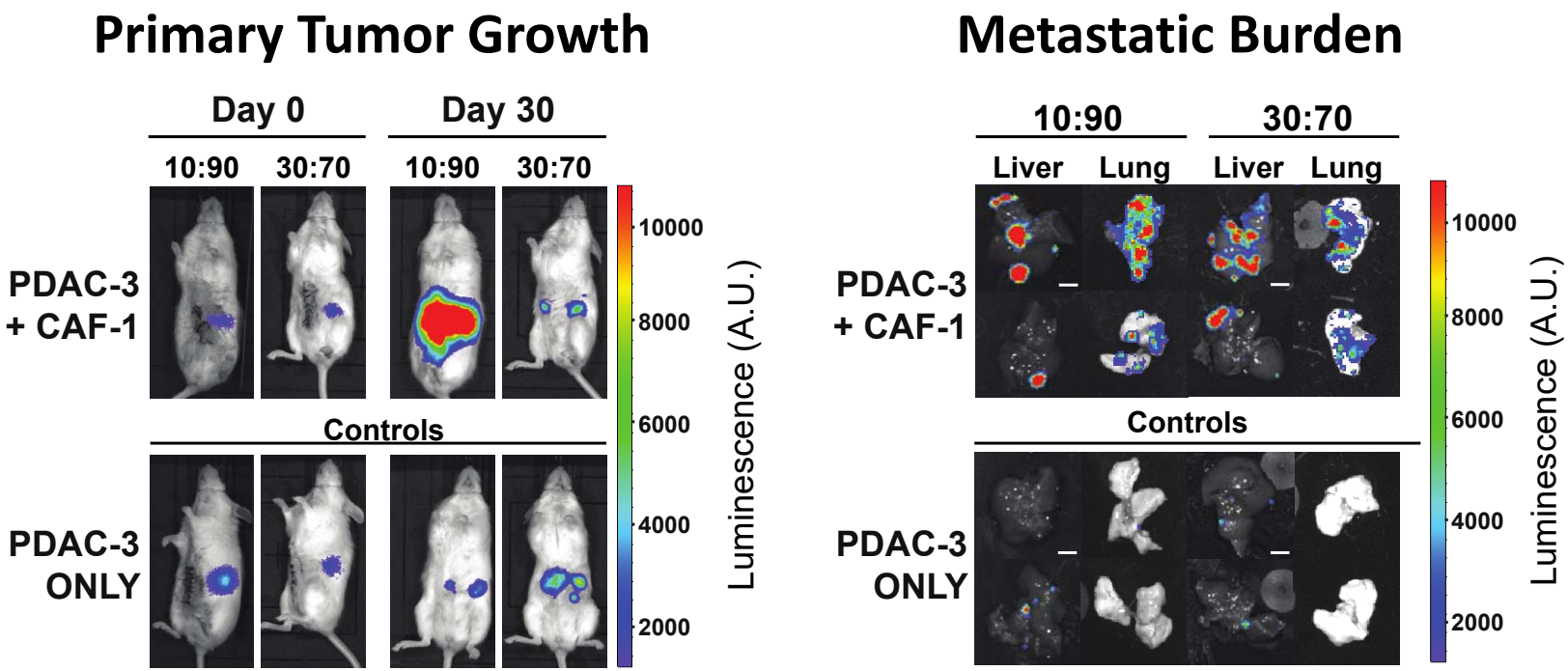
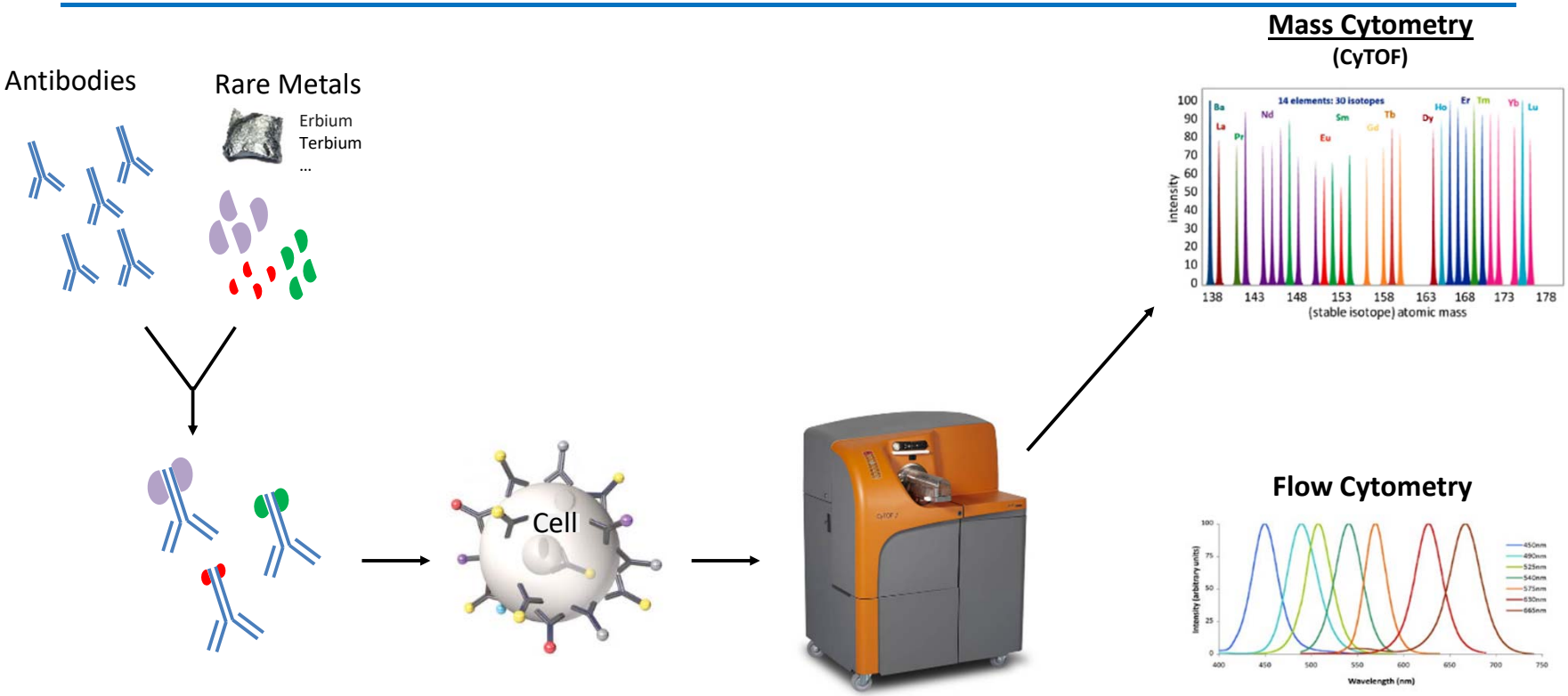


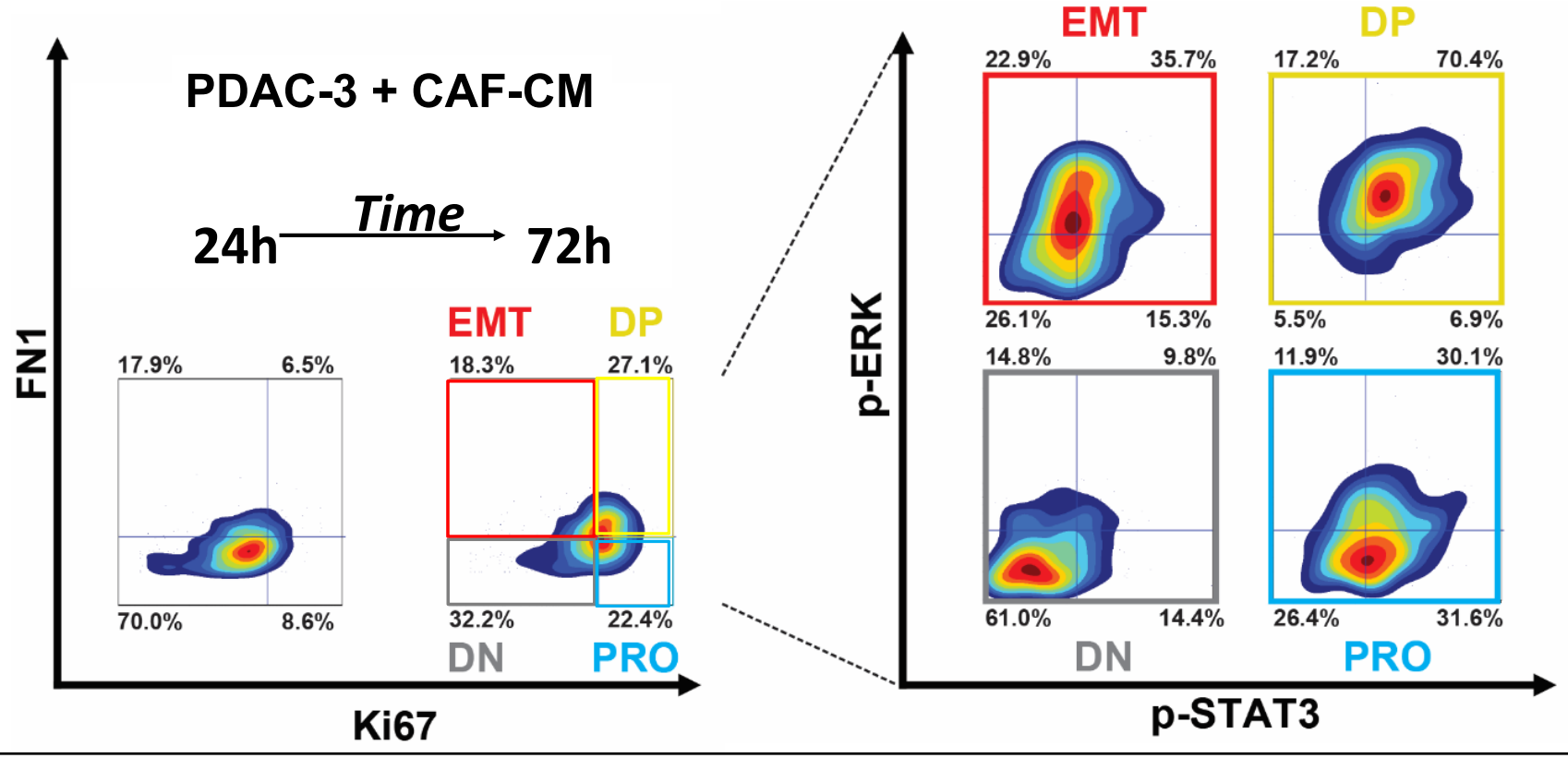
Different proportions of CAFs alters PDAC behavior *in vivo*



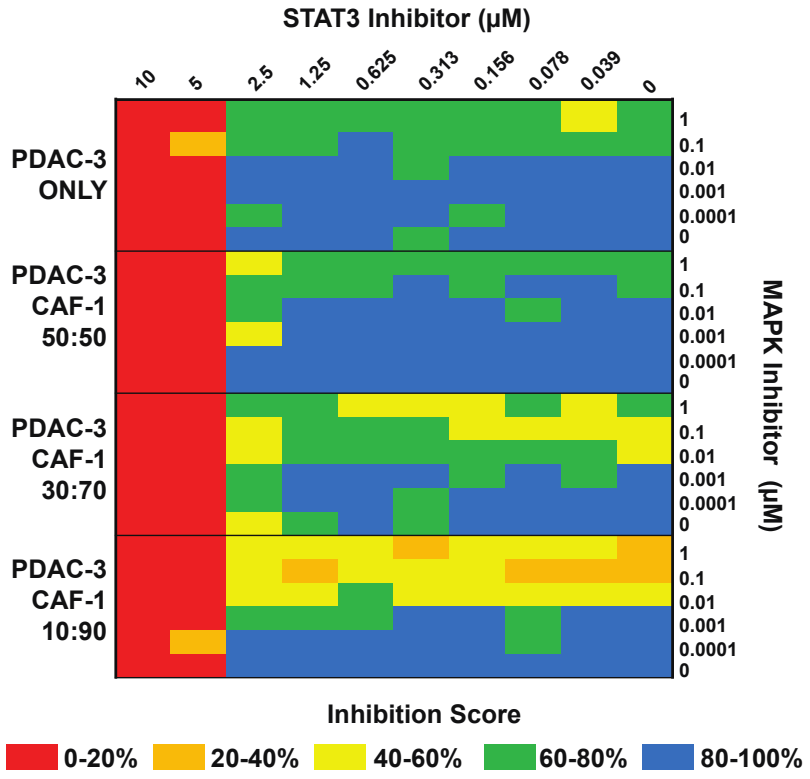
Mass Cytometry (CyTOF) – Single Cell Proteomics



CyTOF Identifies MAPK and STAT3 Single Cell Signaling Enriched in EMT and PRO Phenotypes

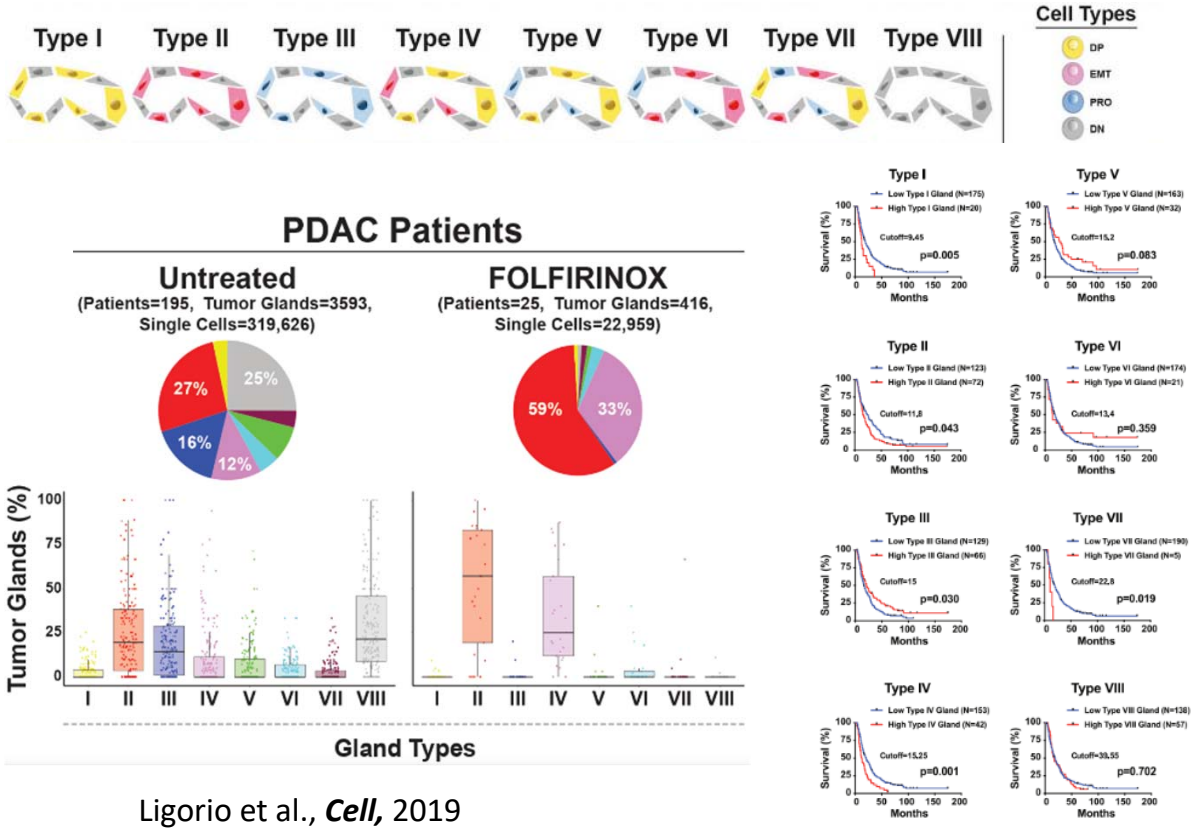


Combination MAPK and STAT3 Inhibitors as a Therapeutic Strategy for High CAF Stromal Tumors



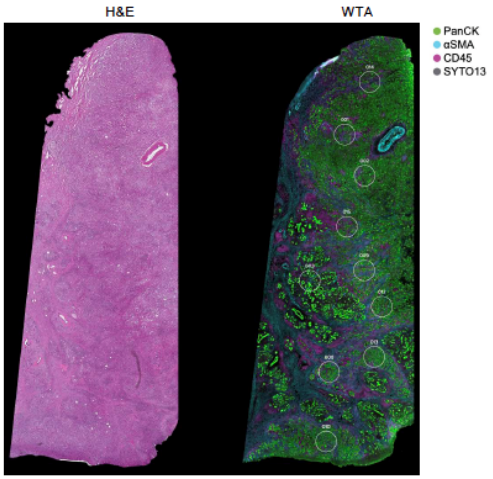
Plasticity leads to chemoresistance in PDAC patients

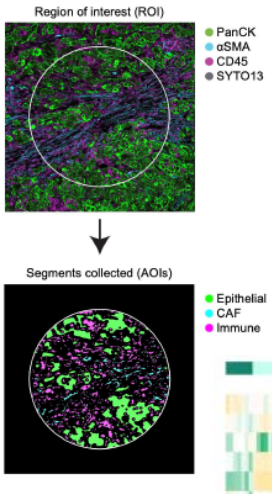
- Neoadjuvant FOLFIRINOX tumors enriched for mesenchymal tumor glands
- Patients with tumors enriched for mesenchymal glands have worse prognoses



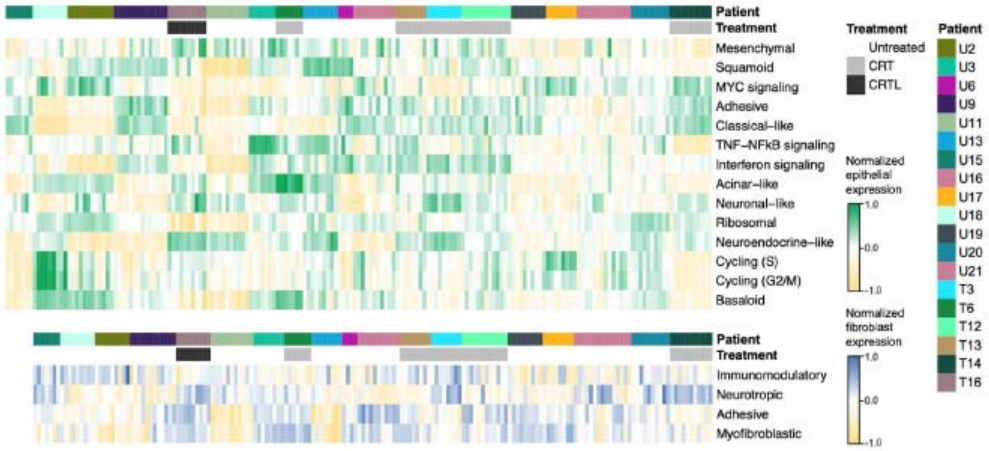
Ligorio et al., ***Cell,*** 2019

Next Generation Spatial Transcriptomics





NanoString GeoMx

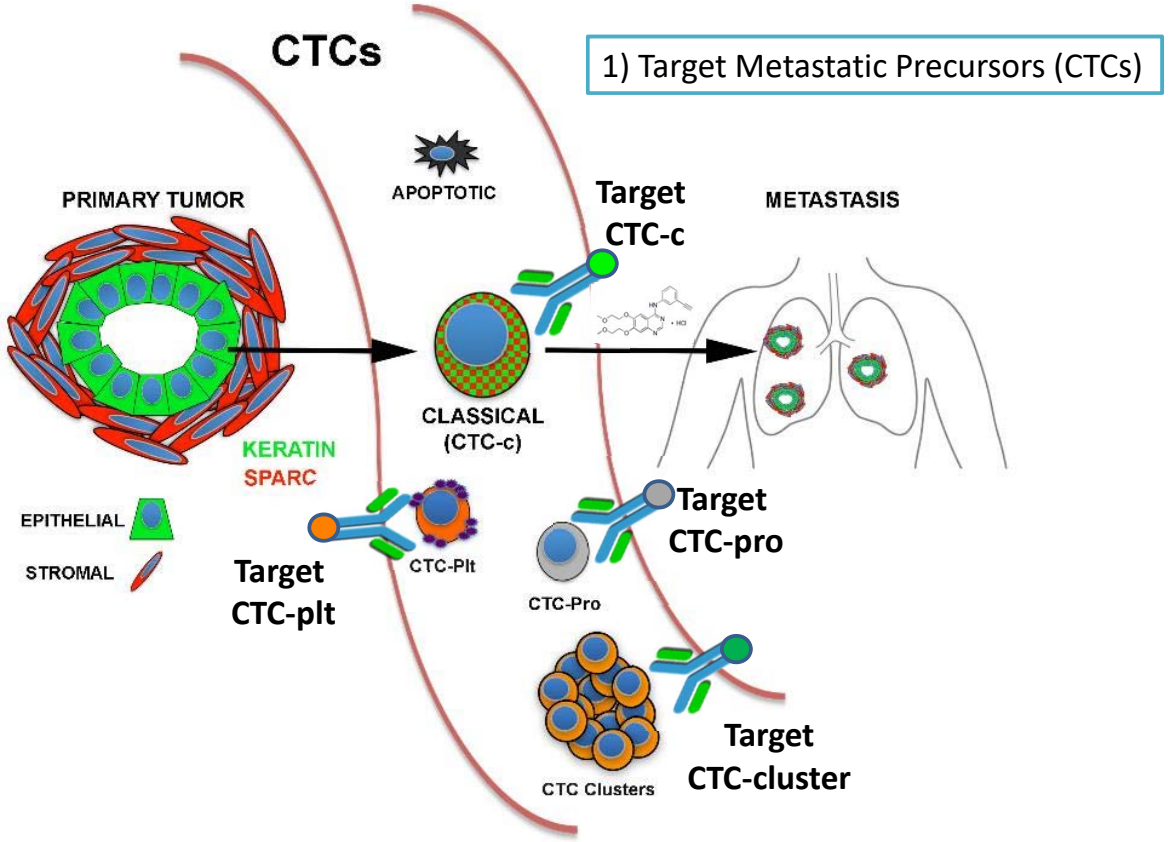


Hwang et al. (Revision)

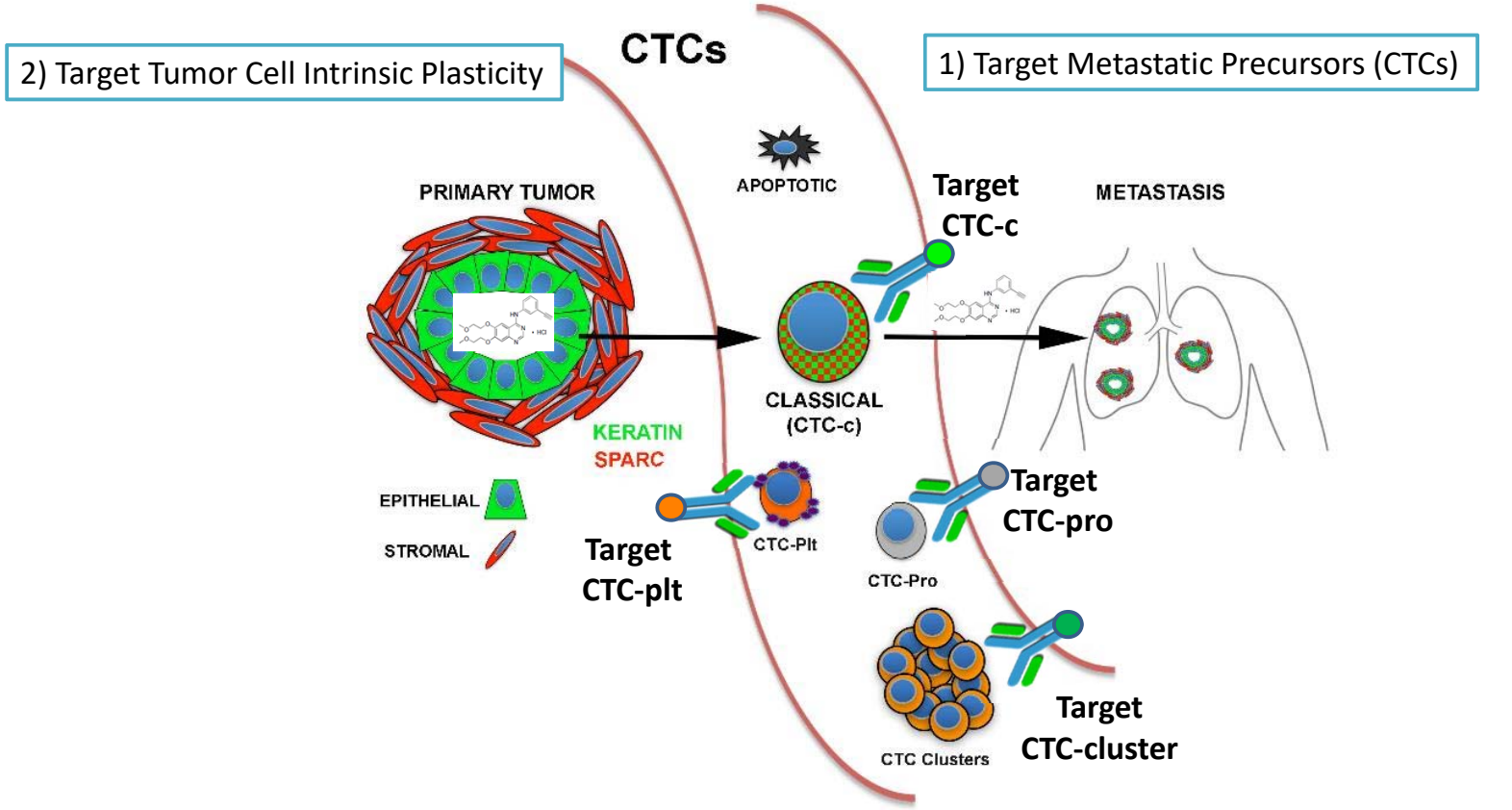
Summary: PDAC-CAF Interactions

- Stromal CAFs is a Driver of Single Cell Heterogeneity in PDAC
- PDAC-CAF Interactions result in enhanced EMT and metastasis
- Identification of combination therapies (MEK+STAT3) and PDAC-CAF interacting proteins (TGF-β) as therapeutic candidates
- Spatial Transcriptomics to understand effects of therapies on single cell subpopulations in human tumors

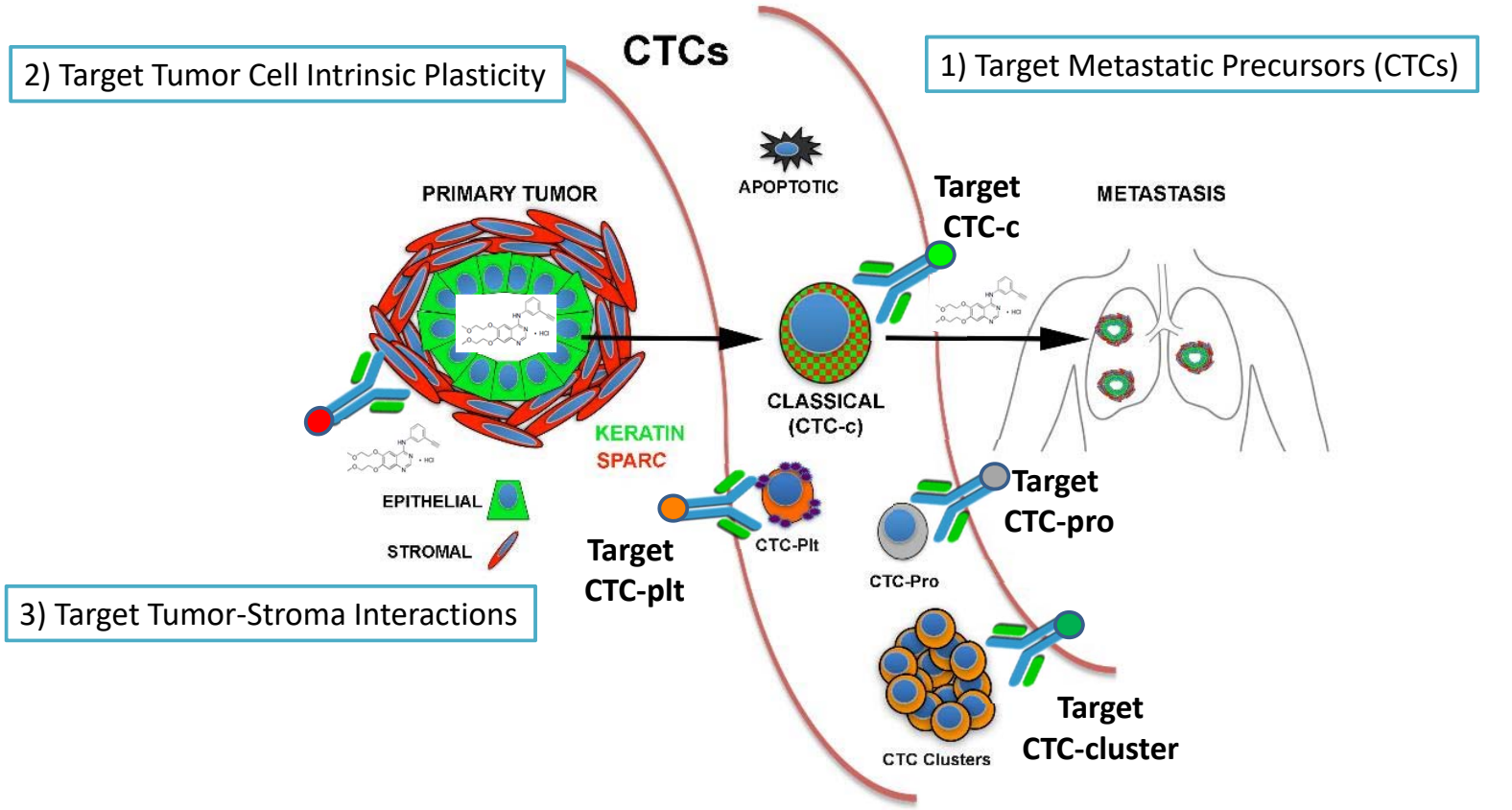
Points of Intervention Targeting EMT Plasticity



Points of Intervention Targeting EMT Plasticity



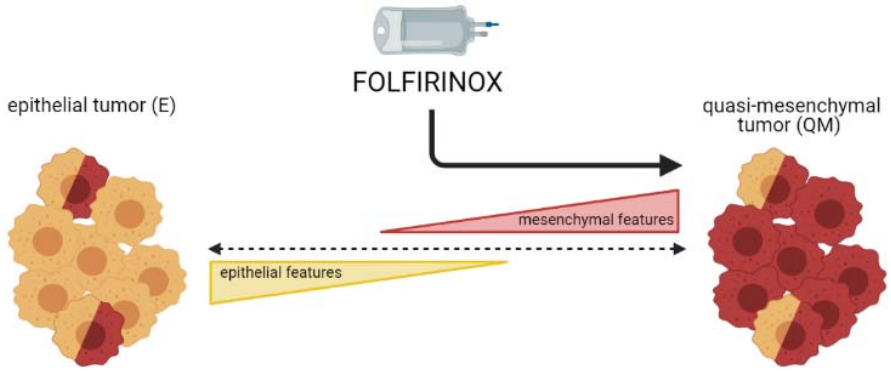
Points of Intervention Targeting EMT Plasticity

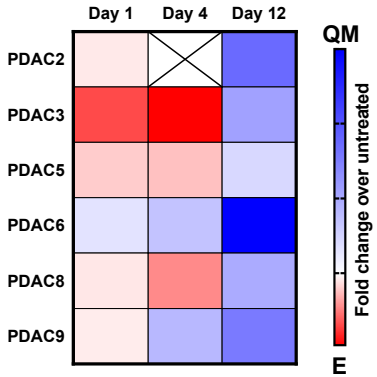


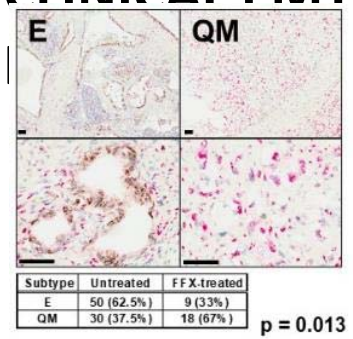
Biomarker Translation to the Clinic

EMT Plasticity leads to chemoresistance in PDAC

- Treatment of PDAC cell lines with FOLFIRINOX induces the mesenchymal state
- Neoadjuvant FOLFIRINOX patient PDAC tumors enriched for mesenchymal cells
- **CLIA EMT RNA-ISH assay operational for patient selection and pharmacodynamic response**



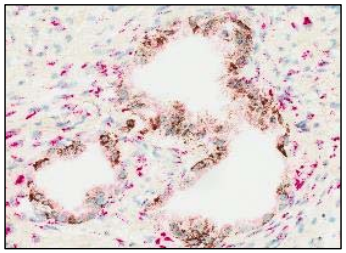




Porter, ***PNAS***, 2019

Precision Medicine: EMT RNA-ISH

EMT Status for Patient Selection in Clinical Trials



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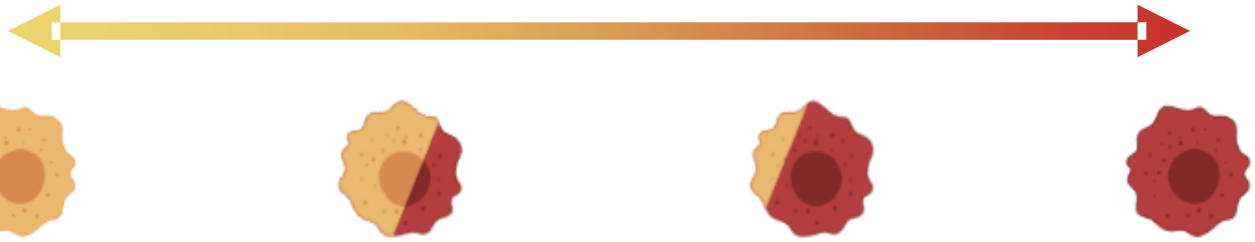
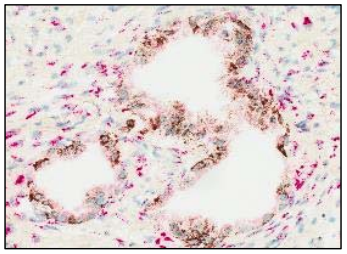


Precision Medicine: EMT RNA-ISH

EMT Status for Patient Selection in Clinical Trials



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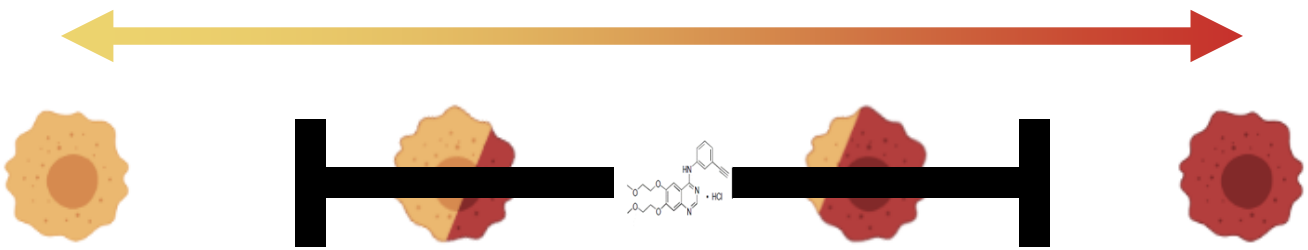

Evaluate Plasticity Drugs to Alter Tumor Heterogeneity

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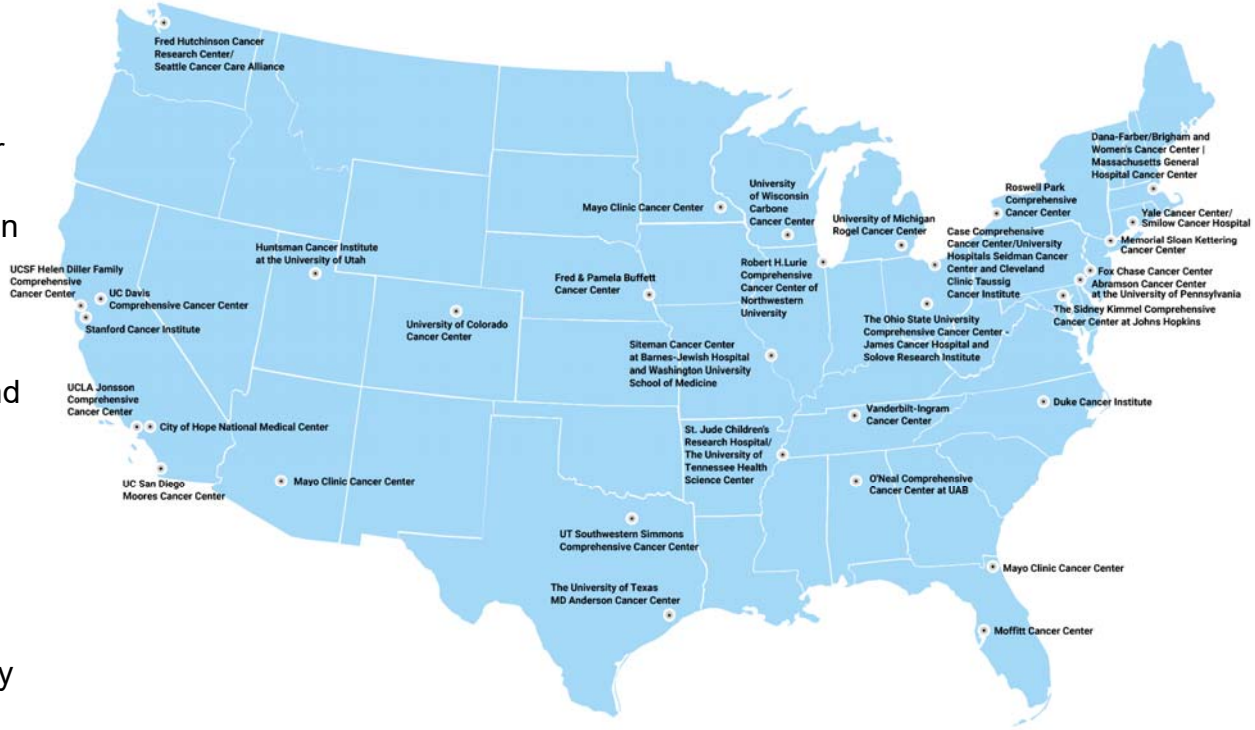

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