GU Liquid Biopsy Updates
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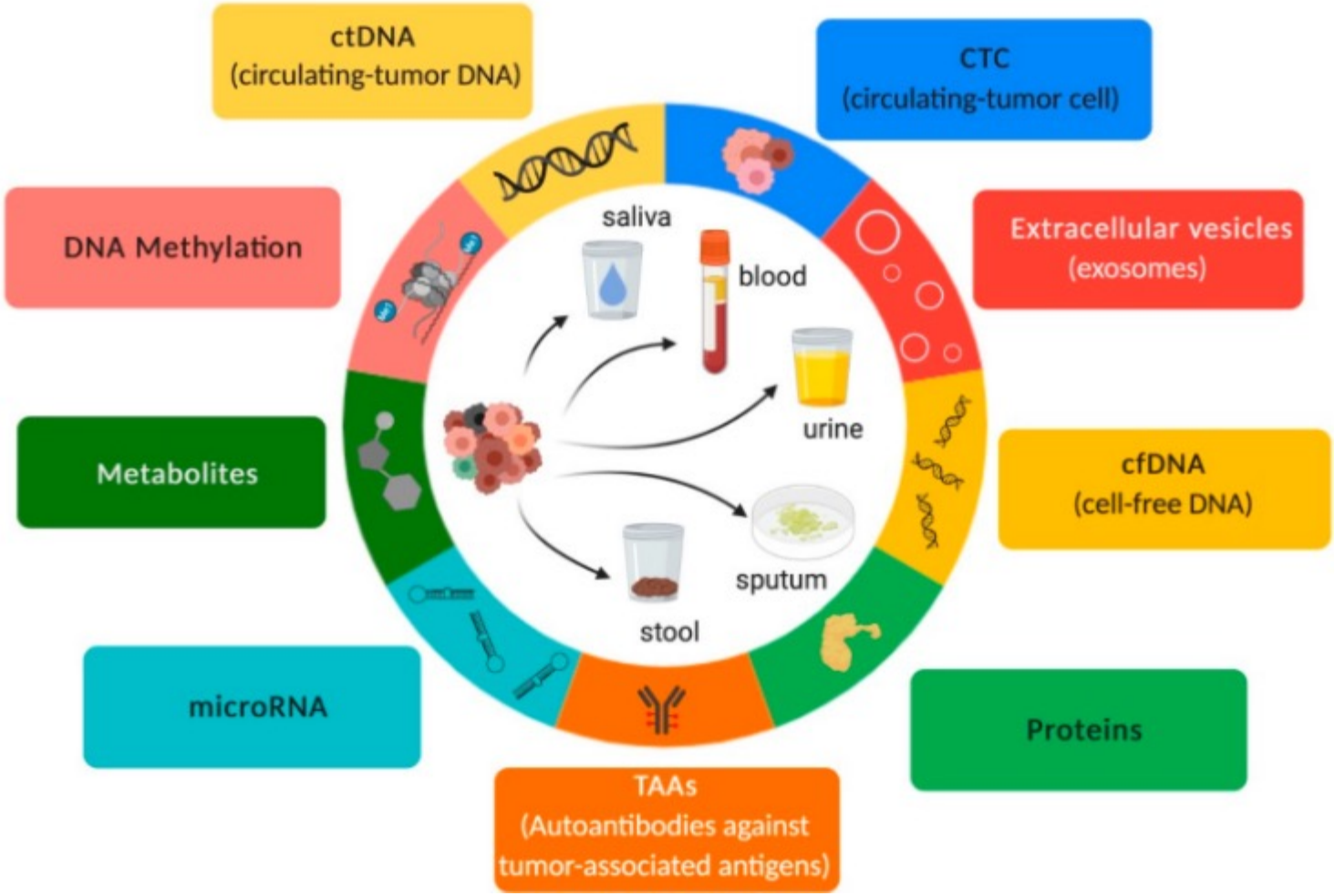
Agenda

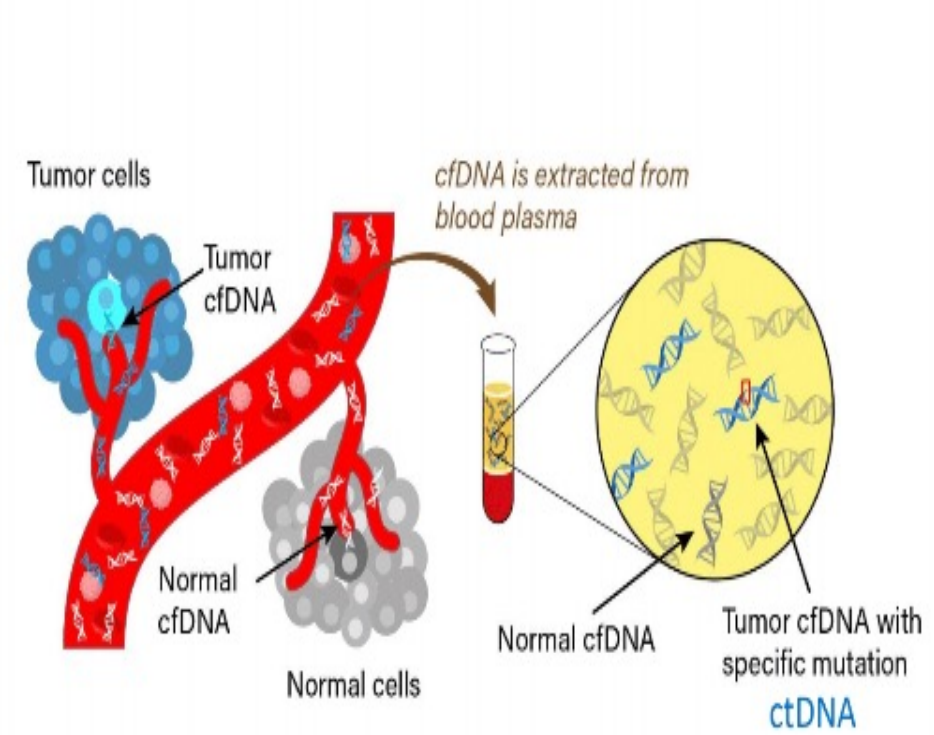
1. Liquid Biopsy Overview
2. Tumor Informed vs Tumor Agnostic
3. CHIP mutation
4. Urothelial Cancer
5. Prostate Cancer
6. Research Questions for the future

Liquid Biopsy Overview

Liquid Biopsy

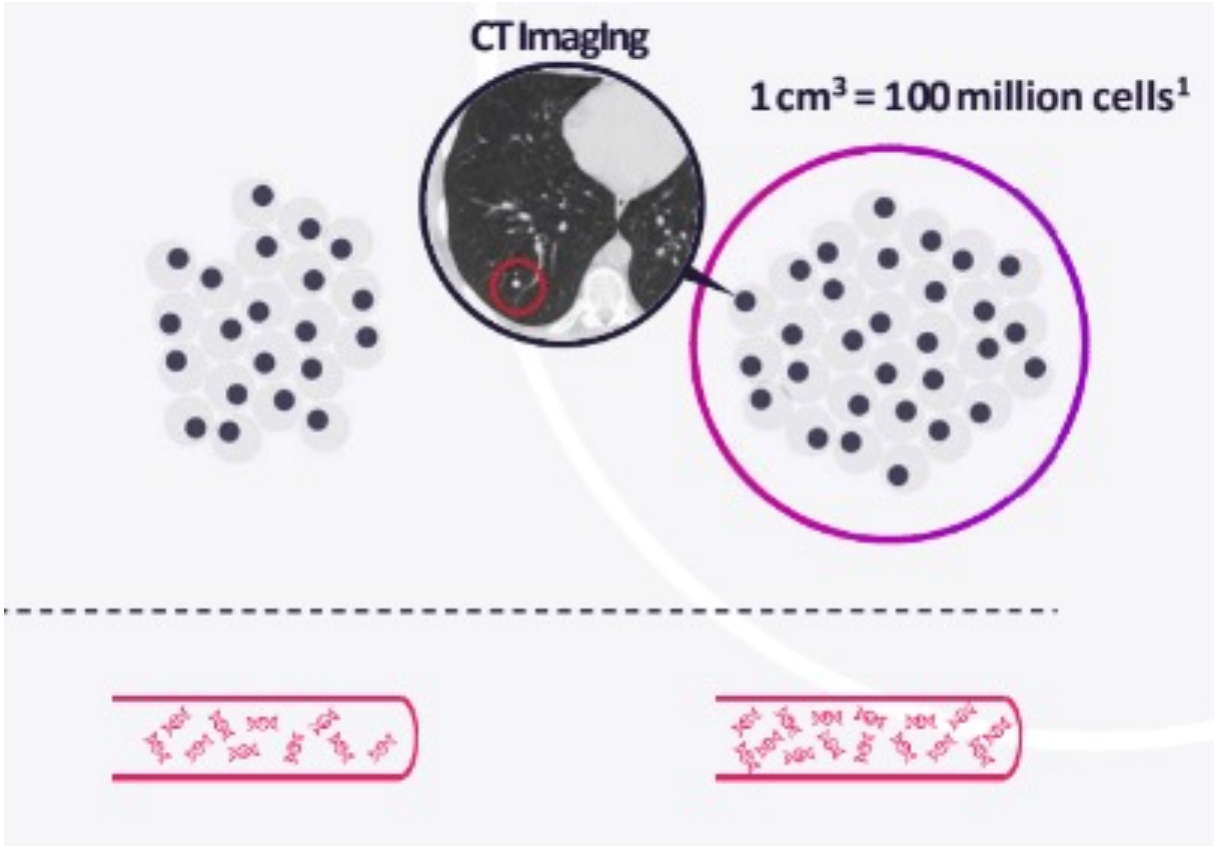


What is ctDNA

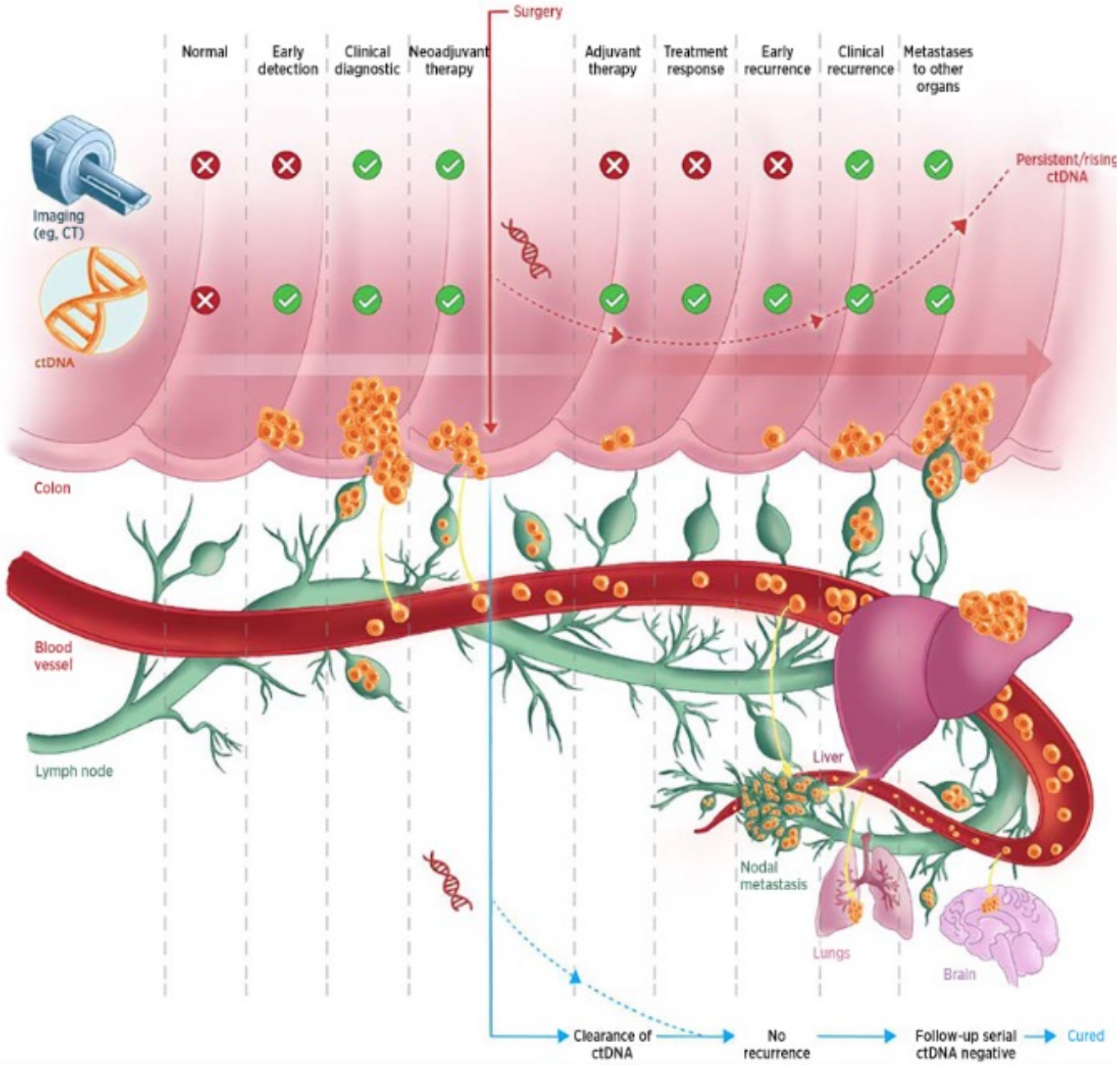


- Small fragments of tumor derived DNA
- Half-life – 2 hours
- Proliferative cancers

Imaging to ctDNA

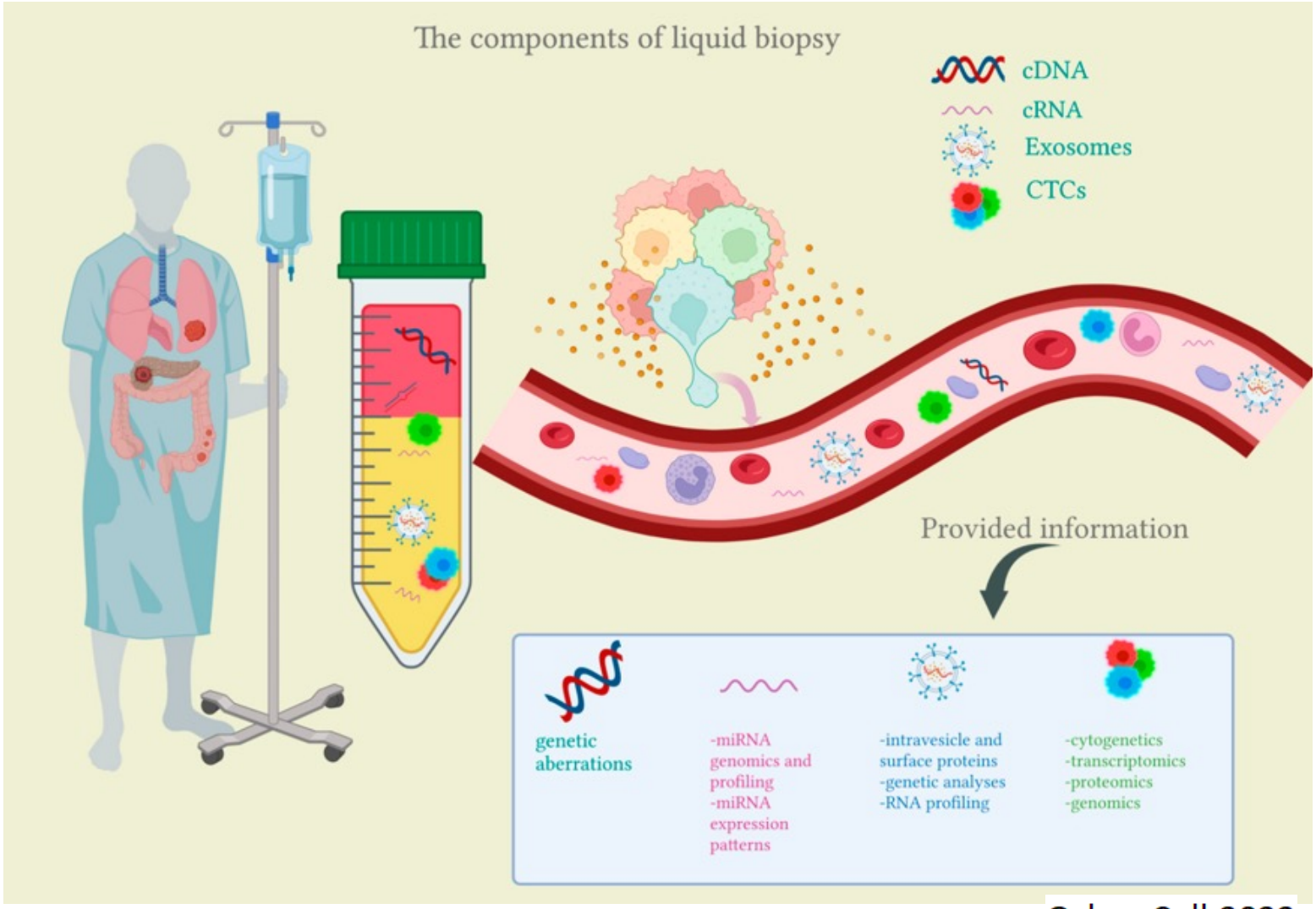


Shields, International Journal of Molecular Sciences 2022



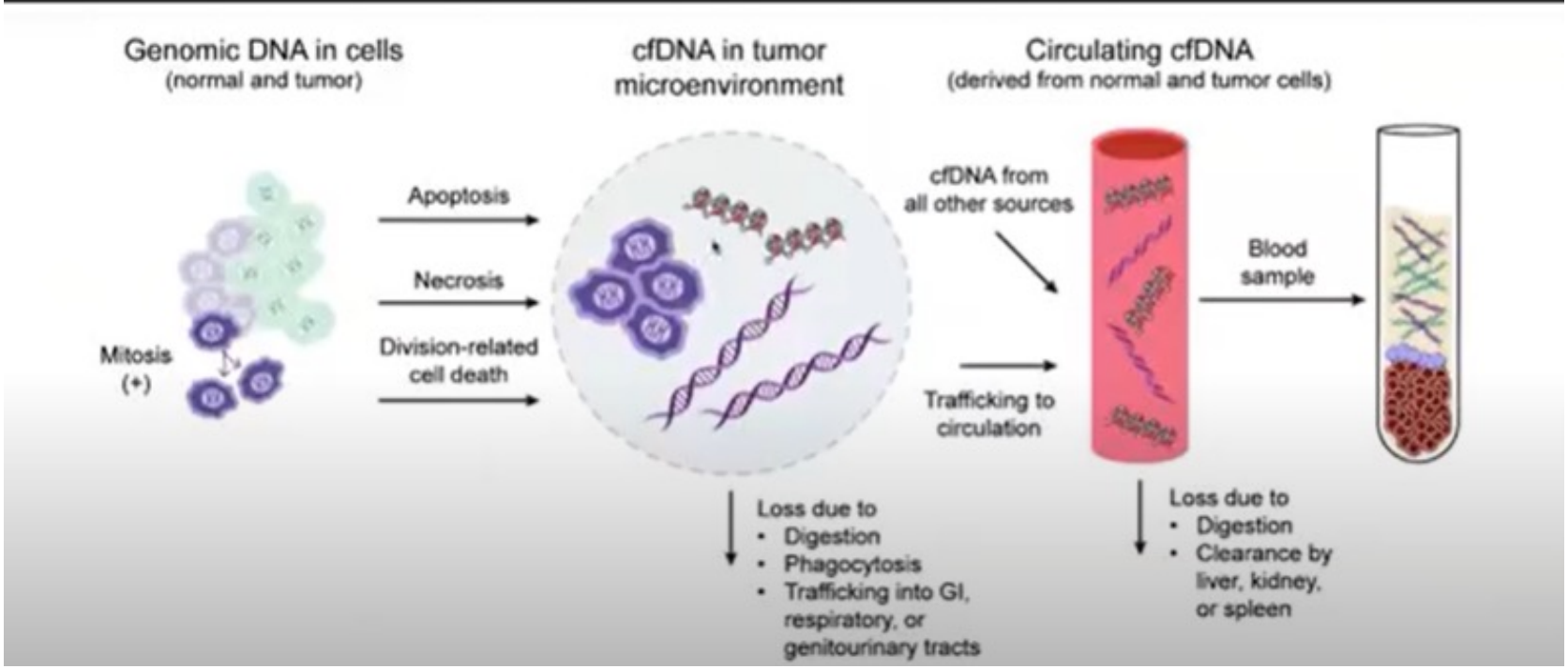
Kasi, ASCO Post 2023

Components of liquid biopsy



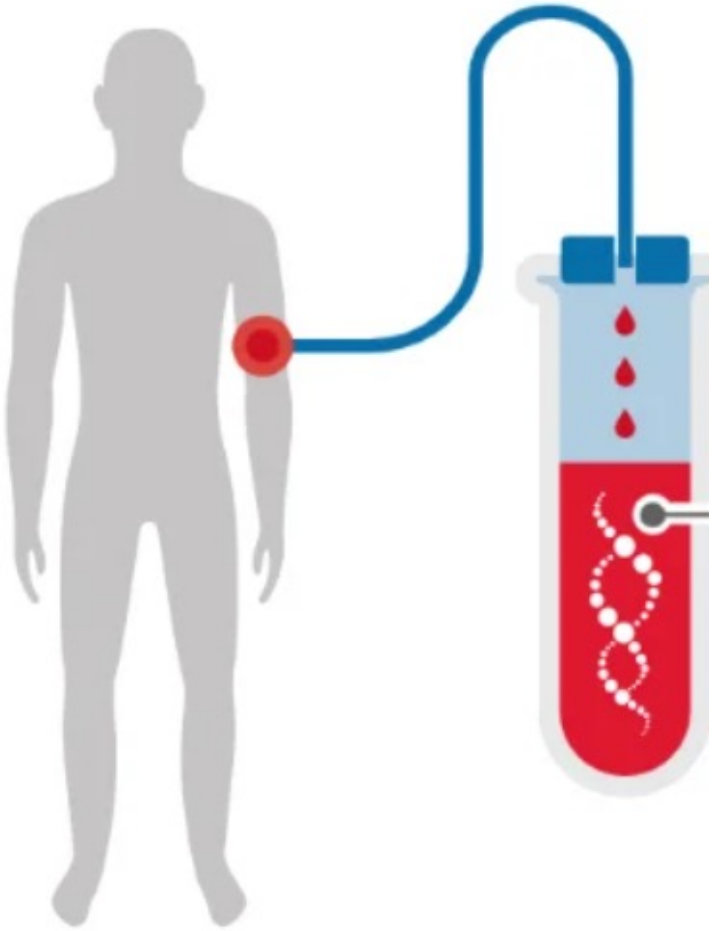
Galos, Cell 2022

Depiction of origin and fates of circulating tumor DNA relative to cell-free DNA

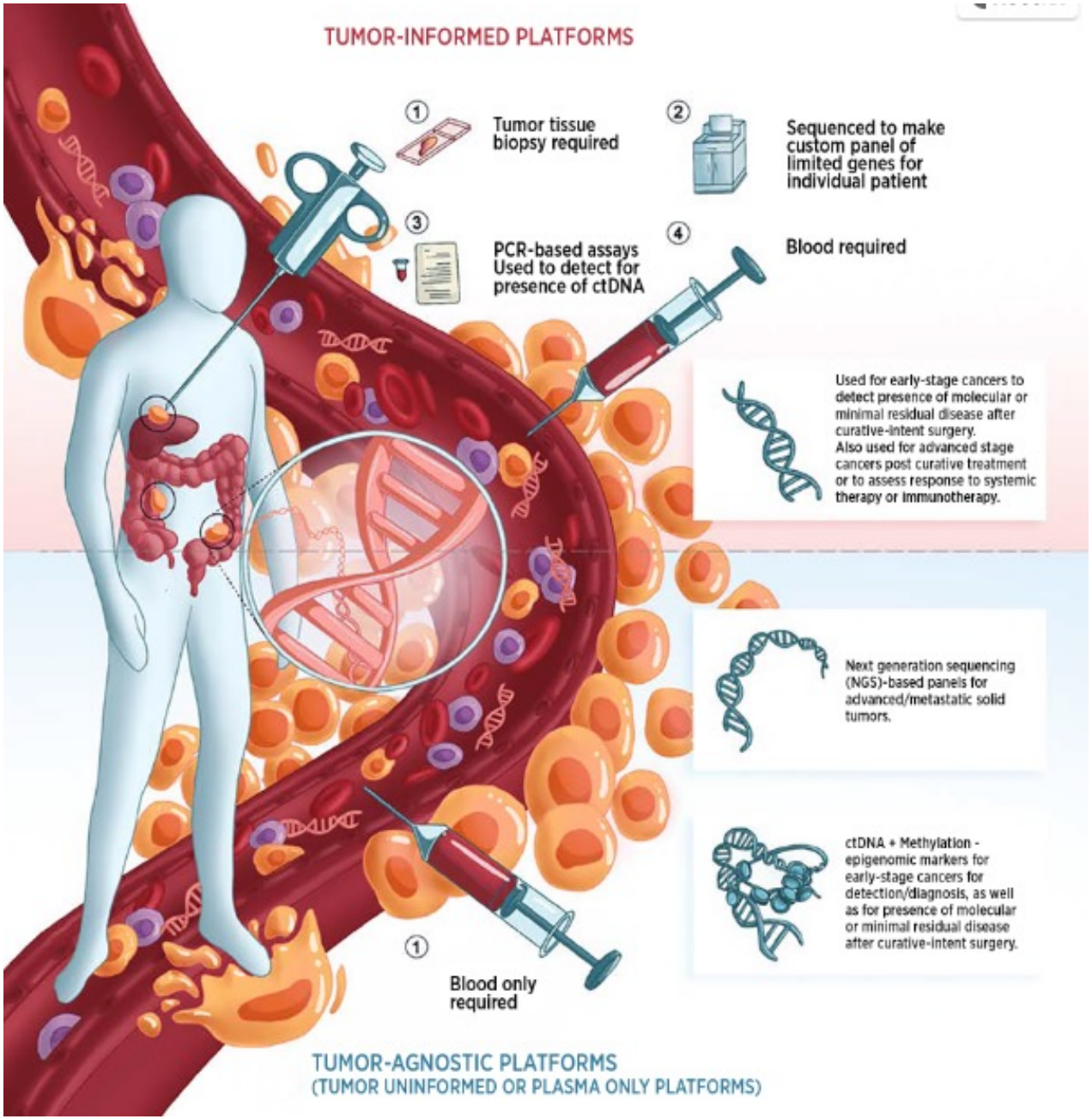


What is included in cell free DNA?

- ctDNA – cancer cells, multiple locations
- Normal cell free DNA from hematopoietic cells (and non-hematopoietic cells)
- Clonal hematopoietic mutations with mutations (CHIP)



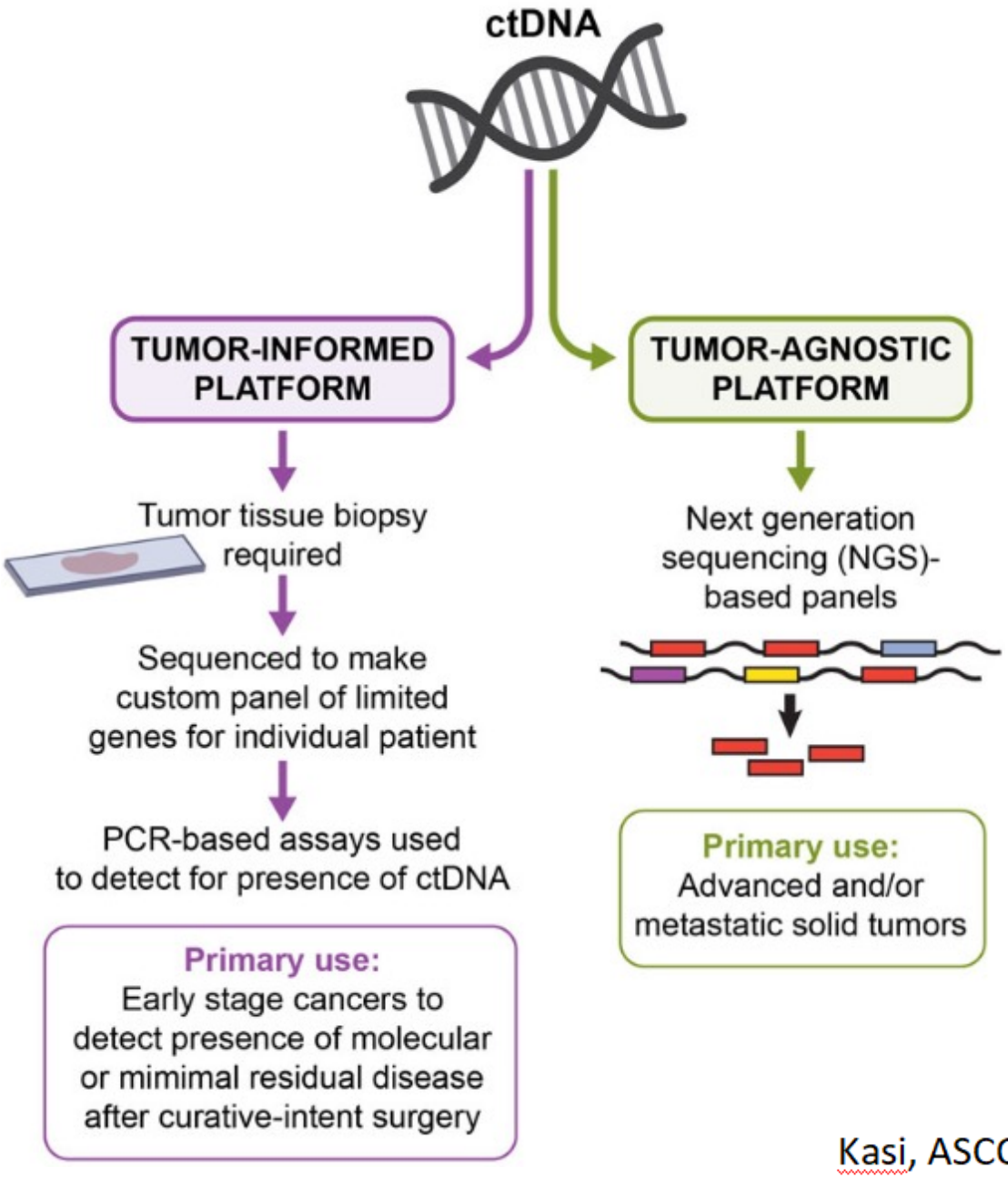
ctDNA Platforms
Tumor informed vs Tumor Agnostic



Kasi, ASCO Post 2022

ctDNA testing Platforms

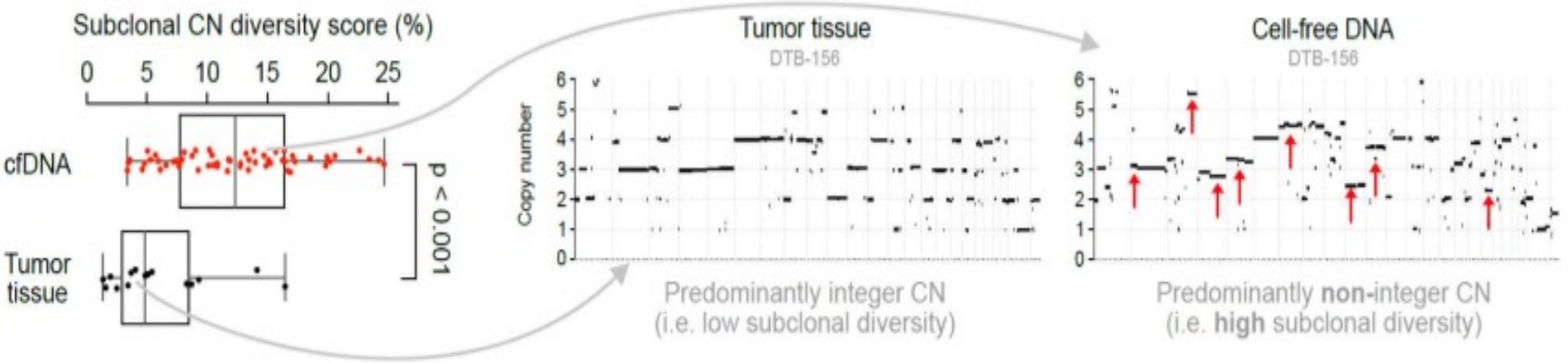
- Tumor Informed
  - Personalized for each cancer patient
  - Tissue biopsy sent to create a "barcode"
  - Liquid biopsy picks up barcode from serial blood tests
  - Example: Bladder Cancer
- Tumor Agnostic
  - ctDNA +Epigenetic markers
  - Methylation signatures
  - Example: Prostate Cancer somatic mutations

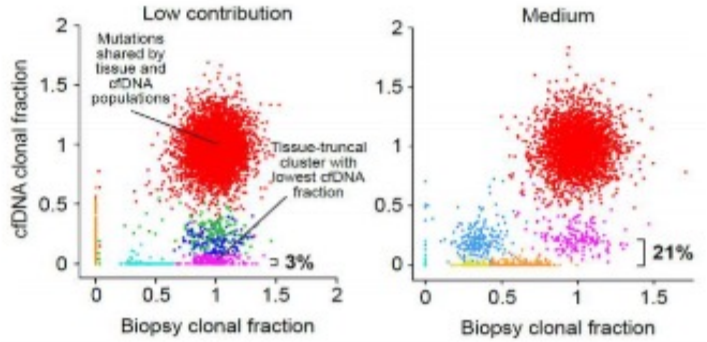


Kasi, ASCO Daily 2020

CHIP Mutation: Cautionary Tale

ctDNA is multiple metastatic foci





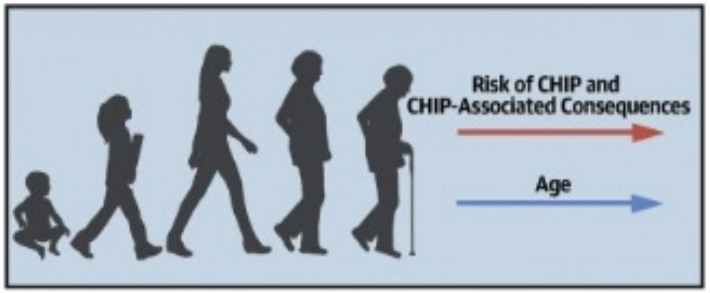
The contribution of individual metastatic foci to total ctDNA is often low

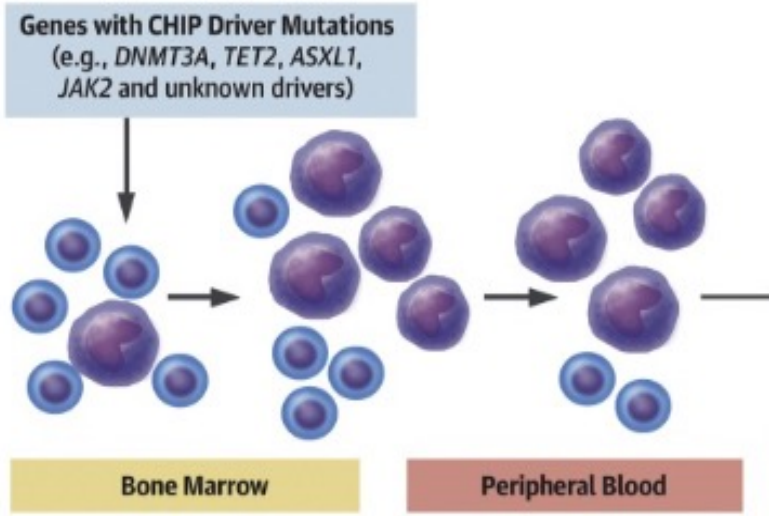
= *ctDNA is derived from multiple metastases*

Herberts, Annala, Sipola, *et al. Nature 2022*

CHIP

- Clonally expanded hematopoietic cells that occur during aging
- Included in liquid biopsies
- Can harbor somatic mutations including ATM, BRCA.





Khetarpal, JACC 2019

JAMA Oncology | Brief Report

Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference

Kendal Jensen, MD, PhD; Eric Q. Konnick, MD; Michael T. Schweizer, MD; Alexandra O. Sokolova, MD; Petros Grivas, MD, PhD; Heather H. Cheng, MD, PhD; Nola M. Klemfuss, MHA; Mallory Beightol, BS, MB; Evan Y. Yu, MD; Peter S. Nelson, MD; Bruce Montgomery, MD; Colin C. Pritchard, MD, PhD

DESIGN, SETTING, AND PARTICIPANTS We report a case series of 69 patients with advanced prostate cancer (metastatic disease or with rising PSA following localized therapy) who had cfDNA variant testing with a large panel cancer next generation sequencing assay (UW-OncoPlexCT). To determine the source of variants in plasma, we tested paired cfDNA and whole blood control samples. The study was carried out in an academic medical center system reference laboratory.

MAIN OUTCOMES AND MEASURES Prevalence and gene spectrum of CHIP interference in patients with prostate cancer undergoing cfDNA testing.

RESULTS We detected CHIP variants at 2% or more variant fraction in cfDNA from 13 of 69 men with prostate cancer (19%; 95% CI, 10%-30%). Seven men (10%; 95% CI, 4%-20%) had CHIP variants in DNA repair genes used to determine PARPi candidacy, including *ATM* (n = 5), *BRCA2* (n = 1), and *CHEK2* (n = 1). Overall, CHIP variants accounted for almost half of the somatic DNA repair gene variants detected. Participant CHIP variants were exponentially correlated with older age (R^2 = 0.82). CHIP interference variants could be distinguished from prostate cancer variants using a paired whole-blood control.

CHIP Mutation

- In case series, up to 10% of patients had CHIP interference used for eligibility of PARP inhibitor.
- Prostate cancer patients are at risk of being misdiagnosed as eligible for PARP therapy.
- Look for liquid biopsy that provide match profiling of WBC as a control

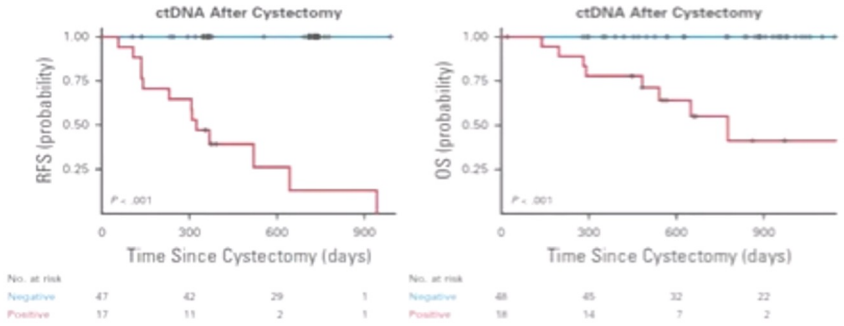
Urothelial Cancer

Residual disease

Detection of ctDNA indicates residual cancer

- Locally advanced bladder cancer (n = 68)
  - Neo-adjuvant chemo → Cystectomy → Surveillance

- ctDNA detection after Cx = imminent relapse; median lead time = 96d

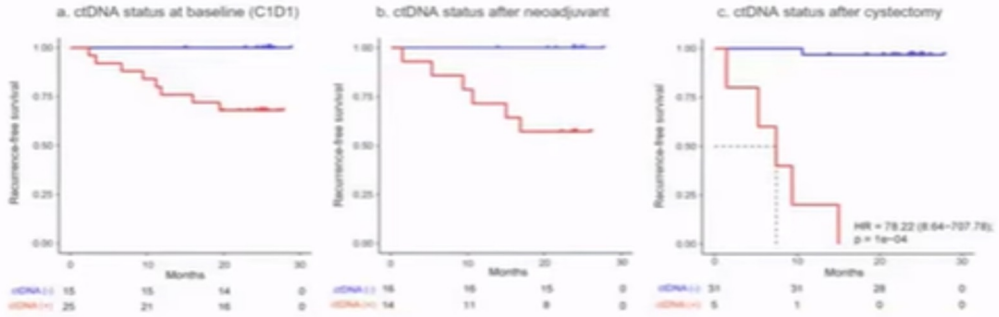


Christensen et al., J Clin Oncol 2019

Abacus study

Detection of ctDNA indicates residual cancer: neoadjuvant setting

- ABACUS phase II of neoadjuvant atezo in MIBC (T2-4aN0M0)
- Presence of ctDNA associated with shorter RFS pre-treatment, after neoadjuvant therapy, and after surgery

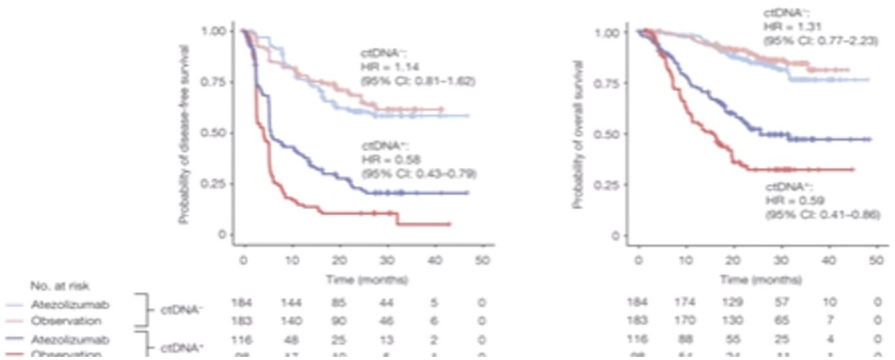


Szabados *et al.*, Eur Urol 2022

IMvigor010

Detection of ctDNA indicates residual cancer: adjuvant setting

- IMvigor010 randomized phase III of atezolizumab versus observation after surgery for MIBC
- Longer disease-free and overall survival for ctDNA-positive patients when treated with atezolizumab



ctDNA to identify patients at increased risk of relapse, who may benefit from adjuvant atezolizumab to treat MRD?

Powles, Nature 2021

ASCO GU 2023

Utility of ctDNA in predicting outcome and pathological complete response in patients with bladder cancer as a guide for selective bladder preservation strategies

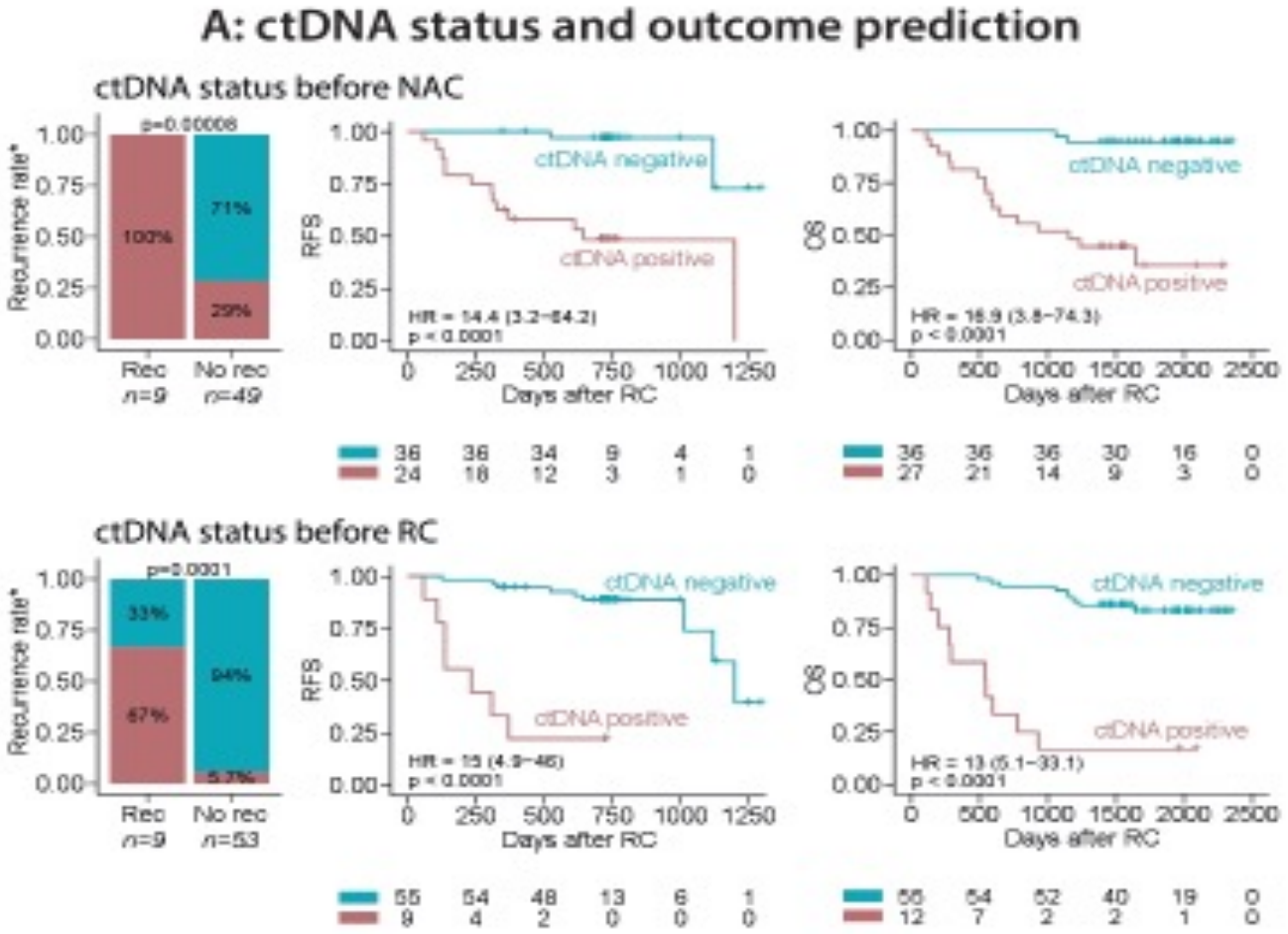
Dyrskjot, ASCO GU 2023

Methods

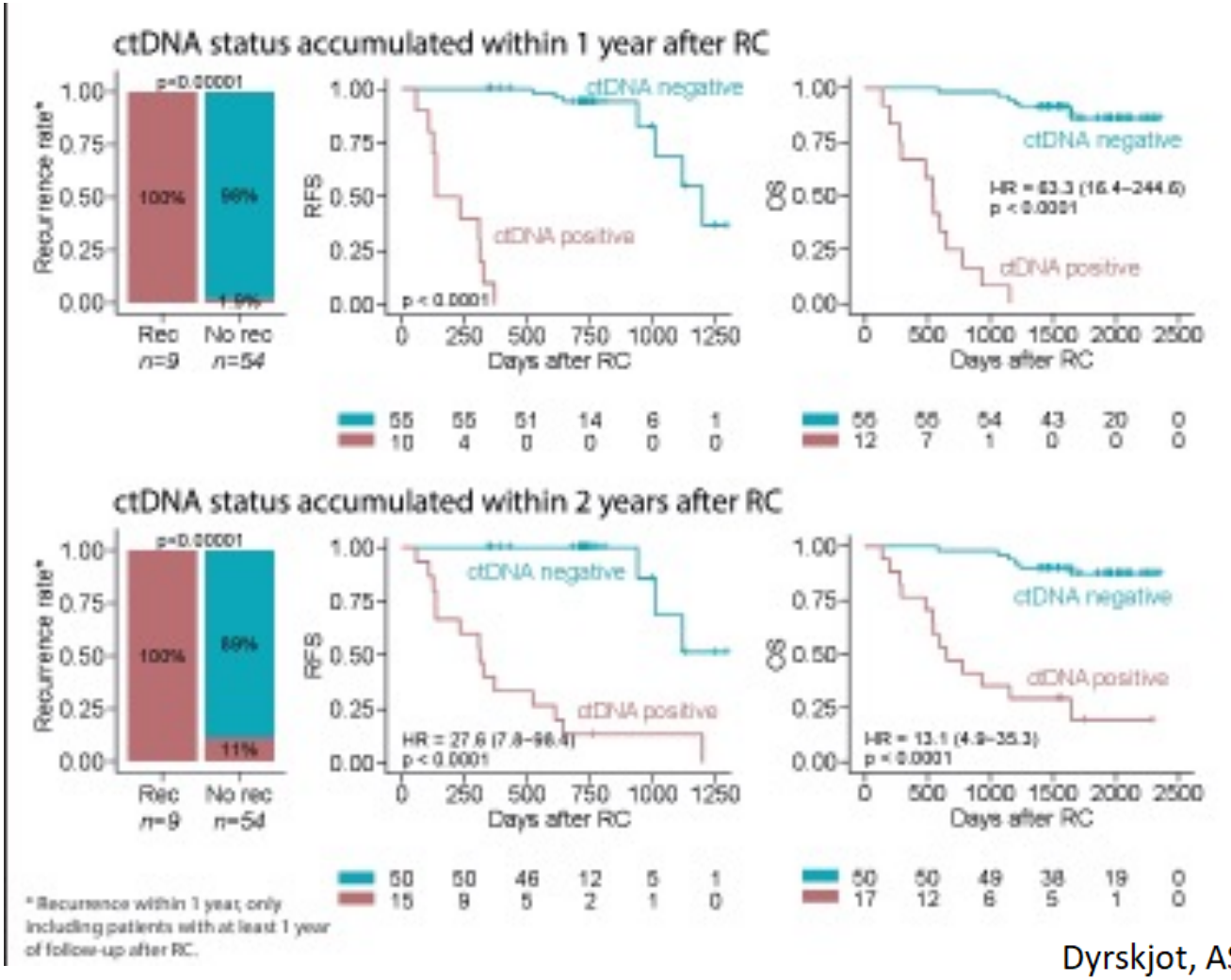
- 68 patients w/ MIBC who received NAC prior to cystectomy.
- Updated median follow-up of 58.94 months (range: 7.19-81.77) post-cystectomy.
- ctDNA was analyzed at baseline (before NAC; N=64), and prior to cystectomy (N=65) using a commercially available assay [redacted] Pathway analysis was used to compare ctDNA-positive and ctDNA-negative patients who failed to achieve pCR.

Dyrskjot, ASCO GU 2023

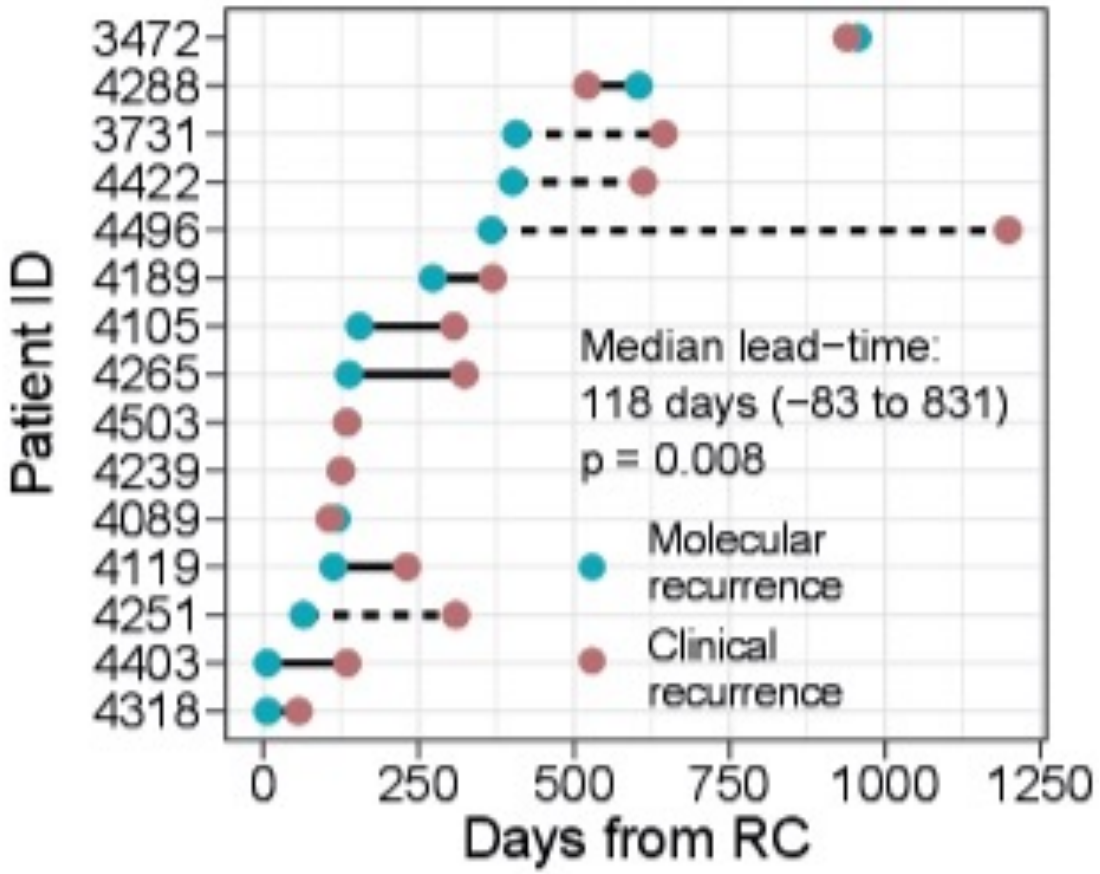
Utility of ctDNA



Dyrskjot, ASCO GU 2023



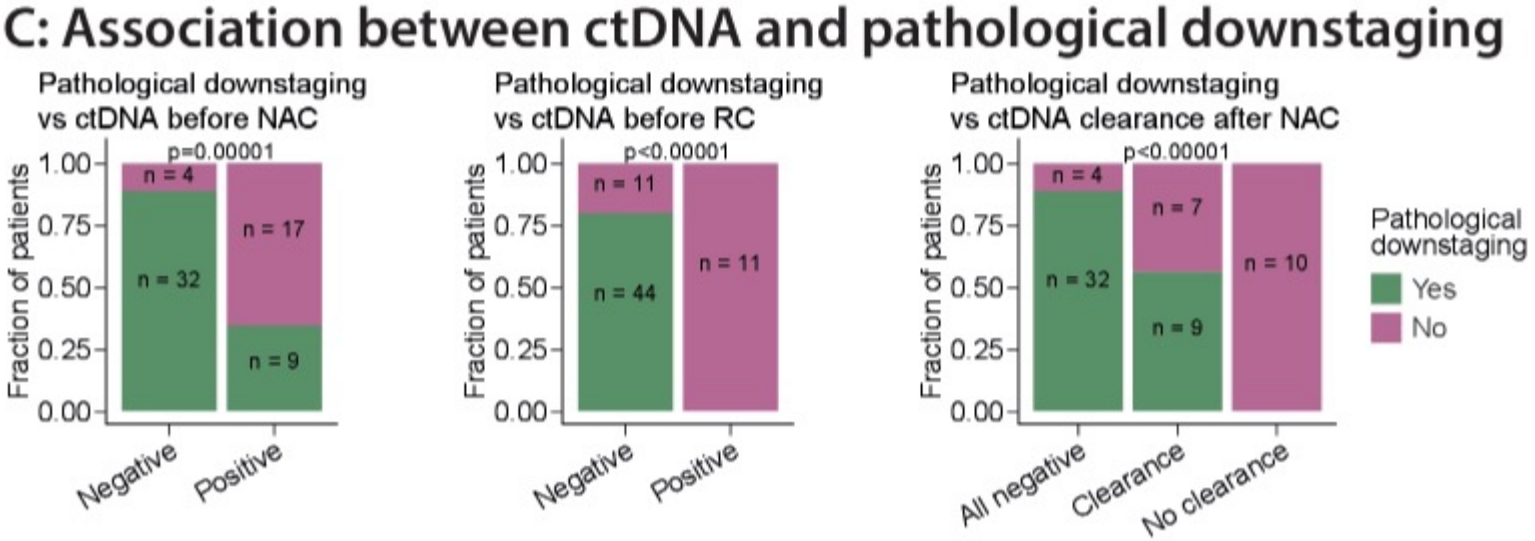
Dyrskjot, ASCO GU 2023



Lead-time in days between molecular recurrence (ctDNA positive) and clinical recurrence (radiographic imaging positive)

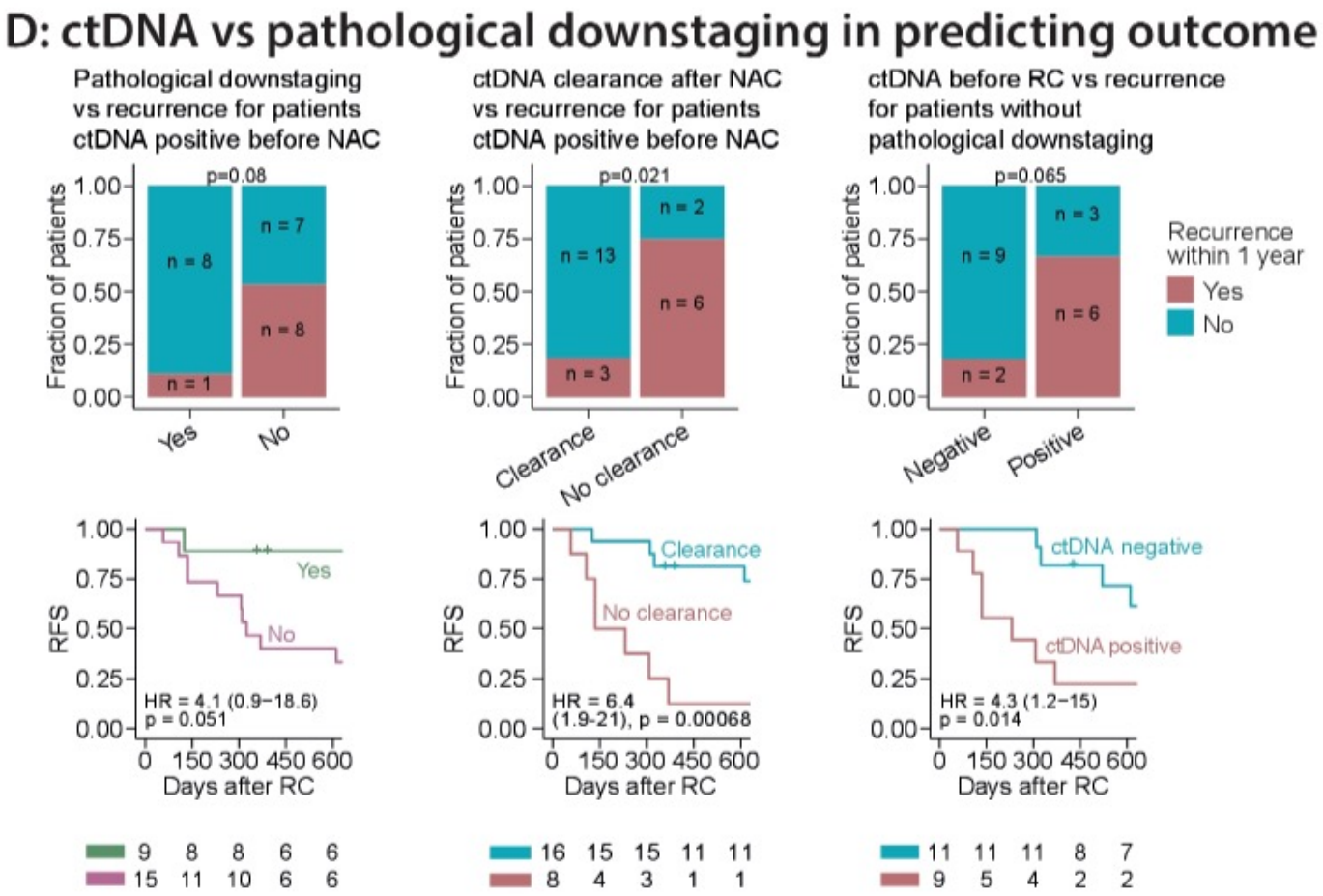
Dyrskjot, ASCO GU 2023

ctDNA and pathology downstaging



Dyrskjot, ASCO GU 2023

Outcomes



Dyrskjot, ASCO GU 2023

Results

- 64 patients with ctDNA results available at baseline, 59.4% (38/64) tested ctDNA-negative, and of these 84.2% (32/38) achieved pCR.
- Furthermore, 40.6% (26/64) tested ctDNA-positive, and only 34.6% (9/26) achieved pCR.
- Prior to cystectomy, 83.9% (52/62) of patients were ctDNA-negative, and 80.7% (42/52) achieved pCR, while none of the ctDNA-positive patients achieved pCR (positive predictive value 100%; negative predictive value 80.8%).

Results

- Probability of ctDNA-negative patients to achieve pCR was significantly higher than ctDNA-positive patients ($p<0.0001$).
- Notably, ctDNA-positive patients without pCR demonstrated significantly poorer RFS and OS compared to the ctDNA-negative patients,
- Prior to cystectomy: RFS; HR=5.2, $p=0.0078$, OS; HR=4.8, $p=0.012$).
- ctDNA status at baseline and before cystectomy was a better predictor of RFS compared to pCR (HR=8.5, $p<0.0001$, HR=14, $p<0.0001$, respectively).

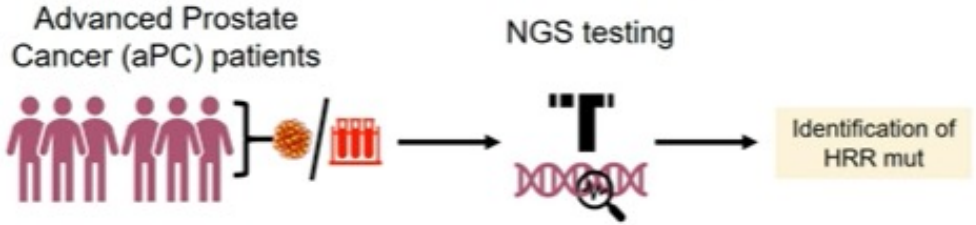
Conclusion

- Absence of ctDNA was significantly associated with pCR both at baseline and prior to cystectomy
- Larger cohorts are warranted to test the prognostic value of ctDNA for patient selection for avoiding cystectomy

Prostate Cancer

HRR mutation concordance between liquid biopsy and tissue

Homologous Recombination Repair (HRR) mutation concordance as a tool in prostate cancer (PC) testing



In a large real-world (RW) database, we determined:

- **Concordance** between plasma ctDNA and primary tumor tissue (PT) and/or metastatic tissue (MT)

  Genes of interest – *BRCA1*, *BRCA2*, and *ATM*

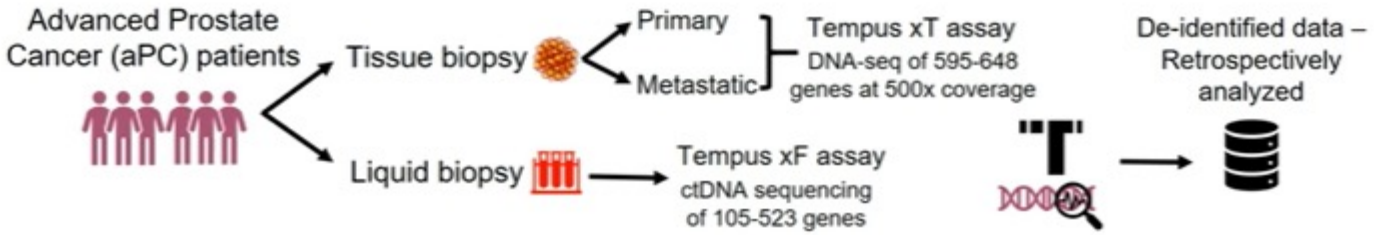
  Patient cohort – Prostate Cancer patients who received both LB and tissue NGS any time during standard of care (SOC) management

- The **utility of LB** to detect **actionable mut** in these **HRR genes** and demonstrate the utility of combined LB and tissue testing

Shen, ASCO GU 2023

Methodology

Methodology adopted to evaluate Homologous Recombination Repair (HRR) mutation concordance



- Paired analysis from Primary Tumor (PT), Metastatic Tumor (MT) and Liquid Biopsy (LB) of patients
- The prevalence of a germline and/or somatic mut in *BRCA1*, *BRCA2*, or *ATM* was reported
- The sensitivity of the LB to identify observed HRR mut in tissue was also reported
- Concordance between pairs was evaluated by Cohen's kappa statistic with 95% CI.

Shen, ASCO GU 2023

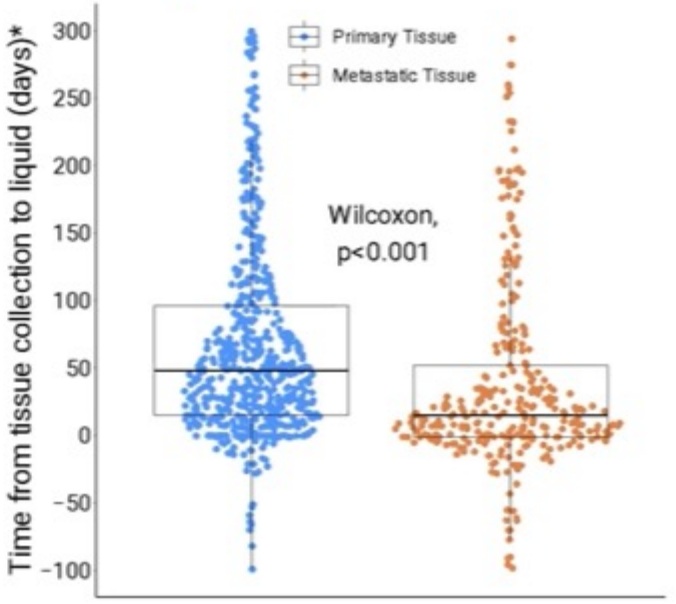
Demographic

Time from tissue collection to liquid was significantly shorter in MT vs LB analyses compared to PT vs LB

Characteristic	PT vs LB, N = 1074[1]	MT vs LB, N = 451[1]
Age at Diagnosis	66 (60, 72)	64 (58, 72)
Unknown	3	12
Race		
White	434 (69%)	197 (70%)
Black or African American	147 (23%)	54 (19%)
Other	27 (4.3%)	20 (7.1%)
Asian	24 (3.8%)	12 (4.2%)
Unknown	442	168
Ethnicity		
Hispanic or Latino	80 (19%)	40 (25%)
Unknown	648	291
Match Type		
tumor/normal match	975 (91%)	403 (89%)
tumor only	99 (9.2%)	48 (11%)
HRR+, tissue (PT/MT)	94 (8.8%)	46 (10%)
HRR+, liquid (LB)	67 (6.2%)	47 (10%)

1 Median (IQR), n (%)

Demographic characteristics of the patient cohort analyzed



*y-axis truncated at 300 and -100

Median: PT vs LB – 174 days, MT vs LB – 21 days

ASCO Genitourinary Cancers Symposium #GU23

PRESENTED BY: John Shen, MD

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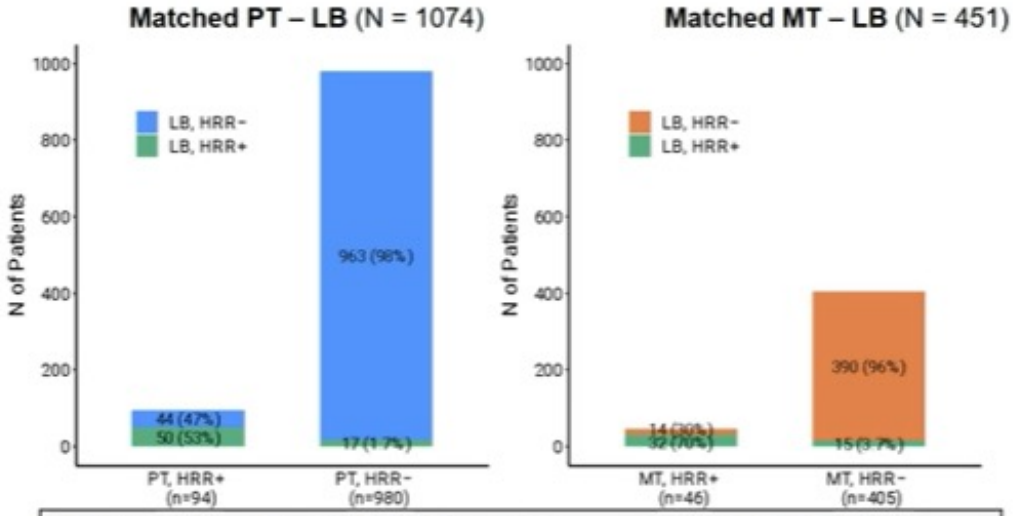
KNOWLEDGE CONQUERS CANCER

Shen, ASCO GU 2023

Results

Agreement of HRR detection between tissue and liquid



Characteristic	Matched PT - LB[1], N = 1074	Matched MT - LB[1], N = 451
Sensitivity	53% (43%-64%)	70% (54%-82%)
Specificity	98% (97%-99%)	96% (94%-98%)
+Predictive Value	75% (63%-84%)	68% (53%-81%)
- Predictive Value	96% (94%-97%)	97% (94%-98%)
Cohen's Kappa	0.59 (0.50 – 0.68)	0.65 (0.54 – 0.77)

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1statistic (95% C.I)

ASCO Genitourinary Cancers Symposium

ASCO American Society of Clinical Oncology — Knowledge Conquers Cancer

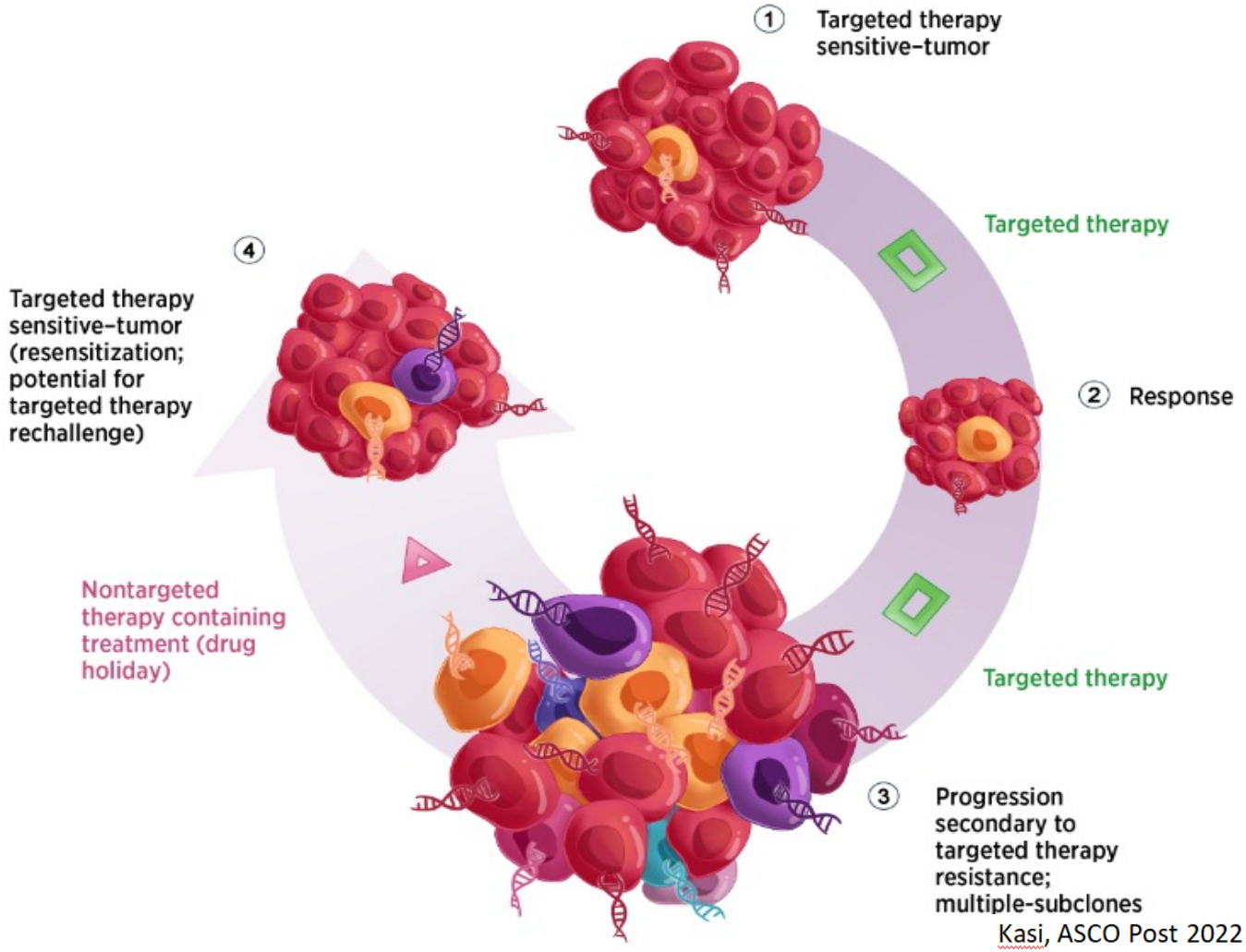
Shen, ASCO GU 2023

Conclusion

- Blood ctDNA from study showed BRCA1, BRCA2, and ATM somatic mutations showed greater concordance with liquid biopsy and metastatic tissue
- Liquid biopsy identifies up to 70% of mutations in metastatic tissue
- Negative liquid biopsy result could be non diagnostic (rather than a TRUE negative)
- Consider tissue biopsy

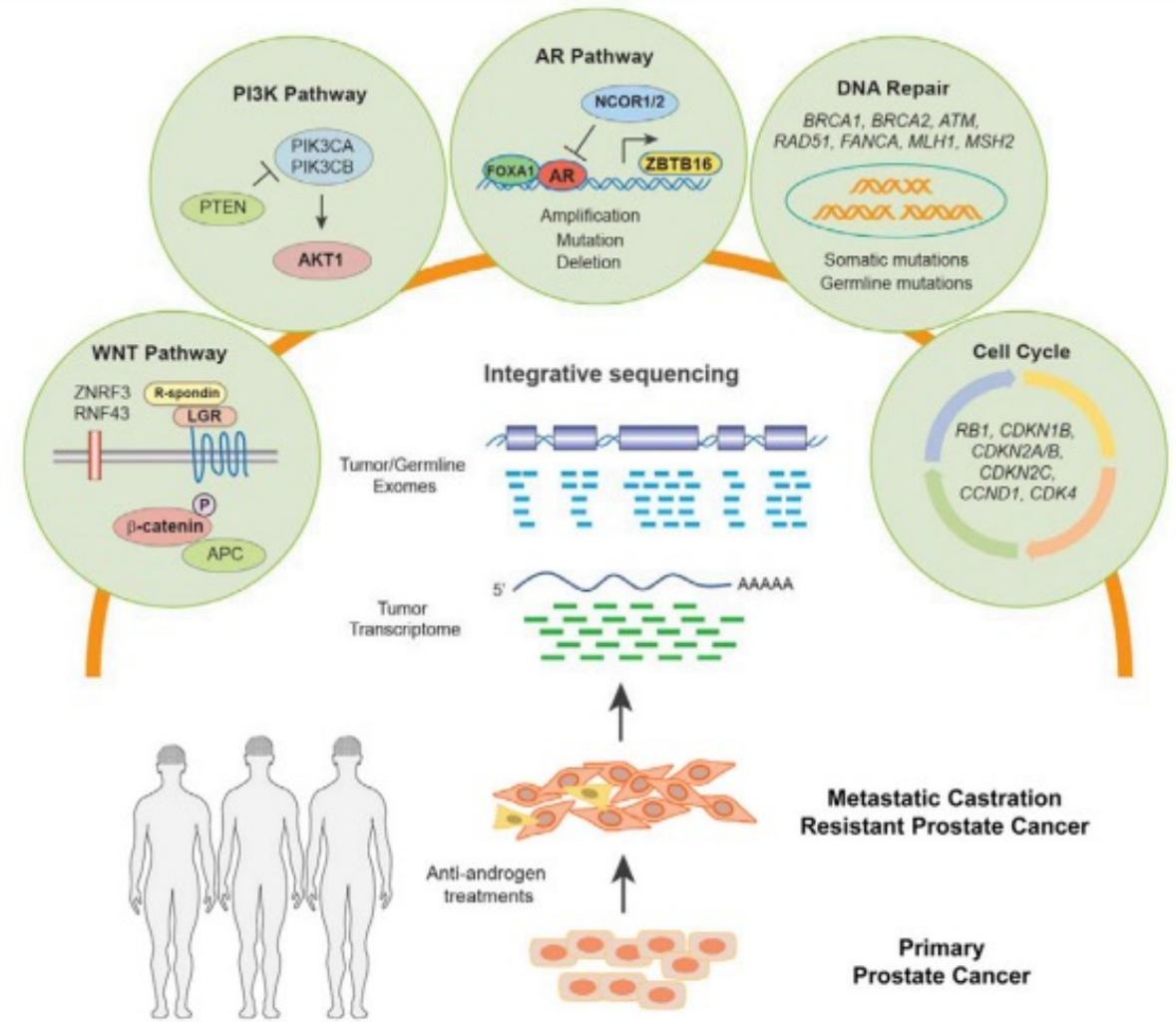
Research questions for the future

Recycle Treatments?



Kasi, ASCO Post 2022

Alpelisib? Capivasertib? Abemaciclib? Platinum Doublet? PARP inhibitor?



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