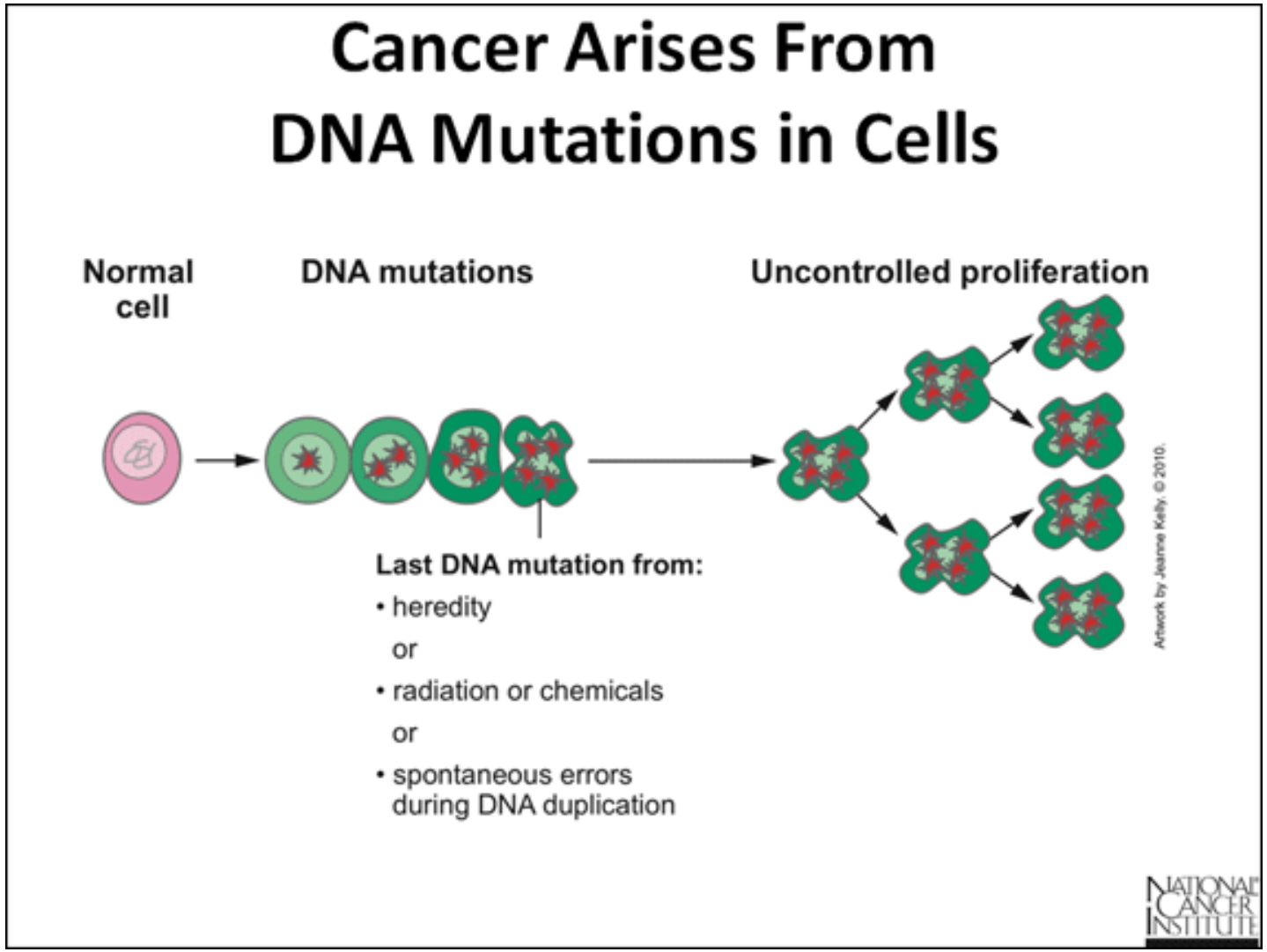
Researching a Personalized Approach to Treating Men with Prostate Cancer

Gillian Vandekerkhove

PhD Candidate

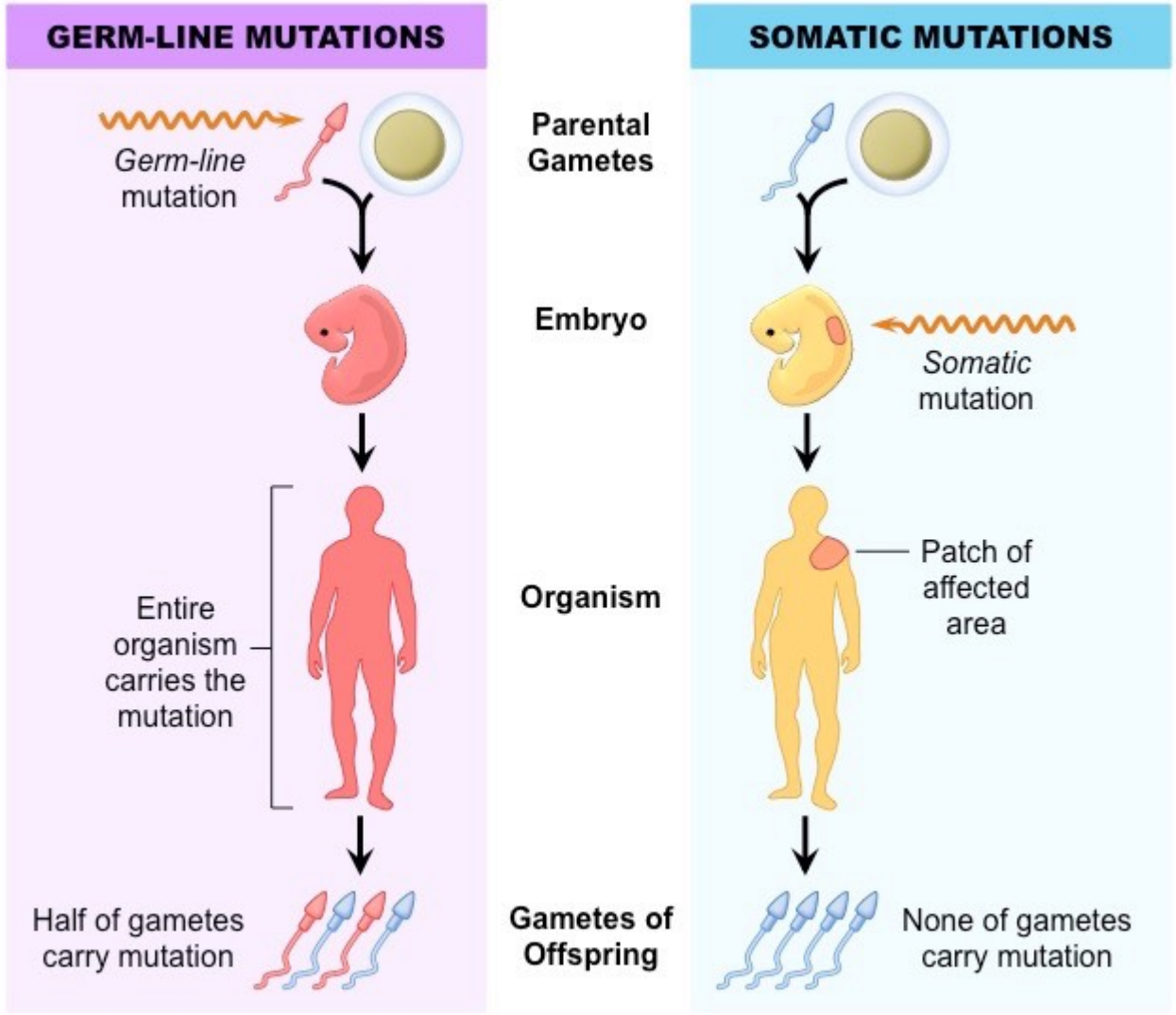
Vancouver Prostate Centre | UBC Experimental Medicine

The role of DNA mutation in cancer



Types of mutation: germline & somatic

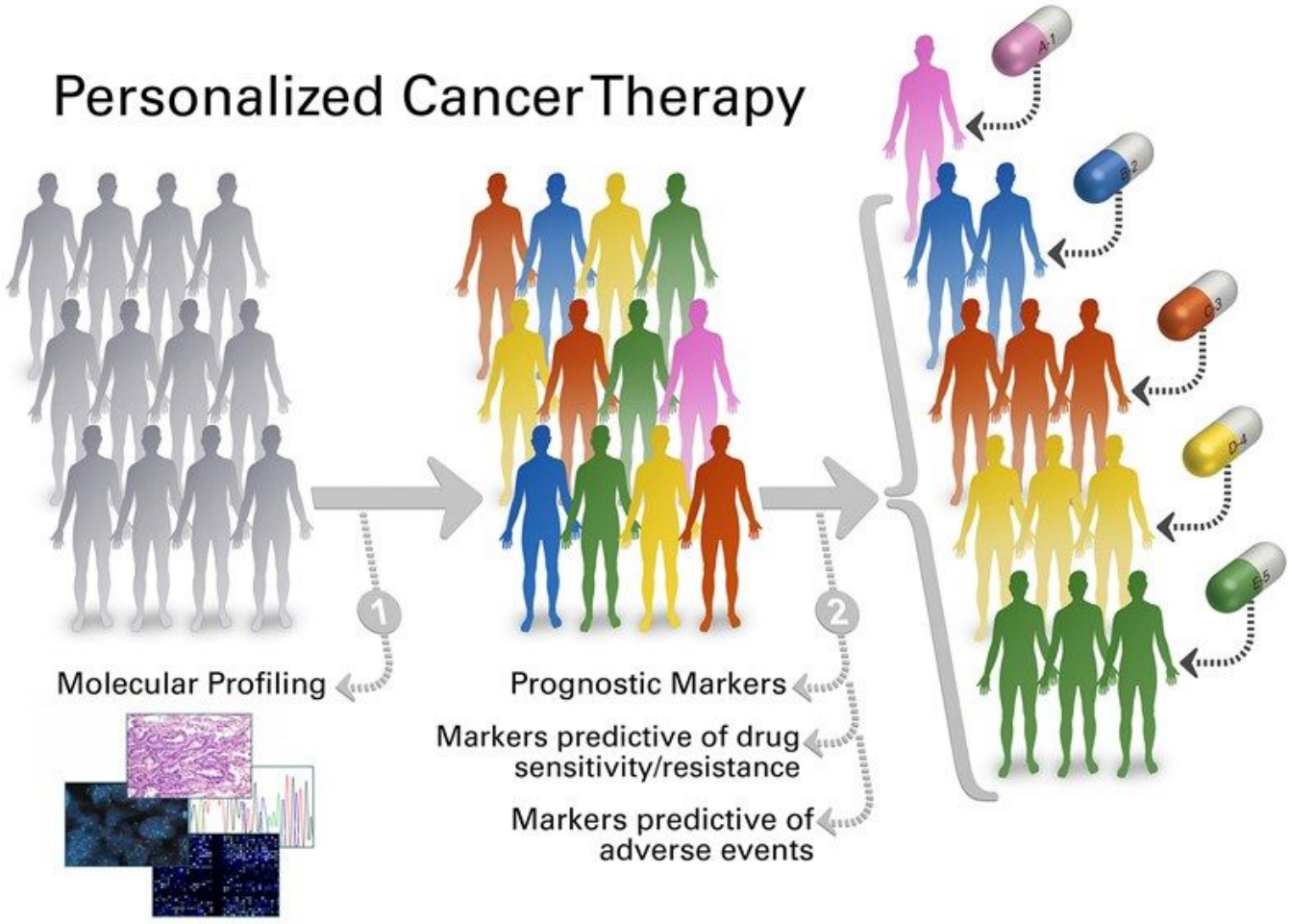
- **Germline mutations** are inherited and predispose to cancer (e.g. BRCA)
- **Somatic mutations** are acquired during life and cannot be passed on to children
- Germline mutations are important in prostate cancer!
  - Primary relatives of men with PC have two-fold risk of developing PC
  - Risk is higher in early onset cancers



Mutations in prostate cancer

- The mutations driving each cancer are different!
  - Cancer to cancer type
  - Patient to patient

- Targeted therapies require the ‘target’ mutation to be present



Treatment of metastatic prostate cancer

Localized prostate cancer recurrence

Metastatic at diagnosis

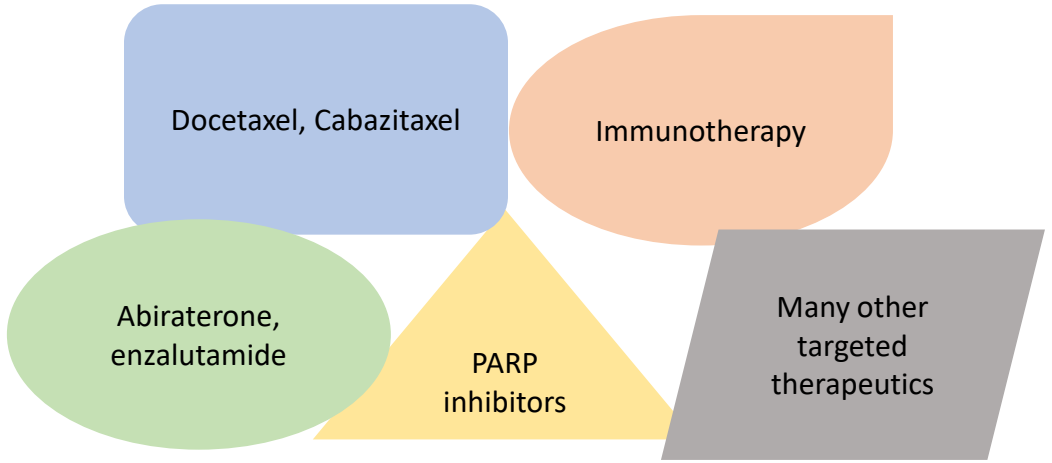
Metastatic prostate cancer

Androgen deprivation therapy & combinations

Metastatic castration-resistant prostate cancer

Standard therapies

Experimental therapies



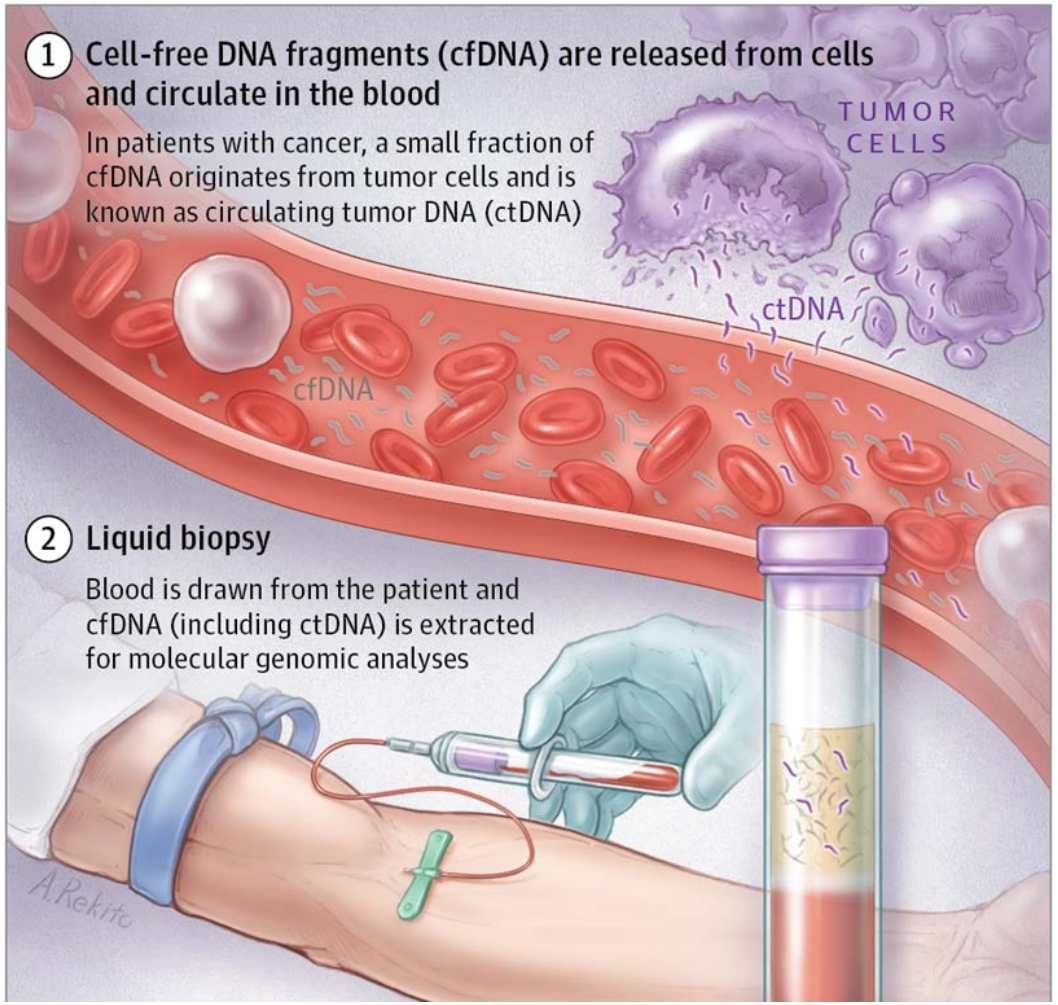
Biomarkers can help guide treatment

- What is a biomarker?
  - A biological molecule (i.e. protein, DNA) found in blood, other body fluids, or tissues
  - May be used to see how well the body responds to a treatment for a disease or condition
  - *Example:* prostate-specific antigen (PSA) levels in the blood are used for prostate cancer screening/diagnosis

- Biomarkers help determine which therapy to give a patient, and when, to optimize treatment

Biomarker sources in metastatic prostate cancer

- Diagnostic biopsy tissue may not reflect *current* tumor
- Metastatic tissue biopsy is not routine
- Plasma cell-free DNA offers an alternative
  - Minimally-invasive
  - Source of tumor material to study DNA mutations



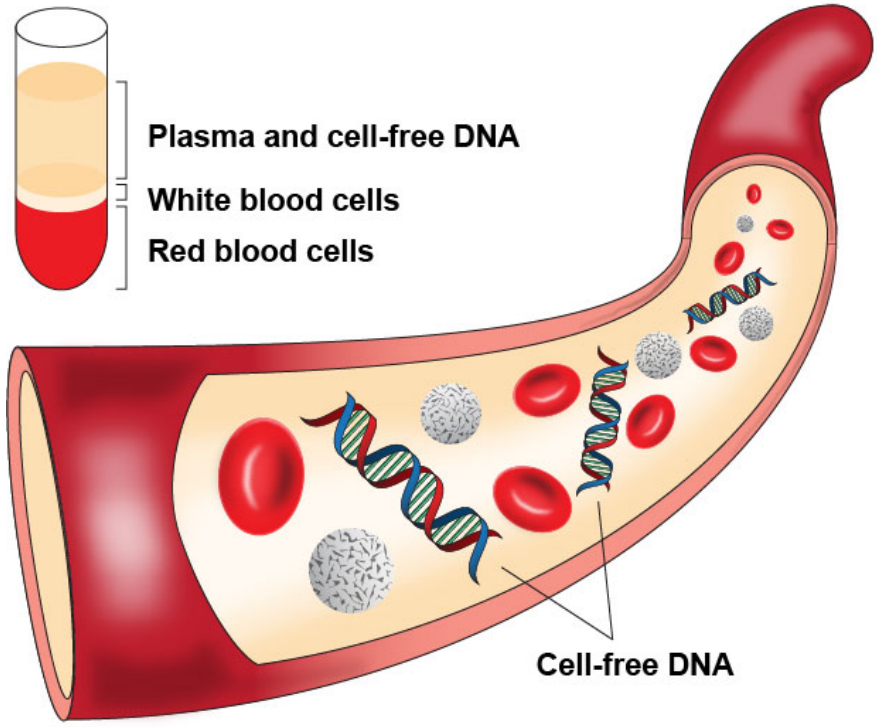
Husain and Velculescu, JAMA 2017; 318:1272-1274

Cell-free DNA (cfDNA) is present in everyone's circulating bloodstream

- DNA is released by cells into the bloodstream
- Increased cfDNA is observed in cancer patients vs. healthy controls

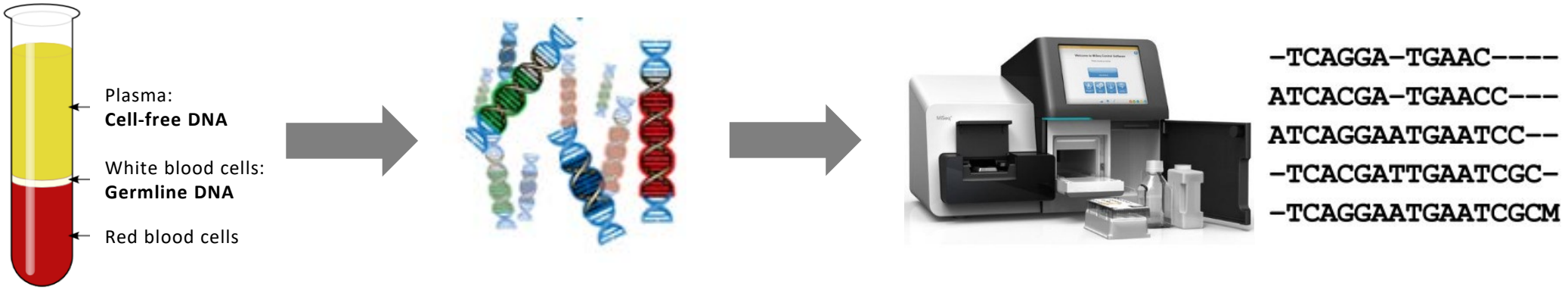
	Amount of cfDNA in 1mL of blood plasma	**DNA Copies** in 1mL of blood plasma
Average healthy person	5-10 ng	750-1500
Prostate cancer patient	Average 20 ng	3000

- A portion of total cfDNA is tumor-derived (circulating tumor DNA)



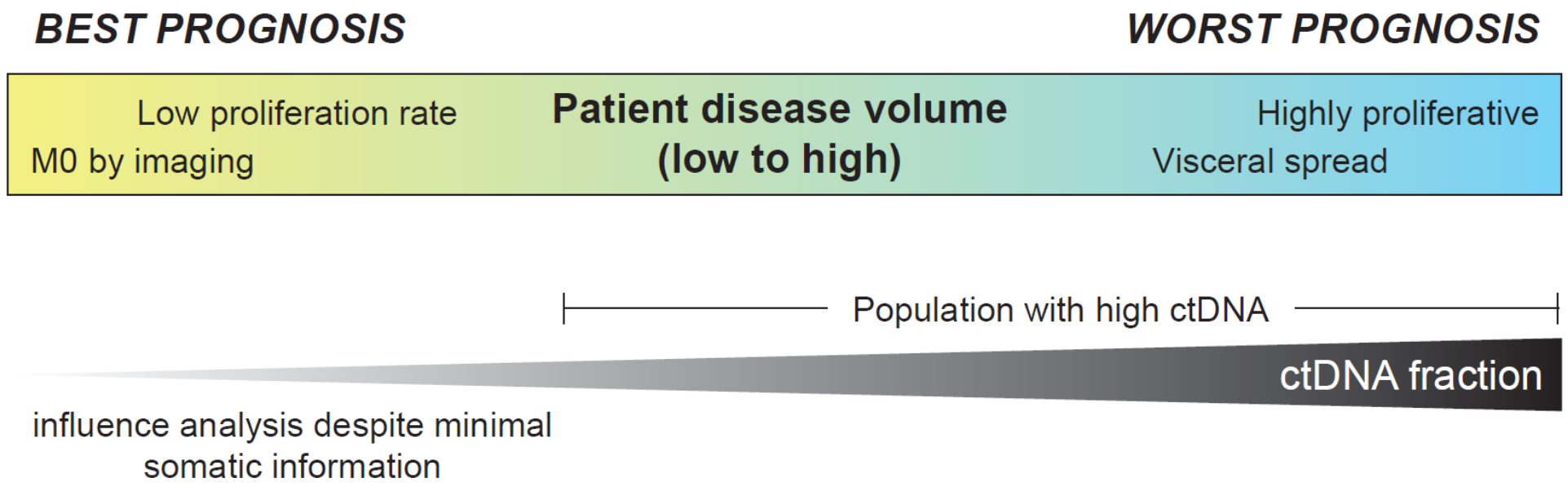
Cell-free DNA (cfDNA) sequencing reveals tumor mutations

- A portion of total cfDNA is tumor-derived (circulating tumor DNA, ctDNA)
- Germline DNA and cfDNA are sequenced separately
  - Identify germline (inherited) mutations
  - Identify mutations in circulating tumor DNA



Circulating tumor DNA (ctDNA) is abundant in men with metastatic prostate cancer

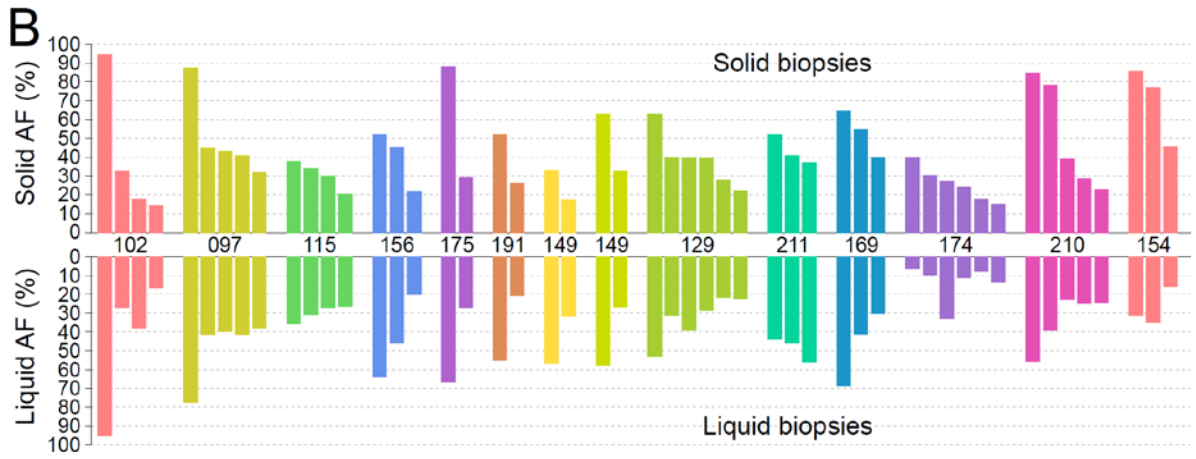
- However, amount of ctDNA is highly variable (undetectable to >80% of total cell-free DNA)



Wyatt *et al*., JAMA Oncology 2016; Warner *et al*., BJUI 2018

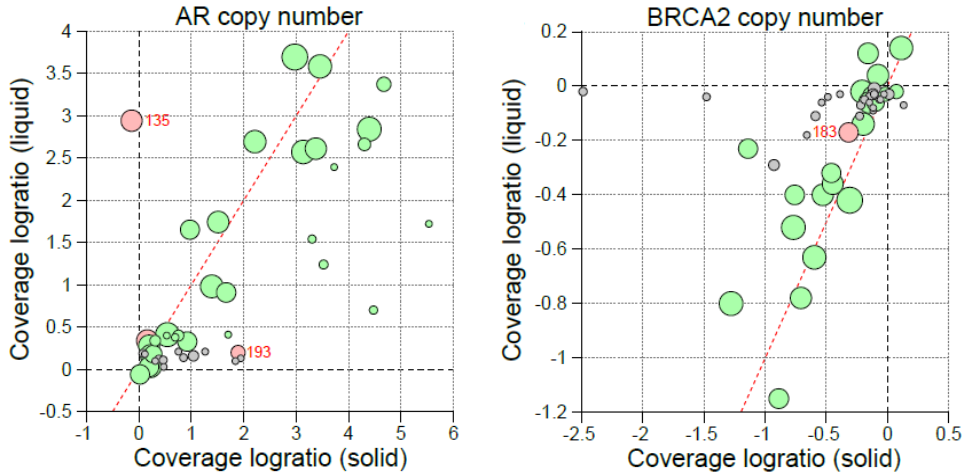
Mutations are concordant between ctDNA and matched metastatic tissue biopsy

- Study lead by Dr. Wyatt examined liquid and solid biopsy pairs from 45 men with metastatic prostate cancer



Similar mutation profiles, ctDNA vs tissue

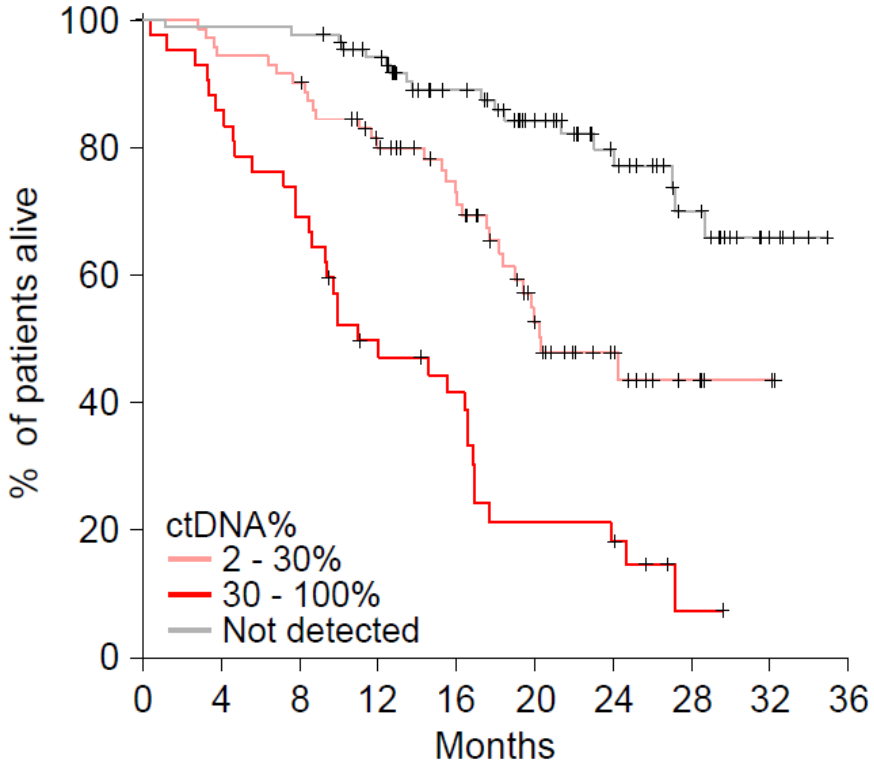
Similar gene copy numbers, ctDNA vs tissue



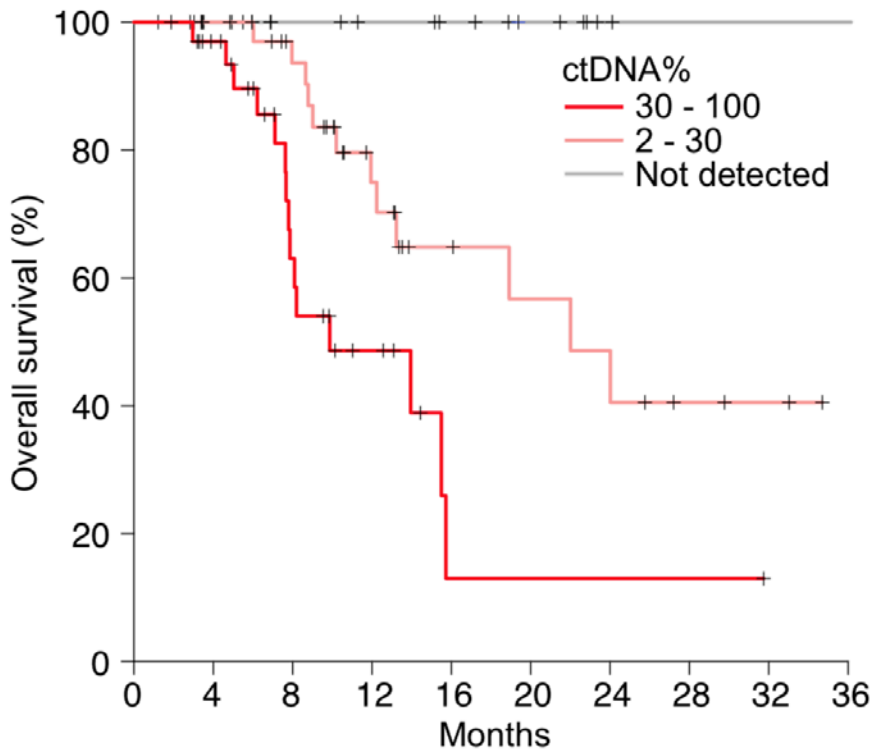
Wyatt, Annala, *et al.*, J Natl Cancer Inst. 2017

ctDNA abundance as a prognostic biomarker

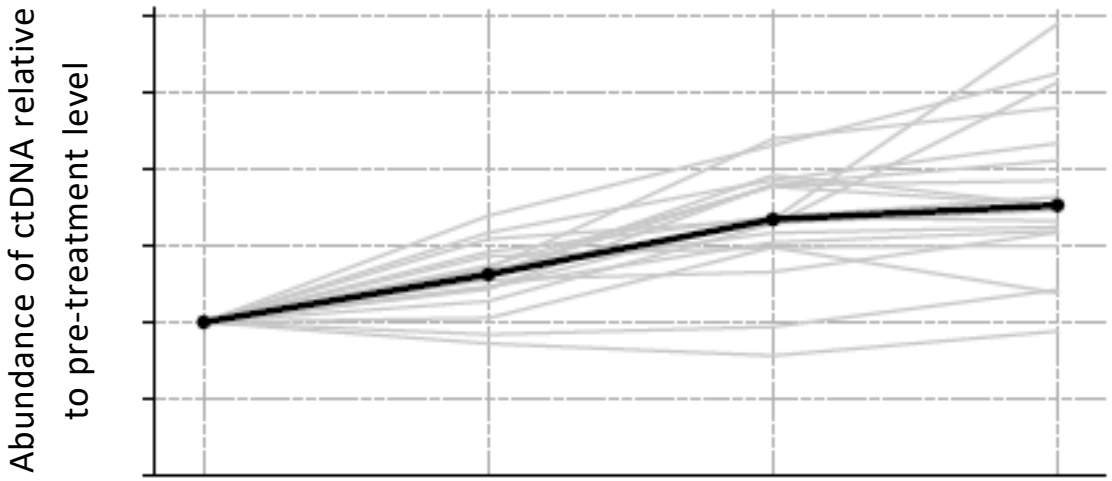
First line mCRPC general population (n = 202)
Khalaf et al., ASCO 2018



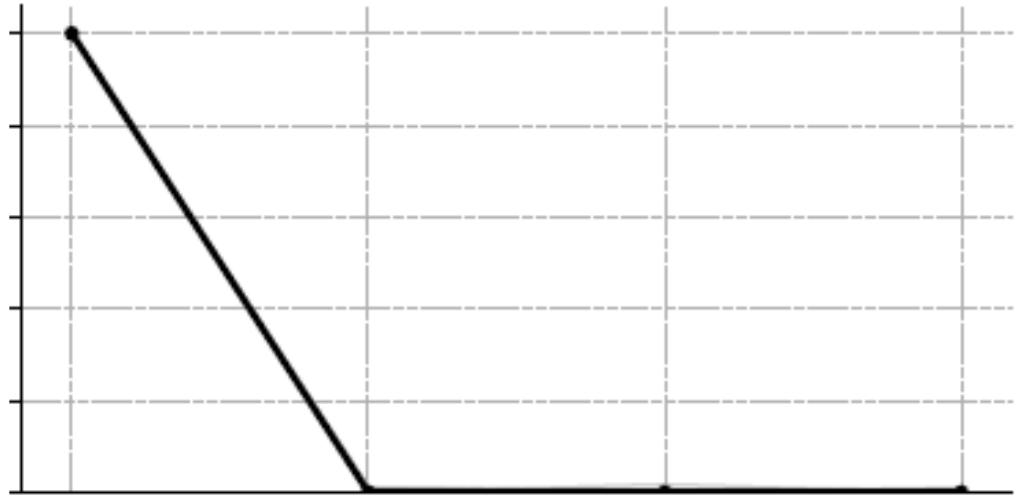
First line mCRPC poor prognosis (n = 95)
Chi et al., ESMO 2018



Monitoring ctDNA levels to predict response to therapy



ctDNA levels increase at each collection
– patient did not respond to therapy

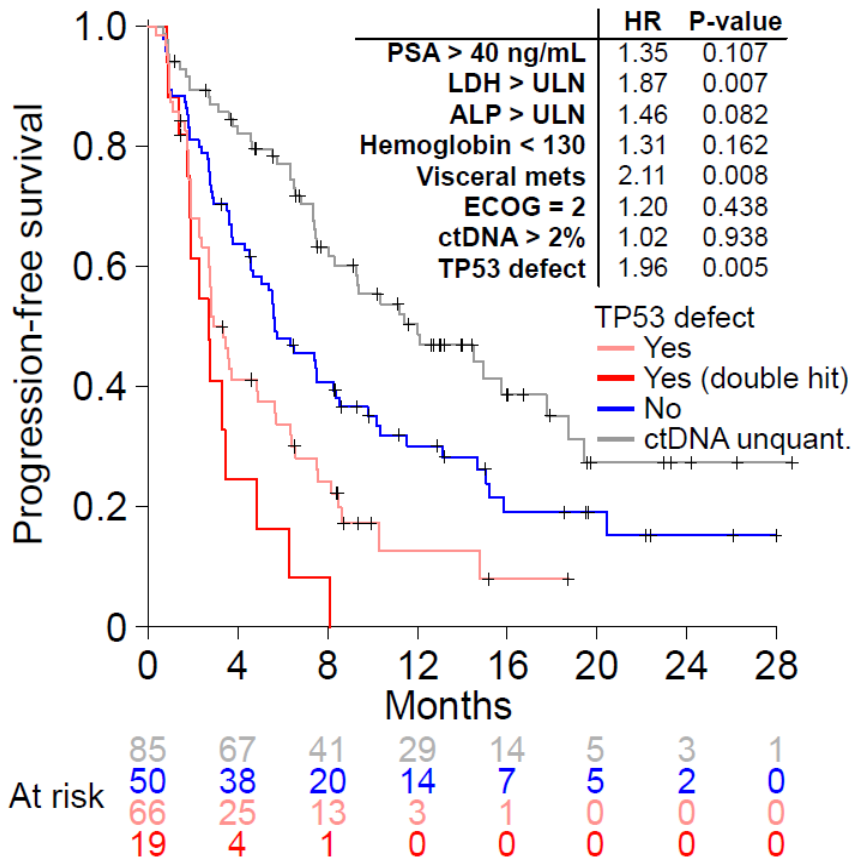


ctDNA undetectable after therapy initiated
– patient dramatic response to therapy

Sundahl, Vandekerkhove, *et al.* Eur Urol 2019

TP53 mutations are independently associated with poor outcomes

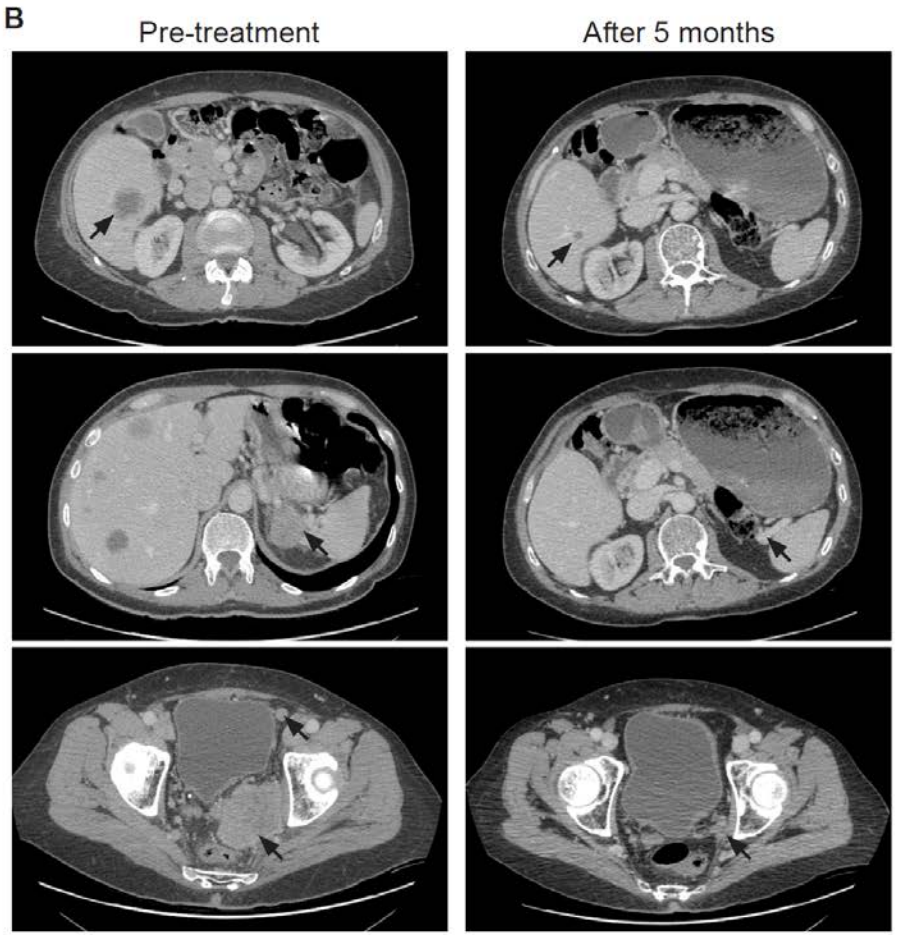
- Metastatic castration-resistant prostate cancer patients
- Receiving abiraterone / enzalutamide



Annala *et al.,* Cancer Discovery 2018; Chi *et al*., ASCO 2017; ClinicalTrials.gov: NCT02125357

BRCA2 deletion and response to platinum and PARP inhibition

- Analysis of DNA from tissue & cfDNA from plasma both revealed deletion of the *BRCA2* gene
- *BRCA2* gene is involved in repairing damaged DNA
- Patient experienced enduring response to therapies that targeted DNA repair defects



Chedgy et al. Clin Genitourin Cancer. 2016

Studying disease evolution in response to therapy with serial cfDNA samples

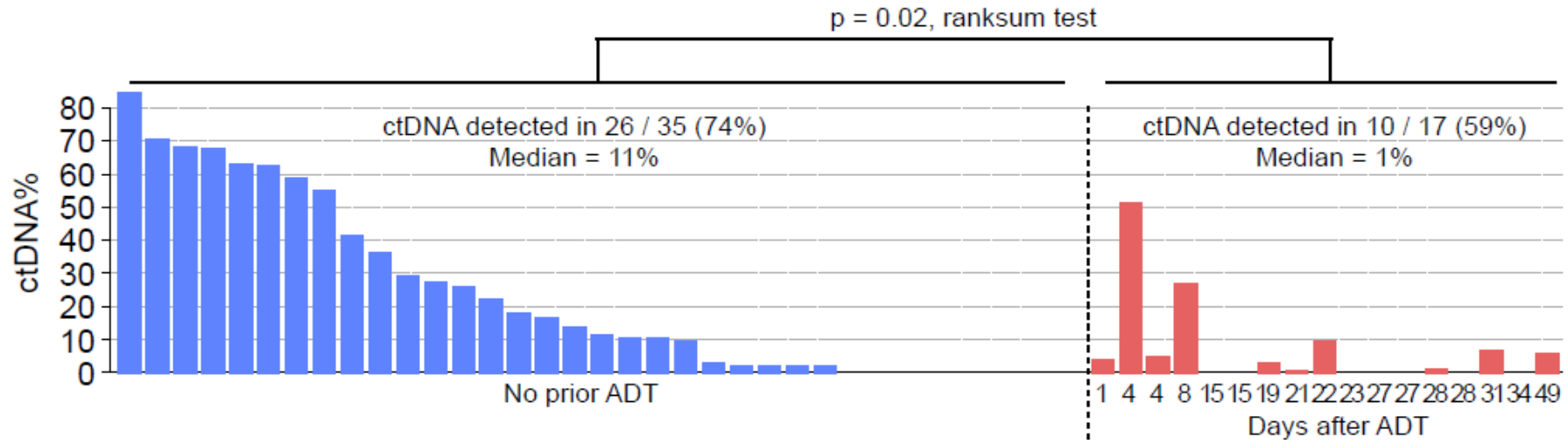
- Compare mutations present prior to treatment to those found at development of therapy resistance

- Example case:
  - Patient with a germline (inherited) *BRCA2* mutation that prevents *BRCA2* from functioning
  - Initial great response to PARPi (causes cell death if the cell cannot repair DNA)
  - Developed progressive disease after 6 months
  - Serial ctDNA samples revealed development of ‘reversion mutations’
  - The cancer cells restore function to *BRCA2*!

Quigley, *et al.* Cancer Discovery 2017

Presence of ctDNA in metastatic prostate cancer at diagnosis

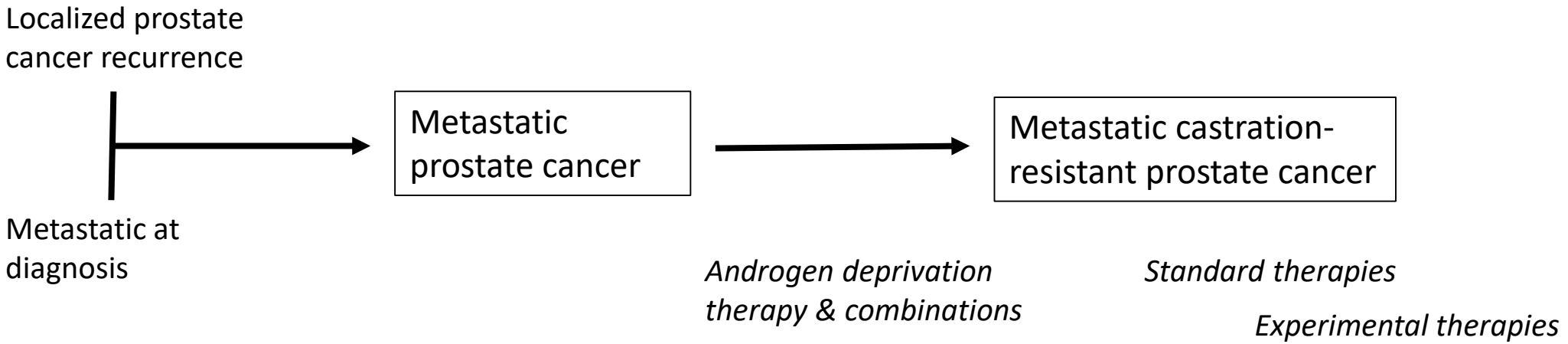
- ctDNA is abundant in patients with de novo metastatic prostate cancer



- Sequencing ctDNA provides complementary information to diagnostic prostate biopsy

Vandekerkhove, Struss, Annala et al. Eur Urol. 2019

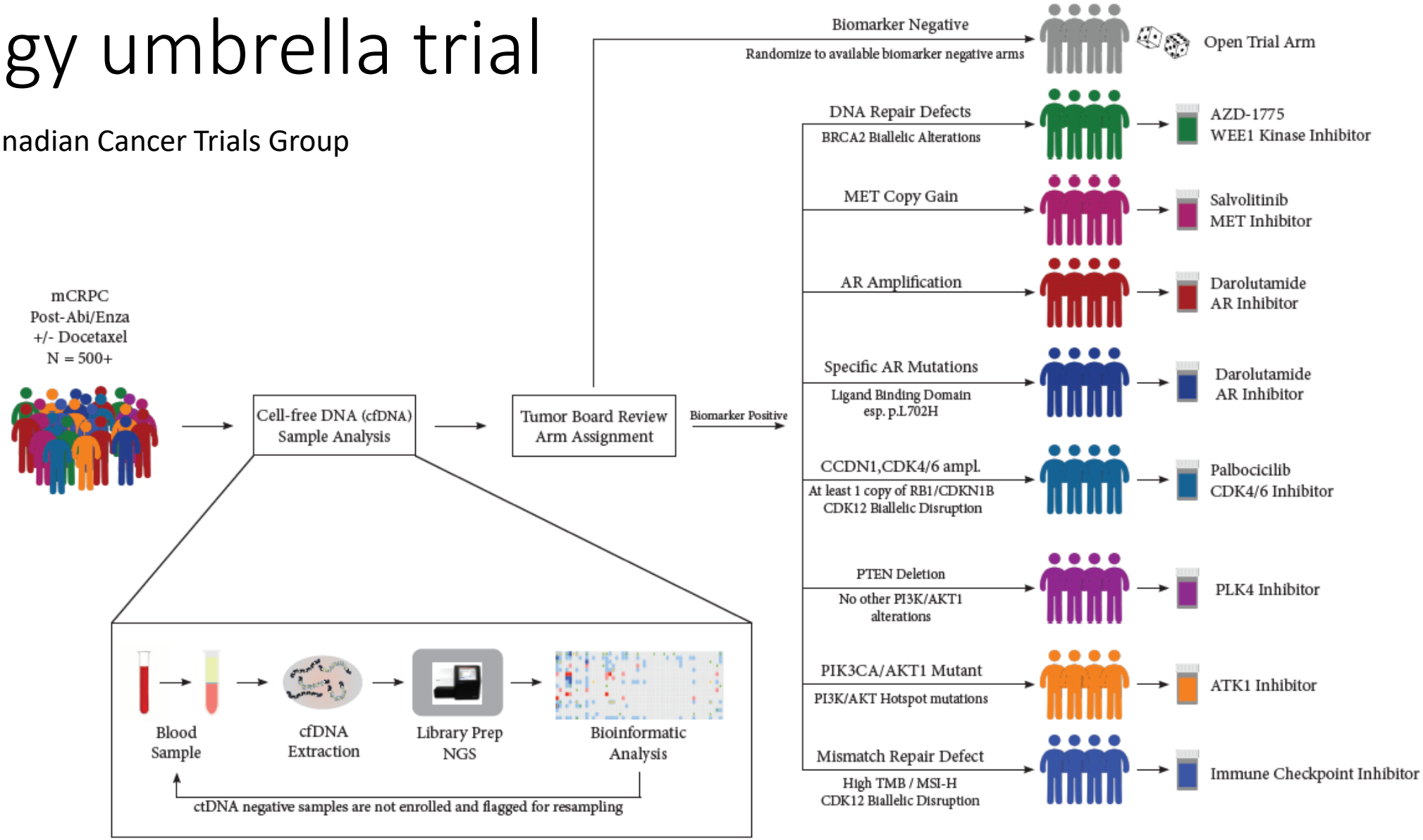
Implementing biomarkers to guide treatment



- Most cfDNA work is correlative
- To change clinical practice we need prospective evaluation of biomarkers

On-going phase II precision oncology umbrella trial

- Dr. Kim Chi; Canadian Cancer Trials Group



ClinicalTrials.gov: NCT03385655

Acknowledgments

- Alexander Wyatt and team at VPC/UBC
  - Matti Annala
  - Kevin Beja
  - Evan Warner
  - Sinja Taavitsainen
  - Yulia Loktionova
  - Cameron Herberts
  - Elie Ritch
  - Jack Bacon
  - Werner Struss
  - Elena Schonlau
  - Andrew Murtha
  - Amanda Wong
- *Vancouver Prostate Centre & University of British Columbia*
  - Martin Gleave, Peter Black
- *Institute of Biosciences and Medical Technology, Tampere*
  - Heini Kallio, Teuvo Tammela, Matti Nykter
- *BC Cancer, Vancouver*
  - Daniel Khalaf, Steven Yip, Simon Fu, Lucia Nappi, Jean-Michel Lavoie
  - Bernie Eigl, Christian Kollmannsberger
  - Kim Chi
- Patients and Their Families!