

The future of APC management: In Biomarkers

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DISCLOSURES

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Sanofi-Aventis, Millennium Pharma, Eli-Lilly, and Janssen

PATENTS:

Listed as co-inventor on patents in the diagnostic and treatment fields for ETS fusions (Harvard/Michigan), EZh2 (Michigan), SPOP (Cornell), and AURKA (Cornell)

OFF-LABEL USE OF DRUGS WILL BE DISCUSSED

Co-Founder and stock holder of THUCYDX, LLC.

Definitions

A **prognostic biomarker** is one that indicates an increased (or decreased) likelihood of a future clinical event, disease recurrence or progression in an identified population. Prognostic biomarkers are measured at a defined baseline, which may include a background treatment

A **predictive biomarker** is used to identify individuals who are more likely to **respond to exposure** to a particular medical product or environmental agent. The response could be a symptomatic benefit, improved survival, or an adverse effect.

Given for lab tests (CLIA/CLEP):

Accuracy

Reproducibility

Sensitivity

Specificity

FDA-NIH **Biomarker** Working Group.

Silver Spring (MD): Food and Drug Administration (US);

Bethesda (MD): National Institutes of Health (US); 2016

CRPC Patient and acquisition of samples for testing

Buccal sample

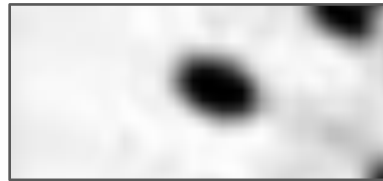


Germline DNA

Genetic testing (e.g., BRCA1/2)

Control normal sample for genomics

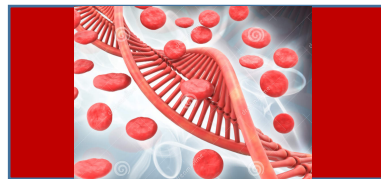
Tumor sample



Tumor DNA/RNA/Protein

For genomic sequencing,
transcriptomic sequencing, etc.

Blood sample



Tumor and normal DNA/RNA/Protein fraction

cfDNA, CTC, metabolites, etc.



Advanced Prostate Cancer

5%, 10%, and 20%

5% have MSI or MMR alterations

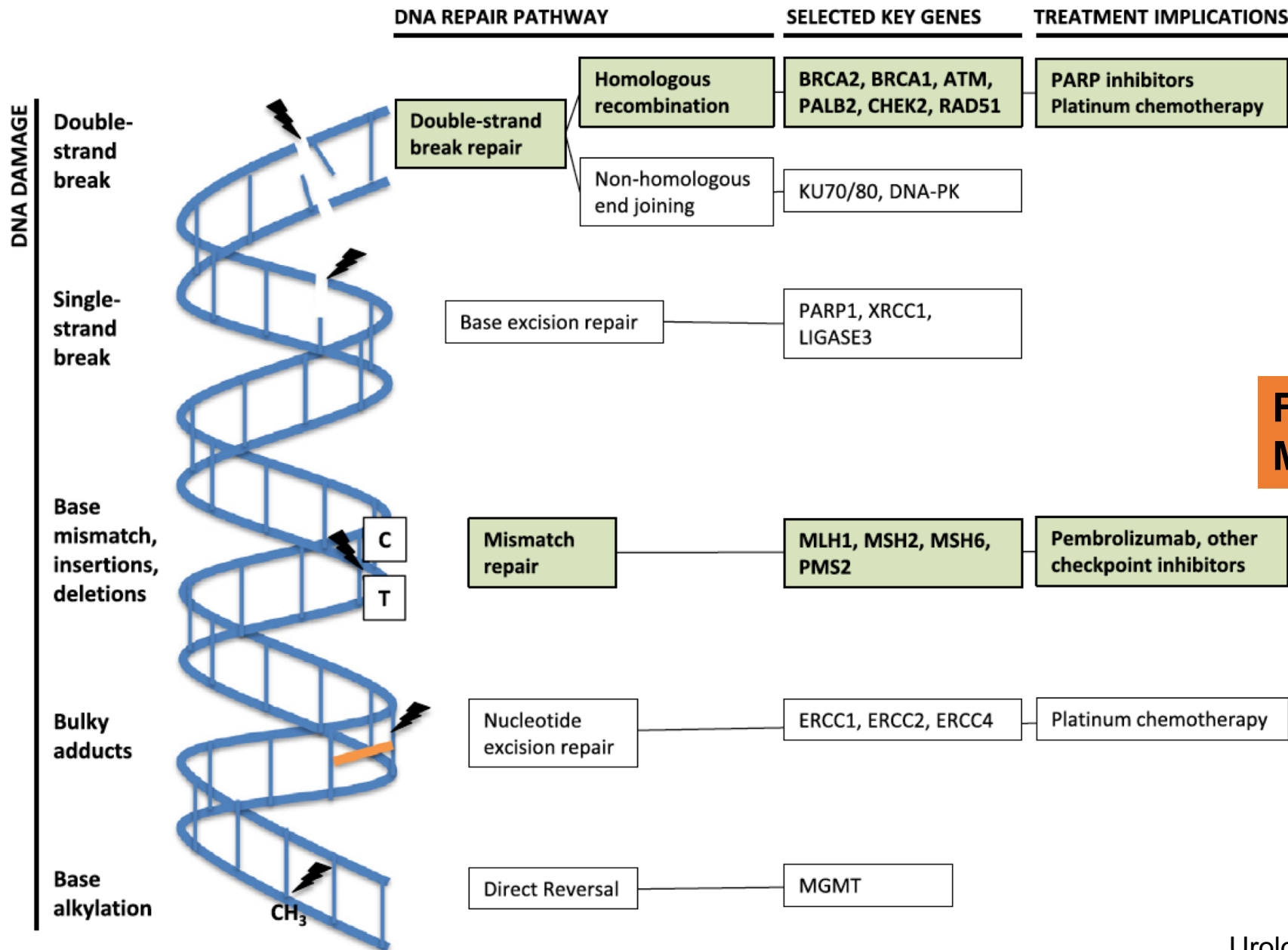
Immunotherapy FDA

10% have germline DRM (e.g. BRCA)

PARPi or Platinum-based Tx/ Family implications

20% have DRM somatic-germline

PARPi or Platinum-based Tx



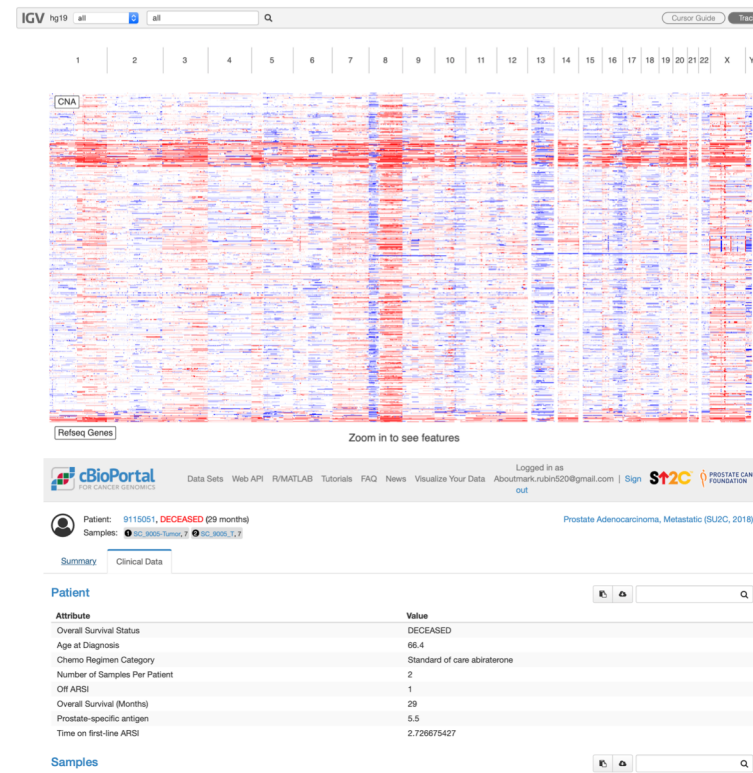
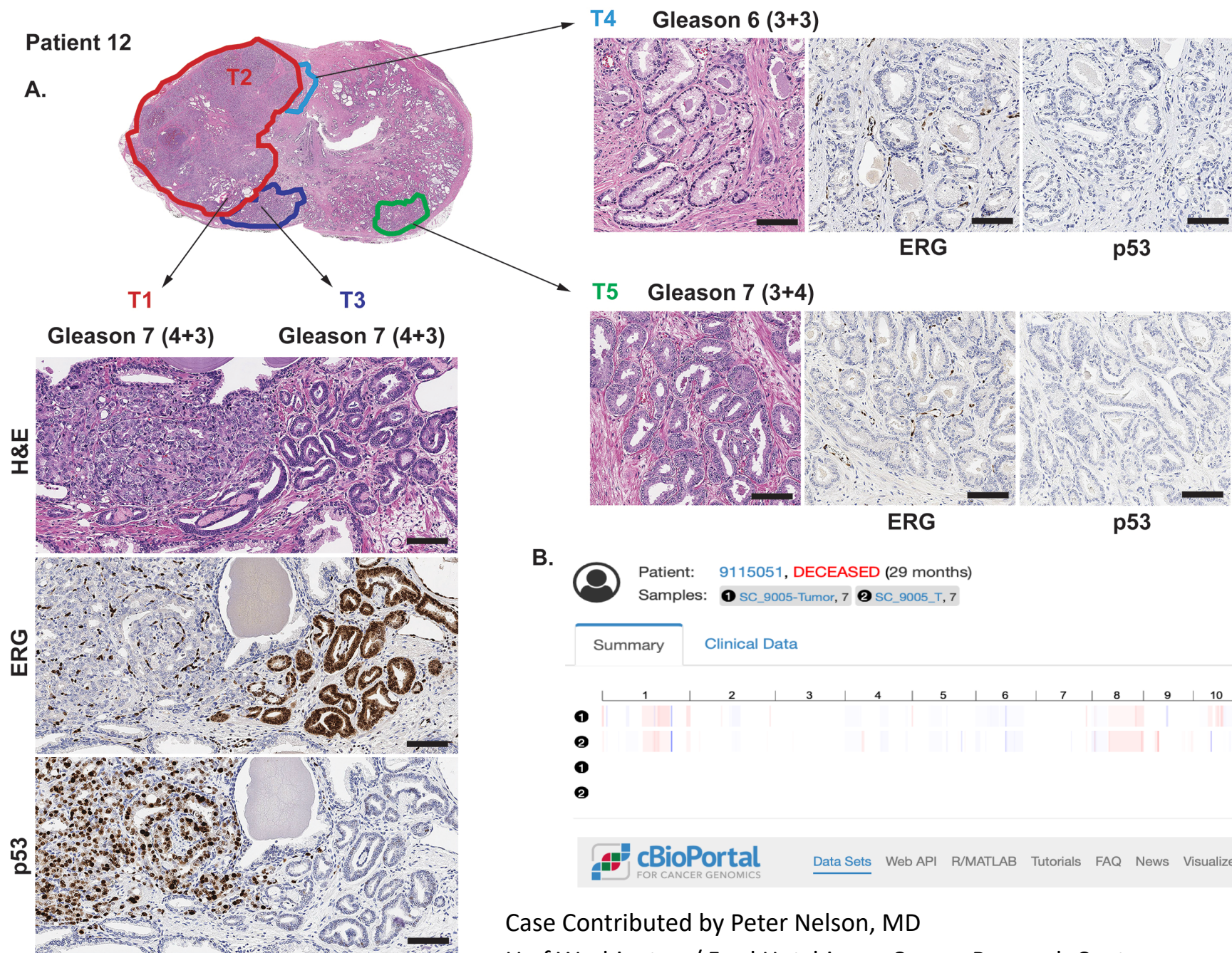
20%

FDA (May 2017) approval for MSI and MMR deficiency

5%

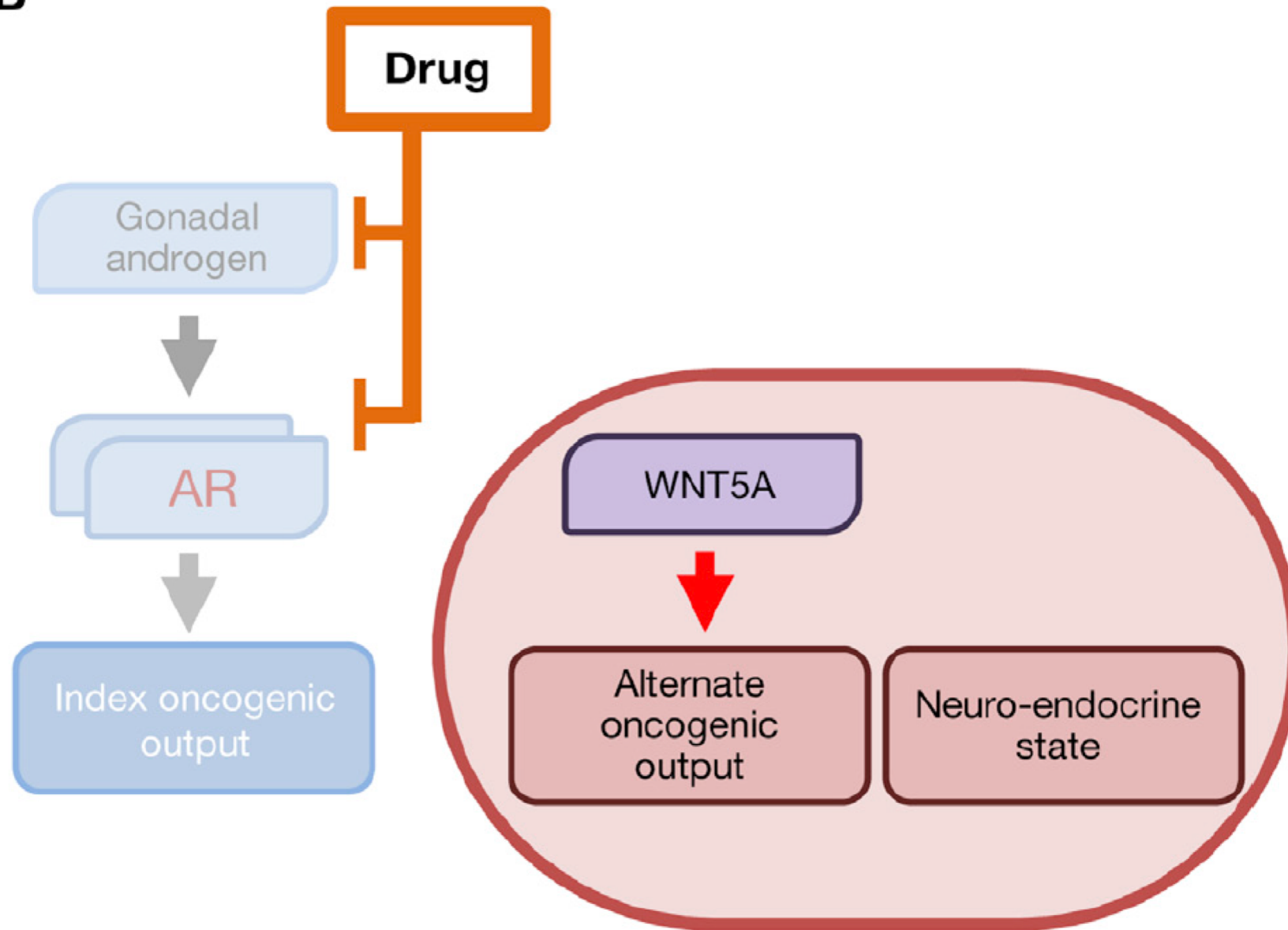
What is Needed Next?

1. Overcome Heterogeneity

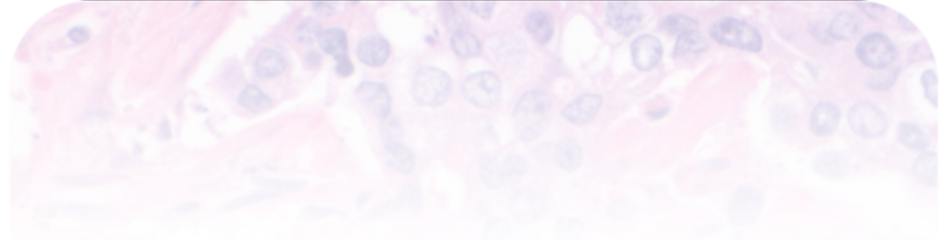
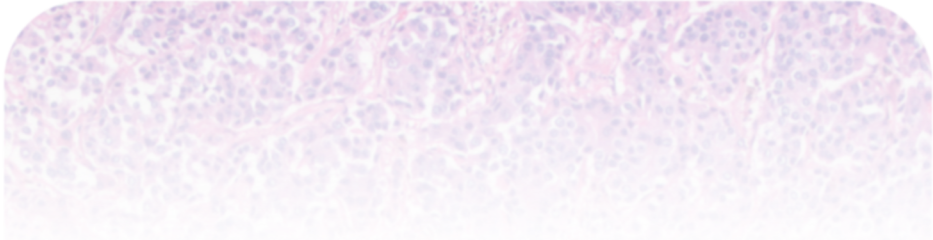
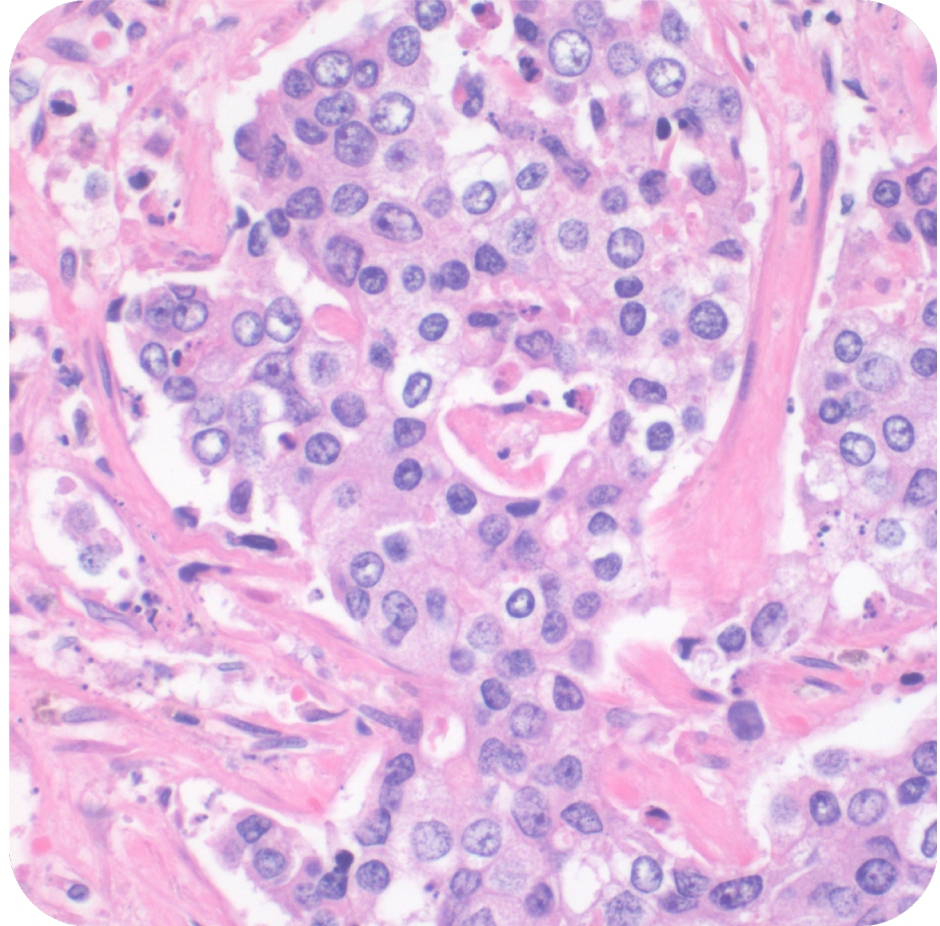
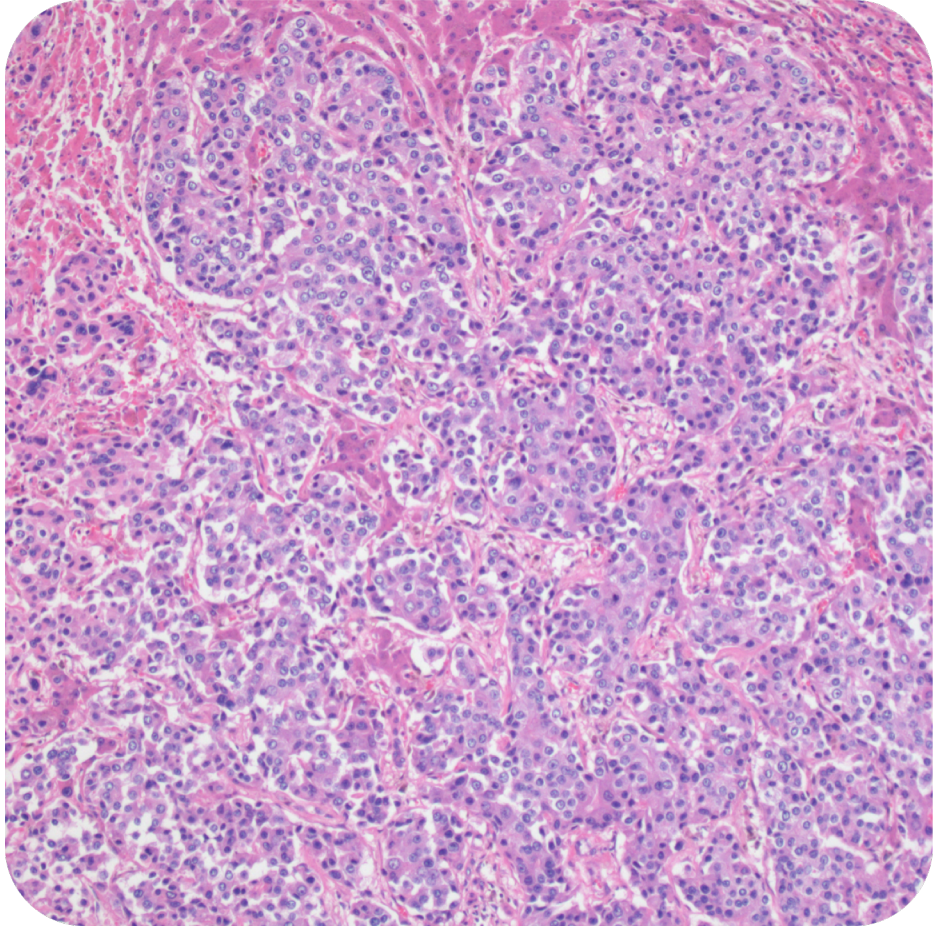


Case Contributed by Peter Nelson, MD
U of Washington / Fred Hutchinson Cancer Research Center

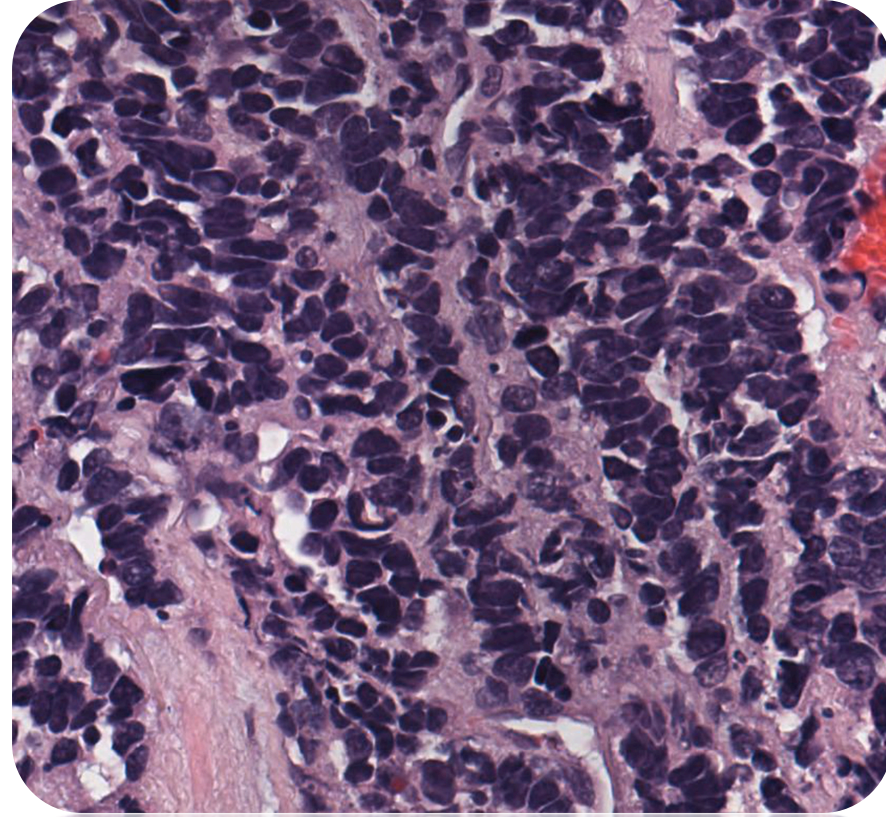
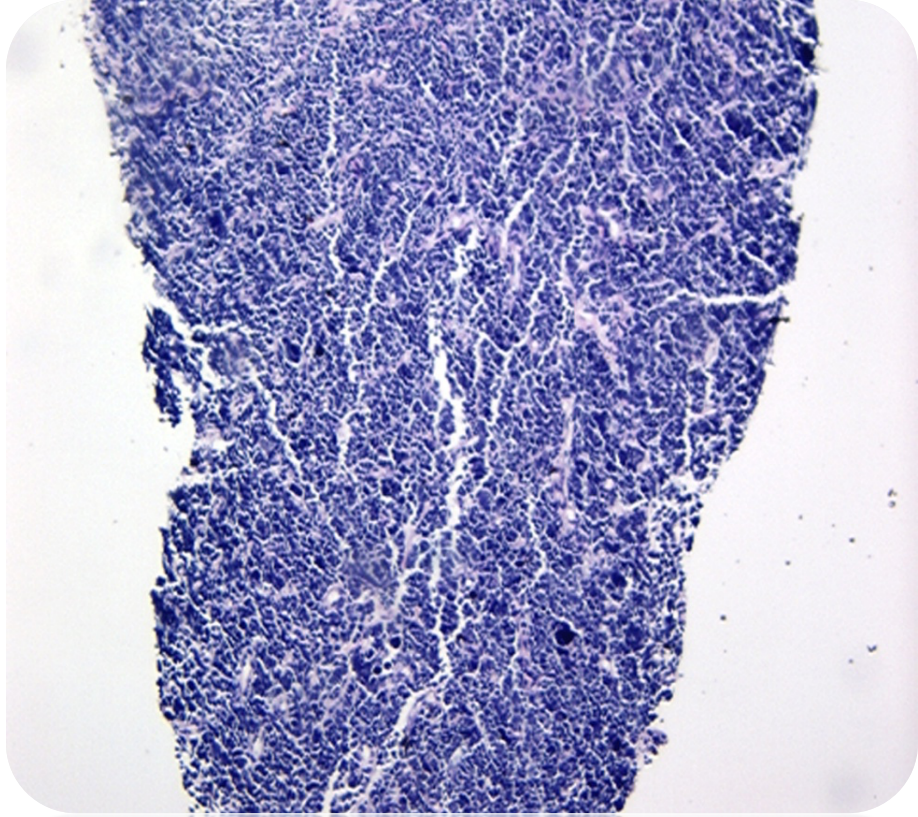
Cyrta, Prandi, et al., in preparation

B

Diagnosis: Prostate Cancer, adenocarcinoma

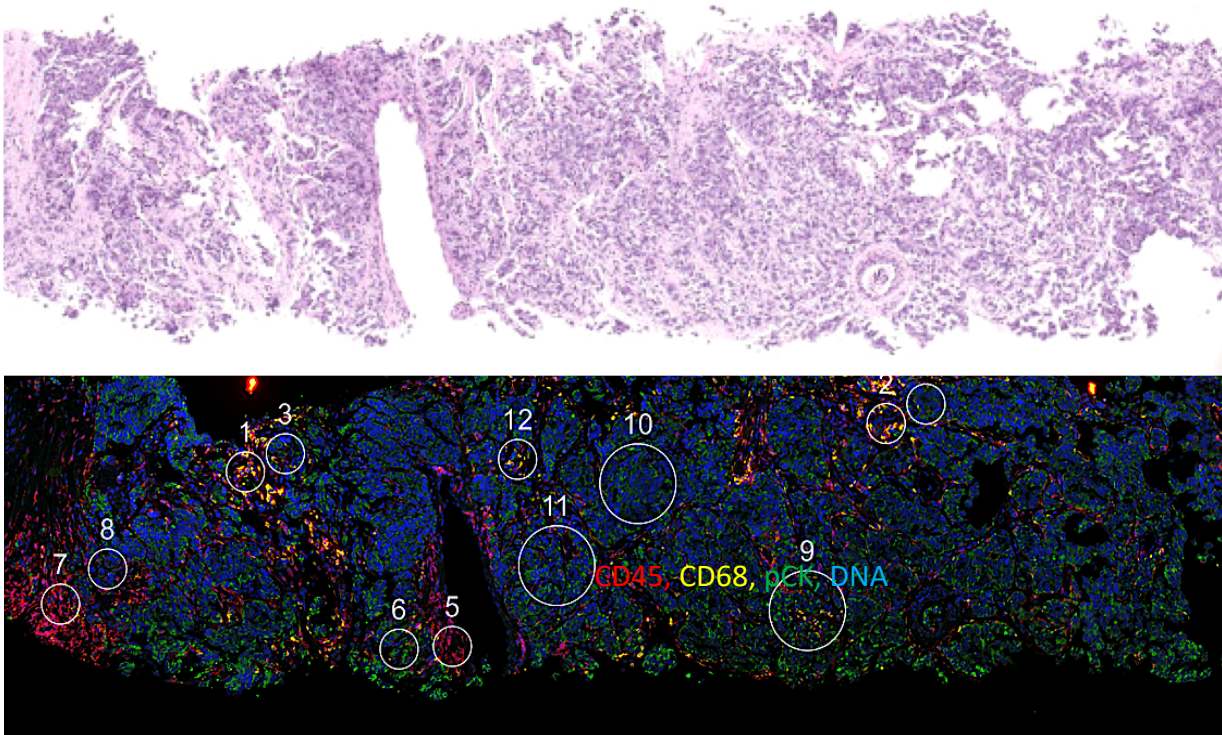


Diagnosis: Small Cell/Neuroendocrine Prostate Cancer

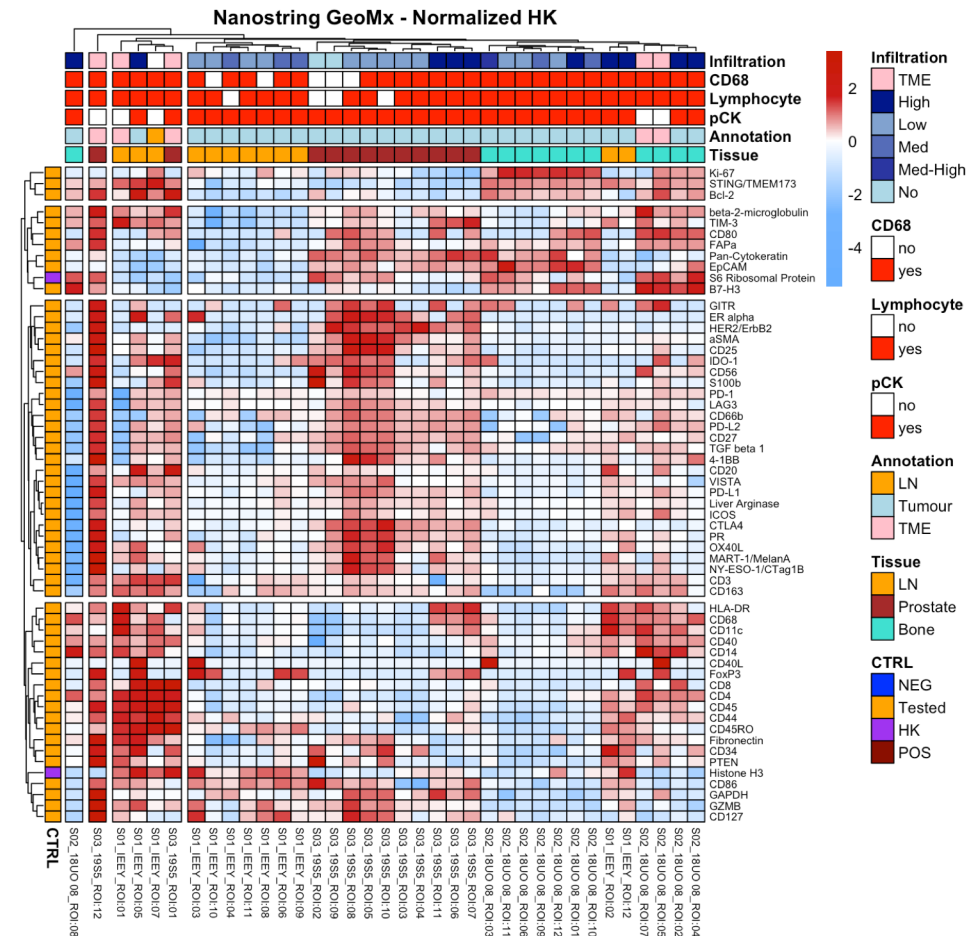


One Example to address heterogeneity: Geospatial immune landscaping

ROI selection

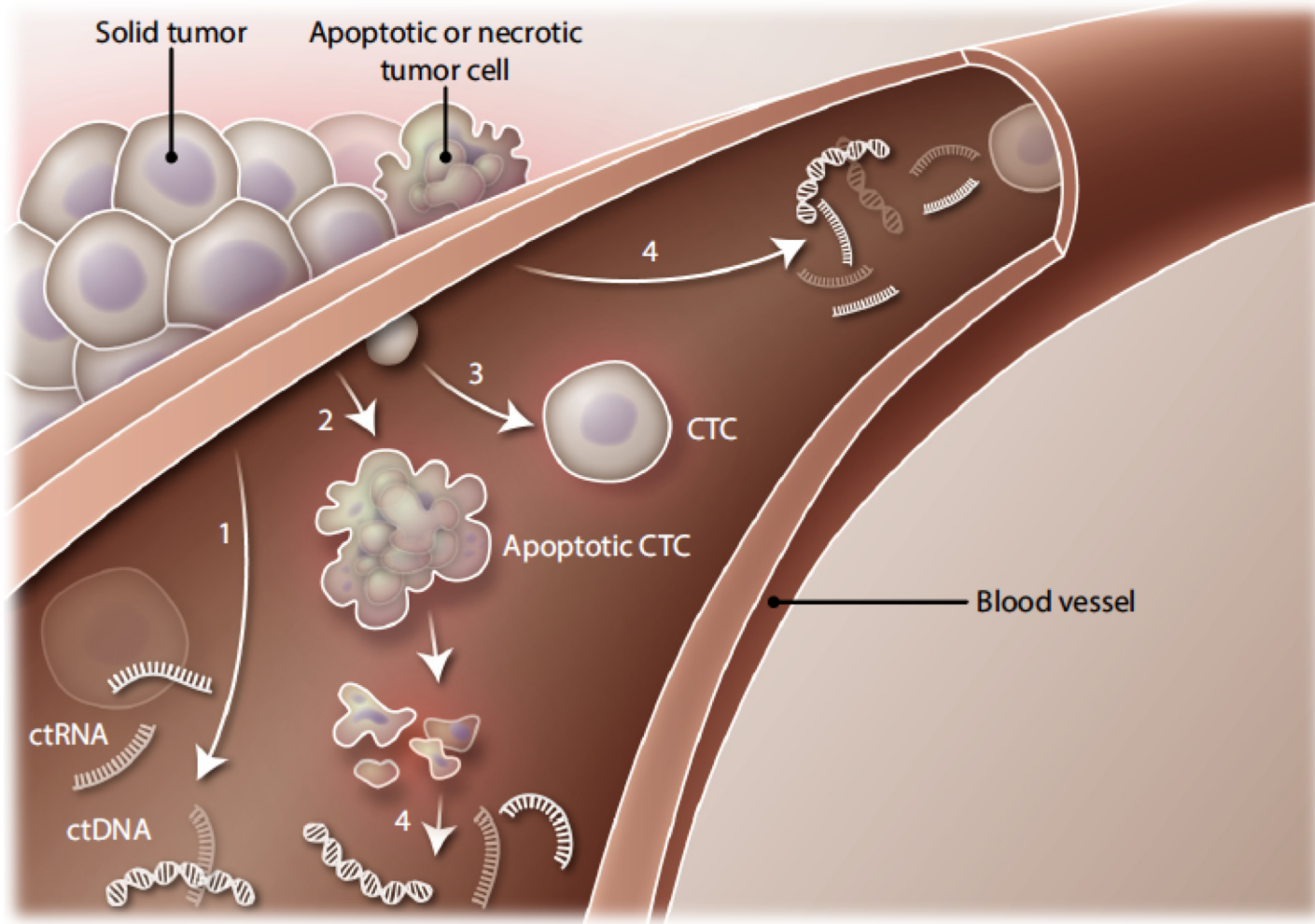


Nanostring GeoMx



But also single cell sequencing...

What is next for CRPC Diagnostics



Liquid biopsy to overcome limits of multiple metastasis biopsies to capture heterogeneity and/or serial biopsies

CIRCULATING BIOMARKERS FOR ADADVANCED PCA:

Non-Invasive Approaches to Monitor PCA evolution

Assay	Pros	Cons	Example
CTC-EpCAM	FDA approved	Epithelial selection	CELLSEARCH
CTC without selection (AR-V7, PTEN, etc)	Unbiased	Not regulatory approved	Epic Sciences
Plasma cfDNA (ctDNA)	Monitor genomic alterations (NGS)	Signal/noise	Attard/Demichelis et al. Wyatt et al.
Oncosomes/Exosomes	Potential informative packets of RNA/DNA	Research grade	
RNA (lncRNA,mRNA, miRNA)	Disease/tissue specificity	Clinical and research grade	T2- ERG/PCA3/SCHLAP1/AR- v7

2. Develop robust assays for prediction

From the blood: What is predictive? Prognostics? Reproducible?

cfDNA (tumor DNA)

AR-V7

AR gain

AR mutations

Other (neuroendocrine differentiation)

Most studies are not exploring these parameters together



Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade

Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman, MD; Ahmet Zehir, PhD; Jinru Shia, MD; Philip Jonsson, PhD; Zsofia K. Stadler, MD; Preethi Srinivasan, BA; Vincent P. Laudone, MD; Victor Reuter, MD; Jedd D. Wolchok, MD, PhD; Nicholas D. Socci, PhD; Barry S. Taylor, PhD; Michael F. Berger, PhD; Philip W. Kantoff, MD; Charles L. Sawyers, MD; Nikolaus Schultz, PhD; David B. Solit, MD; Anuradha Gopalan, MD; Howard I. Scher, MD

Figure 1. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) in Prostate Cancer

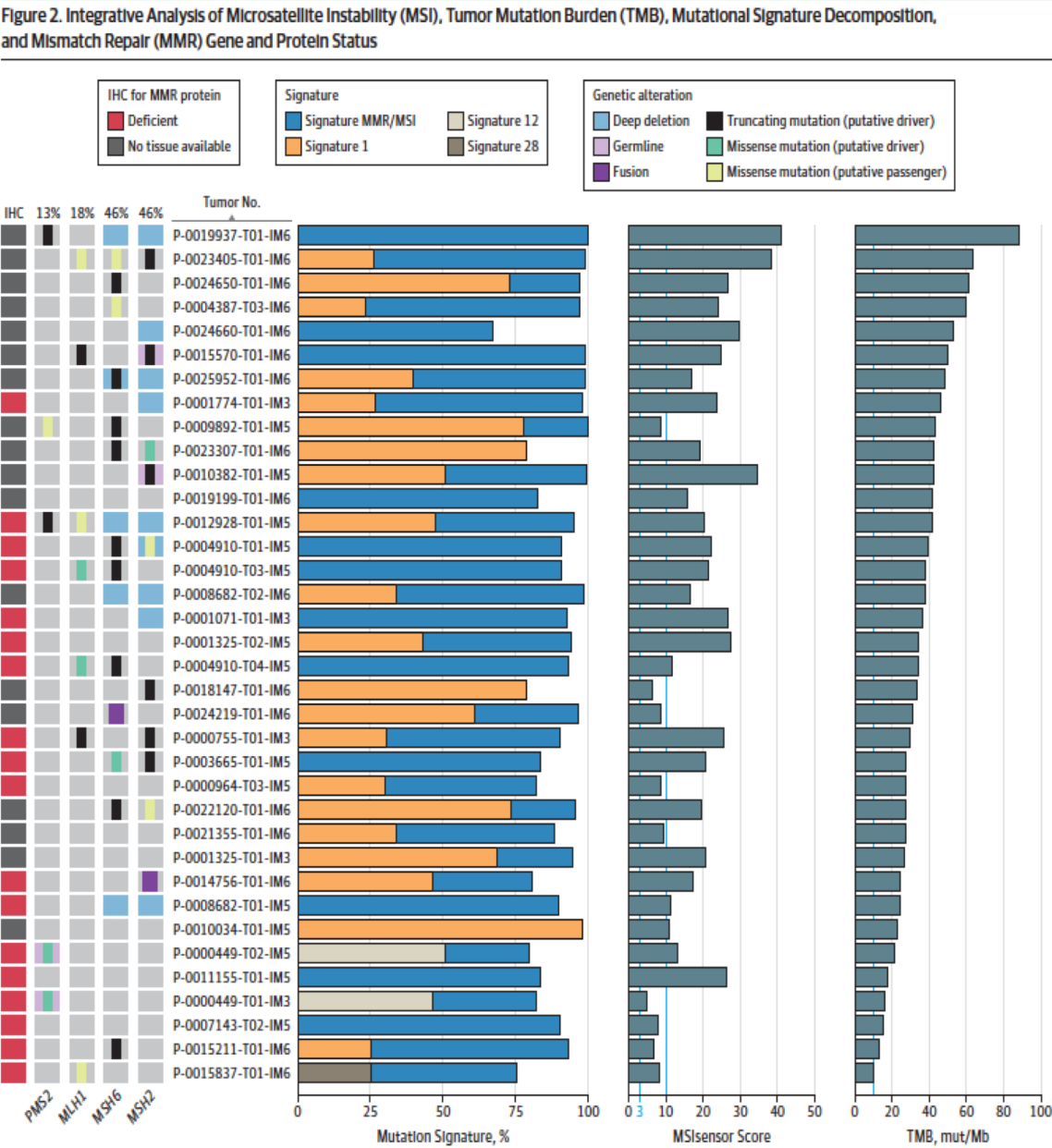
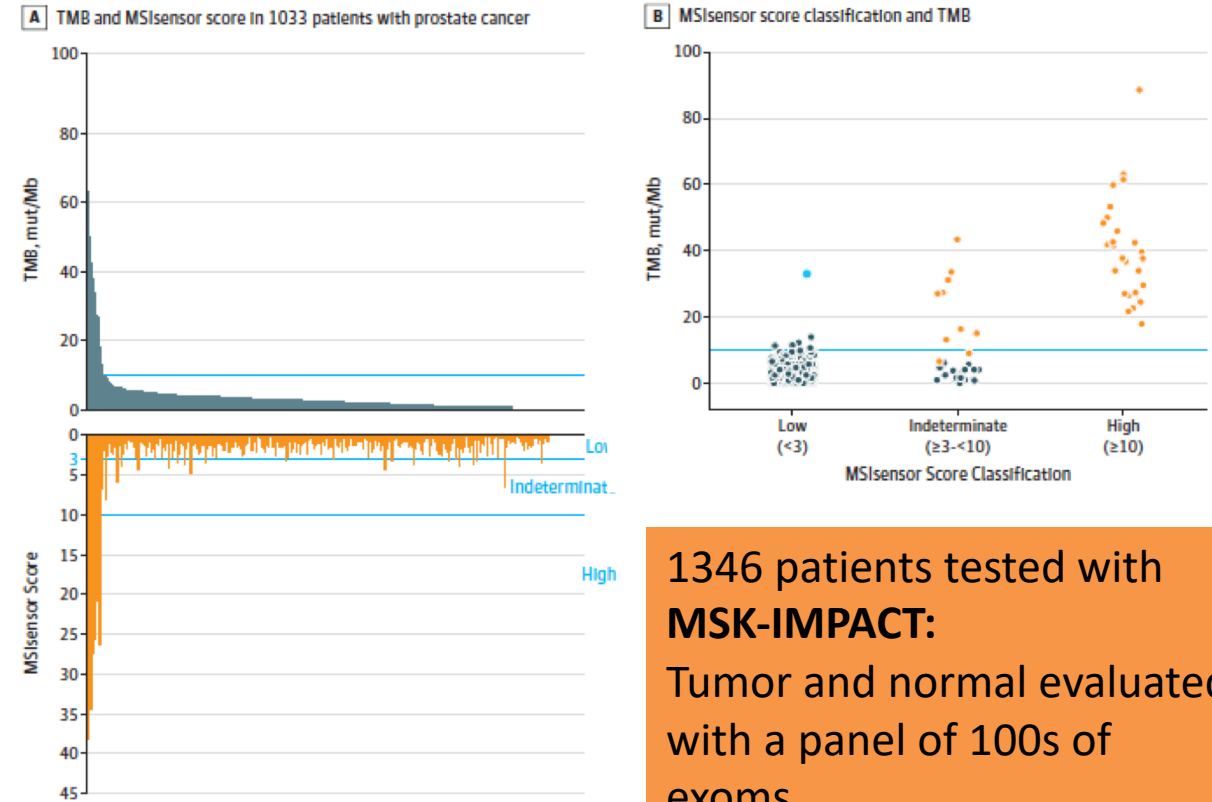
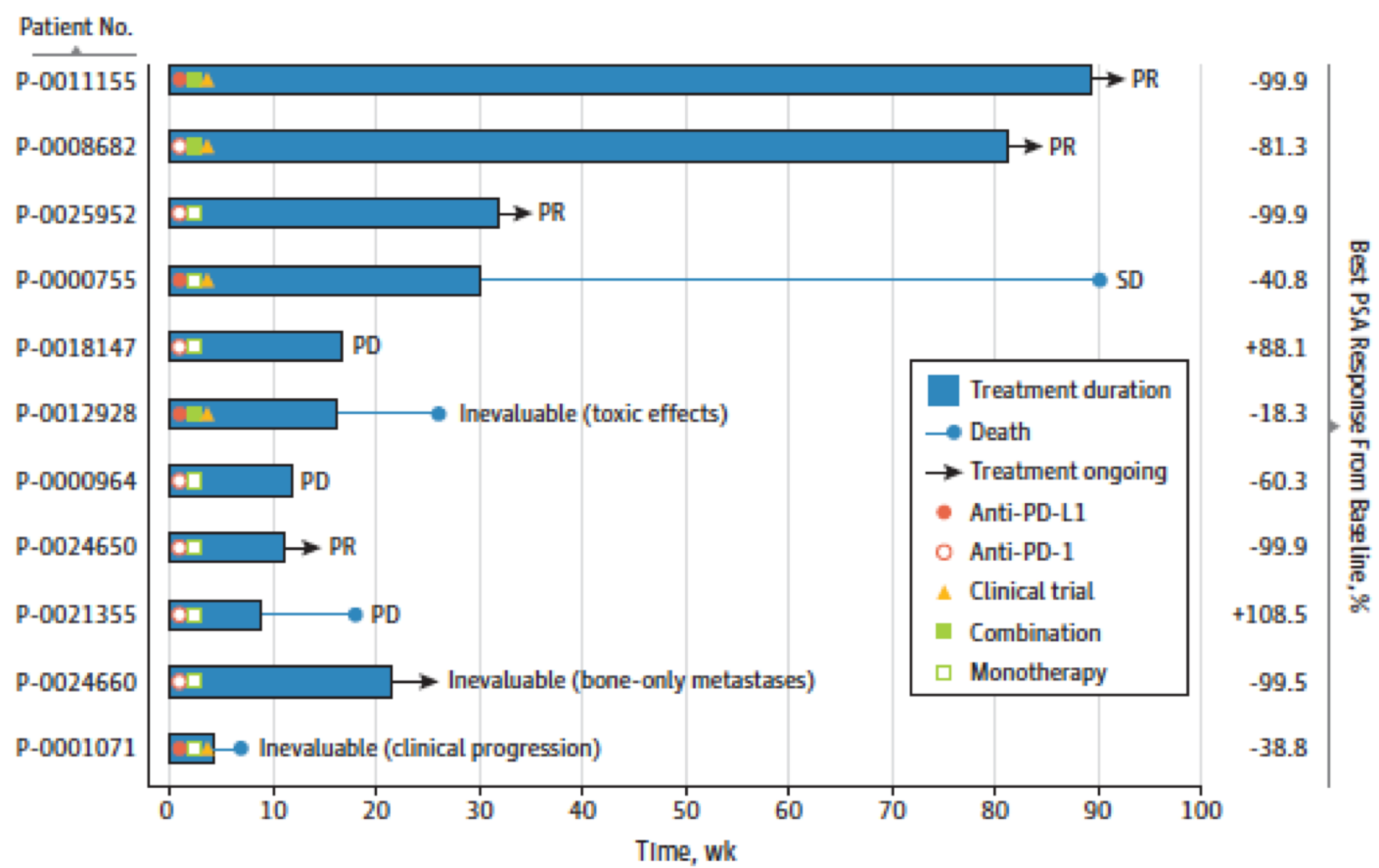


Figure 4. Responses to Immune Checkpoint Blockade In Microsatellite Instability-High and Mismatch Repair Deficient (MSI-H/dMMR) Prostate Cancer



Overview of Tests that are Ready/Promising*

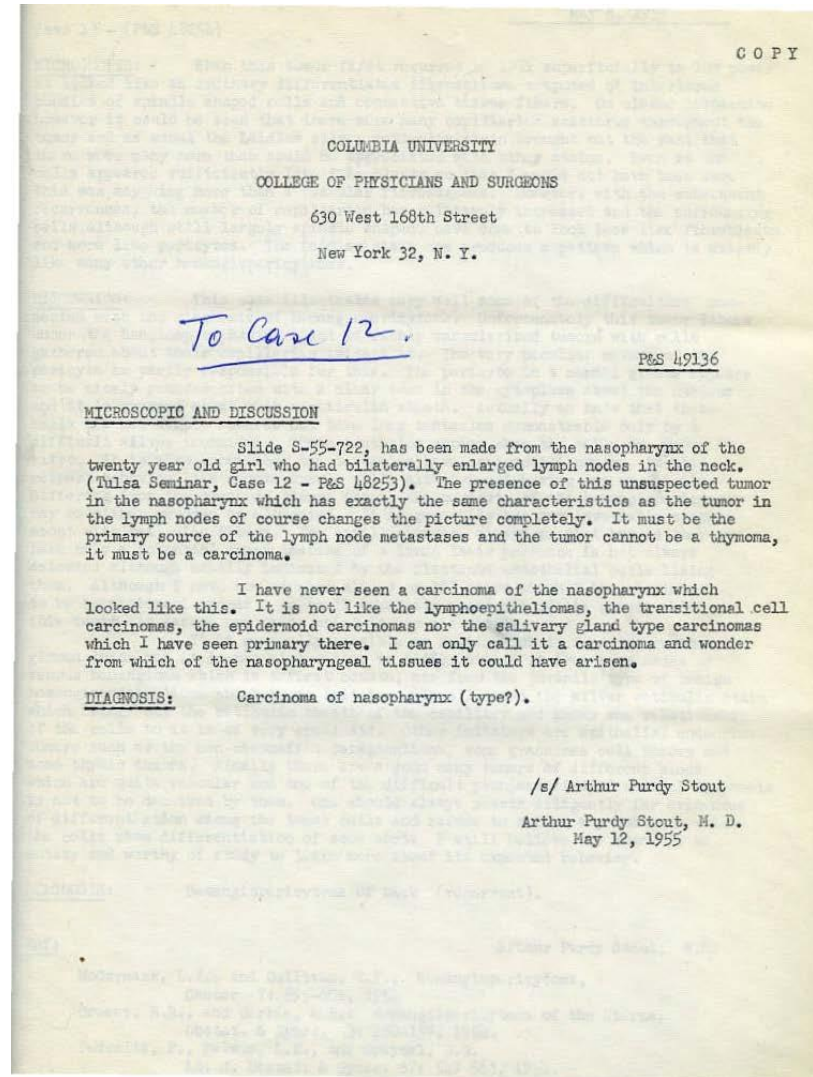
- a. **MSI testing**
- b. **DNA repair status** (“BRCAness”-assay for BRCA1/2/ATM,PALB2) for mutation/loss or HR signature useful for platinum therapy or PARPi
- c. **Loss of AR** lack of response to AR therapy (AR-V7, mutations)
- d. **cfDNA** amount associated with prognosis
- e. **PTEN loss** - possibly response to AKT inhibitor (de Bono CCR 2018)
- f. **CDK12 loss** - possibly response to checkpoint blockade
- g. **Loss of TP53/RB1** - short duration of response to AR-therapy--possibly predictive response to platinum
- h. **CTC heterogeneity** (“clusters”) response to docetaxel vs AR therapy
- i. **Pathology** phenotype for NEPC response to platinum
- j. **Double negative (AR- and NE-)** response to FGFRi
- k. **PSMA expression response** to PSMA-drug therapies
- l. **DLL3** expression response to chemoconjugate

*Thanks Pete Nelson
Always comprehensive!

3. Find the people to take on the challenge

Arthur Purdy Stout

Surgeon and then Pathologist



No. 1 Columbia-Presbyterian Medical Center, 168th St., Bway, N. Y. (c) Wm. Frange

Precision Oncology Institute for Pathology



We need to find and develop highly capable pathologist/oncologists to take on the task of precision oncology testing.

