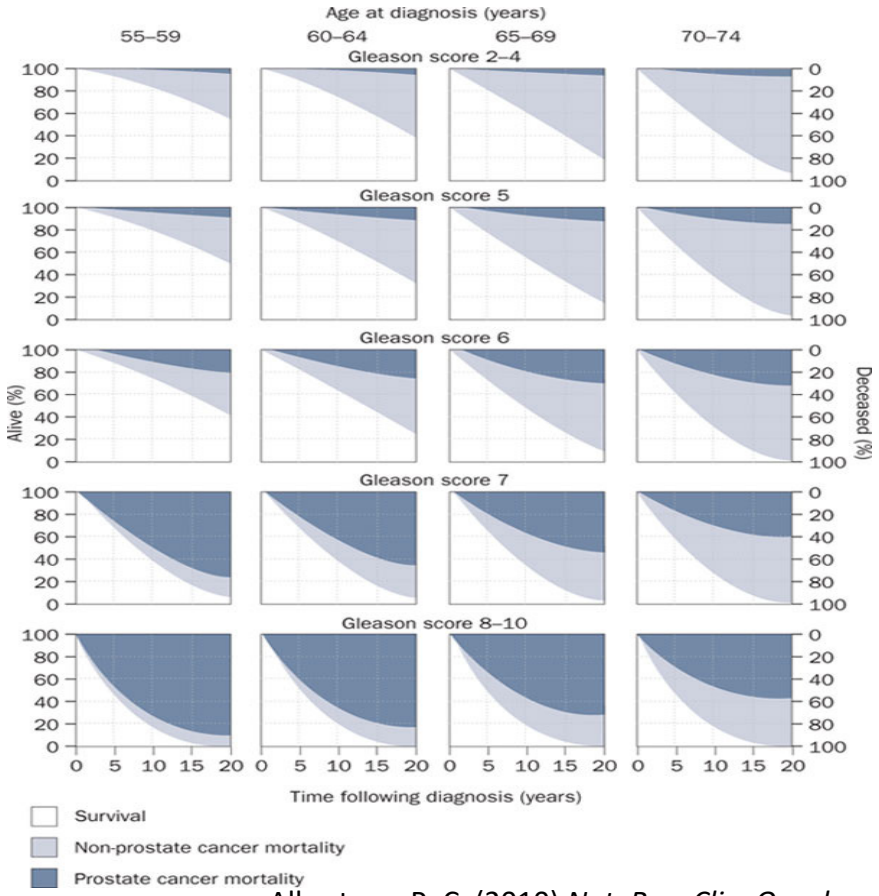
Genomic Subtypes of Prostate Cancer: Moving Towards Clinical Impact

Chris Barbieri, MD, PhD
Assistant Professor of Urology
Assistant Professor of Cell and Developmental Biology
Sandra and Edward Meyer Cancer Center
Weill Cornell Medicine

Prostate Cancer is Clinically Heterogeneous

- **2017:** 161,000 cases, 27,000 deaths
- **Indolent** vs. **aggressive**
- **Overtreatment** of indolent prostate cancer → morbidity/cost
- **Undertreatment** of lethal prostate cancer → continued mortality



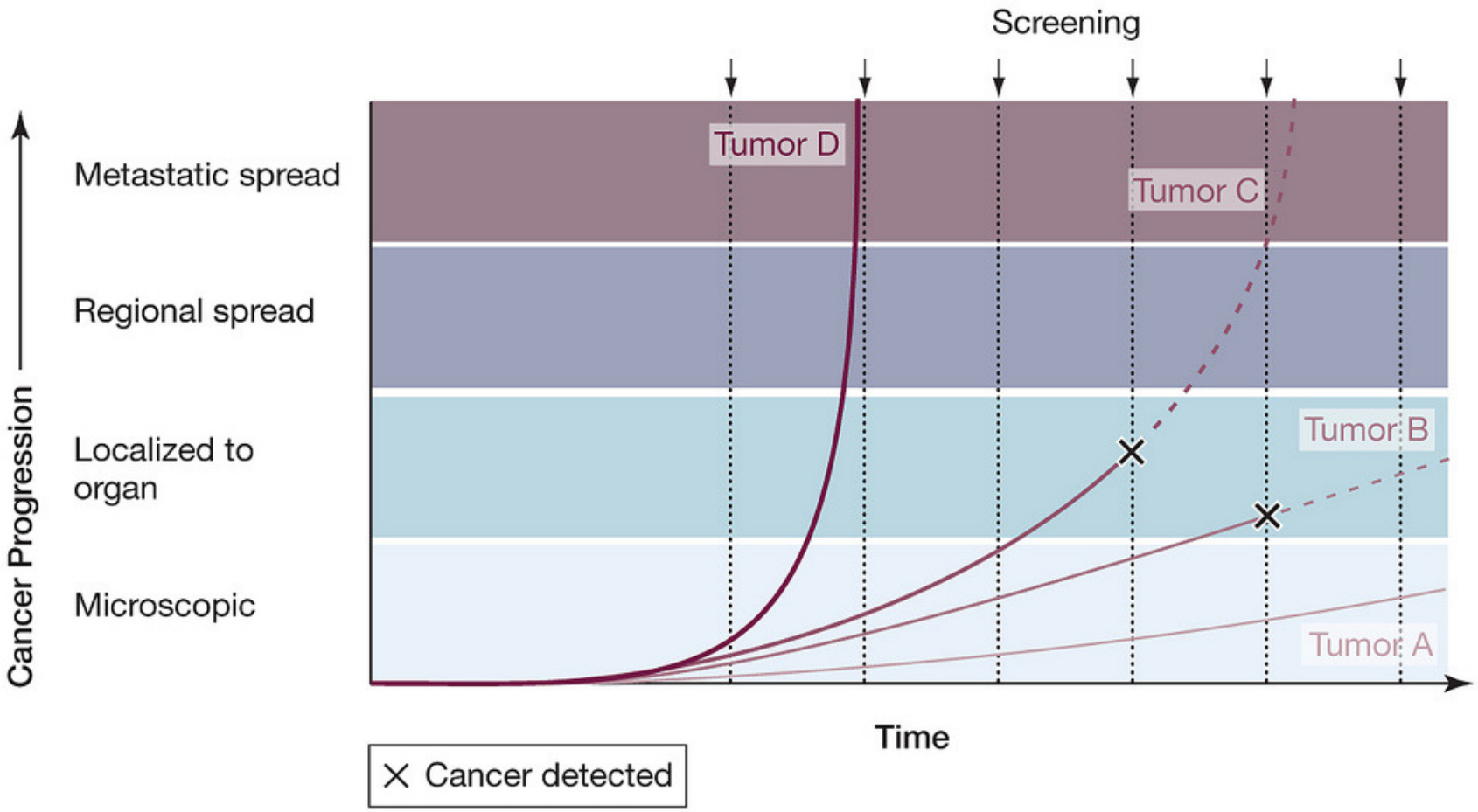
Albertsen, P. C. (2010) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2010.63

Prostate Cancer is Clinically Heterogeneous

- **Aggressive vs. Indolent**
  - Some prostate cancers grow and spread quickly
  - Others grow slowly

- Current information (clinical and pathological data) inadequately tell them apart

Figure 3. Screen Detection Capability Based on Tumor Biology and Growth Rates



Esserman et al.
JAMA. 2009;302(15):1685-1692. doi:10.1001/jama.2009.1498.

Prostate Cancer is Clinically Heterogeneous

Problems with current care

- **Overtreatment** of indolent prostate cancer with radical therapy

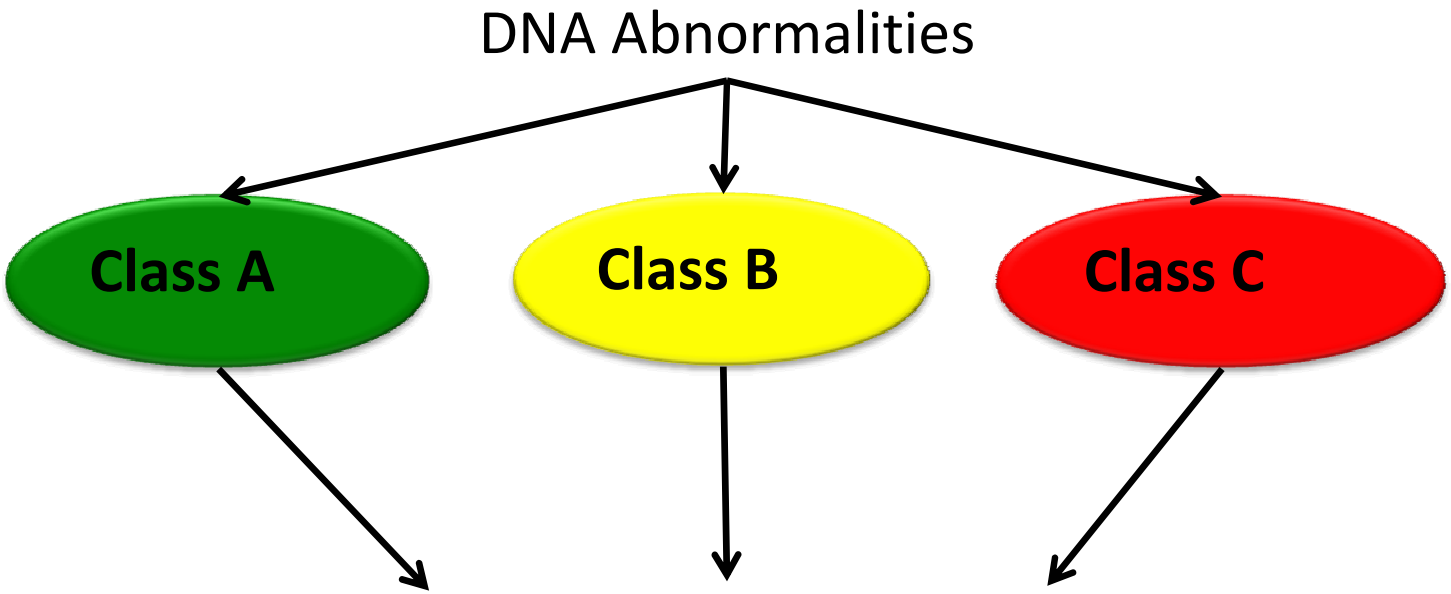
→ high morbidity

- **Undertreatment** of lethal prostate cancer

→ continued mortality

Genomic Classification

Define distinct classes of prostate cancer based on molecular/genomic characteristics



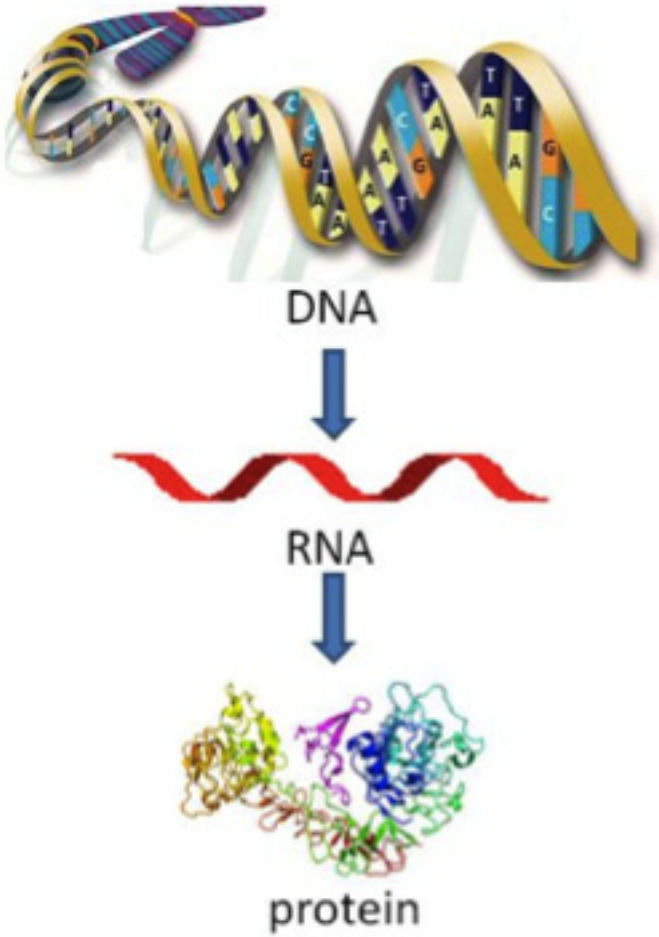
Prognosis

Management Strategy

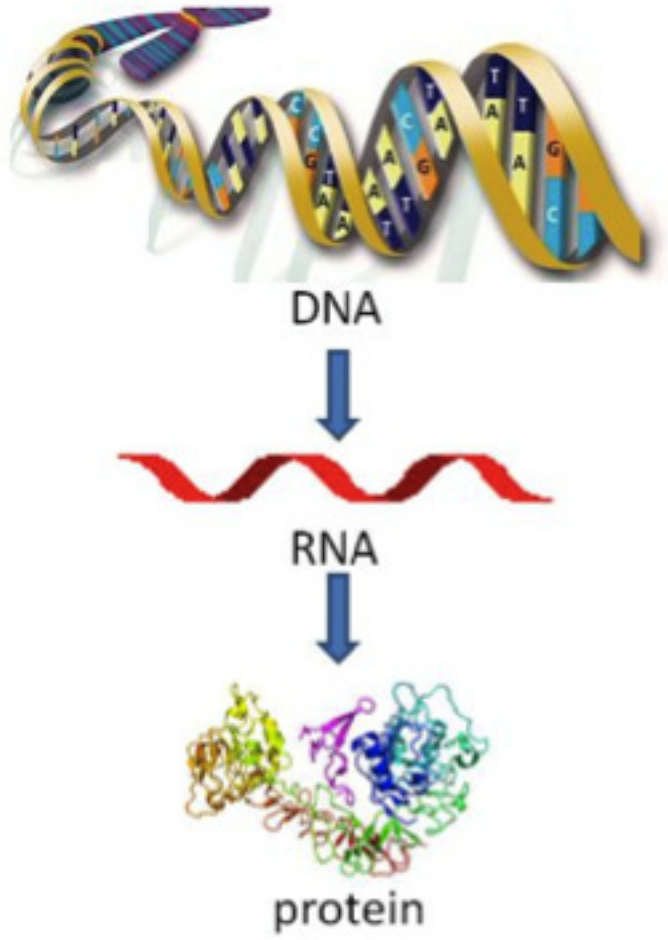
Targeted Therapy: **PRECISION MEDICINE**

What is genomics?

- Study of the structure and function of the **complete set of DNA** in a cell or organism



“Genomics” in modern medicine



Can refer to analysis of **any** molecular information (DNA, RNA, etc) that provides information about biology.

Genome-wide approaches (every single gene)
Vs.
Targeted

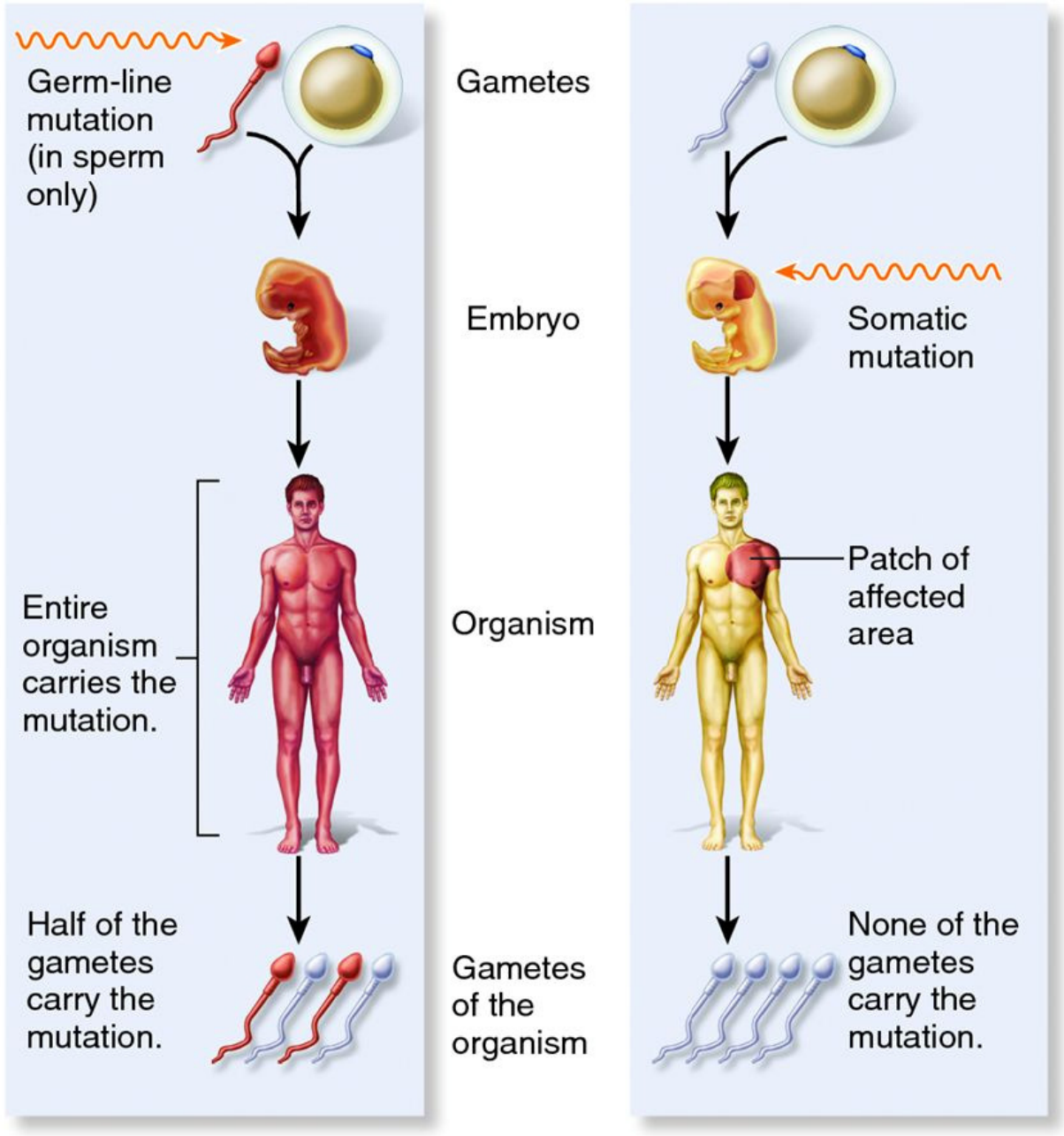
GERMLINE

In every cell

Hereditary

SOMATIC

In the cancer)



Genomic Classification

1. **Defining subclasses**
   - Patterns of molecular alterations
2. **Subclass-specific model systems**
   - Relevant context based on observations in human disease
   - Utilizing to learn about underlying biology
3. **Clinical impact** of subclasses

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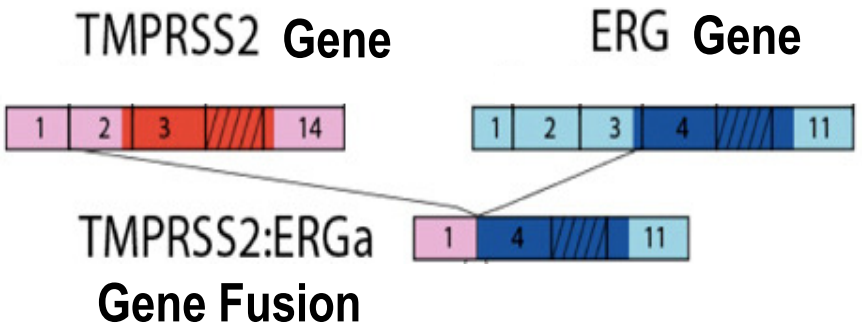
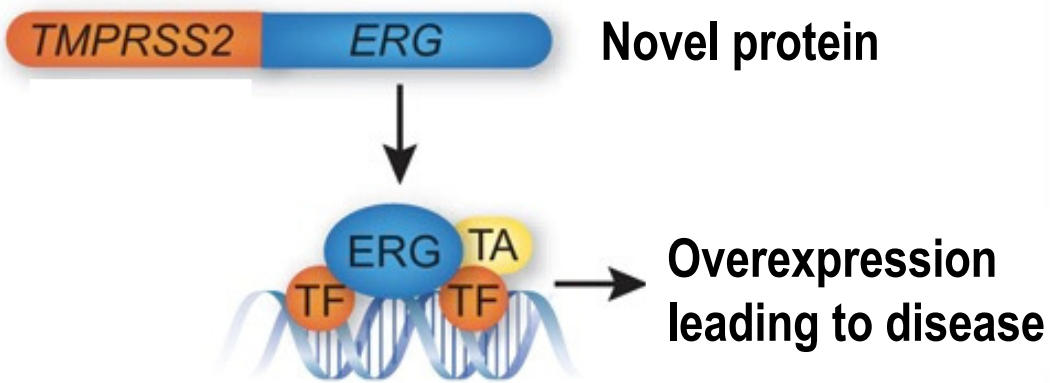
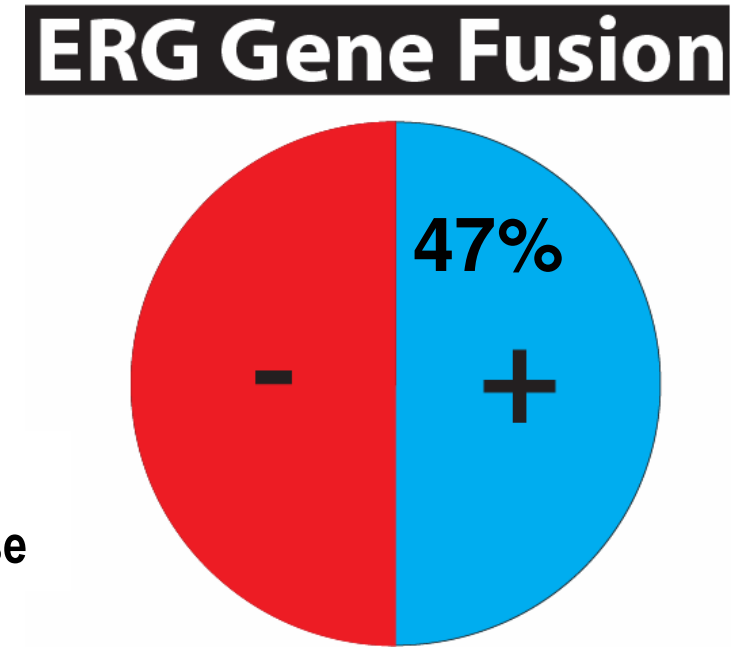
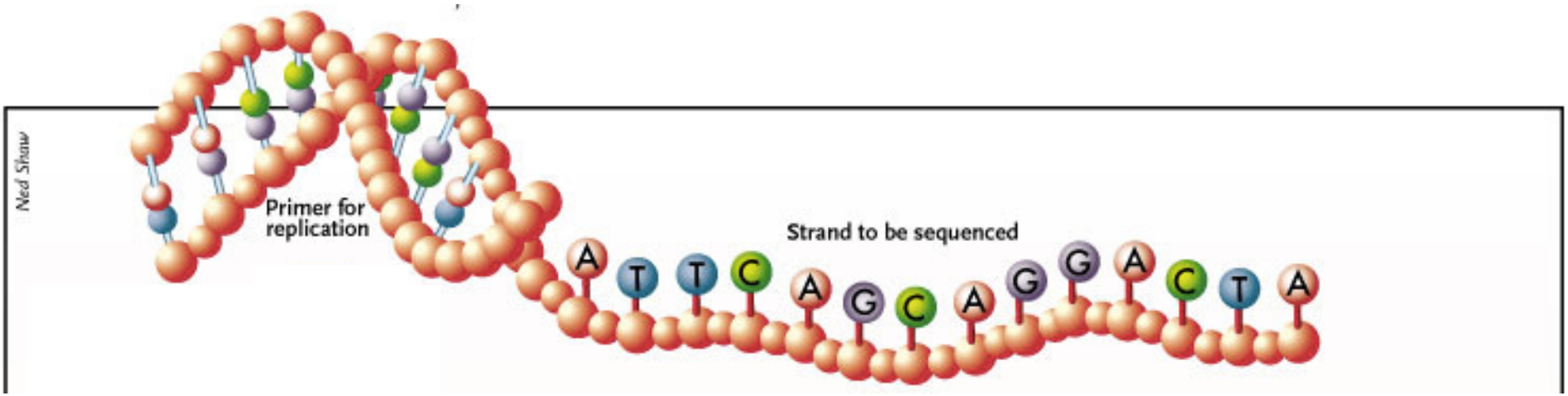
ERG gene fusions:
A starting point for molecular classification







WCMC a leader in state-of-the-art DNA sequencing for prostate cancer



7 prostate cancer whole genomes
Berger et al, *Nature* 2011

112 whole exomes
Barbieri et al, *Nature Genetics* 2012

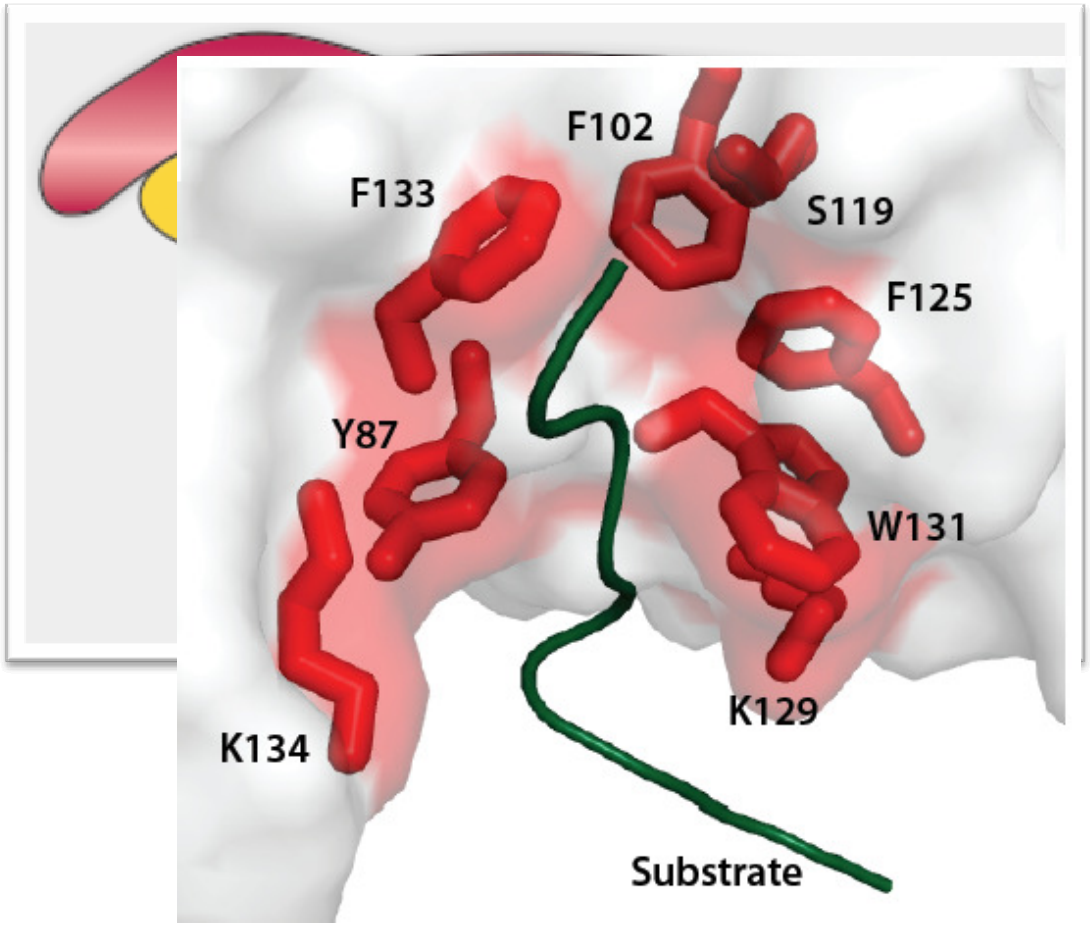
57 whole genomes
Baca et al, *Cell* 2013

SPOP mutations in Prostate Cancer

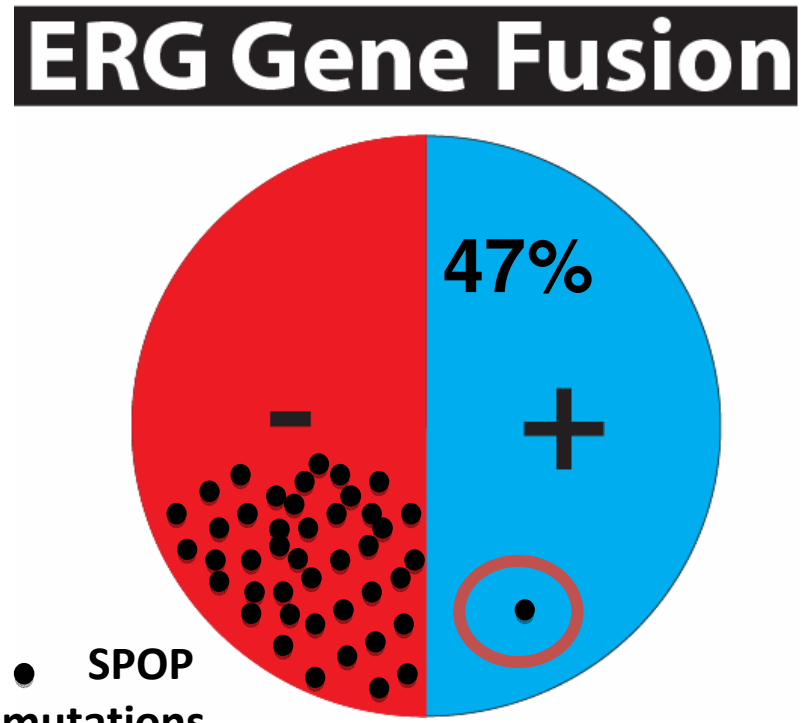
Prostate Cancer Samples (N= 453)

↓

SPOP mutations **10%** (45 of 453)



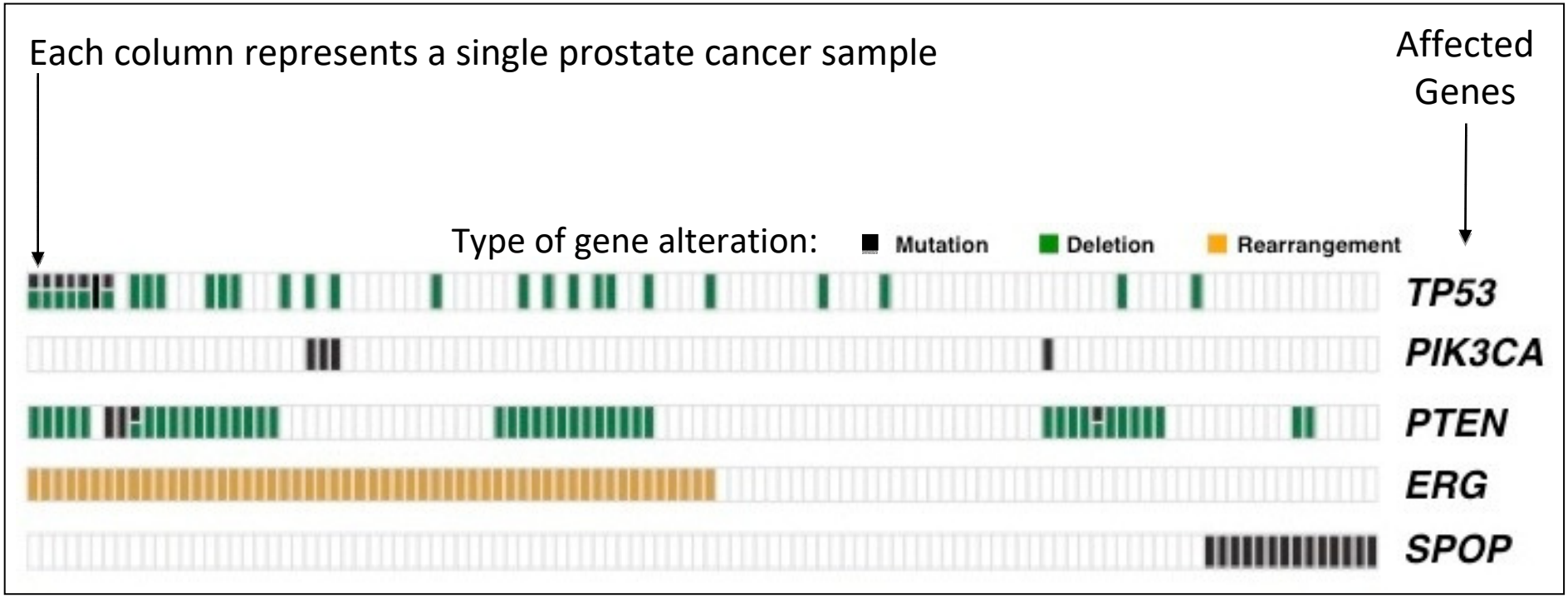
SPOP mutation & ERG rearrangement



SPOP mutation	ERG rearrangement +	ERG rearrangement -
+	1	43
-	190	202

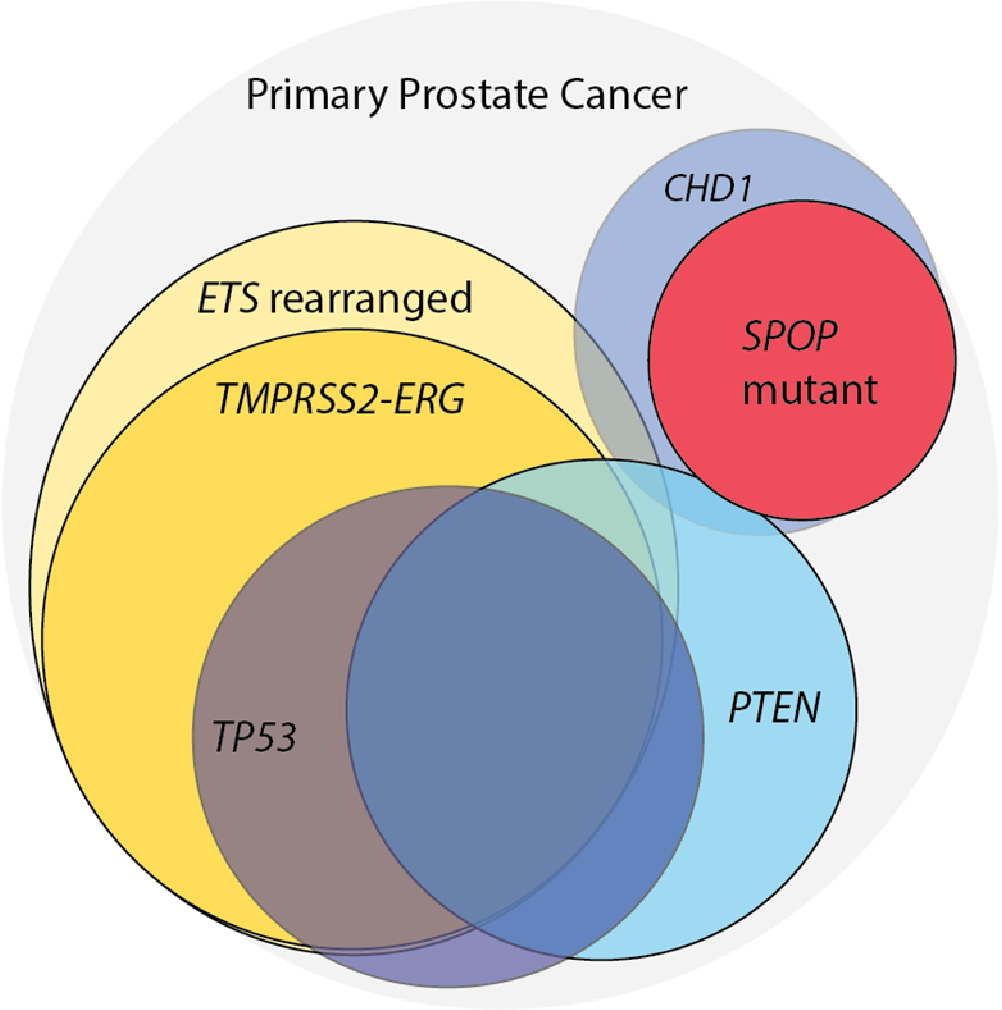
Combined cohorts
(n=436)
P<0.0001

SPOP mutations define a distinct molecular class of prostate cancer

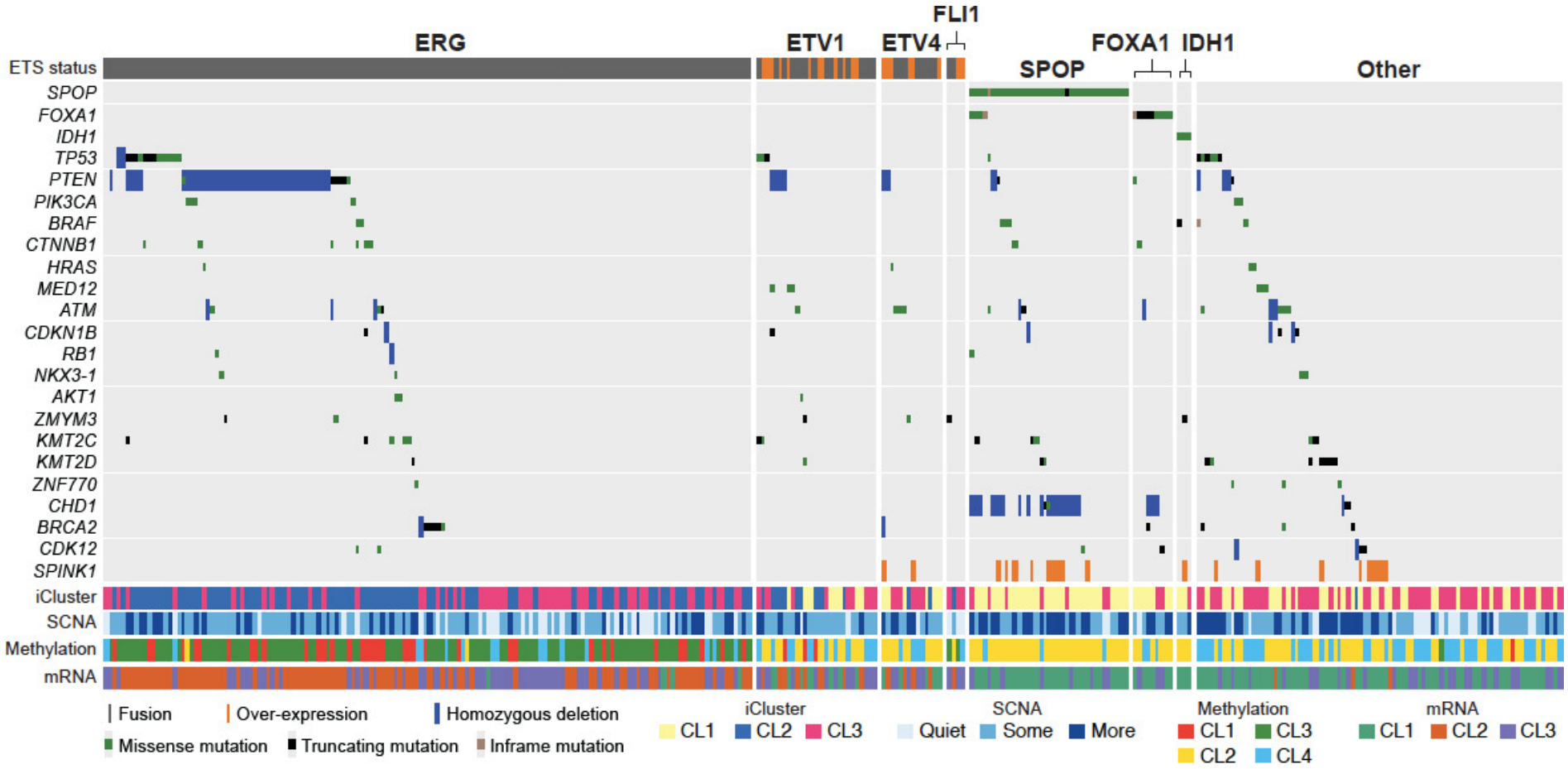


Barbieri et al, Nature Genetics 2012

SPOP mutation defines a distinct molecular class of prostate cancer

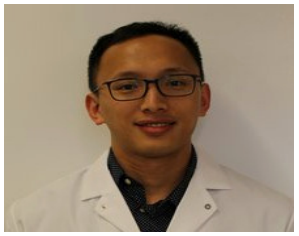


The Cancer Genome Atlas (TCGA)

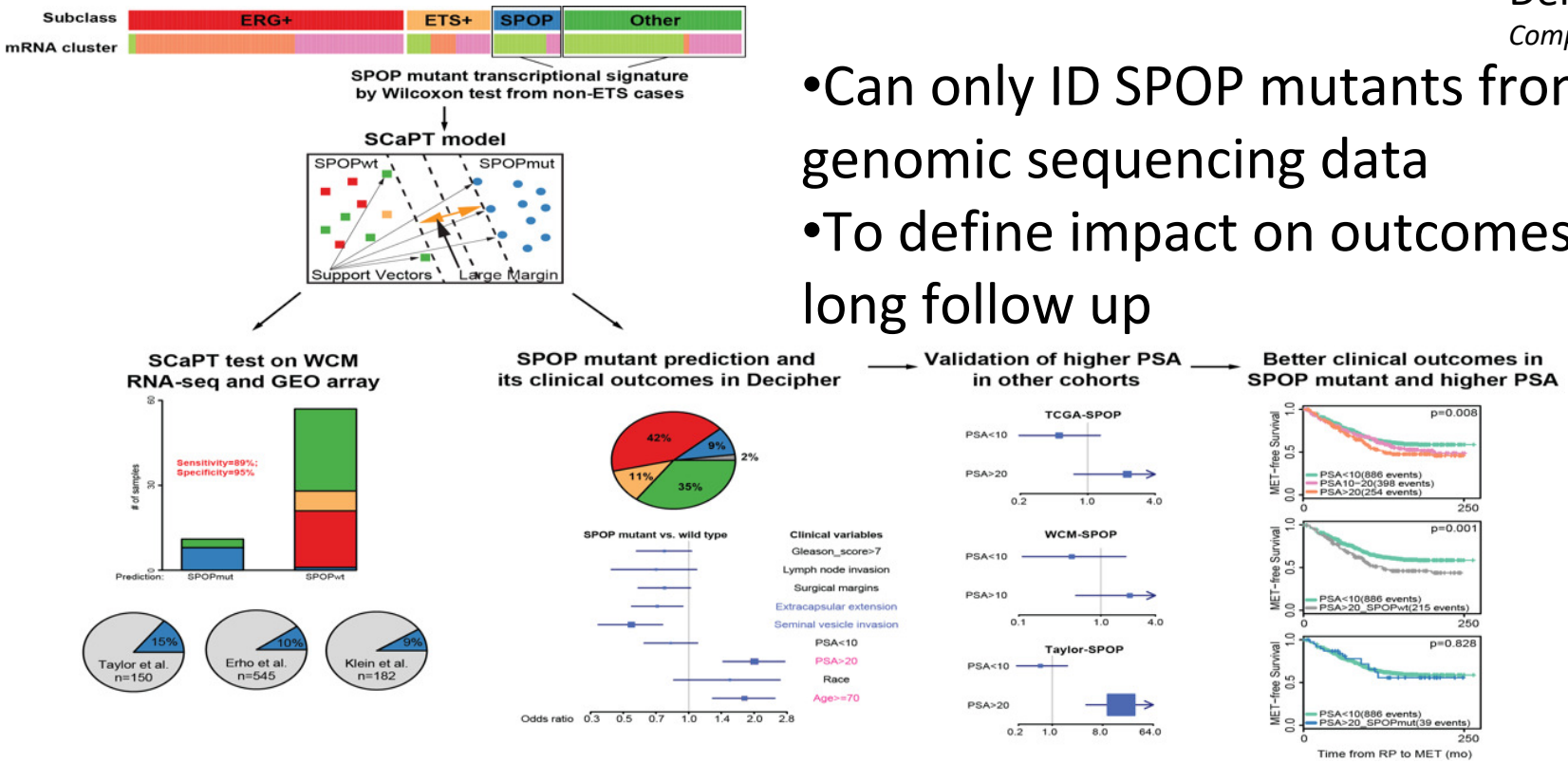


TCGA et al, Cell 2015

IMPACT OF SPOP MUTATION ON PATIENT OUTCOMES

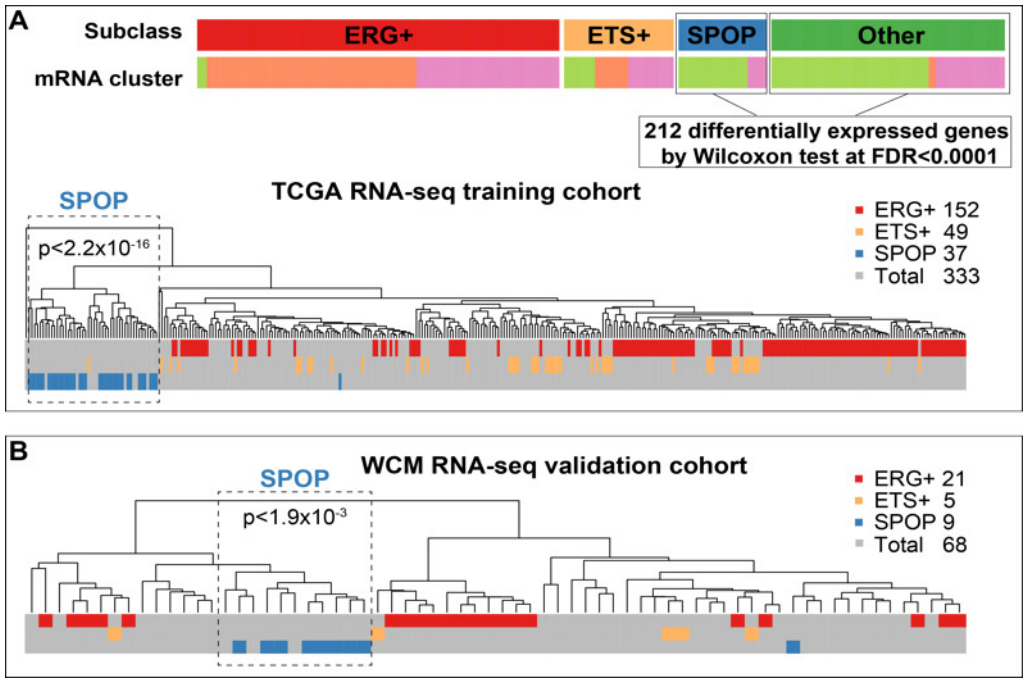


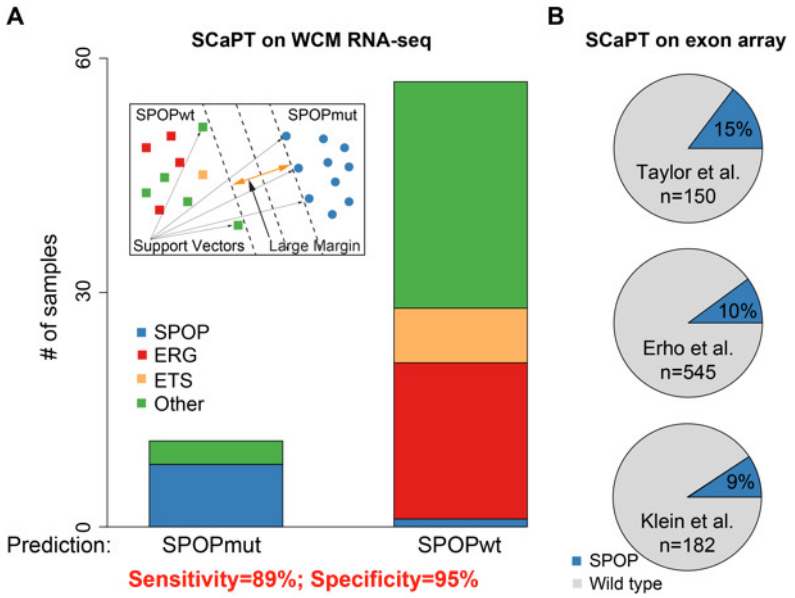
Deli Liu, PhD
Computational Biologist



- Can only ID SPOP mutants from genomic sequencing data
- To define impact on outcomes, need long follow up

Building an SPOP-mutant classifier





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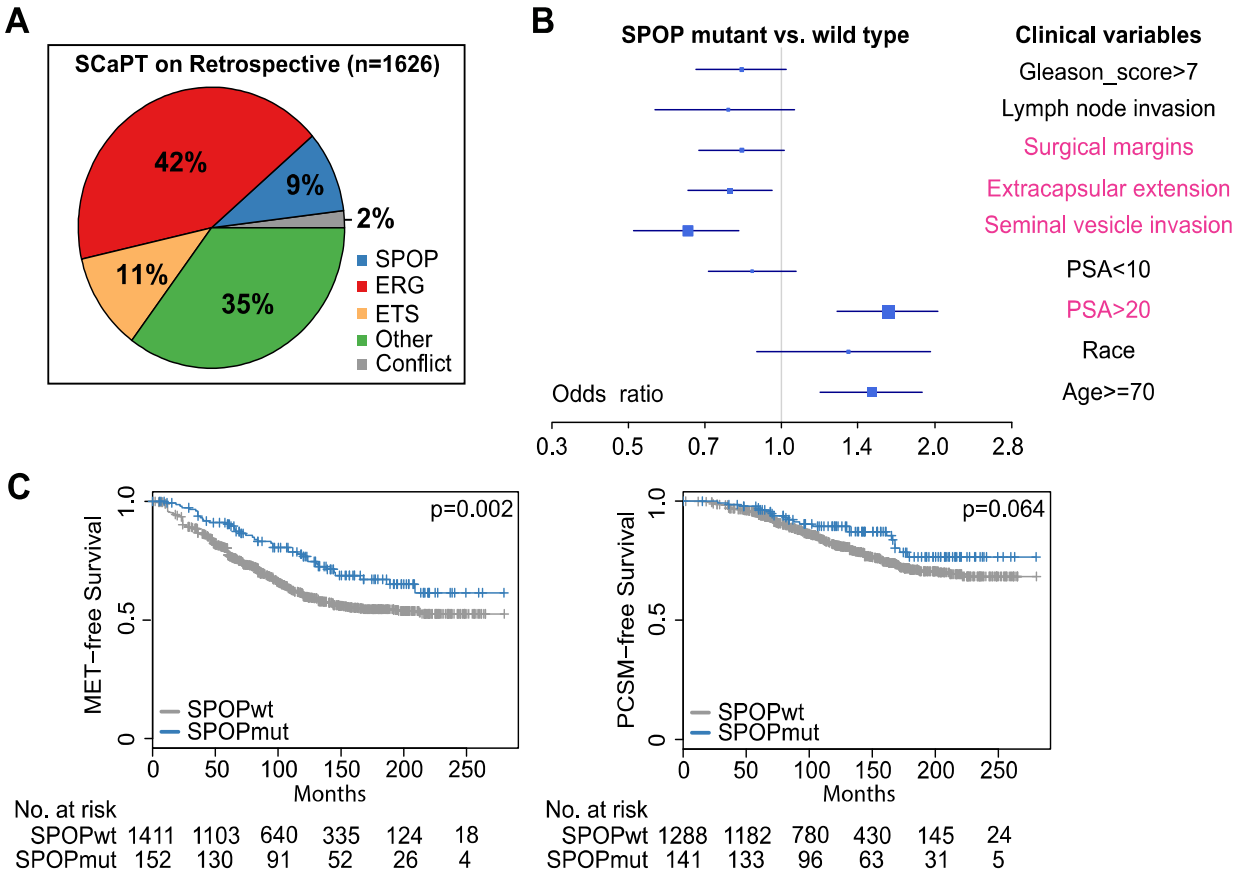
DECIPHER
BY GENOME DX

- Gene expression:
  - Affymetrix Exon arrays
- 6 Retrospective cohorts
  - 1742 radical prostatectomy patients
- Robust clinical annotation and long follow up (decades)

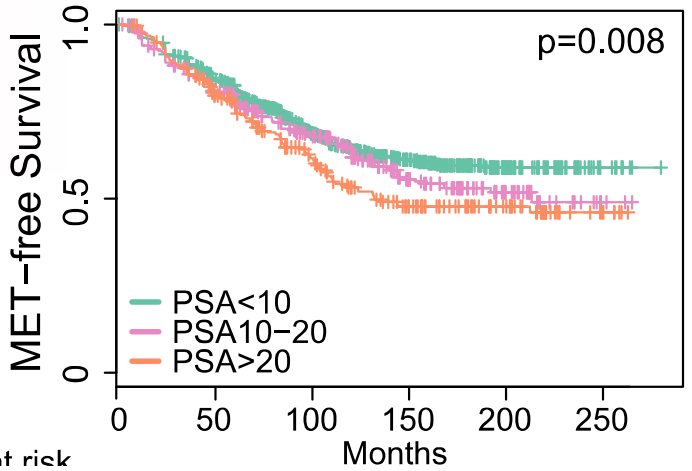
- Prospective cohort
  - (n > 6500)
  - SPOP mutant → **High PSA Lower stage**

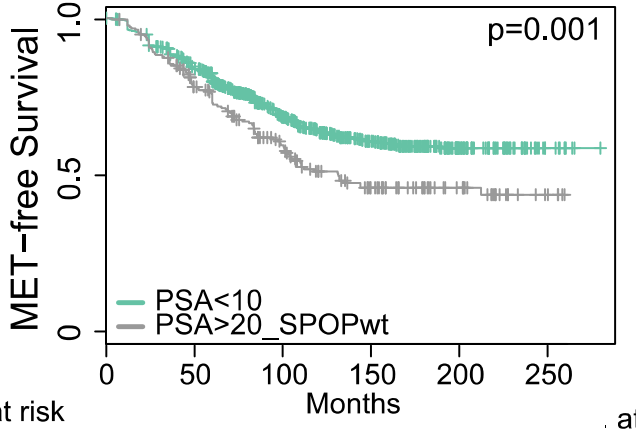


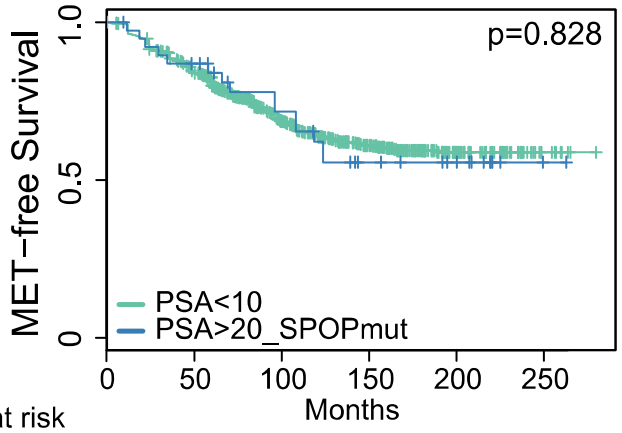
Molecular subtype impacts interpretation of PSA and risk

2017 AUA/ASTRO Guidelines

TABLE 3: Risk Stratification for Localized Prostate Cancer	
Very Low Risk	PSA <10 ng/ml AND Grad AND no core with >50% i
Low Risk	PSA <10 ng/ml AND Grad
Intermediate Risk	PSA 10-<20 ng/ml OR Gra · Favorable: Grade Gr · Unfavorable: Grade Group 3 (with PSA < 20)
High Risk	PSA ≥20 ng/ml OR Grade







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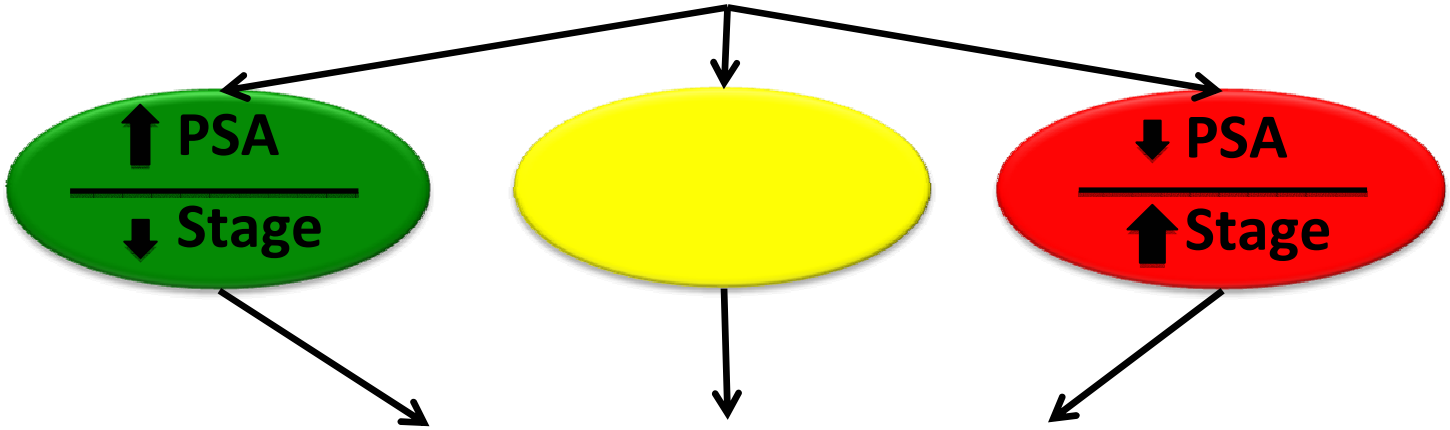
Genomic Classification



Pre-treatment risk stratification?

Post-treatment recurrence?

Treatment response in metastatic disease?

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Prostate Cancer is Clinically Heterogeneous

- **Indolent** vs. **aggressive**
- Current information inadequately distinguish

Problems with current care

- **Overtreatment** of indolent prostate cancer with radical therapy

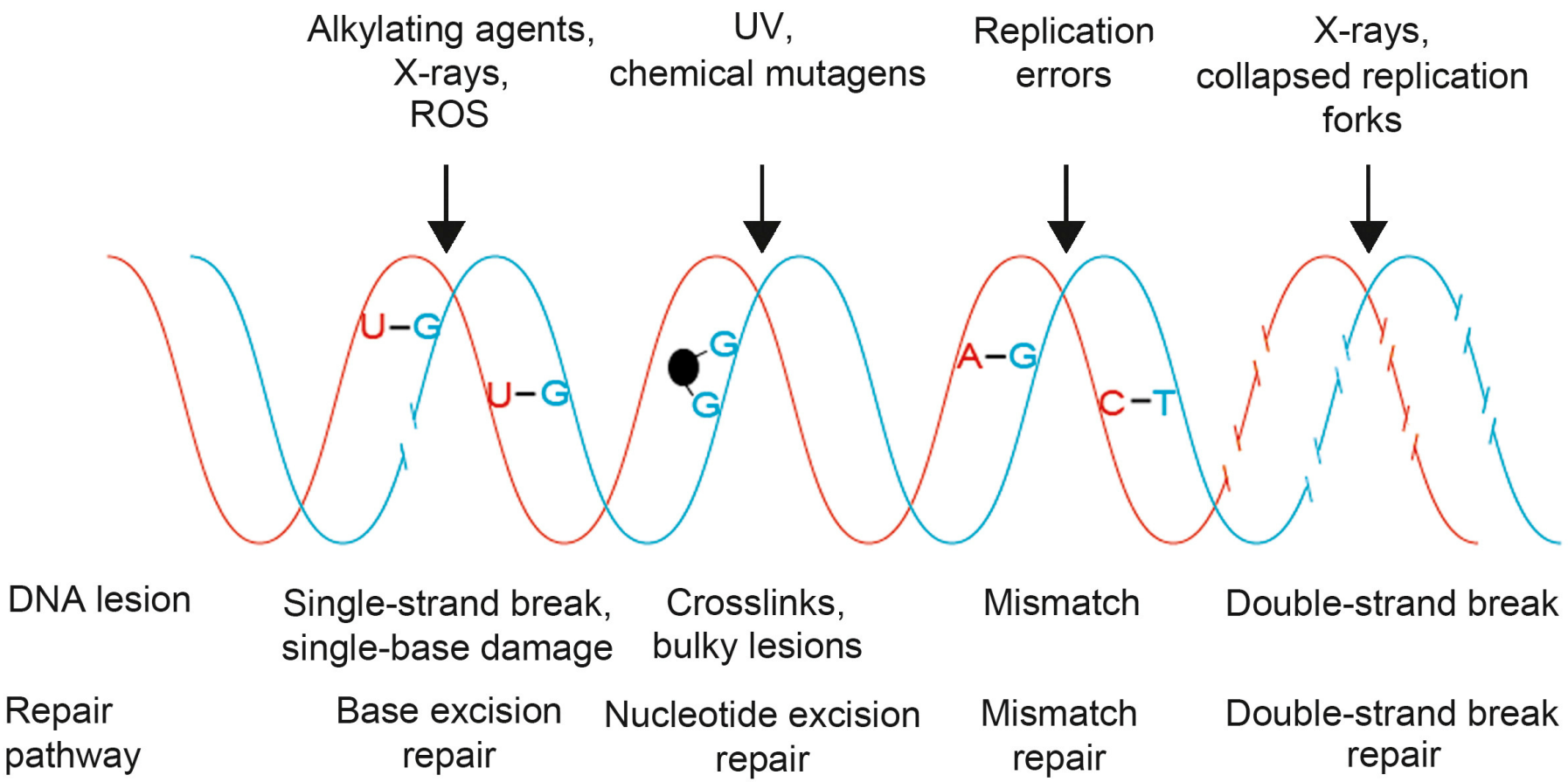
→high morbidity

- **Undertreatment** of lethal prostate cancer

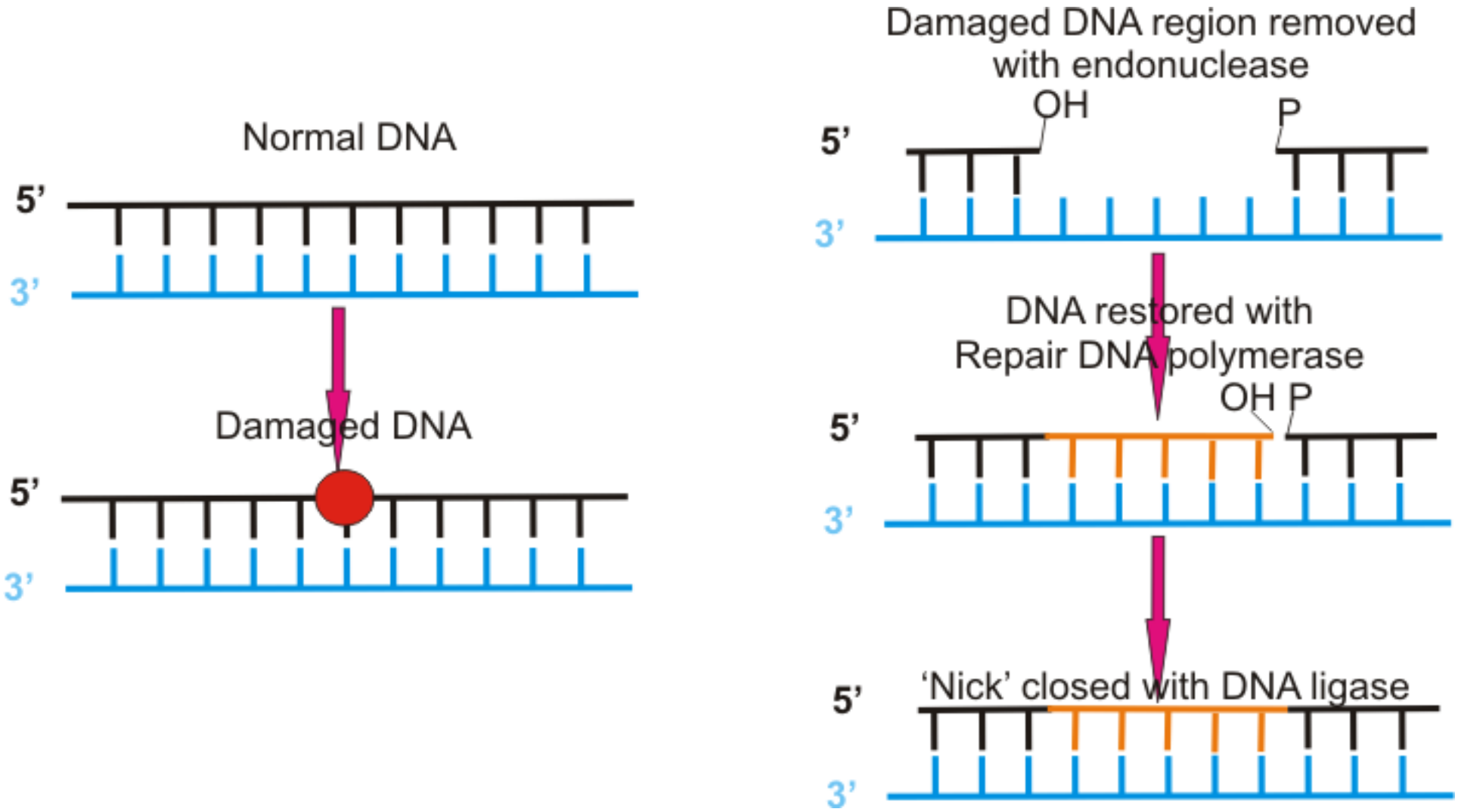
→continued mortality

HOW TO MATCH THE RIGHT TREATMENTS TO THE RIGHT PATIENTS?

DNA Damage and Repair in Prostate Cancer



DNA Repair



https://commons.wikimedia.org/wiki/File:Dna_repair.png

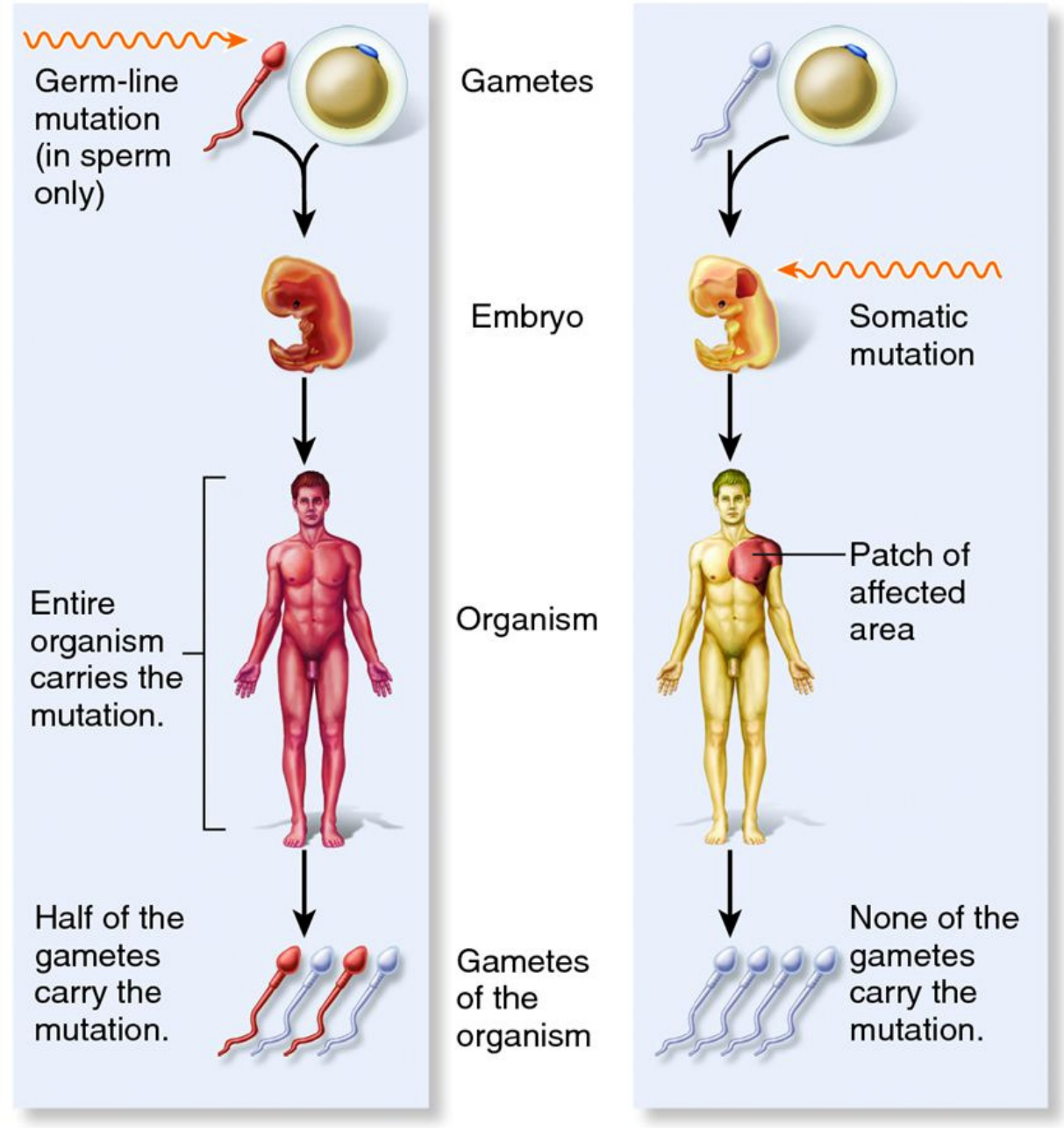
GERMLINE

In every cell

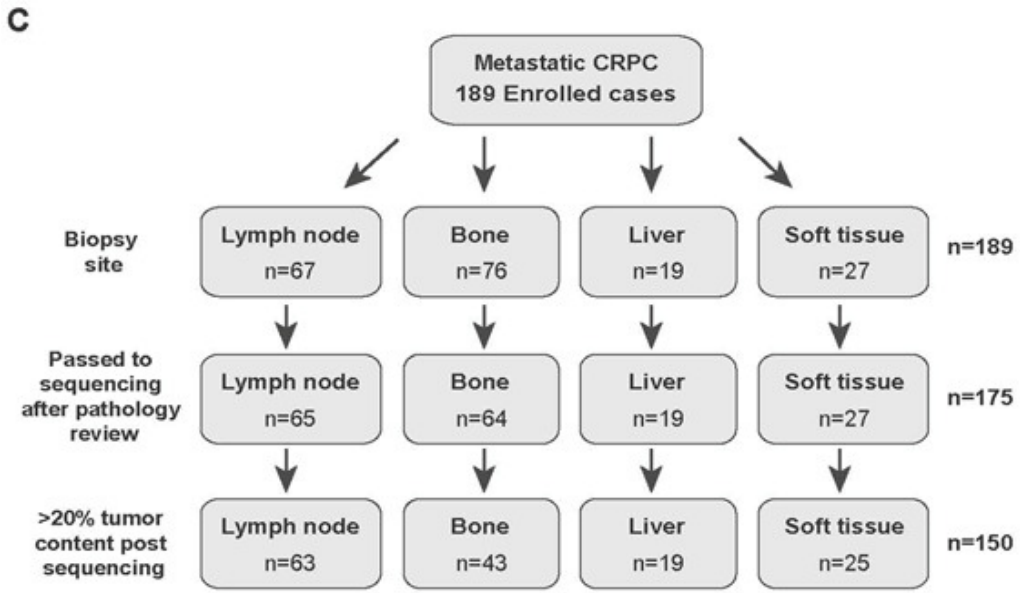
Hereditary

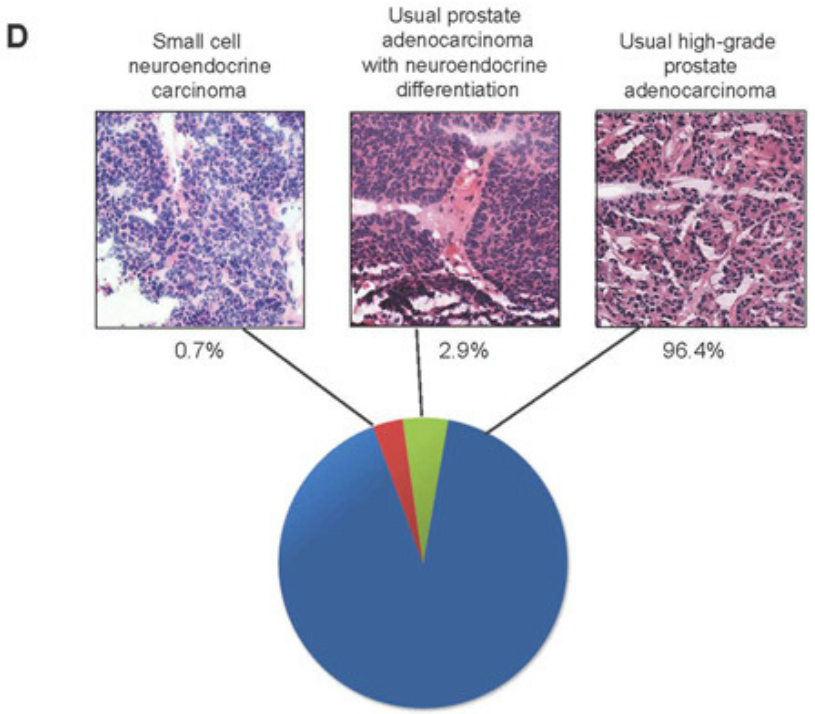
SOMATIC

In the cancer



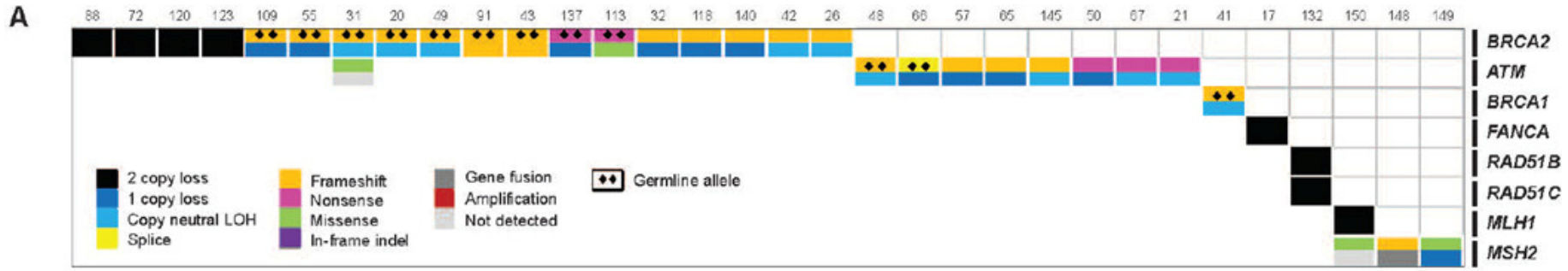
SU2C/PCF CRPC 500: Metastatic Prostate Tumors





Cell. 2015 May 21; 161(5): 1215–1228.

Metastatic Prostate Tumors



About 20% of castration-resistant metastatic prostate cancers had mutations in DNA repair genes.

Cell. 2015 May 21; 161(5): 1215–1228.

Original Article

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

The NEW ENGLAND JOURNAL of MEDICINE

August 4, 2016

- Inherited mutations in DNA-repair genes found in **nearly 12%** of **men with metastatic prostate cancer**, as compared with 2.7% in an unselected general population.

Germline DNA-Repair Gene Mutations in Metastatic Prostate Cancer.

Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)

General population

2.7%

Localized cancers

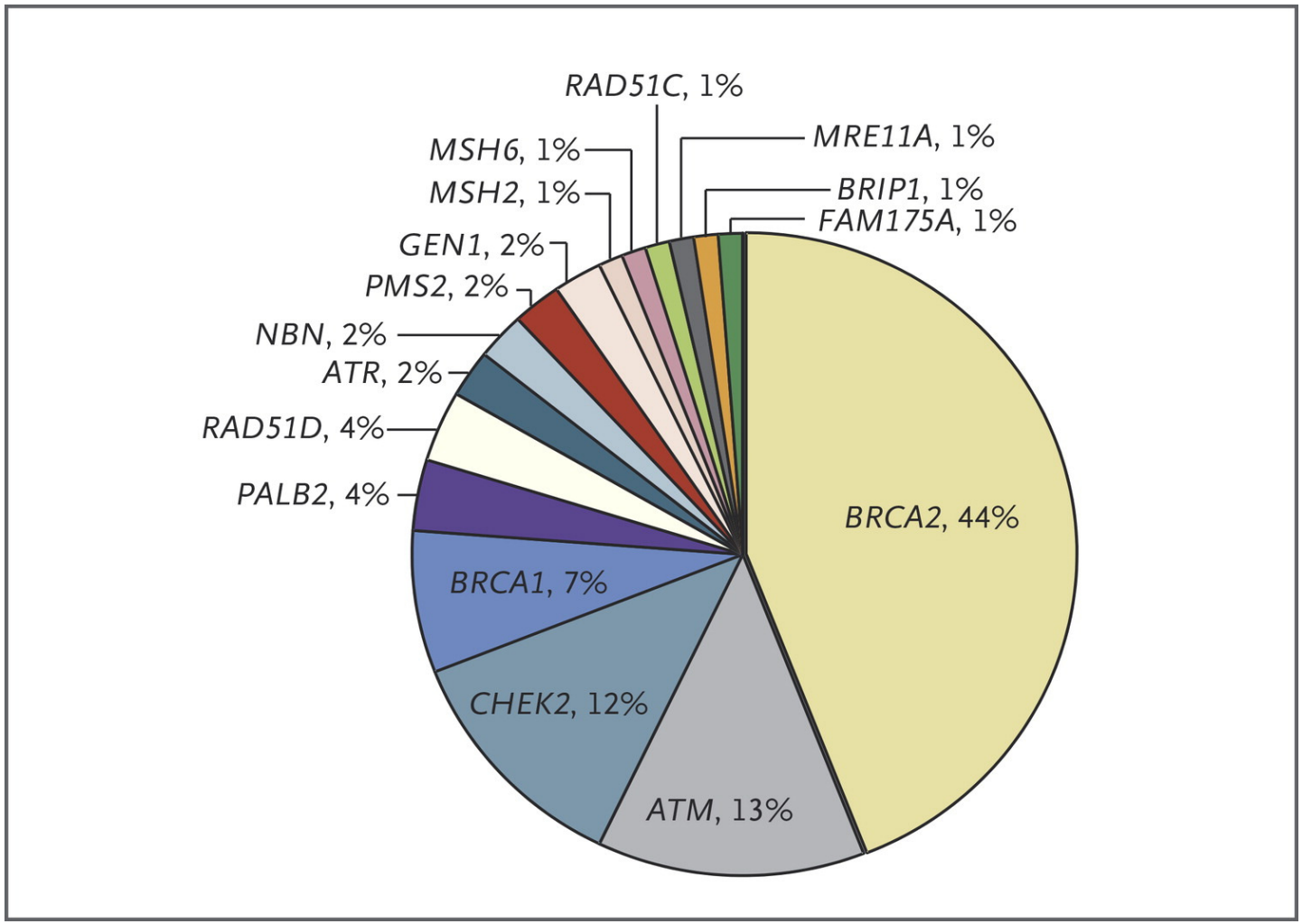
4.6%

Metastatic cancers

11.8%

Pritchard CC et al. N Engl J Med 2016;375:443-453.

Distribution of Presumed Pathogenic Germline Mutations.



Pritchard CC et al. N Engl J Med 2016;375:443-453.

Conclusions

- In our multicenter study, the incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8%, which was significantly higher than the incidence among men with localized prostate cancer.
- The frequencies of germline mutations in DNA-repair genes among men with metastatic disease **did not differ significantly according to age at diagnosis or family history of prostate cancer**.

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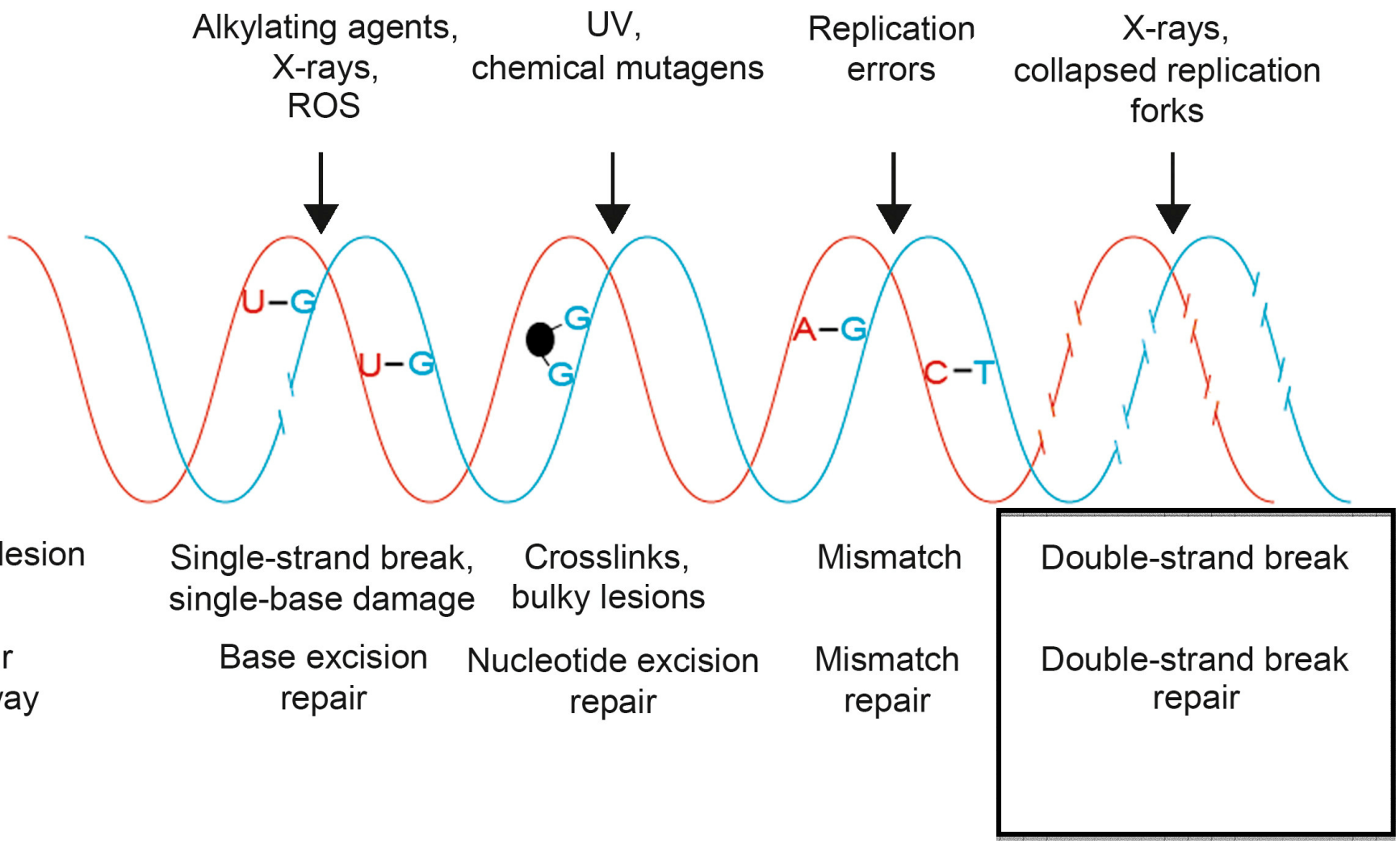
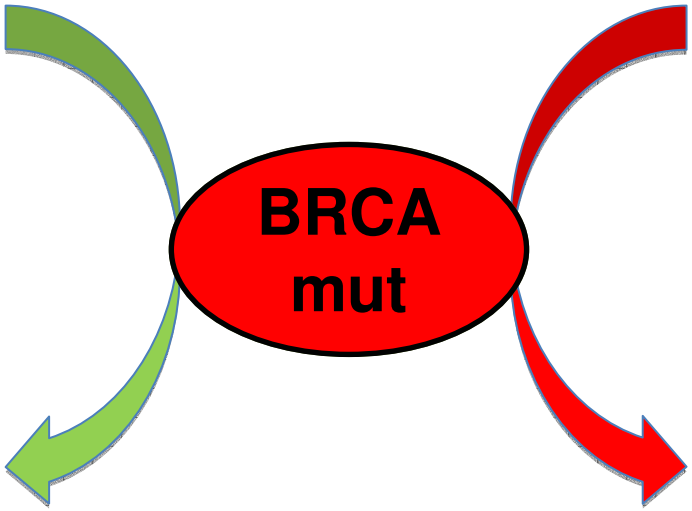
DNA Repair in Prostate Cancer



DNA break repair defects

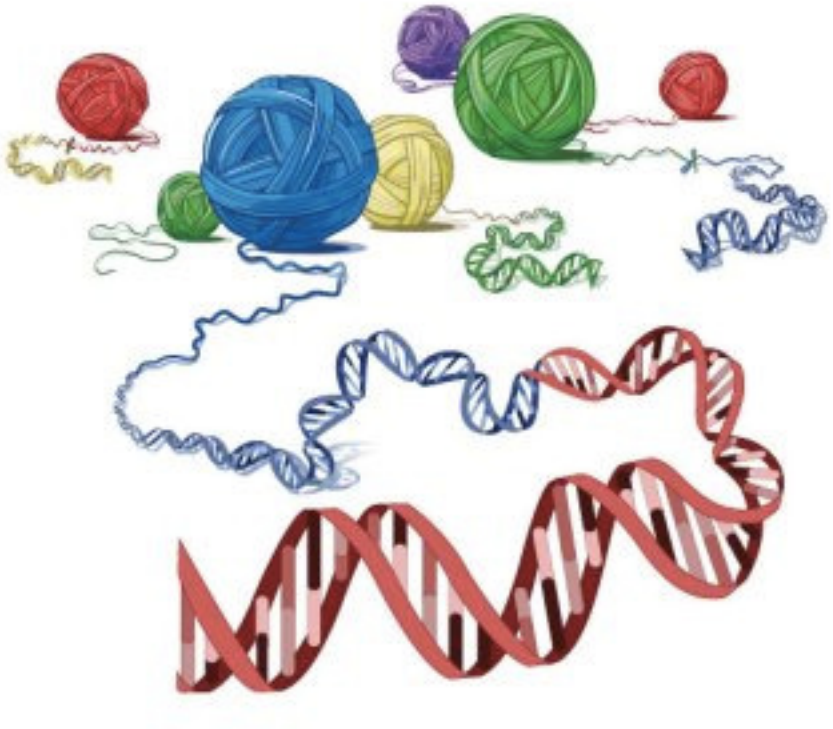
Double-strand DNA break



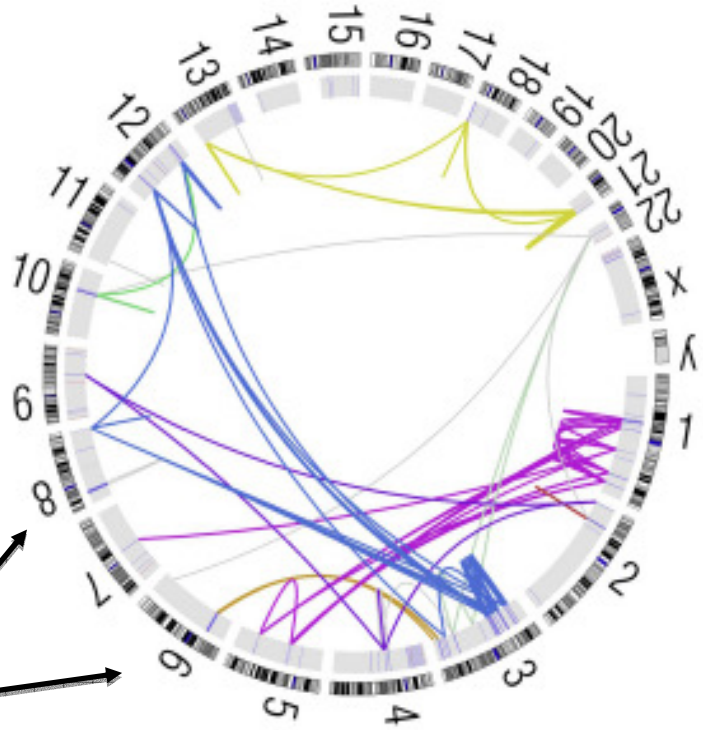
Error-free Repair Mechanism

Error-prone Repair Mechanism

DNA Rearrangements in Prostate Cancer



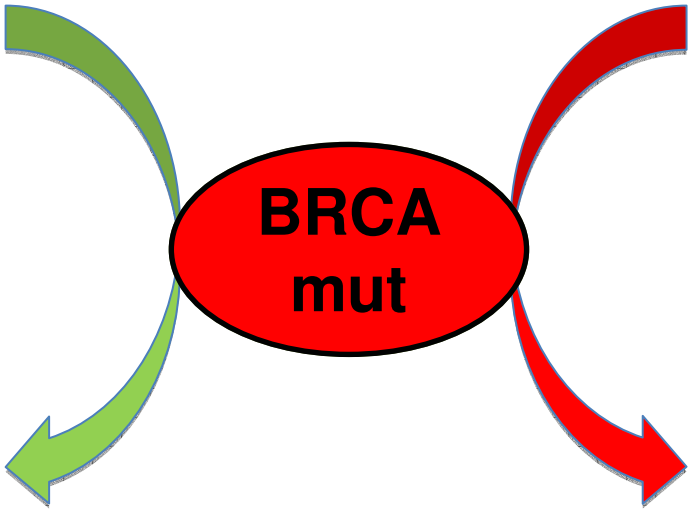
Complex patterns of DNA rearrangements



Chromosome numbers

DNA break repair defects

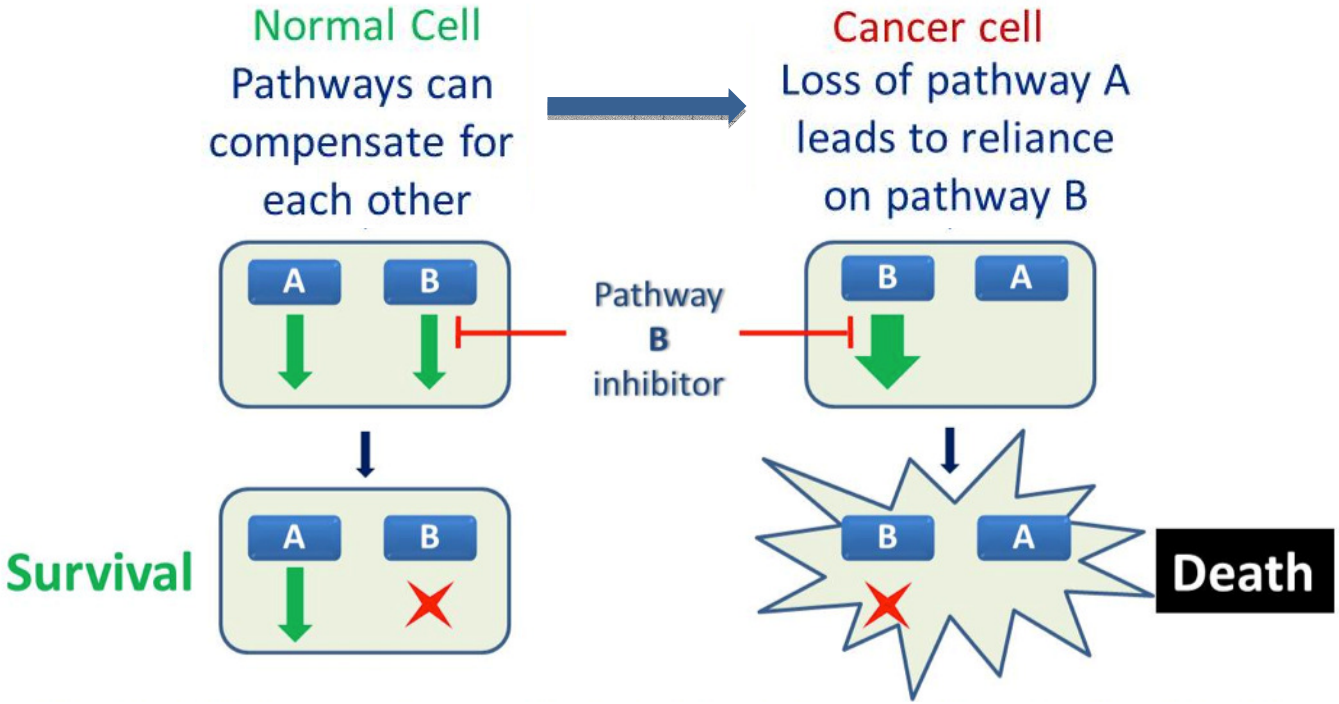
Double-strand DNA break



Error-free Repair Mechanism

Error-prone Repair Mechanism

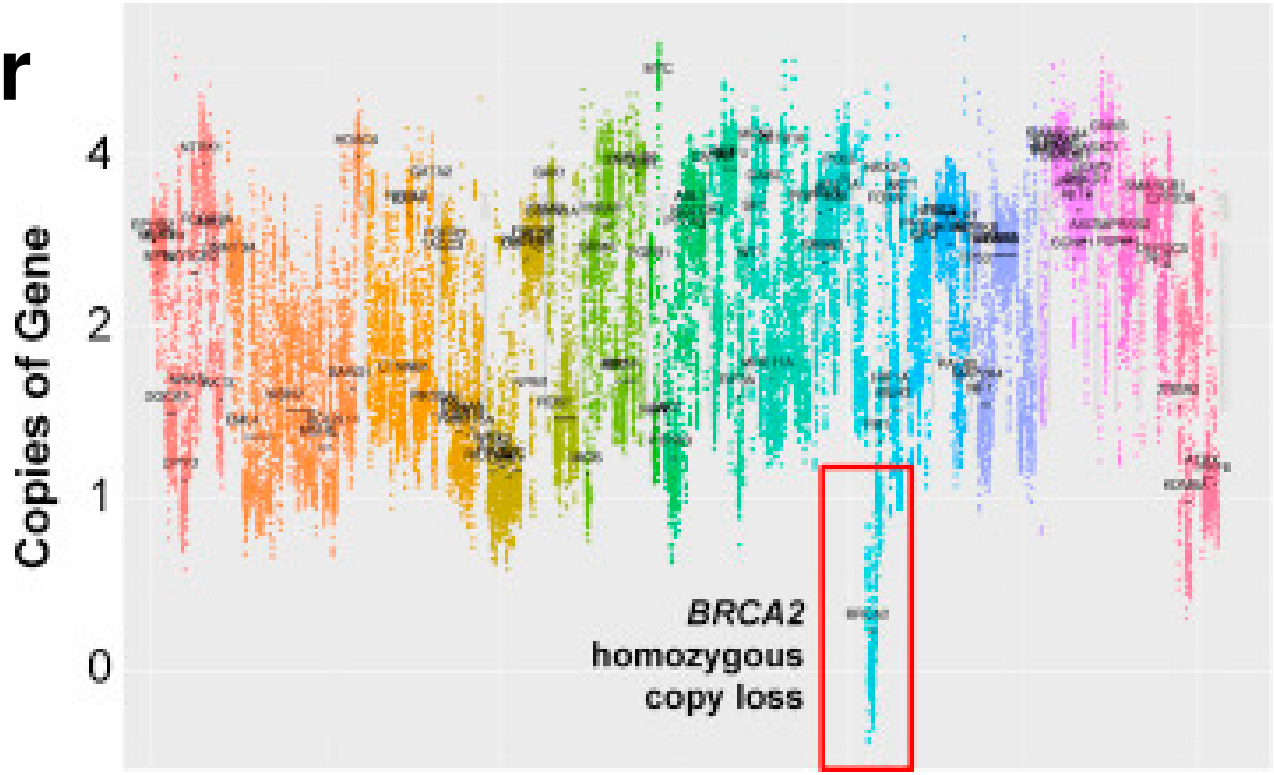
DNA Repair as an Achilles Heel in Cancer: Synthetic Lethality



Sensitivity to specific DNA damaging agents

Opportunity for novel therapeutic interventions

DNA repair defects in prostate cancer



Heather H. Cheng, Colin C. Pritchard, Thomas Boyd, Peter S. Nelson, Bruce Montgomery

Biallelic Inactivation of BRCA2 in Platinum-sensitive Metastatic Castration-resistant Prostate Cancer

European Urology, Volume 69, Issue 6, 2016, 992–995

http://dx.doi.org/10.1016/j.eururo.2015.11.022

DNA repair defects make prostate cancer sensitive to DNA damaging therapy

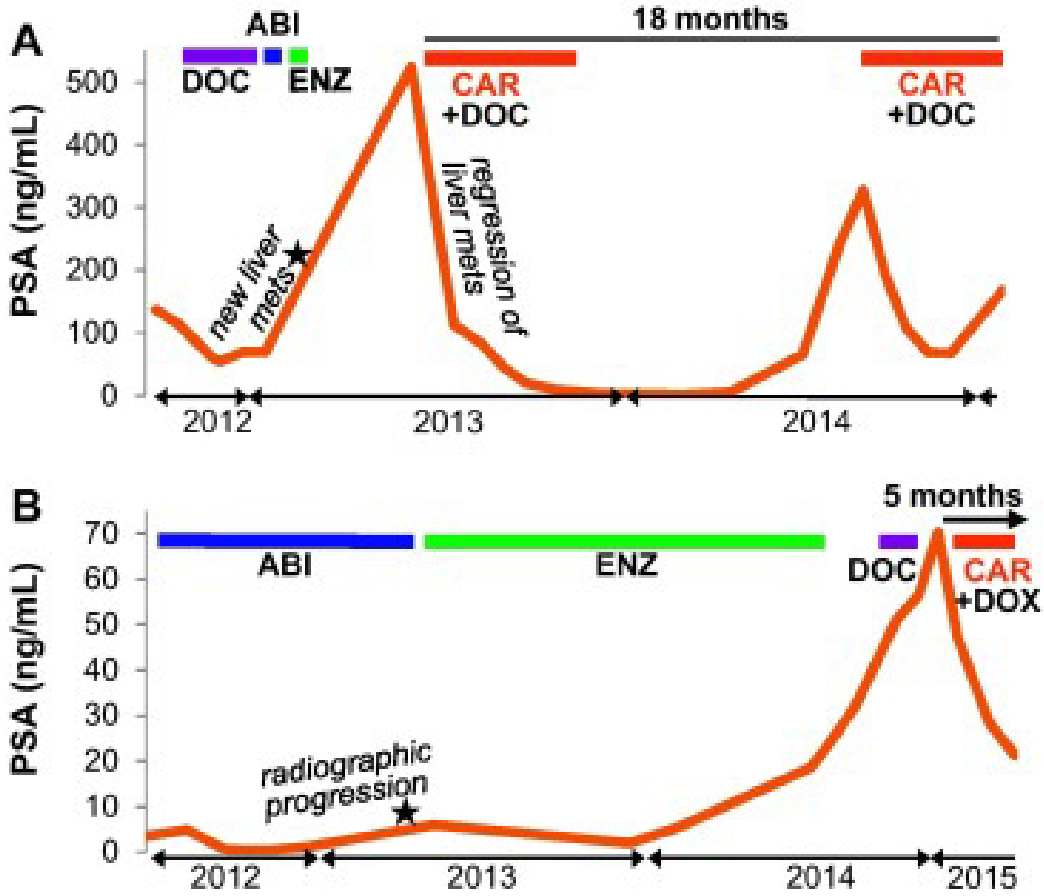


Fig. 1. Clinical treatment course and prostate-specific antigen response. (A) Patient 1, (B) patient 2, (C) patient 3. Platinum chemotherapies are in bold red type. Stars denote time of metastatic biopsies.ABI = abiraterone; CAR = carboplatin; CIS = cisplatin;...

Heather H. Cheng, Colin C. Pritchard, Thomas Boyd, Peter S. Nelson, Bruce Montgomery

European Urology, Volume 69, Issue 6, 2016, 992–995

http://dx.doi.org/10.1016/j.eururo.2015.11.022

Original Article

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

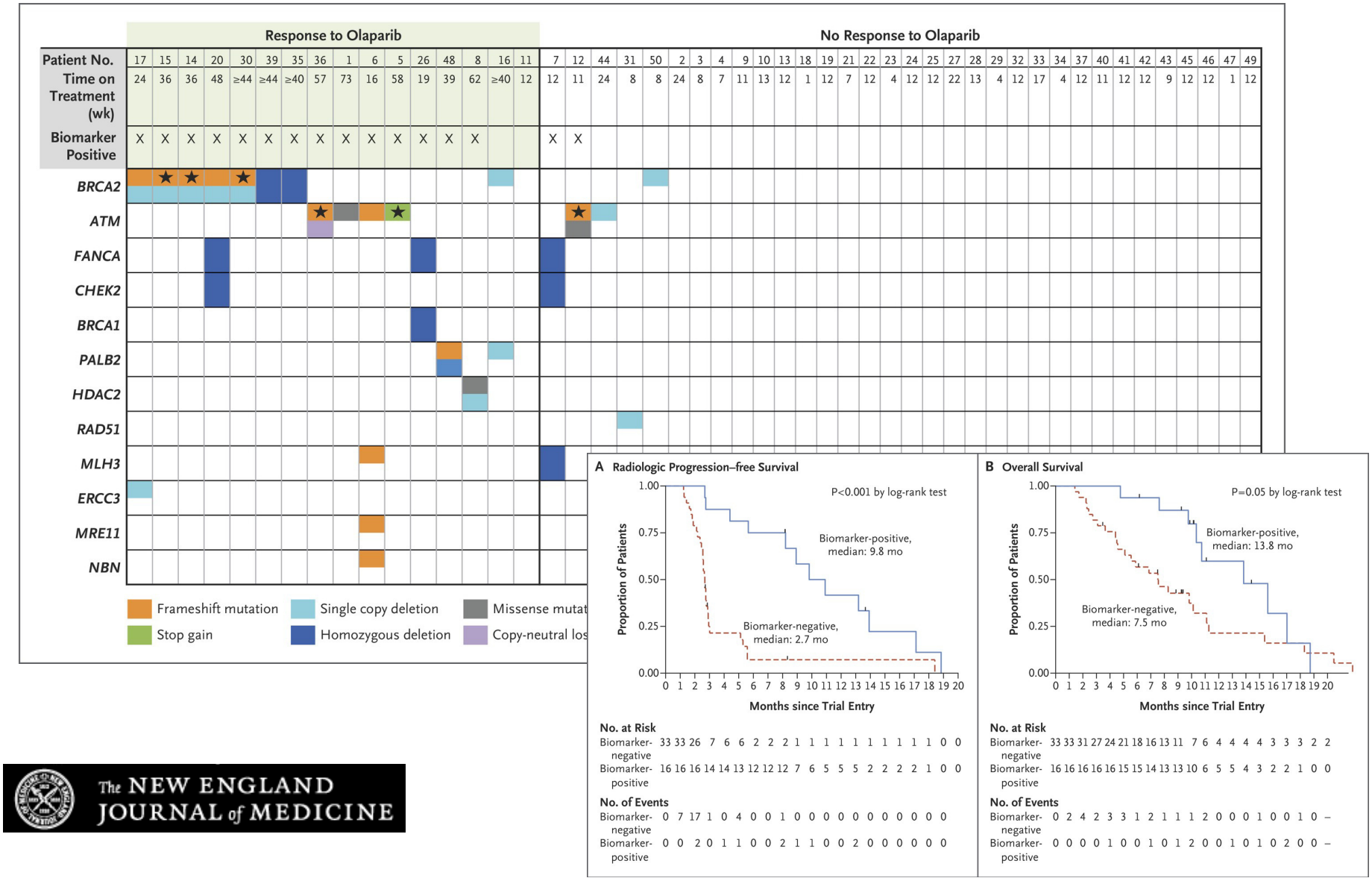
Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., …., Rosalind Eeles, M.D., Ph.D., Gerhardt Attard, M.D., Ph.D., Christopher J. Lord, Ph.D., Alan Ashworth, Ph.D., Mark A. Rubin, M.D., Karen E. Knudsen, Ph.D., Felix Y. Feng, M.D., Ph.D., Arul M. Chinnaiyan, M.D., Ph.D., Emma Hall, Ph.D., and Johann S. de Bono, M.B., Ch.B., Ph.D.

October 29, 2015

The NEW ENGLAND JOURNAL of MEDICINE

- 49 patients with metastatic, castration-resistant prostate cancer
- PARP inhibitor olaparib
- Anemia and fatigue were the major toxic effects.

14/16 patients with response has defects in DNA repair genes



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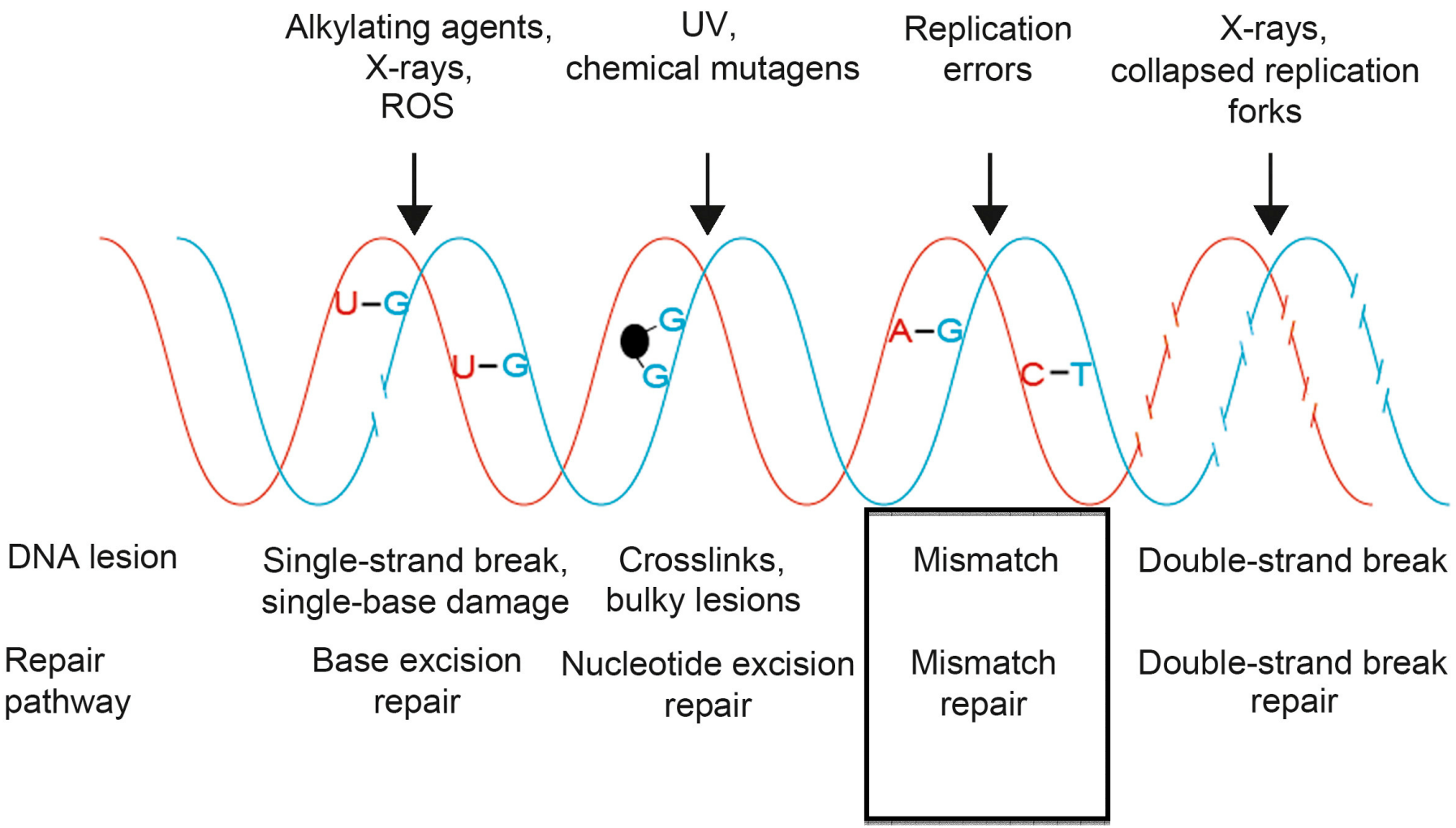
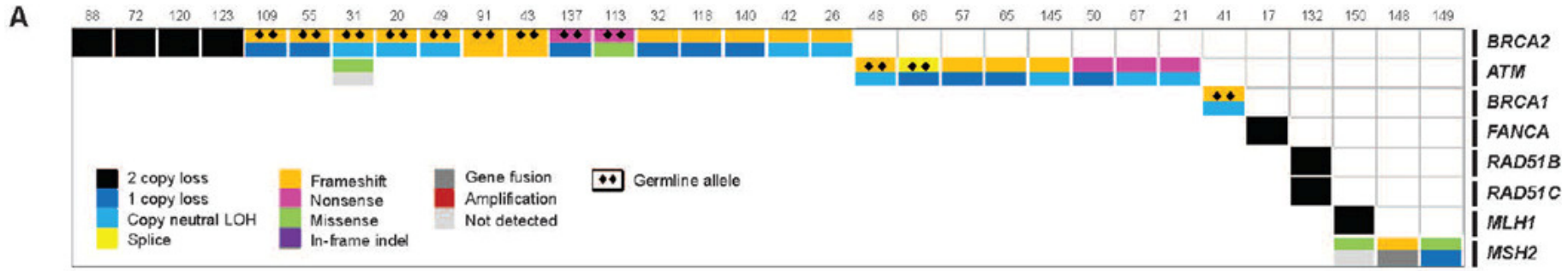
DNA Repair in Prostate Cancer



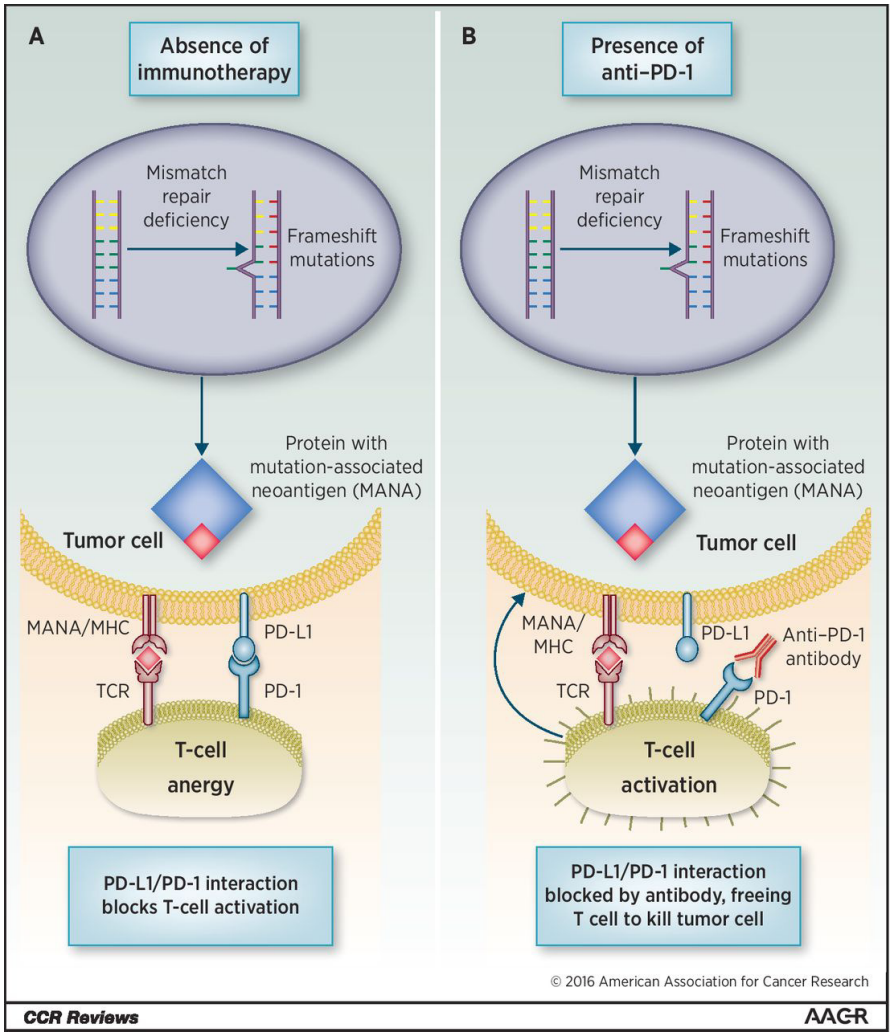
Metastatic Prostate Tumors



About 5% of castration-resistant metastatic prostate cancers have mutations in mismatch repair genes.

Cell. 2015 May 21; 161(5): 1215–1228.

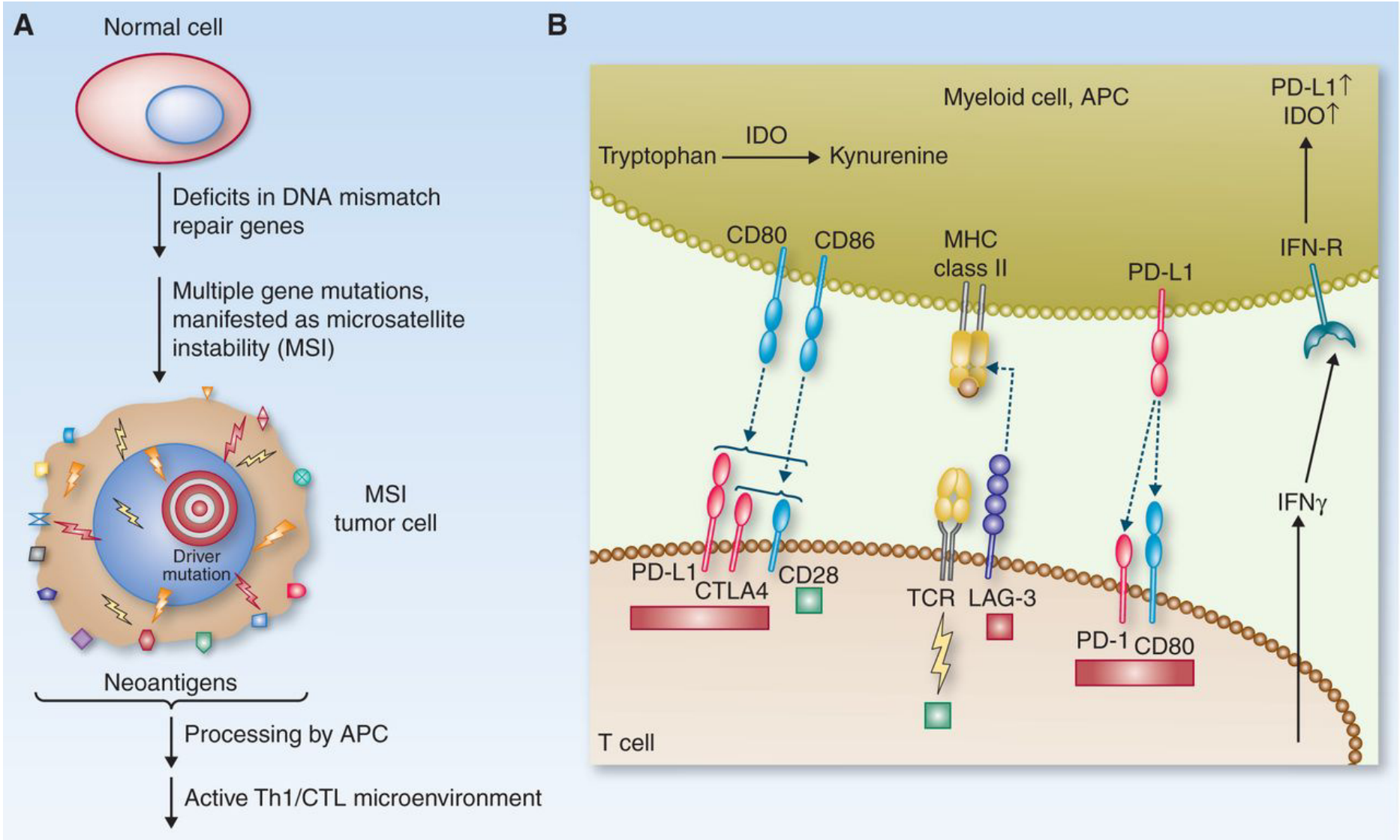
Proposed relationship between MSI status and immunologic response.



Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Clinical Cancer Research
AACR American Association for Cancer Research

Immune microenvironment of MMR cancer.



Yanping Xiao, and Gordon J. Freeman Cancer Discovery 2015;5:16-18

AACR American Association for Cancer Research
CANCER DISCOVERY

May 2017: FDA approves Keytruda (pembrolizumab) for ANY cancer with MMR deficiency

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

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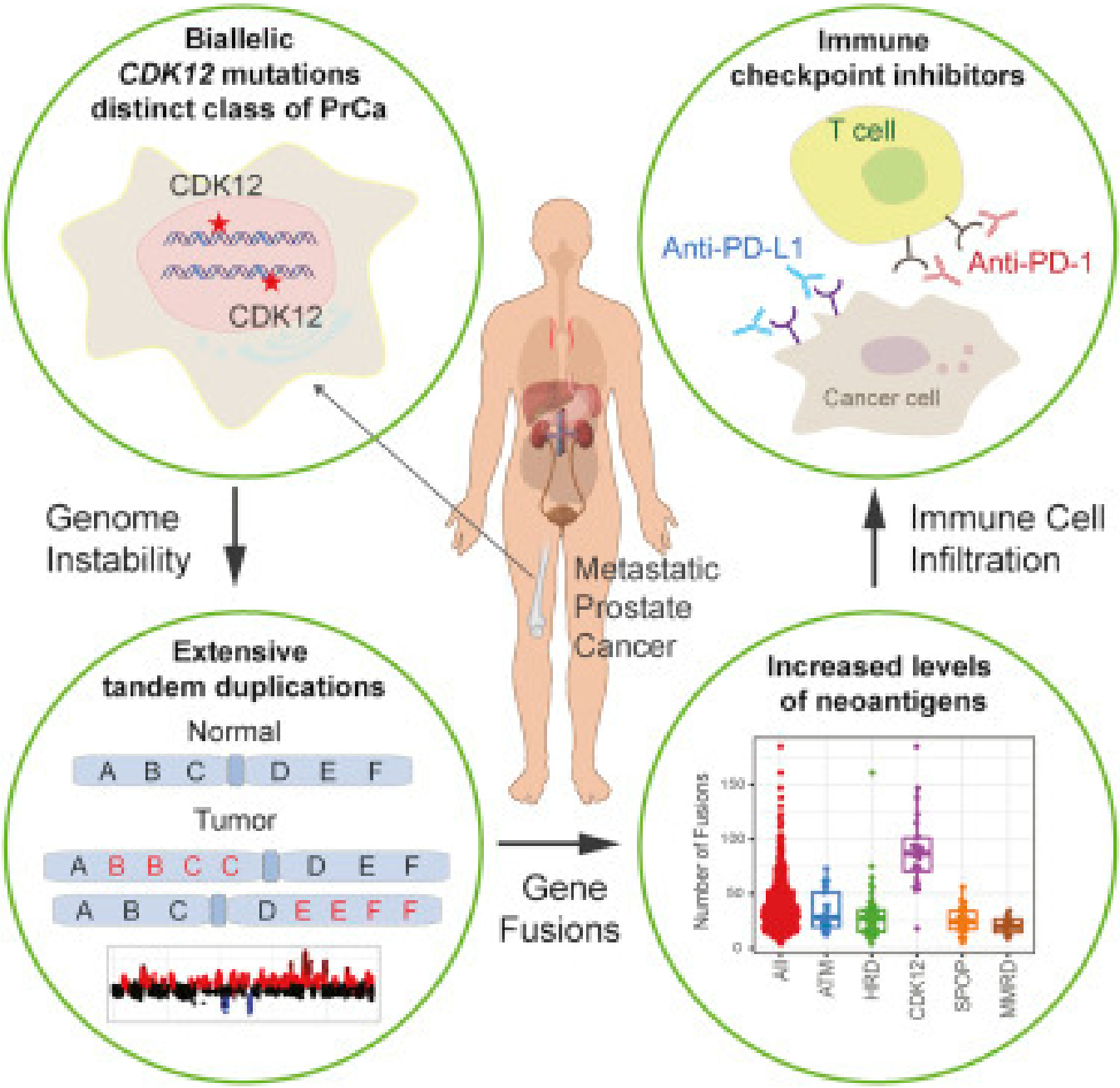
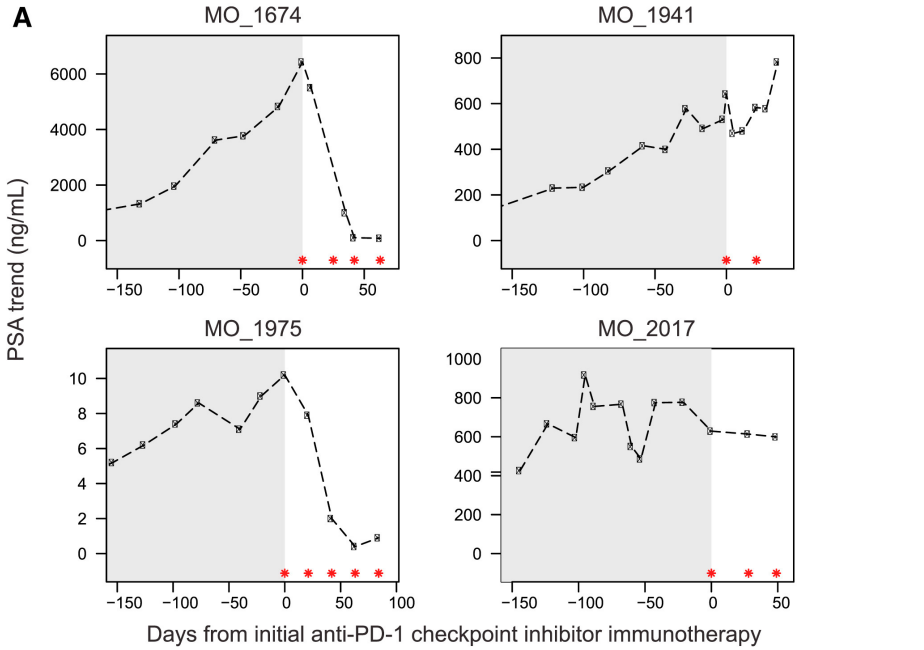
For Immediate Release May 23, 2017

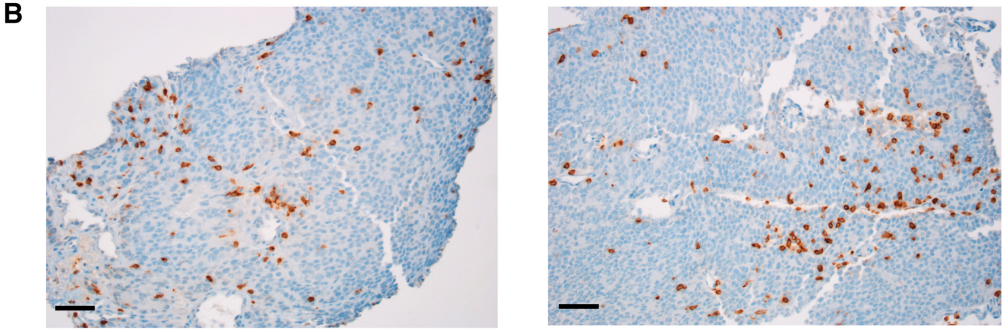
CDK12 mutations define a immunogenic class of prostate cancer

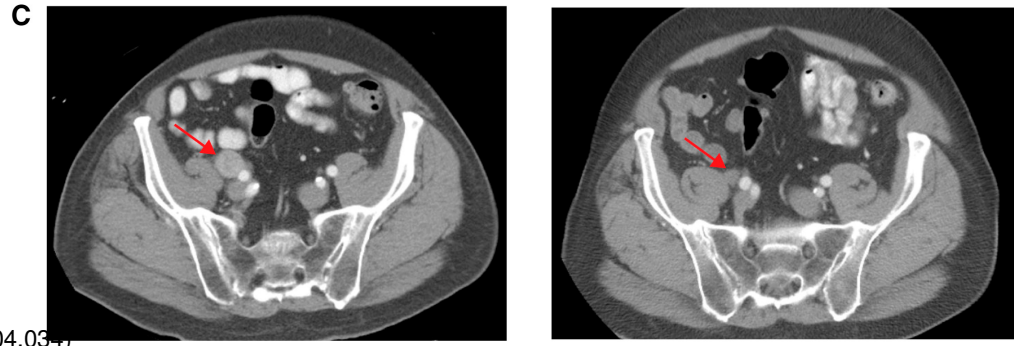


Cell 2018 173, 1770-1782.e14DOI: (10.1016/j.cell.2018.04.034)

Patients with CDK12 mutations may respond better to immune checkpoint inhibitors







Prior to anti-PD-1 immunotherapy
Right external iliac LN, 2.4 cm, PSA 8.9 ng/mL

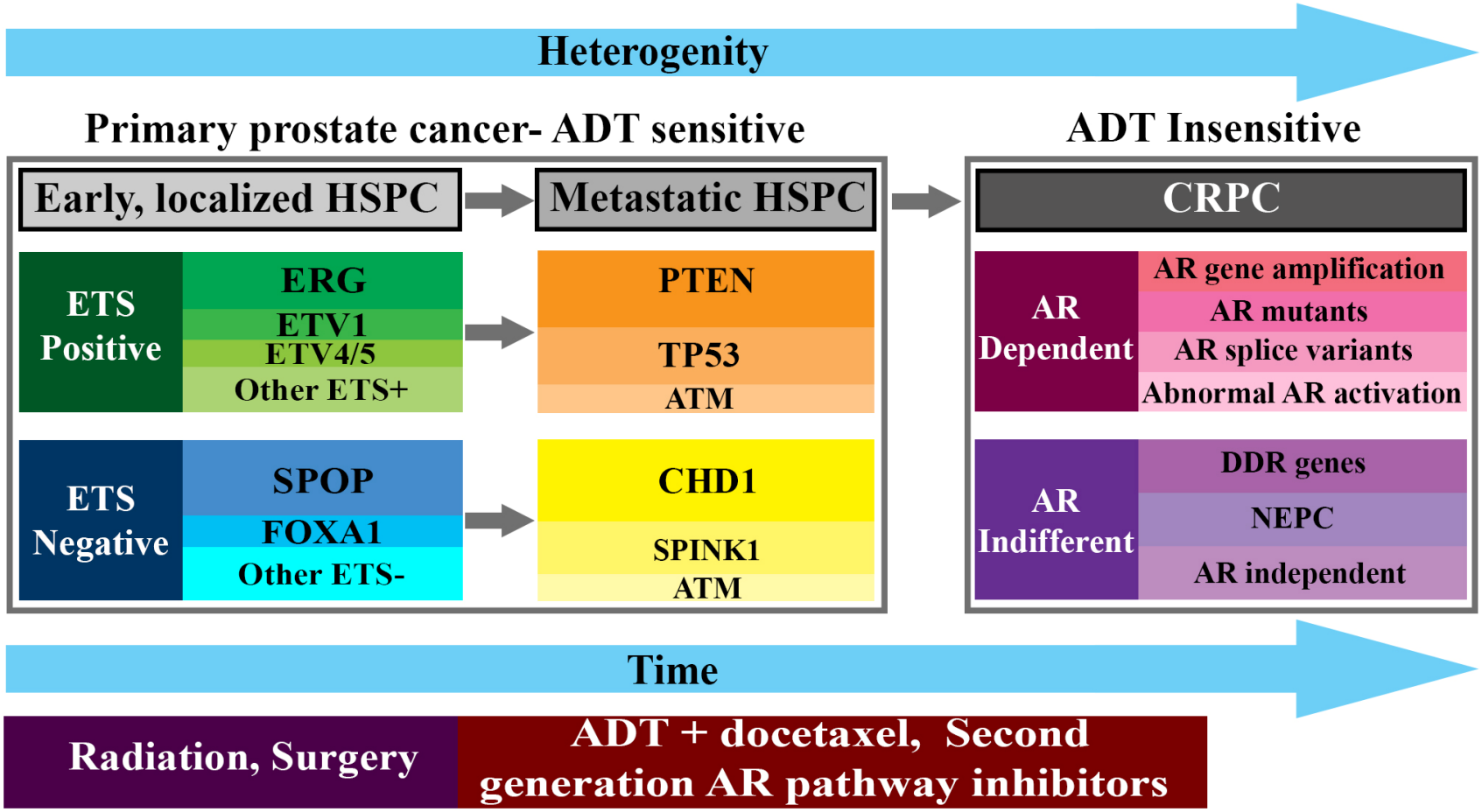
After 4 doses of anti-PD-1 immunotherapy
Right external iliac LN, 1.1 cm, PSA 0.9 ng/mL

Cell 2018 173, 1770-1782.e14DOI: (10.1016/j.cell.2018.04.034)

CONCLUSIONS – DNA repair

- DNA repair defects are common in prostate cancer
  - DNA repair alterations in up to 20% of **CRPC**
  - **Inherited** DNA repair alterations in up to 12% of men with metastatic prostate cancer
- Alterations in DNA repair may be targeted with specific therapies
  - Precision medicine approach to therapy

Distinct molecular classes of prostate cancer



Ongoing research at WCM will help refine the prostate cancer subclasses and develop improved therapeutic approaches