# Prostate cancer in the era of personalized medicine

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# Disclosures

**FUNDING:**
NCI, EDRN, PCF, SU2C/PCF, Starr Cancer Consortium, DOD, SNF, Krebsliga, SPHN, Sanofi-Aventis, Millennium Pharma, Eli-Lilly, Janssen, Roche, Novartis

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

**Scientific Board of Advisors:**
Neogenomics Labs, inc. and LynxDx , inc.

Focus on advanced prostate cancer

Will not cover molecular imagining (e.g., PSMA)

# Why?

ASCO special

# Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

Scott E. Eggener, MD[1]; R. Bryan Rumble, MSc[2]; Andrew J. Armstrong, MD, ScM[3]; Todd M. Morgan, MD[4]; Tony Crispino[5]; Philip Cornford, MD[6]; Theodorus van der Kwast, MD, PhD[7]; David J. Grignon, MD[8]; Alex J. Rai, PhD[9]; Neeraj Agarwal, MD[10]; Eric A. Klein, MD[11]; Robert B. Den, MD[12]; and Himisha Beltran, MD[13]

**TABLE 3.** Description of Assays

| Test(s) | Company | List Price,* USD | Sample Requirement | Clinical Utility/Intended Use | Comments |
|---|---|---|---|---|---|
| Decipher Biopsy and Decipher Postoperative | Decipher Biosciences (formally Genome Dx) | $5,150 | FFPE tissue from prostate biopsy, or | Categorize patients into low/high risk to stratify patients to surveillance *v* treatment (and intensity of treatment) | Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0 |
| | | | Prostate tissue after RP | Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant, or salvage therapy may be warranted | |
| Onco*type* Dx GPS | Genomic Health | $4,520 | Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted | Biopsy-based likelihood of adverse pathologic features (Grade Group ≥ 3 or extracapsular extension); identify those who may benefit from surveillance *v* treatment | GPS ranges from 0 to 100 based on mRNA expression of 17 genes across four pathways |
| Prolaris Biopsy and Prolaris Postprostatectomy | Myriad Genetic Laboratories | $3,900 | FFPE tissue from: prostate tumor biopsy, or prostatectomy specimens | Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management | mRNA expression of cell-cycle progression genes are used to calculate the score; clinical factors are subsequently added for risk assessment |
| ProMark, Proteomic Prognostic test for prostate cancer | MetaMark | $3,900 | Requires tissue collected with patented biopsy kit available from MetaMark | Uses automated image recognition technology to determine the likelihood of Grade Group ≥ 2 or stage ≥ T3b | Expression of 8 proteins; uses automated image recognition technology to generate a score from 1 to 100 indicating the aggressiveness of prostate cancer |

JCO 2020

**TABLE 1.** Summary Boxes Recommendations 1-4

| |
|---|
| **Clinical question 1:** Are there molecular prostate cancer biomarkers with which to identify patients who are most likely to benefit from active surveillance? |
| **Summary:** There are currently commercially available biopsy-based multigene expression classifiers (ie, Decipher, Onco*type* Dx Prostate, and Prolaris) and one protein-based biomarker (ProMark). Each seems to independently improve the prognostic accuracy of clinical multivariable models for identifying men with biologically significant disease. The clinical benefit of integrating these classifiers in selecting patients for surveillance has not been prospectively demonstrated. There are no comparative data indicating that one may be more accurate than another. |
| **Example clinical scenario:** These may be considered, for instance, in select men with NCCN low- or favorable intermediate-risk prostate cancer who might benefit from refined risk classification when considering active surveillance (eg, high-volume Grade Group 1; Grade Group 1 with abnormal DRE or high PSA density; low-volume Grade Group 2). |
| **Recommendation 1.1.** Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate). |
| **Recommendation 1.2.** Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate). |
| **Clinical question 2:** Are there molecular biomarkers with which to diagnose clinically significant prostate cancer? |
| **Summary:** There are commercially available biopsy-based multigene expression classifiers (ie, Decipher, Onco*type* Dx Prostate, and Prolaris) and a protein-based biomarker (ProMark). While these assays may also inform patients considering active surveillance (Recommendation 1), additional prognostic value may contribute to risk stratification and patient counseling when added to standard clinical parameters. The ability of these tests to improve outcomes (quality of life and risk of metastasis or death) has not been prospectively evaluated. Comparative studies between tests have not been reported. |
| **Example clinical scenario:** These may be considered, for instance, in select unfavorable intermediate-risk patients when deciding whether to add androgen-deprivation therapy to radiation therapy. |
| **Recommendation 2.1.** Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate). |
| **Recommendation 2.2.** Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate). |
| **Clinical question 3:** Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation? |

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

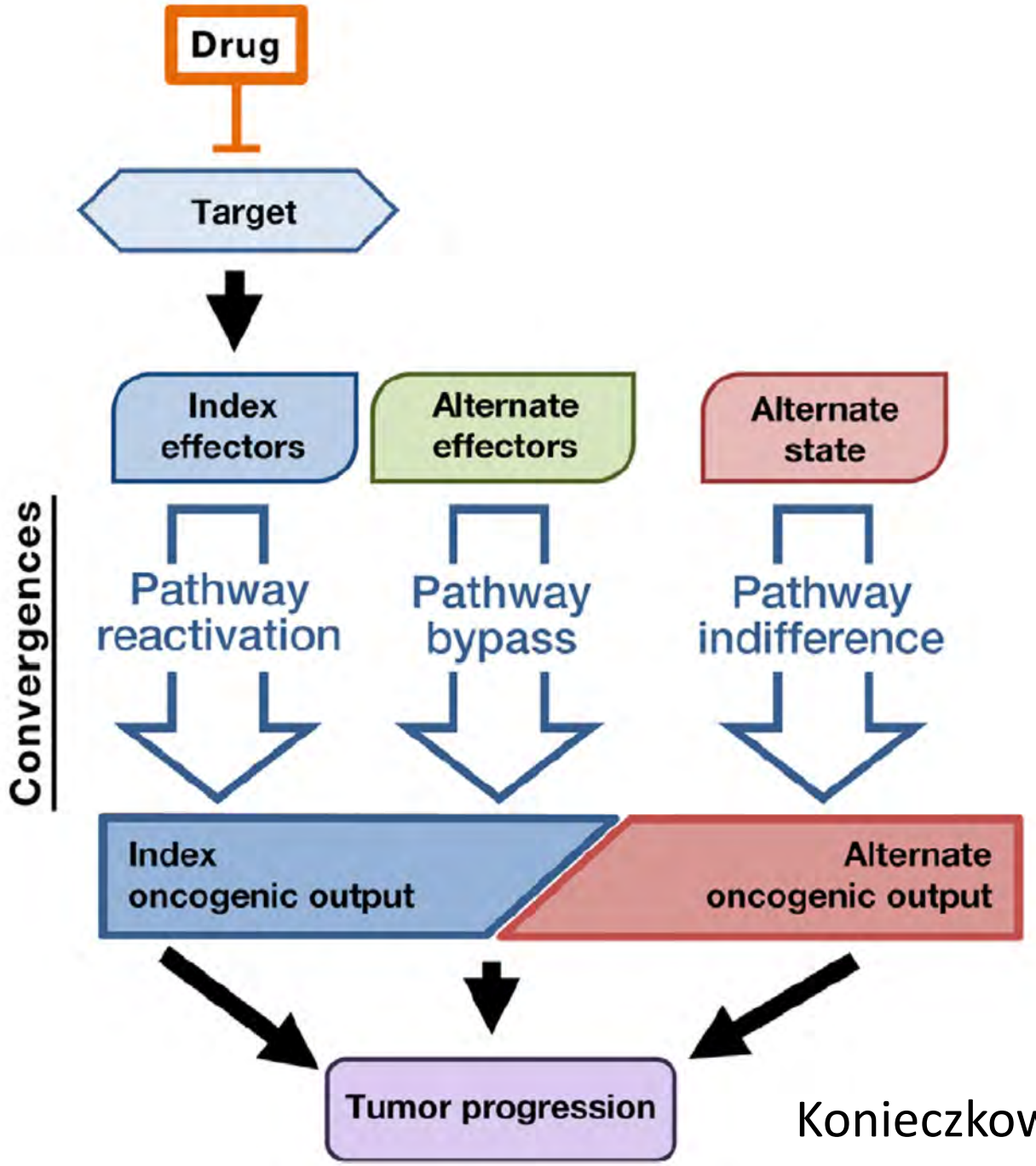
Dan L. Longo, M.D., *Editor*

# Metastatic Prostate Cancer

Oliver Sartor, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D.

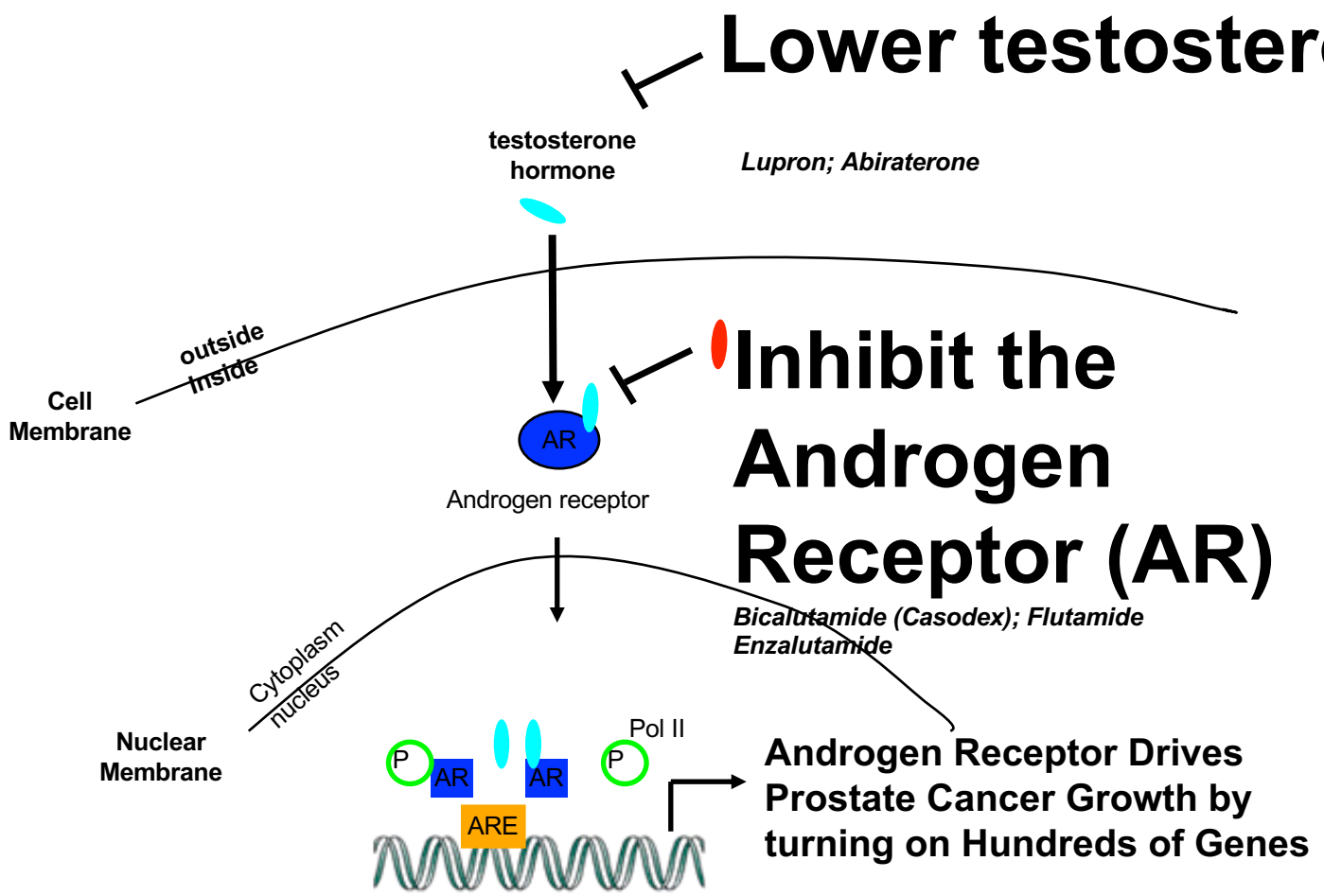
*"The use of advanced genomic analysis is now feasible to a greater extent than ever before. Whether its use improves treatment decisions is not yet clear…**advanced genetics and immunology**, two major drivers of progress in oncology, are not routinely incorporated into the care of patients with prostate cancer."*

NEJM 378;7 February 15, 2018 647

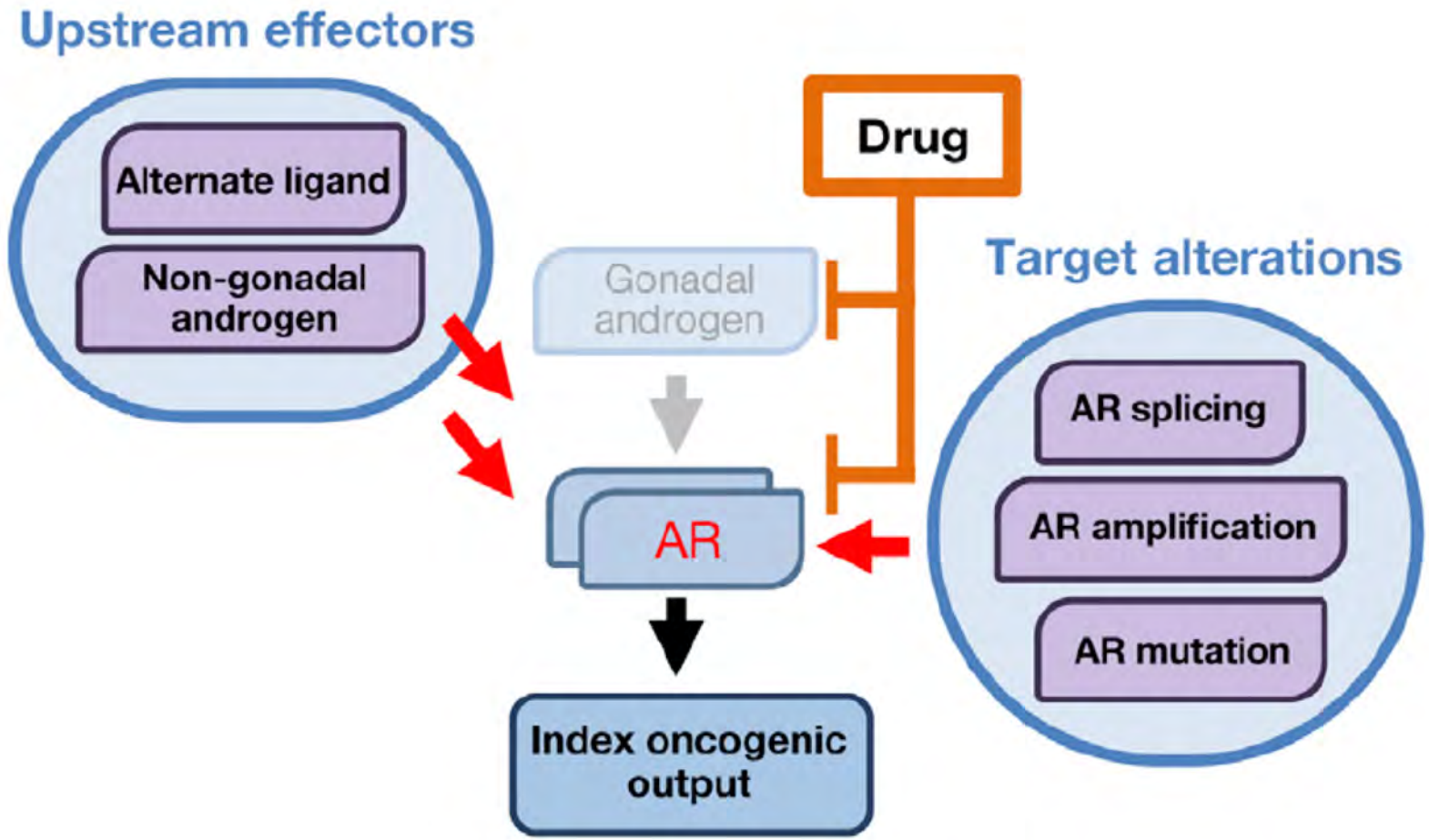



Konieczkowski et al, Cancer Cell 2018

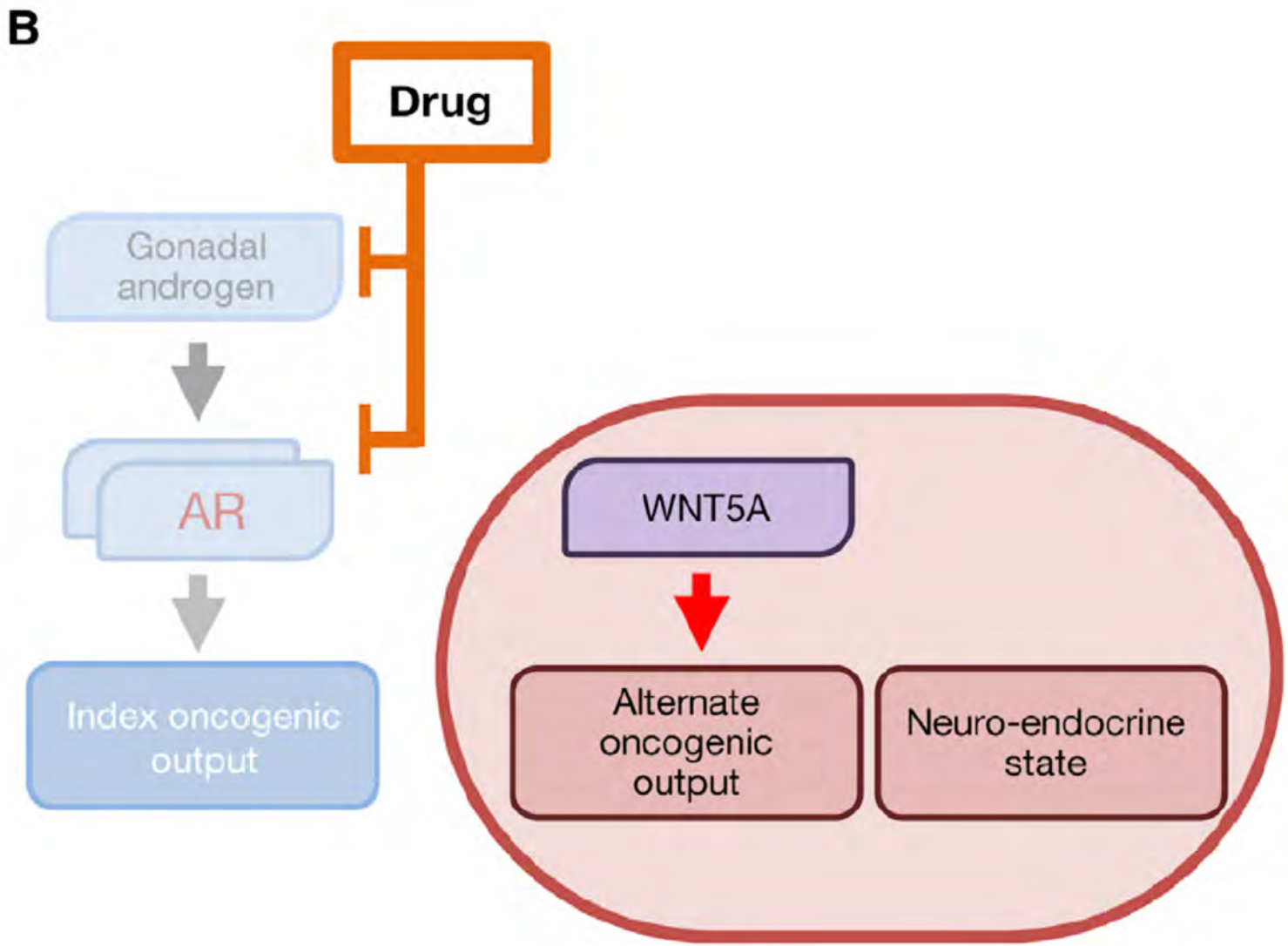
# Androgen receptor signaling inhibitors (ARSi) major therapy




Modified from C. Sawyer



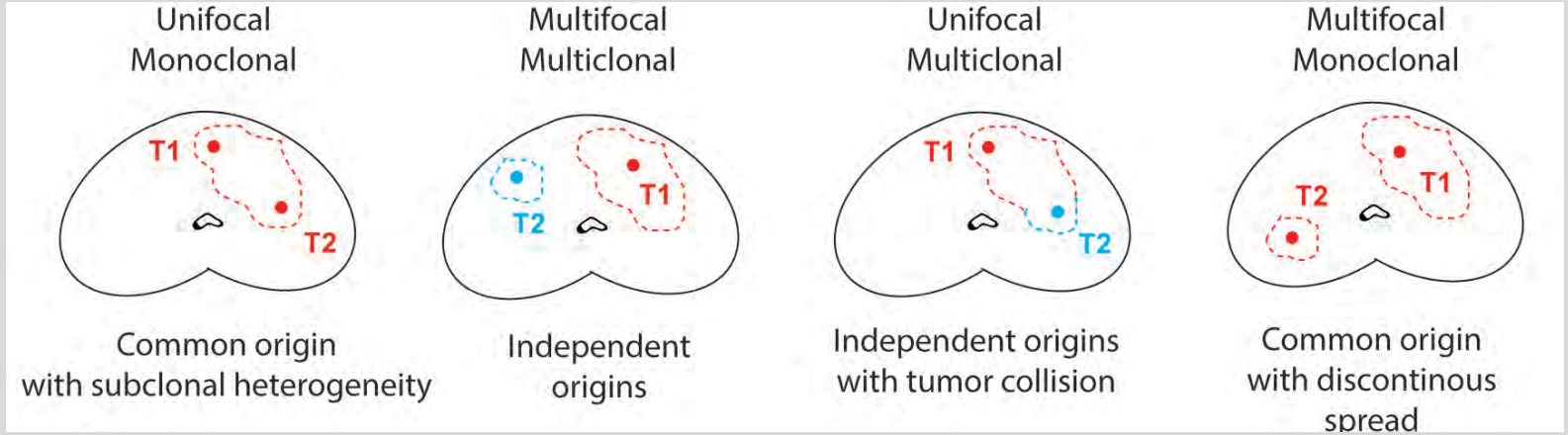

Konieczkowski et al, Cancer Cell 2018




Konieczkowski et al, Cancer Cell 2018

# Heterogeneity Landscape also plays role in resistance

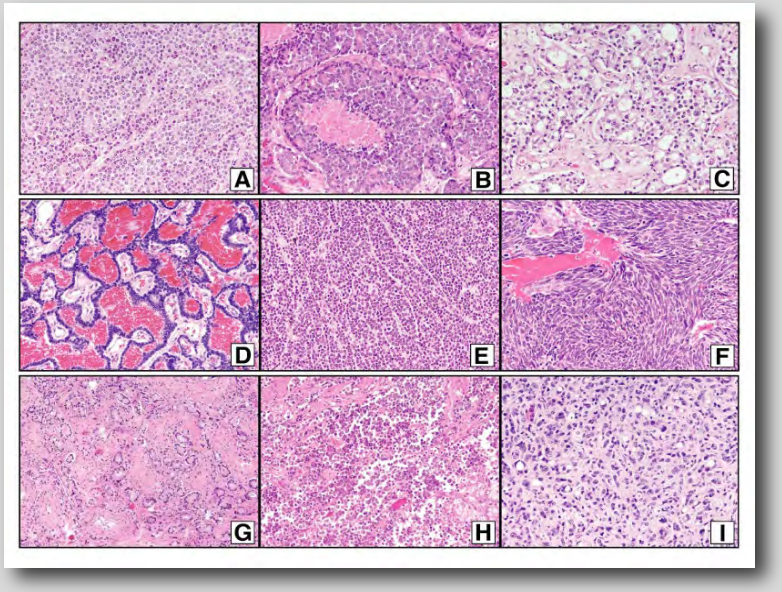
Localized




Cyrta et al., unpublished

Metastatic CRPC


Rubin et al., Clinical Can Res 2000




Shah et al., Can Res 2004

# 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

# Definitions

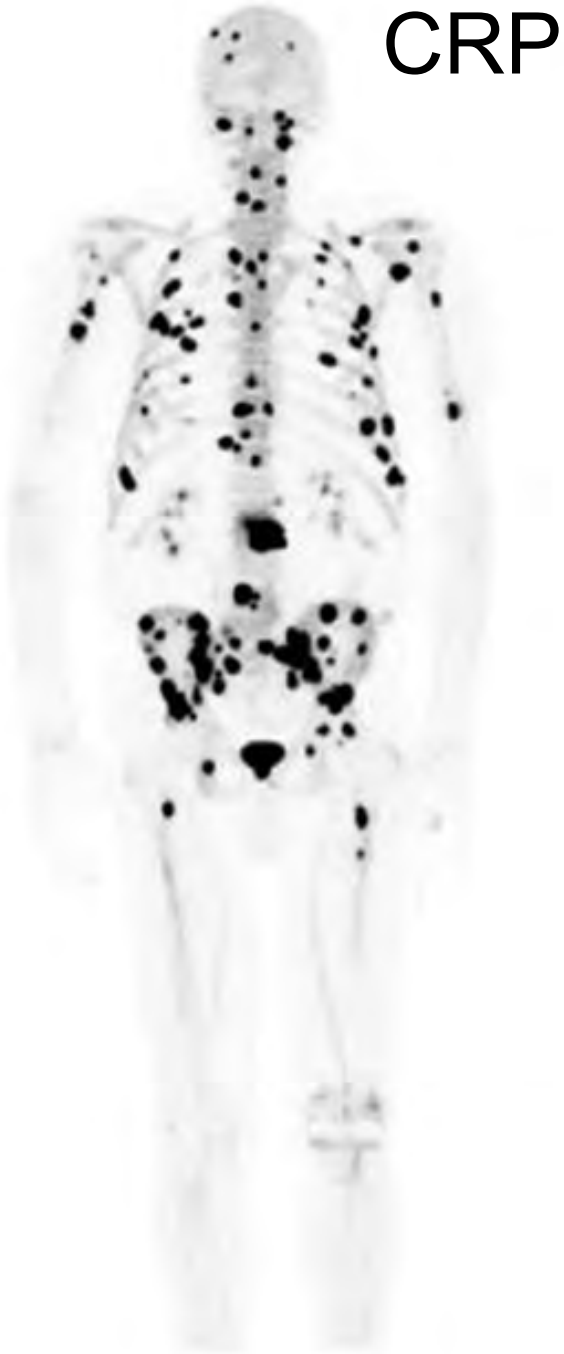
A **prognostic biomarker** is one that indicates an increased (or decreased) likelihood of a future clinical event, disease recurrence or progression in an identified population. Prognostic biomarkers are measured at a defined baseline, which may include a background treatment

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

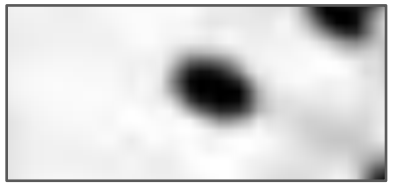


# CRPC Patient and acquisition of samples for testing

Buccal sample

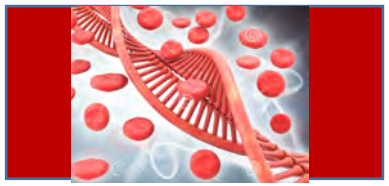
**Germline DNA**
Genetic testing (e.g., BRCA1/2)
Control normal sample for genomics

Tumor sample



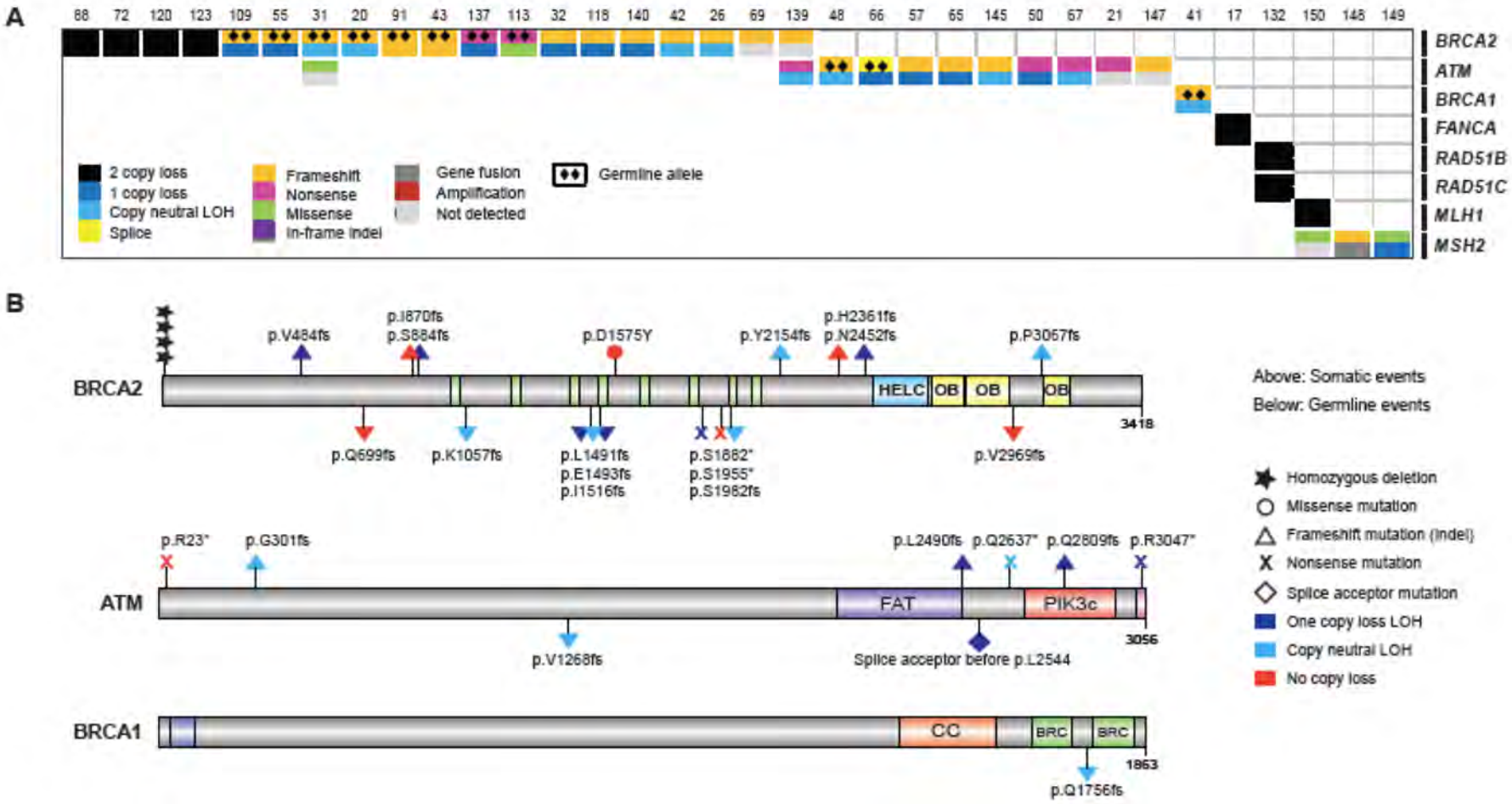
**Tumor DNA/RNA/Protein**
For genomic sequencing, transcriptomic sequencing, etc.

Blood sample



**Tumor and normal DNA/RNA/Protein *fraction***
*cfDNA, CTC, metabolites, etc.*

# Significant alterations in DNA repair genes




Robinson et al, Cell 2015

ELSEVIER

Check for updates

UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 36 (2018) 385–388

Seminars article

# The resounding effect of DNA repair deficiency in prostate cancer

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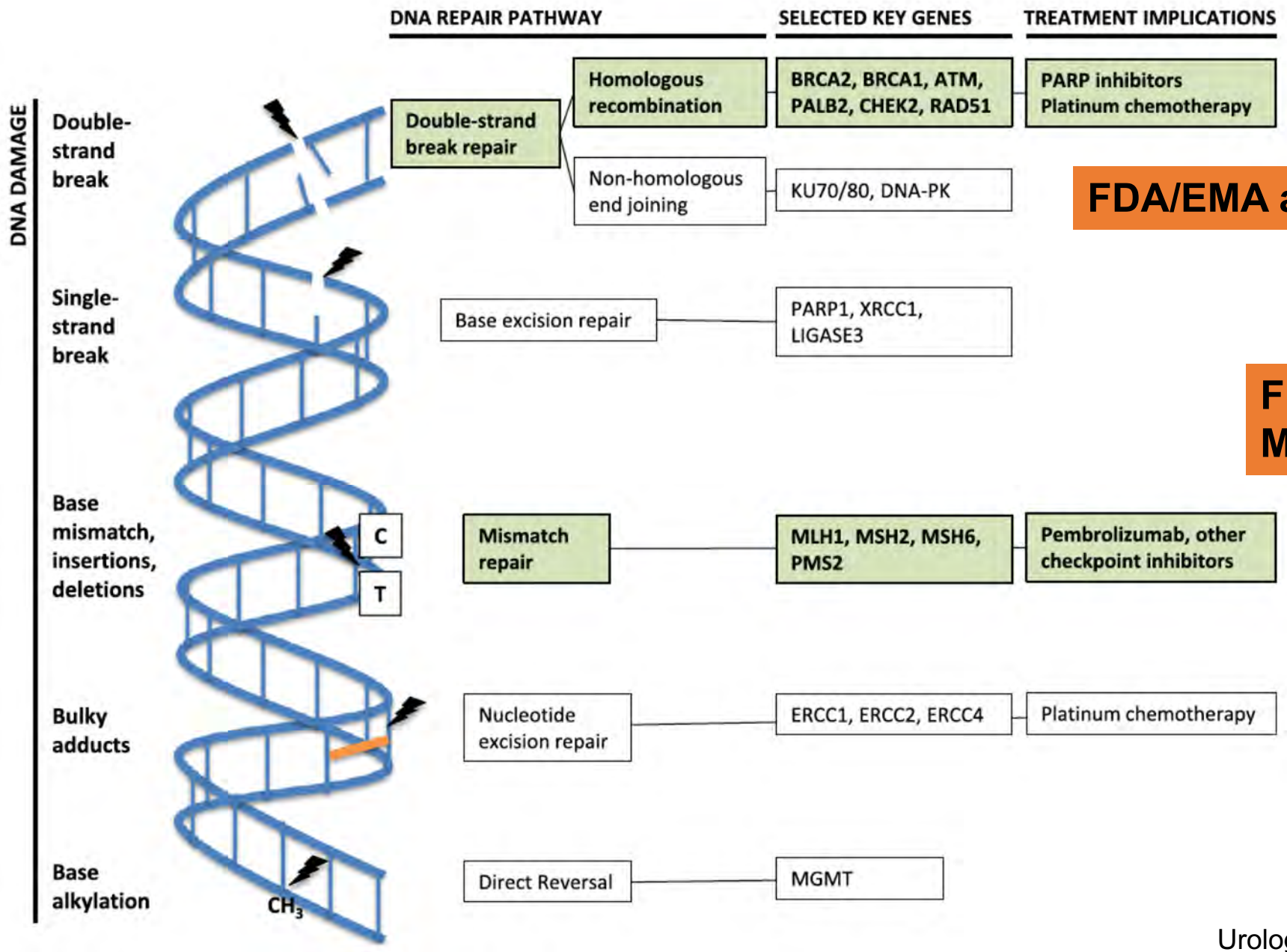
[b] *Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

Urologic Oncology: Sem. and Orig. Invest.
36(**2018**)385–388




20%

**FDA/EMA approval for BRCA1/2, ATM**

**FDA (May 2017) approval for MSI and MMR deficiency**

5%

Urologic Oncology: Sem. and Orig. Invest. 36(2018)385–388

# Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

**Hannah Farmer[1,2]*, Nuala McCabe[1,2]*, Christopher J. Lord[2]*, Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2]†, Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]**

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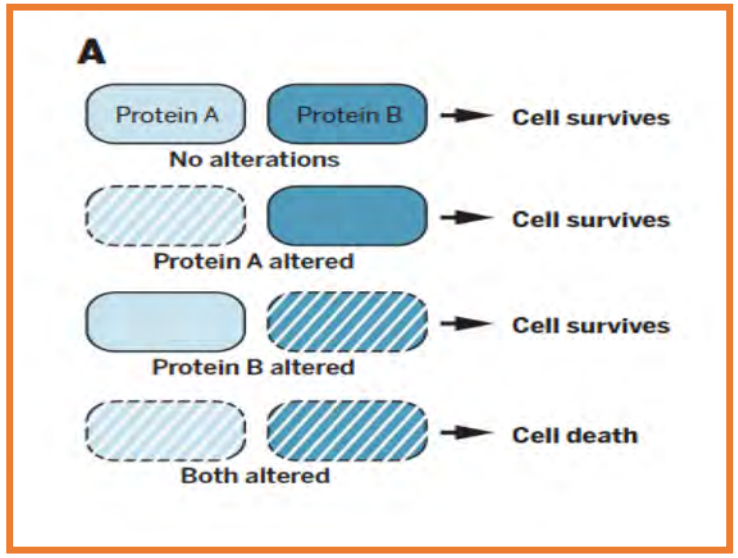
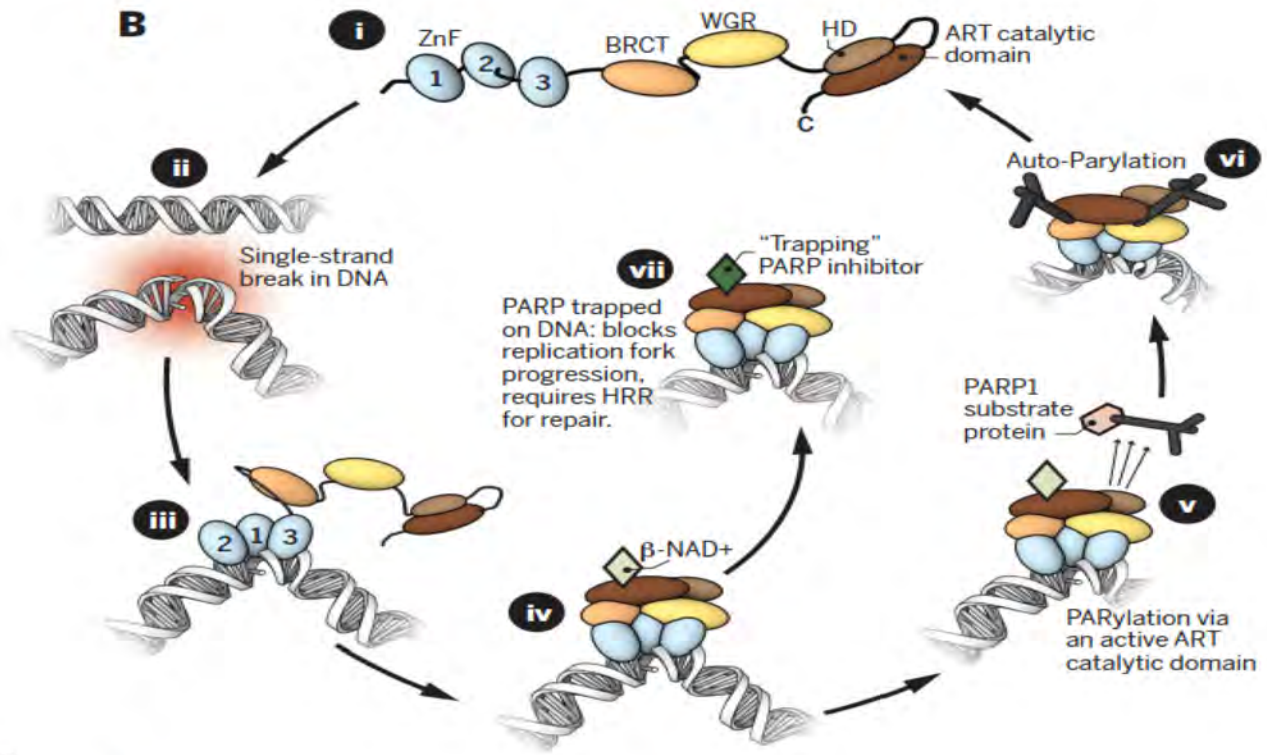
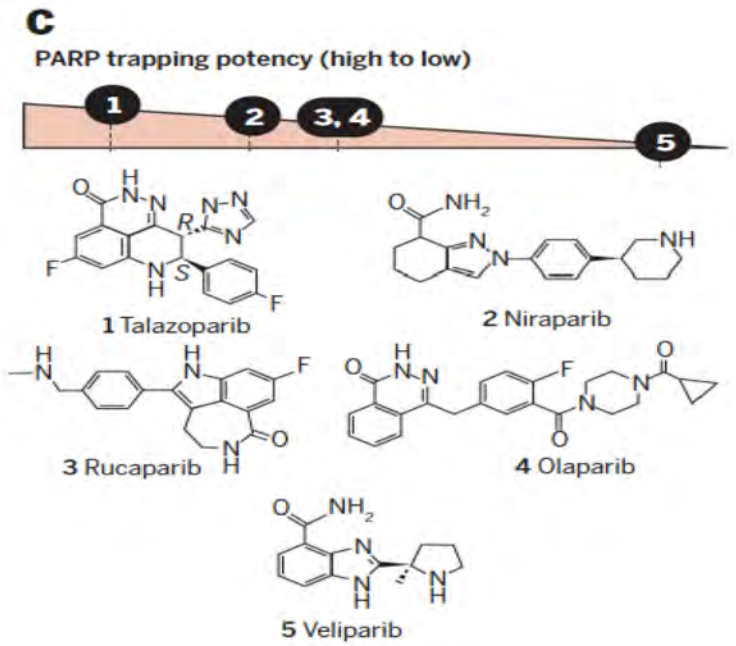
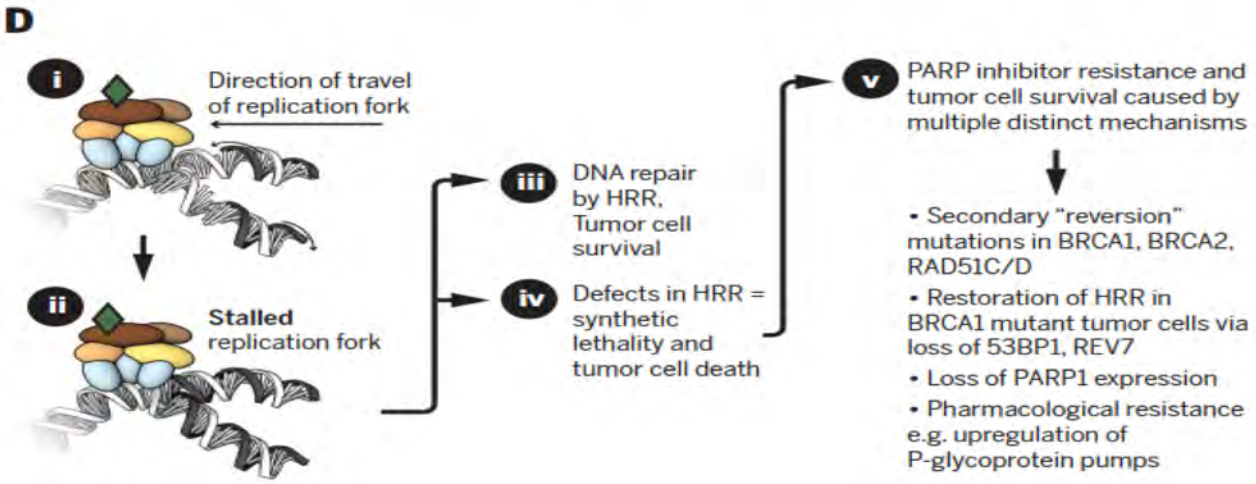
NATURE |VOL 434 | 14 APRIL 2005



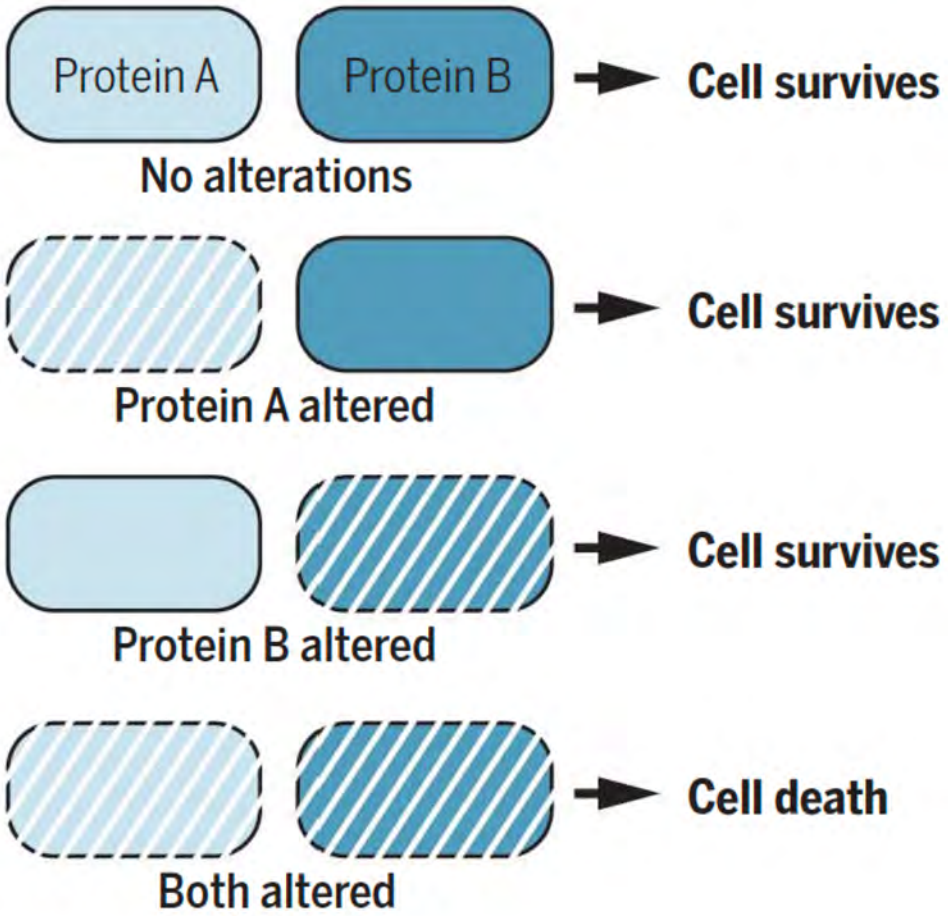



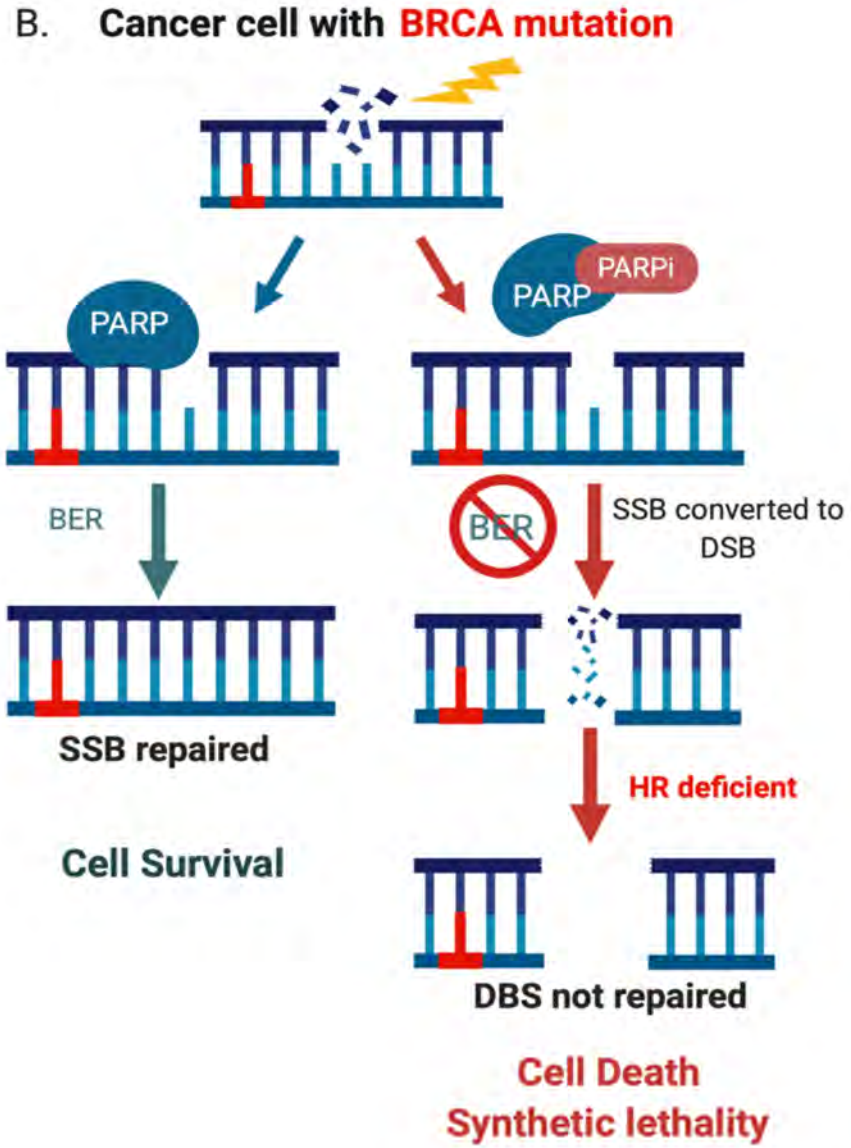






Lord and Ashworth, Science 355, 1152–1158 (2017)

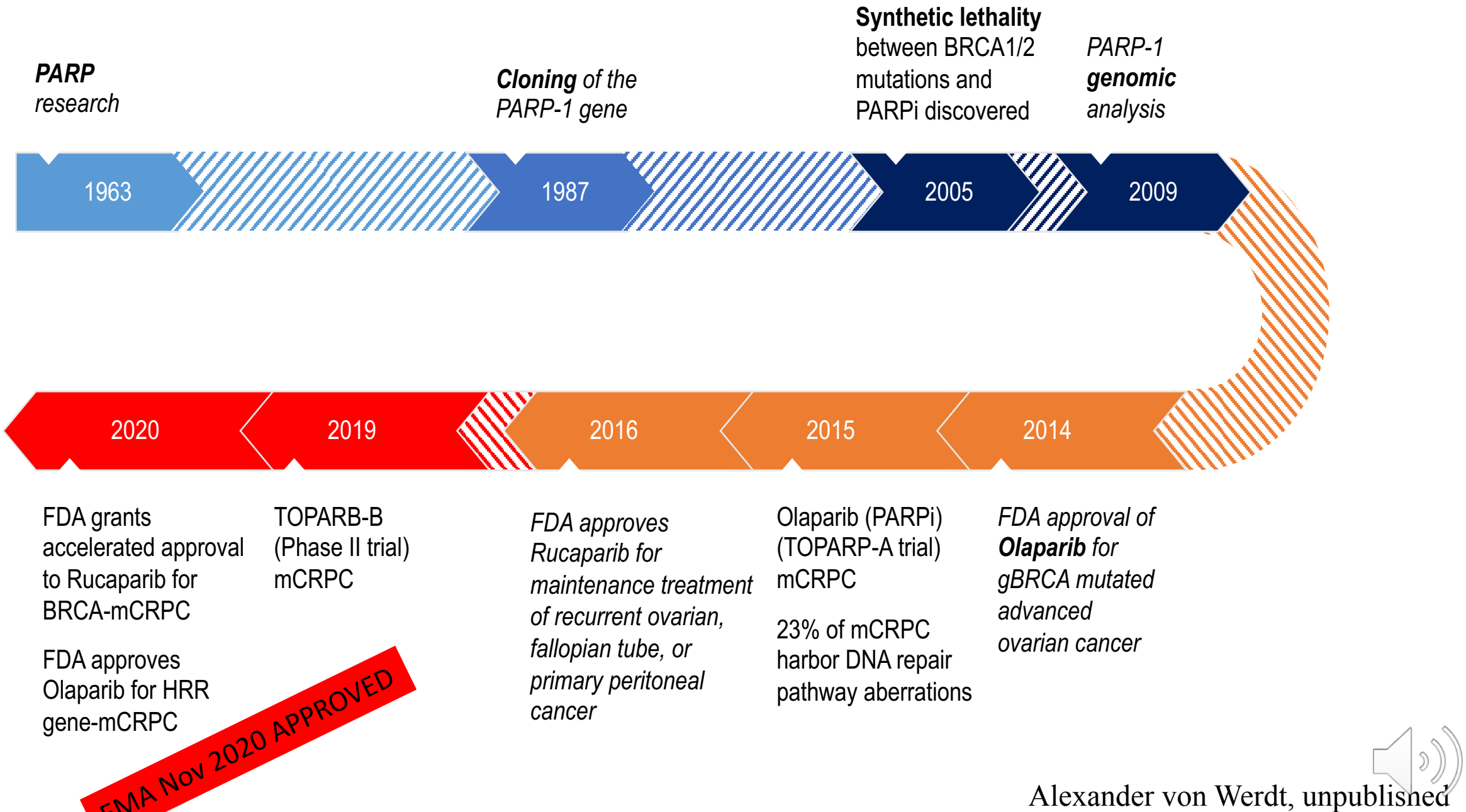
# Synthetic Lethality




Lord and Ashworth, Science 355, 1152–1158 (2017)

Alexander von Werdt, unpublished



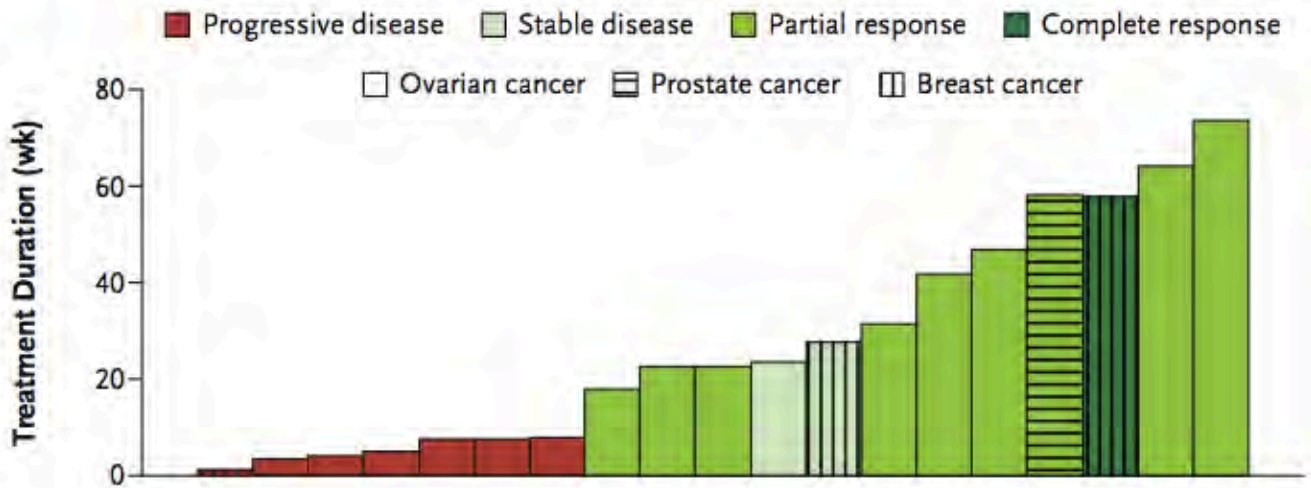

Alexander von Werdt, unpublished

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

# Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.





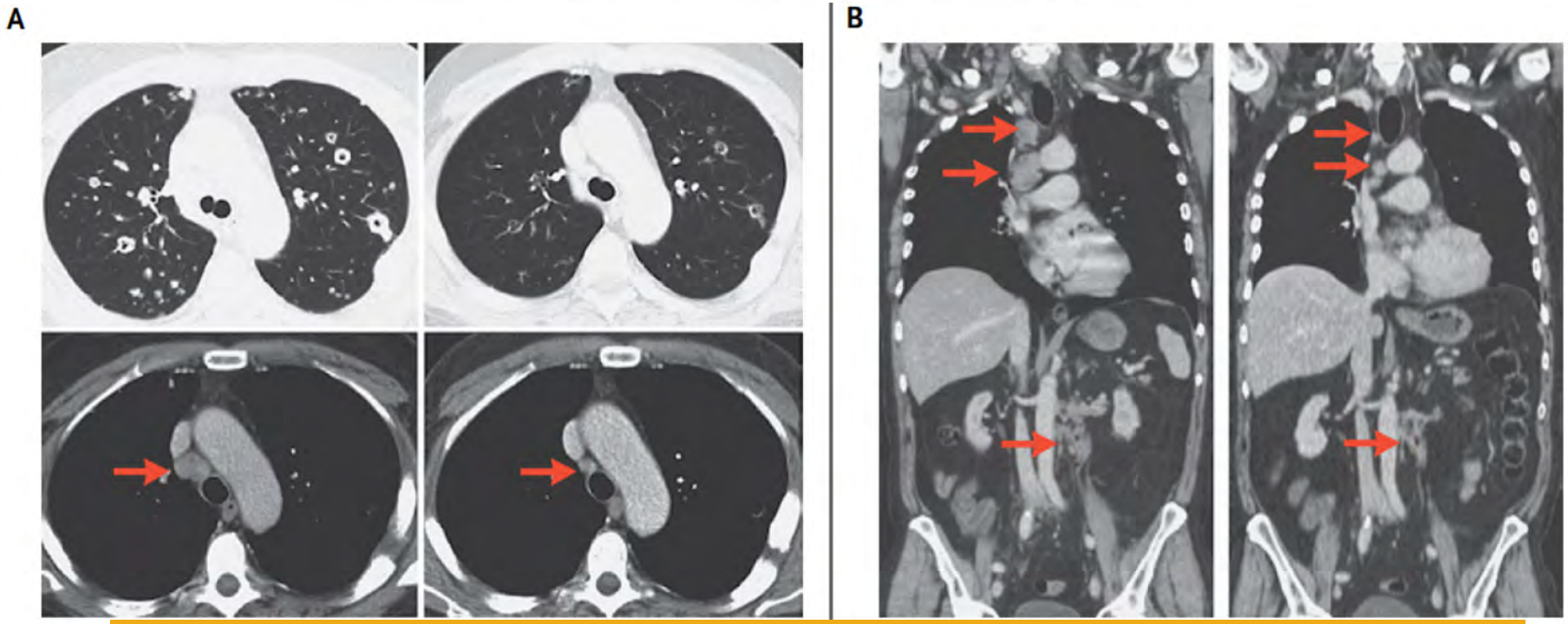

19 BRCA mutated

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

# DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

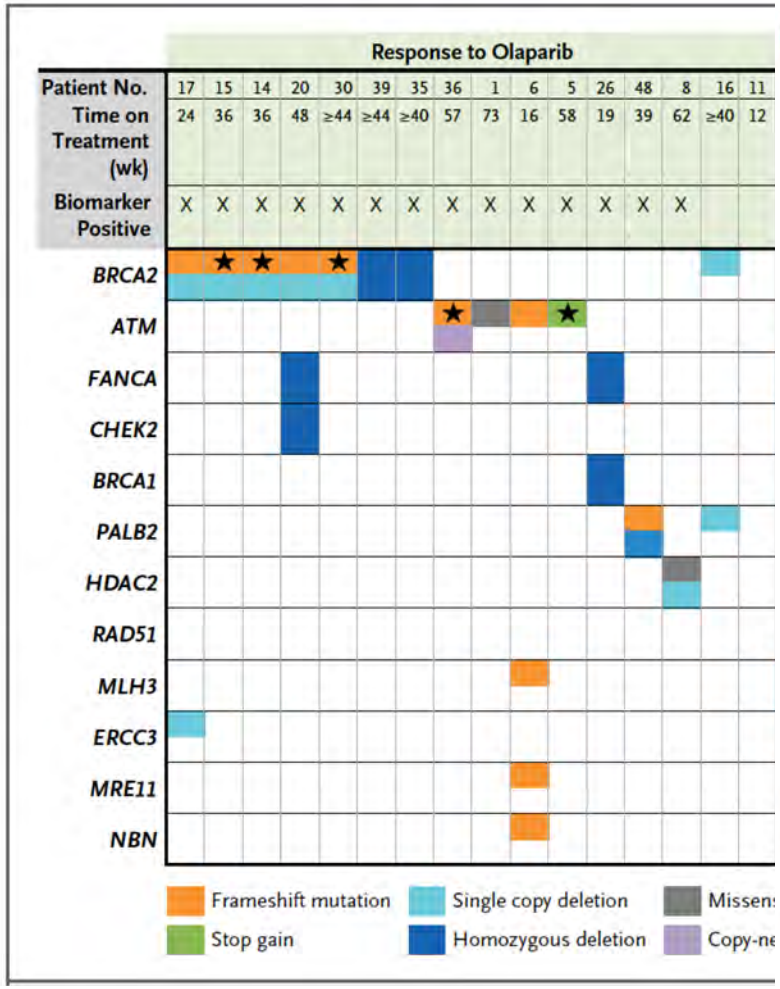
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono



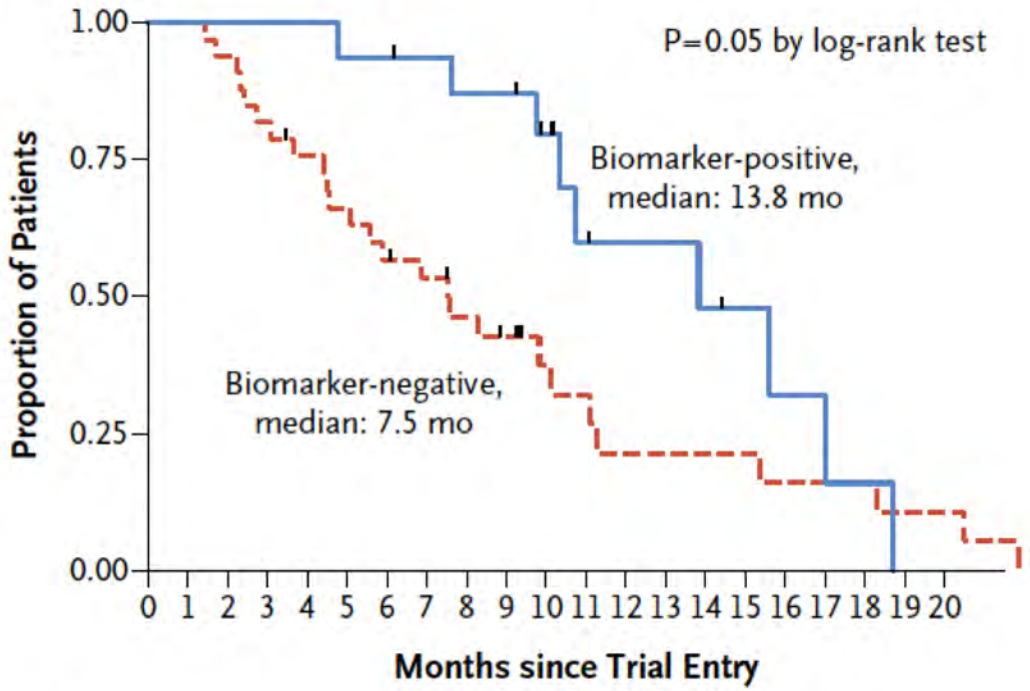

TOPARP Trial shows 30% Long Term Responders



NEJM, Oct 29 2015




**B** **Overall Survival**




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Biomarker-negative | 33 | 33 | 31 | 27 | 24 | 21 | 18 | 16 | 13 | 11 | 7 | 6 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 2 | 2 |
| Biomarker-positive | 16 | 16 | 16 | 16 | 16 | 15 | 15 | 14 | 13 | 13 | 10 | 6 | 5 | 5 | 4 | 3 | 2 | 2 | 1 | 0 | 0 |

**No. of Events**

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Biomarker-negative | 0 | 2 | 4 | 2 | 3 | 3 | 1 | 2 | 1 | 1 | 1 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | – |
| Biomarker-positive | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 0 | 0 | – |

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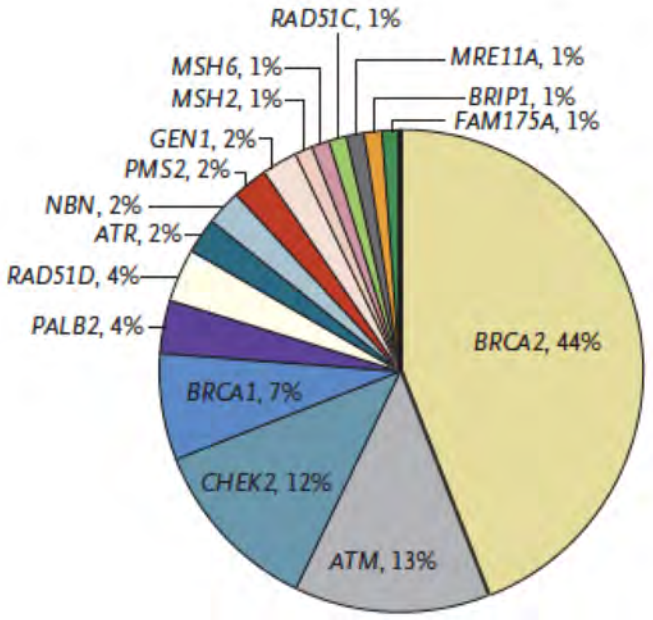
ORIGINAL ARTICLE

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

Table 2. Germline Mutations in Metastatic Cases as Compared with the General Population and Primary Cases.

| Gene | Metastatic Prostate Cancer (N=692)* | Exome Aggregation Consortium (N=53,105)† | TCGA Cohort with Primary Prostate Cancer (N=499) | Metastatic Prostate Cancer vs. Exome Aggregation Consortium | | Metastatic Prostate Cancer vs. TCGA Cohort | |
|---|---|---|---|---|---|---|---|
| | No. of Mutations (% of Men) | | | Relative Risk (95% CI) | P Value | Relative Risk (95% CI) | P Value |
| *ATM* | 11 (1.59) | 133 (0.25) | 5 (1.00) | 6.3 (3.2–11.3) | <0.001 | 1.6 (0.8–2.8) | 0.12 |
| *ATR* | 2 (0.29) | 43 (0.08) | 0 | 3.6 (0.4–12.8) | 0.11 | — | — |
| *BAP1*‡ | 0 | 1 | 0 | — | — | — | — |
| *BARD1*‡ | 0 | 38 (0.07) | 1 (0.20) | — | — | — | — |
| *BRCA1* | 6 (0.87) | 104 (0.22) | 3 (0.60) | 3.9 (1.4–8.5) | 0.005 | 1.4 (0.5–3.1) | 0.32 |
| *BRCA2* | 37 (5.35) | 153 (0.29) | 1 (0.20) | 18.6 (13.2–25.3) | <0.001 | 26.7 (18.9–36.4) | <0.001 |
| *BRIP1*‡ | 1 (0.18) | 100 (0.19) | 1 (0.20) | 0.9 (0.02–5.3) | 1.0 | 0.9 (0.0–4.9) | 1.0 |
| *CHEK2*‡ | 10 (1.87) | 314 (0.61) | 2 (0.40) | 3.1 (1.5–5.6) | 0.002 | 4.7 (2.2–8.5) | <0.001 |
| *FAM175A*‡ | 1 (0.18) | 52 (0.10) | 0 | 1.8 (0.05–10.1) | 0.42 | — | — |
| *GEN1*‡ | 2 (0.46) | 42 (0.08) | 0 | 5.8 (0.7–20.8) | 0.048 | — | — |
| *MLH1* | 0 | 11 (0.02) | 0 | — | — | — | — |
| *MRE11A* | 1 (0.14) | 36 (0.07) | 1 (0.20) | 2.1 (0.1–11.8) | 0.38 | 0.7 (0.0–4.0) | 1.0 |
| *MSH2* | 1 (0.14) | 23 (0.04) | 1 (0.20) | 3.3 (0.1–18.5) | 0.26 | 0.7 (0.0–4.0) | 1.0 |
| *MSH6* | 1 (0.14) | 41 (0.08) | 1 (0.20) | 1.9 (0.05–10.4) | 0.41 | 0.7 (0.0–4.0) | 1.0 |
| *NBN* | 2 (0.29) | 61 (0.11) | 1 (0.20) | 2.5 (0.3–9.1) | 0.19 | 1.4 (0.2–5.2) | 0.40 |
| *PALB2* | 3 (0.43) | 65 (0.12) | 2 (0.40) | 3.5 (0.7–10.3) | 0.05 | 1.1 (0.2–3.1) | 0.76 |
| *PMS2* | 2 (0.29) | 56 (0.11) | 1 (0.20) | 2.7 (0.3–9.8) | 0.17 | 1.4 (0.2–5.2) | 0.40 |
| *RAD51C* | 1 (0.14) | 59 (0.11) | 2 (0.40) | 1.3 (0.03–7.2) | 0.54 | 0.4 (0.0–2.0) | 0.54 |
| *RAD51D* | 3 (0.43) | 40 (0.08) | 1 (0.20) | 5.7 (1.2–16.7) | 0.02 | 2.2 (0.4–6.3) | 0.16 |
| *XRCC2* | 0 | 23 (0.04) | 0 | — | — | — | — |




***Selected*** *DNA repair germline mutations from targeted panel and WES reveal 10-20% frequency* (Pritchard and Nelson, 2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

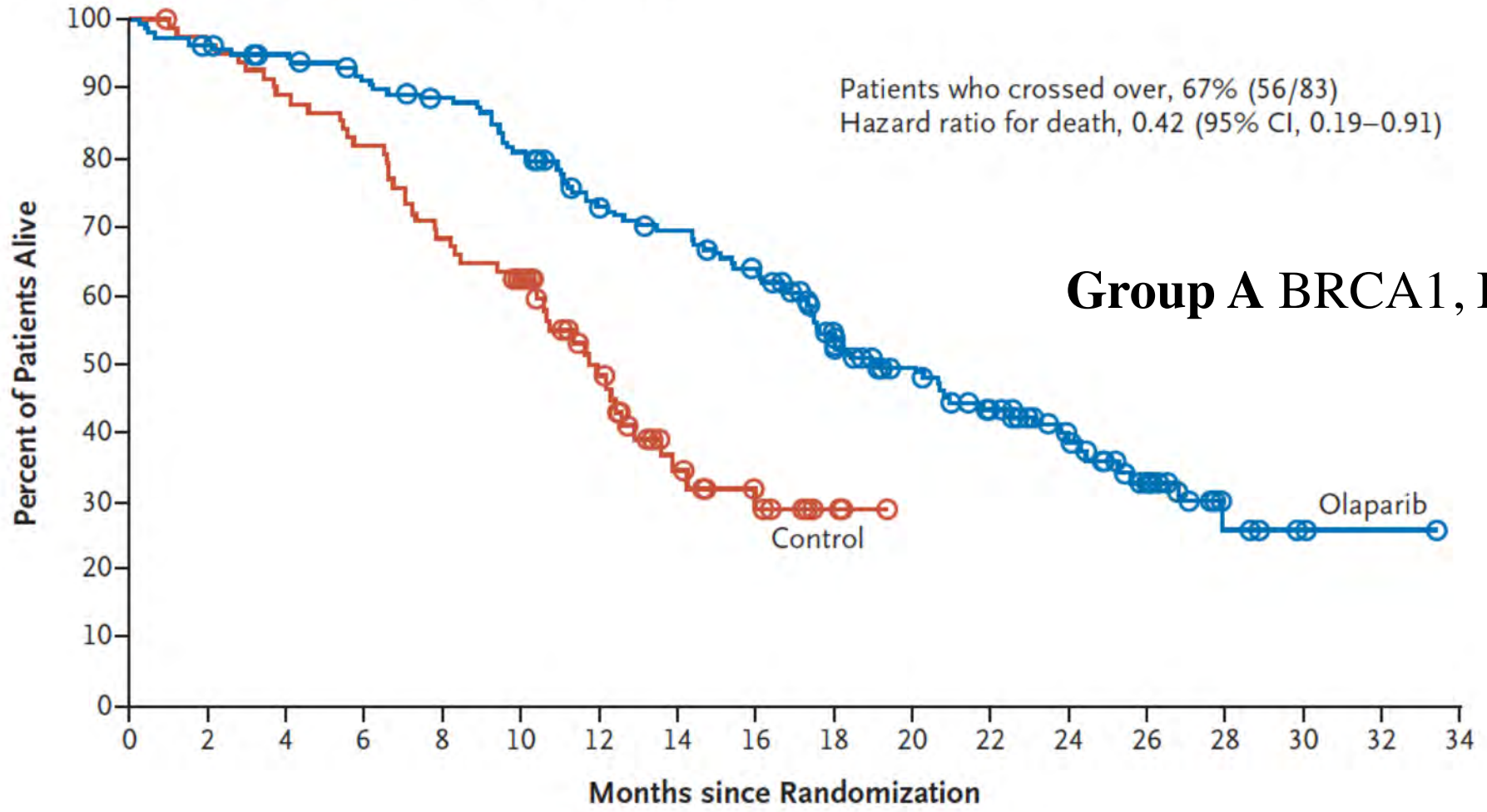
M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

**Group A** BRCA1, BRCA2, ATM

**Group B**: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

NEJM 2020

**B** Crossover-Adjusted Analysis of Overall Survival in Cohort A

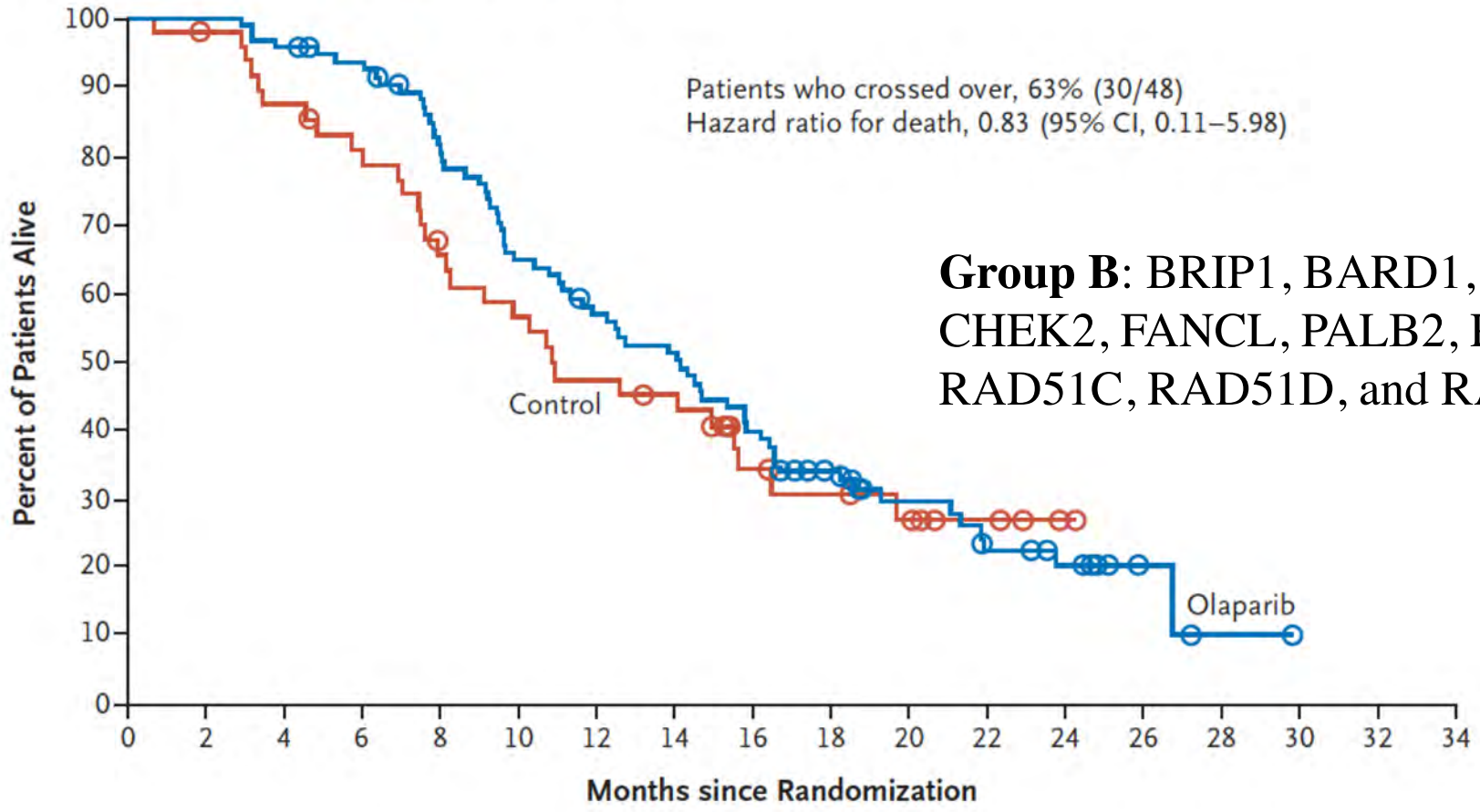



**Group A** BRCA1, BRCA2, ATM

| No. at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 162 | 155 | 150 | 142 | 136 | 124 | 107 | 101 | 91 | 71 | 56 | 44 | 30 | 18 | 6 | 2 | 1 | 0 |
| Control | 83 | 79 | 73 | 67 | 56 | 47 | 29 | 15 | 9 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

NEJM 2020

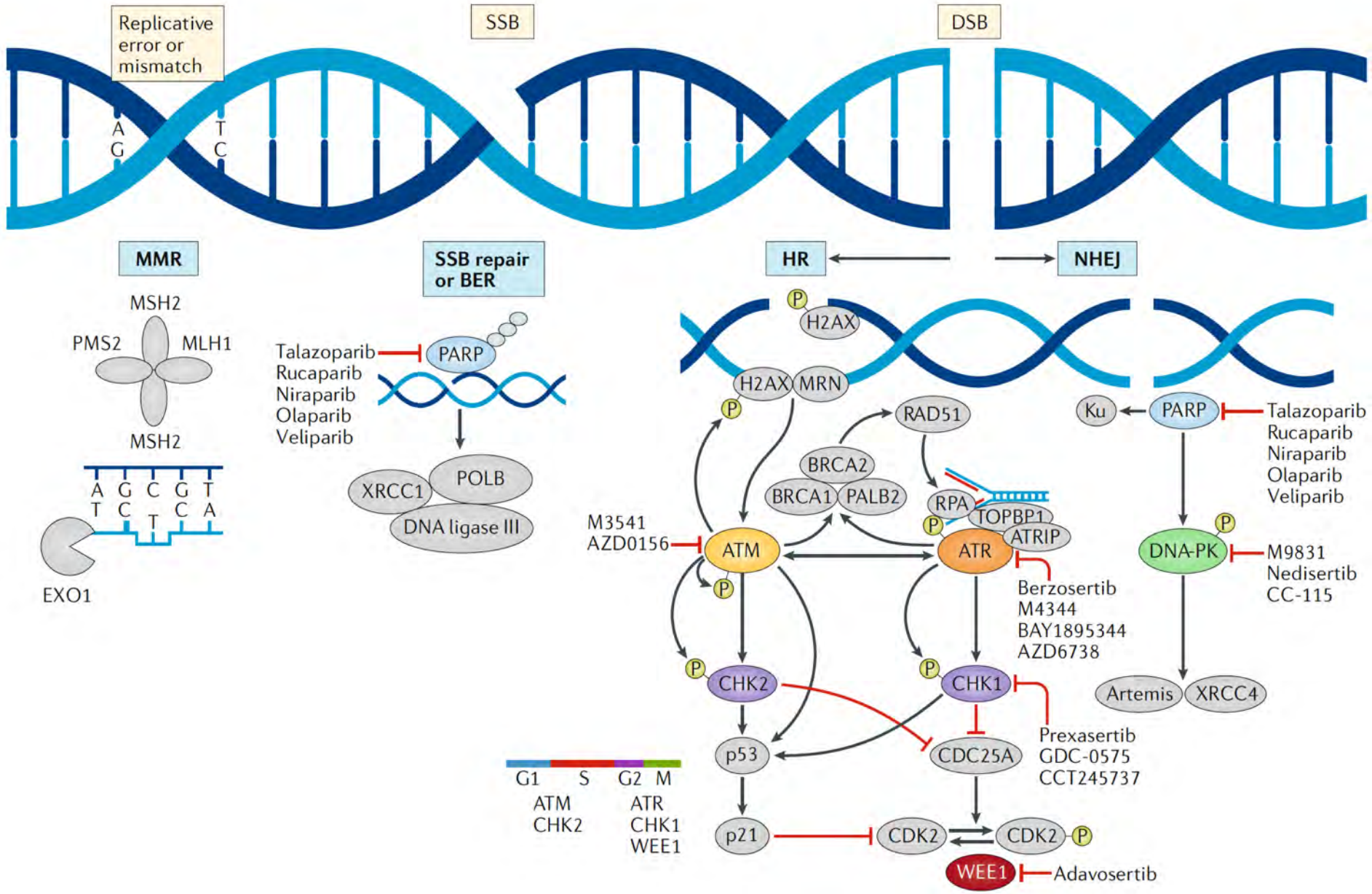
**B** Crossover-Adjusted Analysis of Overall Survival in Cohort B




**Group B**: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

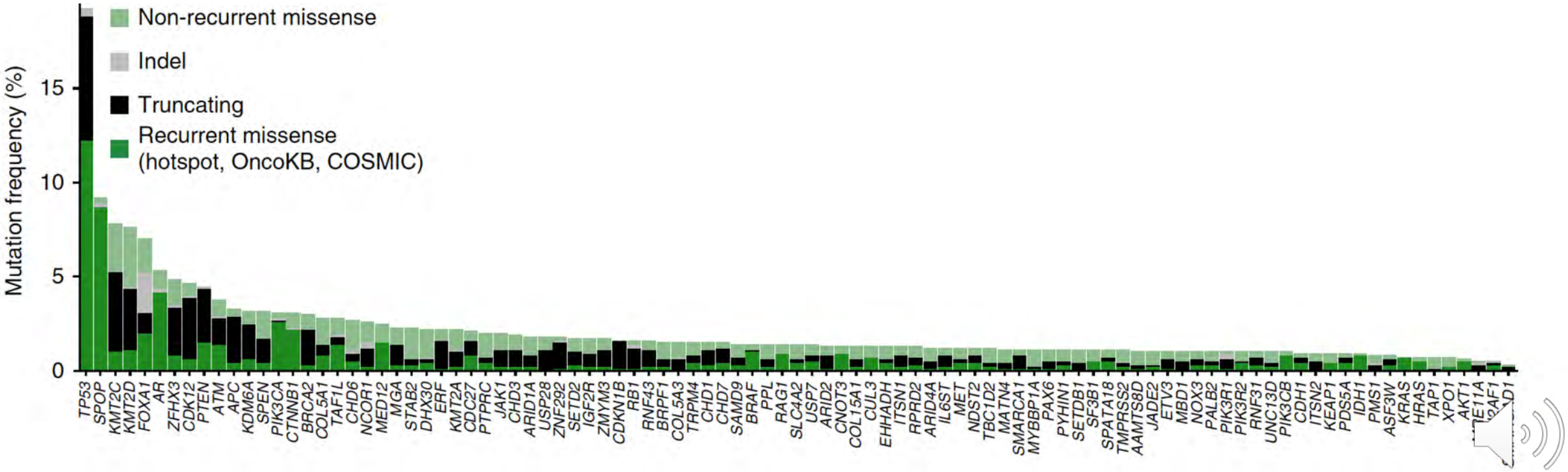
| No. at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 94 | 94 | 90 | 86 | 73 | 58 | 50 | 45 | 35 | 25 | 17 | 12 | 9 | 4 | 1 | 0 | 0 | 0 |
| Control | 48 | 46 | 41 | 37 | 29 | 25 | 21 | 19 | 11 | 9 | 7 | 4 | 1 | 0 | 0 | 0 | 0 | 0 |

NEJM 2020




Pilié et al., Nature Reviews | Clinical Oncology 2019

# long tail of prostate cancer mutations




Armenia et al, ***Nature Genetics***, 2018

cBioPortal FOR CANCER GENOMICS

Data Sets | Web API | R/MATLAB | Tutorials/Webinars | FAQ | News | Visualize Your Data | About | Login

Modify Query

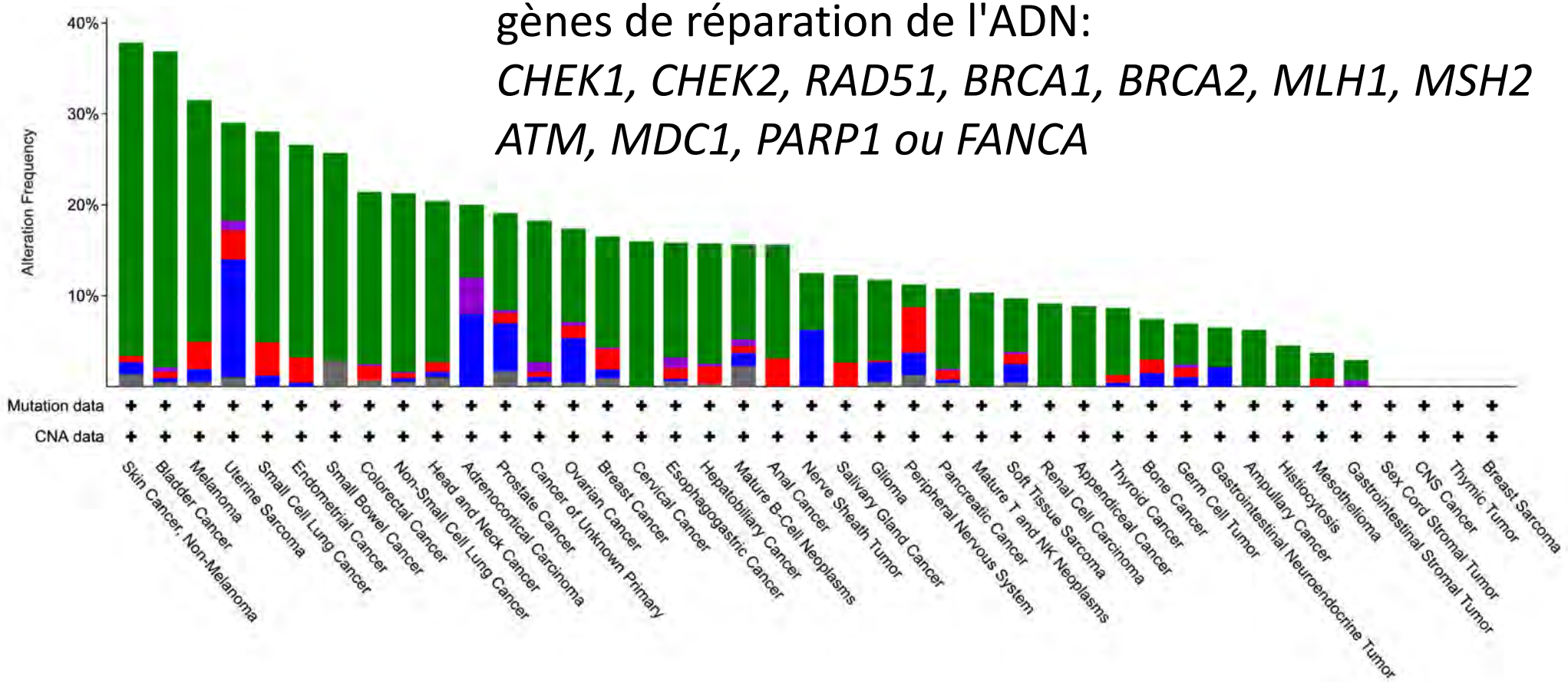
MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017)
Samples with mutation and CNA data (10336 patients / 10945 samples) - CHEK1, CHEK2 & 11 other genes

Queried genes are altered in · 1870 (18%) of queried patients
· 1933 (18%) of queried samples

OncoPrint | Cancer Types Summary | Mutual Exclusivity | Plots | Mutations | Comparison/Survival | CN Segments | Pathways | Download

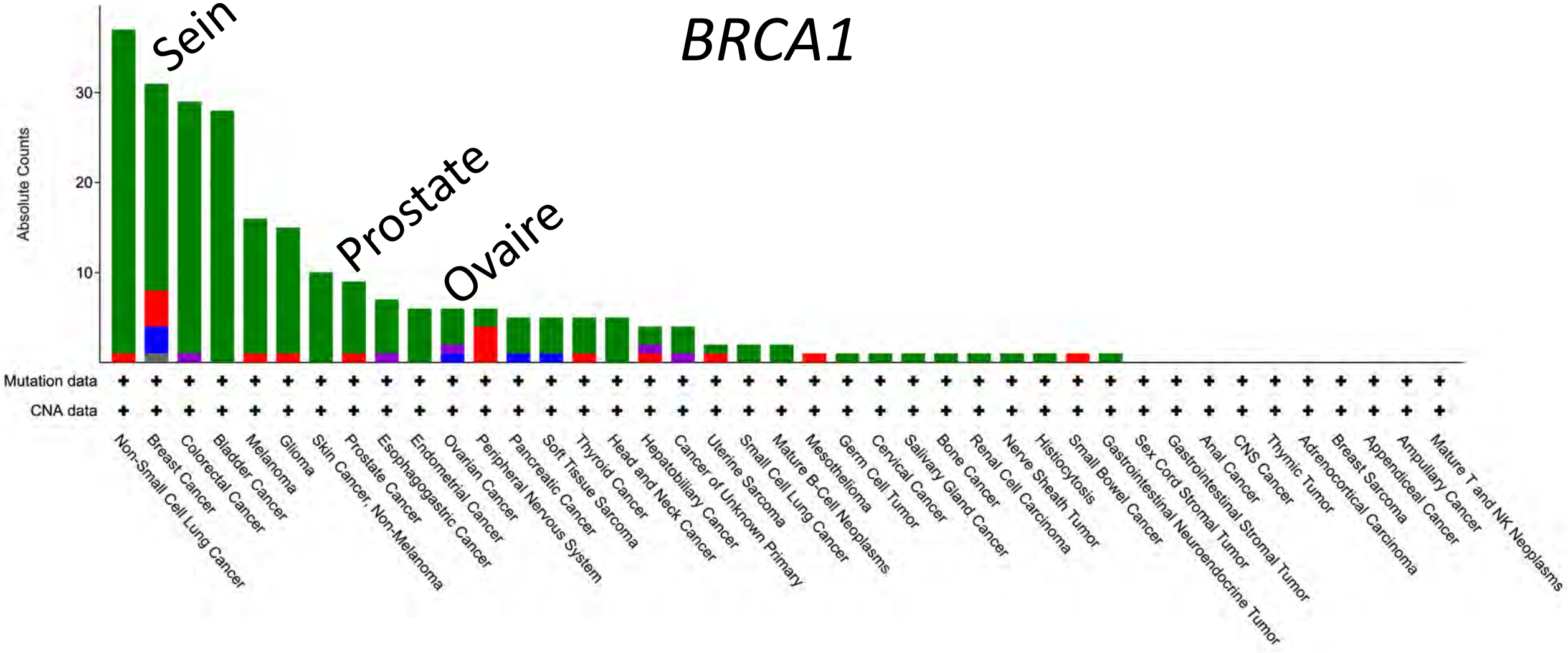
All Queried Genes | CHEK1 | CHEK2 | RAD51 | BRCA1 | BRCA2 | MLH1 | MSH2 | ATM | ATR | MDC1 | PARP1 | FANCF | FANCA

18% des 10336 tumeurs étudiées ont une mutation dans l'un de ces gènes de réparation de l'ADN:
*CHEK1, CHEK2, RAD51, BRCA1, BRCA2, MLH1, MSH2*
*ATM, MDC1, PARP1 ou FANCA*

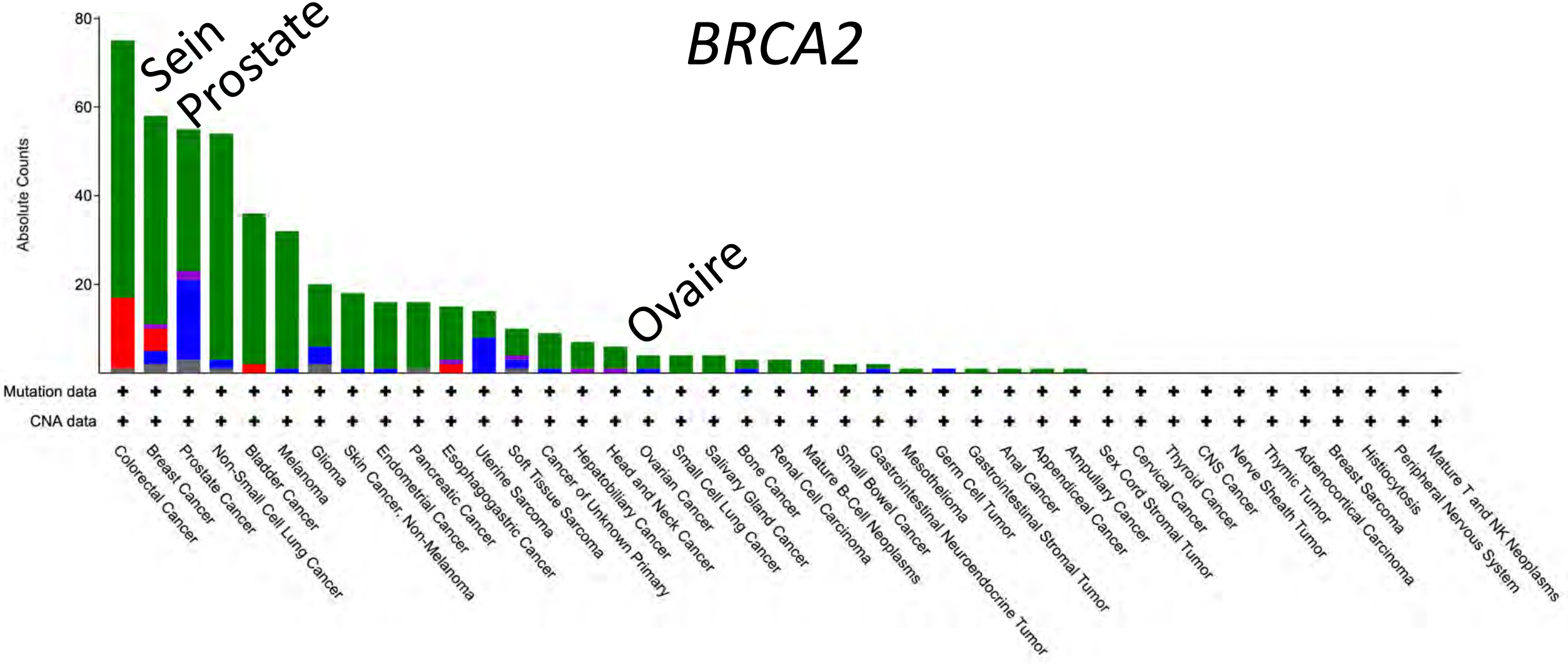



MSKCC-IMPACT, Nature Med 2017

# *BRCA1*


Sein
Prostate
Ovaire
Absolute Counts
30
20
10
Mutation data
CNA data
Non-Small Cell Lung Cancer
Breast Cancer
Colorectal Cancer
Bladder Cancer
Melanoma
Glioma
Skin Cancer, Non-Melanoma
Prostate Cancer
Esophagogastric Cancer
Endometrial Cancer
Ovarian Cancer
Peripheral Nervous System
Pancreatic Cancer
Soft Tissue Sarcoma
Thyroid Cancer
Head and Neck Cancer
Hepatobiliary Cancer
Cancer of Unknown Primary
Uterine Sarcoma
Small Cell Lung Cancer
Mature B-Cell Neoplasms
Mesothelioma
Germ Cell Tumor
Cervical Cancer
Salivary Gland Cancer
Bone Cancer
Renal Cell Carcinoma
Nerve Sheath Tumor
Histiocytosis
Small Bowel Cancer
Gastrointestinal Neuroendocrine Tumor
Sex Cord Stromal Tumor
Gastrointestinal Stromal Tumor
Anal Cancer
CNS Cancer
Thymic Tumor
Adrenocortical Carcinoma
Breast Sarcoma
Appendiceal Cancer
Ampullary Cancer
Mature T and NK Neoplasms

# *BRCA2*


Sein
Prostate
Ovaire
Absolute Counts
80
60
40
20
Mutation data
CNA data
Colorectal Cancer
Breast Cancer
Prostate Cancer
Non-Small Cell Lung Cancer
Bladder Cancer
Melanoma
Glioma
Skin Cancer, Non-Melanoma
Endometrial Cancer
Pancreatic Cancer
Esophagogastric Cancer
Uterine Sarcoma
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Cancer of Unknown Primary
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Head and Neck Cancer
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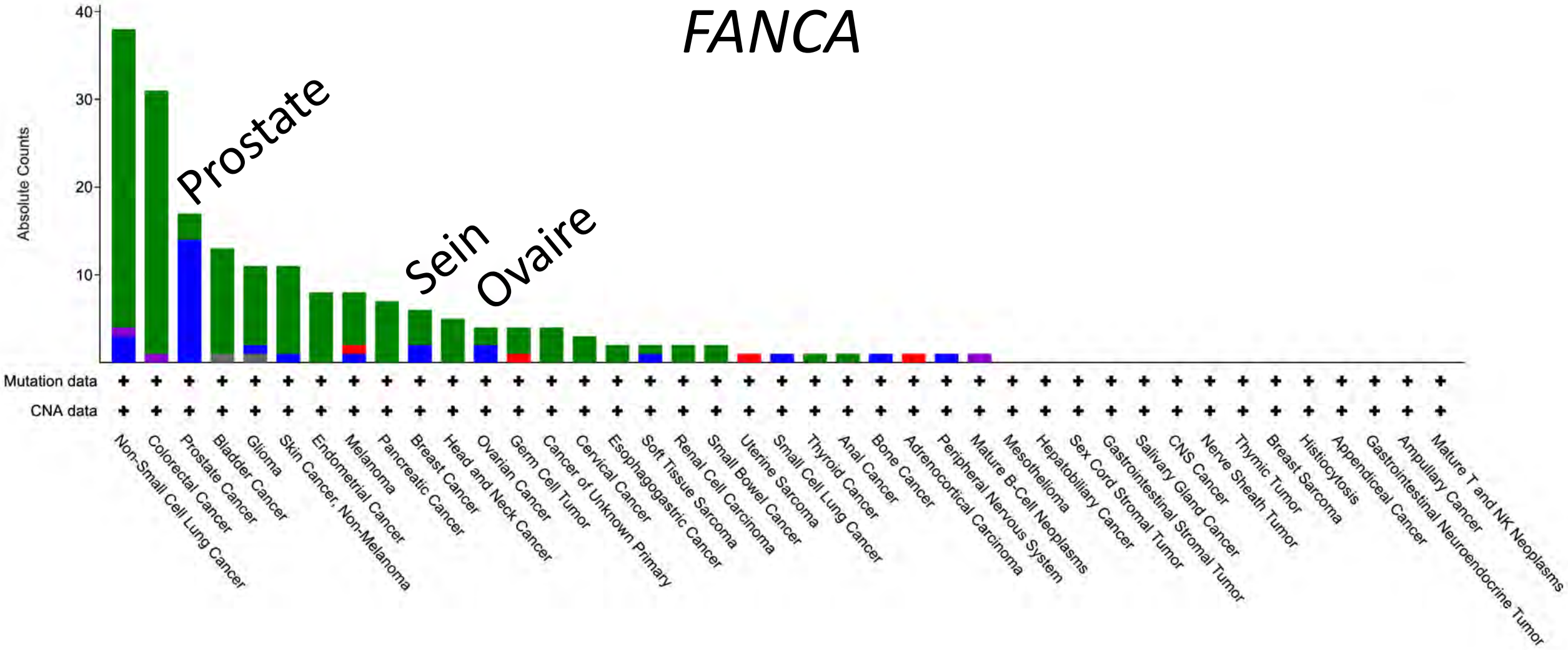
Ampullary Cancer
Sex Cord Stromal Tumor
Cervical Cancer
Thyroid Cancer
CNS Cancer
Nerve Sheath Tumor
Thymic Tumor
Adrenocortical Carcinoma
Breast Sarcoma
Histiocytosis
Peripheral Nervous System
Mature T and NK Neoplasms

# *FANCA*


Absolute Counts
40
30
20
10
Prostate
Sein
Ovaire
Mutation data
CNA data
Non-Small Cell Lung Cancer
Colorectal Cancer
Prostate Cancer
Bladder Cancer
Glioma
Skin Cancer, Non-Melanoma
Endometrial Cancer
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CNS Cancer
Nerve Sheath Tumor
Thymic Tumor
Breast Sarcoma
Histiocytosis
Appendiceal Cancer
Gastrointestinal Neuroendocrine Tumor
Ampullary Cancer
Mature T and NK Neoplasms

Research

JAMA Oncology | Original Investigation

# Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines

Piper Nicolosi, PhD; Elisa Ledet, PhD; Shan Yang, PhD; Scott Michalski, MS, LCGC; Brandy Freschi, MS, CGC; Erin O'Leary, MS, CGC; Edward D. Esplin, MD, PhD; Robert L. Nussbaum, MD; Oliver Sartor, MD

Cross-sectional study of data from 3607 men with a personal history of prostate cancer who underwent germline genetic testing between 2013 and 2018 and were unselected for family history, stage of disease, or age at diagnosis.

Table. Most Frequently Detected Variants in Patients With a Personal History of Prostate Cancer

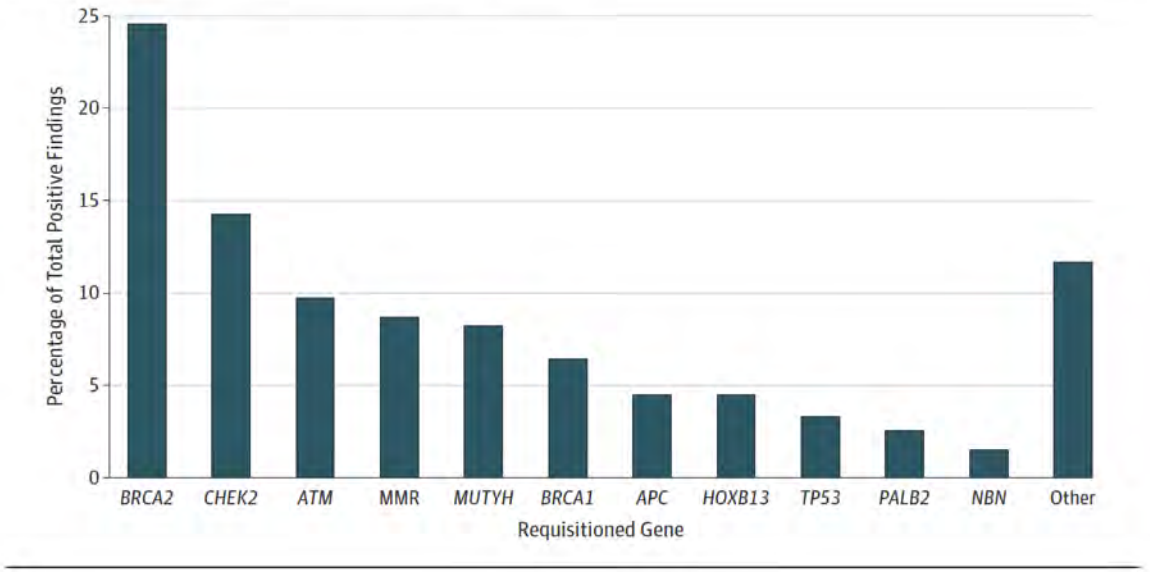
| Gene | No. of Requisitions | Variants of Uncertain Significance Detected | Positive Variants Detected, n = 674, (%) | Positive Variants per Requisition, %[a] |
|---|---|---|---|---|
| *BRCA2* | 3459 | 75 | 164 (24.3) | 4.74 |
| *CHEK2* | 3300 | 71 | 95 (14.1) | 2.88 |
| *ATM* | 3207 | 160 | 65 (9.6) | 2.03 |
| *MUTYH* | 2322 | 27 | 55 (8.2) | 2.37 |
| *BRCA1* | 3436 | 38 | 43 (6.4) | 1.25 |
| *HOXB13* | 2667 | 0 | 30 (4.5) | 1.12 |
| *APC* | 2345 | 76 | 30 (4.5) | 1.28 |
| *MSH2* | 3350 | 48 | 23 (3.4) | 0.69 |
| *TP53* | 3329 | 30 | 22 (3.3) | 0.66 |
| *PALB2* | 3014 | 42 | 17 (2.5) | 0.56 |
| *PMS2* | 3345 | 50 | 18 (2.7) | 0.54 |
| *MSH6* | 3346 | 75 | 15 (2.2) | 0.45 |
| *NBN* | 3145 | 41 | 10 (1.5) | 0.32 |
| *RAD50* | 2173 | 40 | 7 (1.0) | 0.32 |
| *BRIP1* | 2461 | 36 | 7 (1.0) | 0.28 |
| *RAD51C* | 2438 | 21 | 5 (0.7) | 0.21 |
| *RAD51D* | 2689 | 12 | 4 (0.6) | 0.15 |
| *CDKN2A* | 2277 | 6 | 3 (0.4) | 0.13 |
| *CDH1* | 2504 | 28 | 3 (0.4) | 0.12 |
| *NF1* | 2347 | 35 | 2 (0.3) | 0.09 |
| *MLH1* | 3343 | 25 | 2 (0.3) | 0.06 |

DNA Repair mutations are probably more common than previously appreciated
This is not only associated with family history



JAMA Oncology Published online February 7, 2019

Figure. Frequency by Gene of Pathogenic, Likely Pathogenic, and Increased-Risk Allele Variants Detected in This Study




*"229 patients (37%) with the positive variants detected in this study would not have been identified had they been tested using only the NCCN genetic/familial breast and ovarian guidelines"*

New NCCN guidelines rely heavily on Gleason scores.

Conclusion: cost of genetic testing and counseling needs to be weighed against cost of treating late stage cancer
But there are alternate strategies….only provide genetic counseling to those that test positive (VA Model, on-going trial)



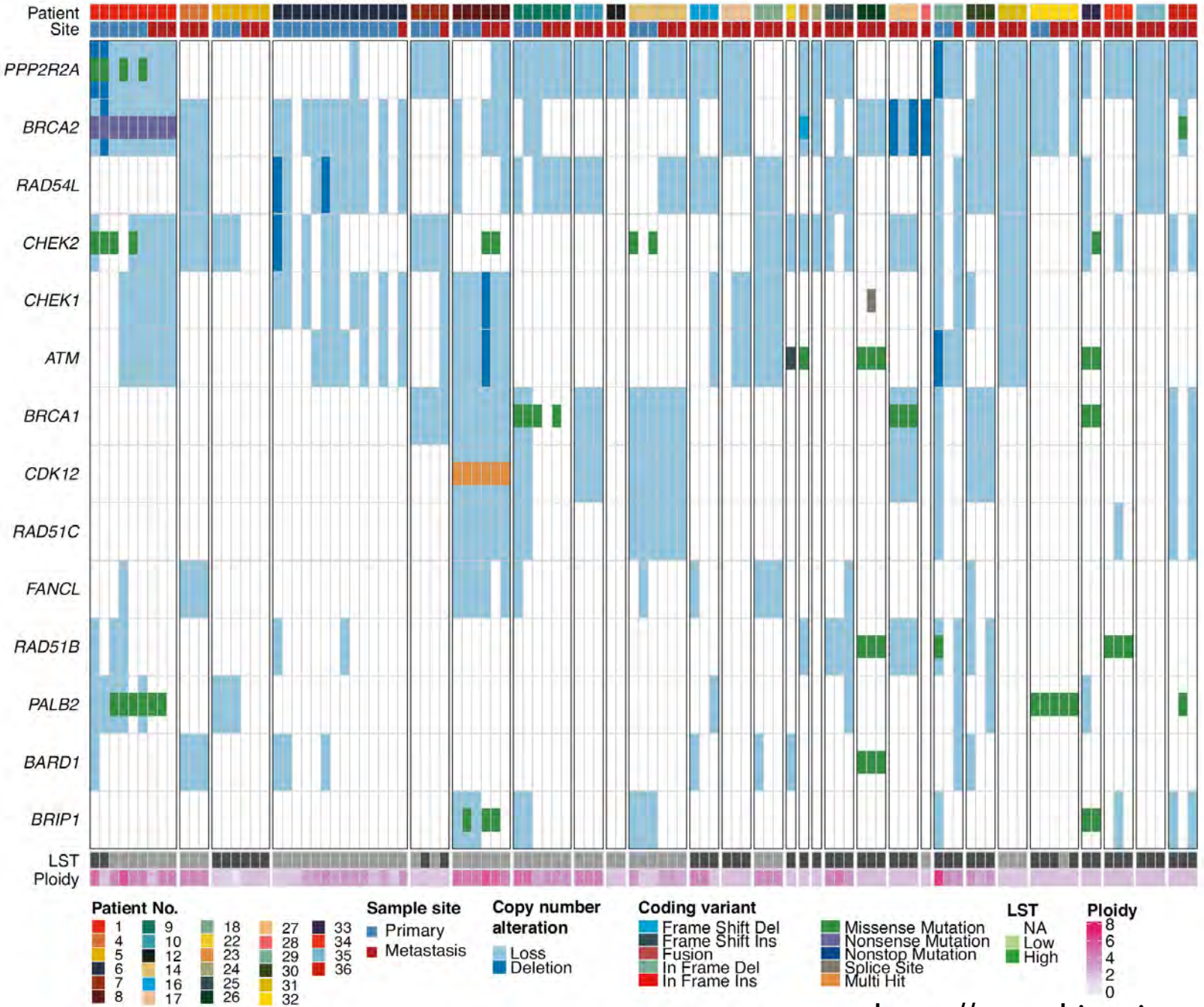
JAMA Oncology Published online February 7, 2019

# *The Genomic Landscape of Prostate Cancer Brain Metastases*

Antonio Rodriguez[1,2 *], John Gallon[3 *], Dilara Akhoundova[4], Sina Maletti[1], Alison Ferguson[1,5], Joanna Cyrta[6], Ursula Amstutz[7], Andrea Garofoli[8], Viola Paradiso[8], Scott A. Tomlins[9], Ekkehard Hewer[2], Vera Genitsch[2], Achim Fleischmann[10], Elisabeth J. Rushing[11], Rainer Grobholz[12], Ingeborg Fischer[12], Wolfram Jochum[13], Gieri Cathomas[14], Lukas Bubendorf[4], Holger Moch[15], Charlotte K.Y. Ng[1], Silke Gillessen Sommer[16,17,18 #], Salvatore Piscuoglio[3,8 #§], and Mark A. Rubin[1,19 #§]

Rodriguez, Gallon et al., in review

https://www.biorxiv.org/content/10.1101/2020.05.12.092296v1




When considering the combination of somatic mutations, copy number alterations, and Large-scale State Transitions, 64.3% of patients (18/28) had evidence of HR defects

Rodriguez, Gallon et al., in review

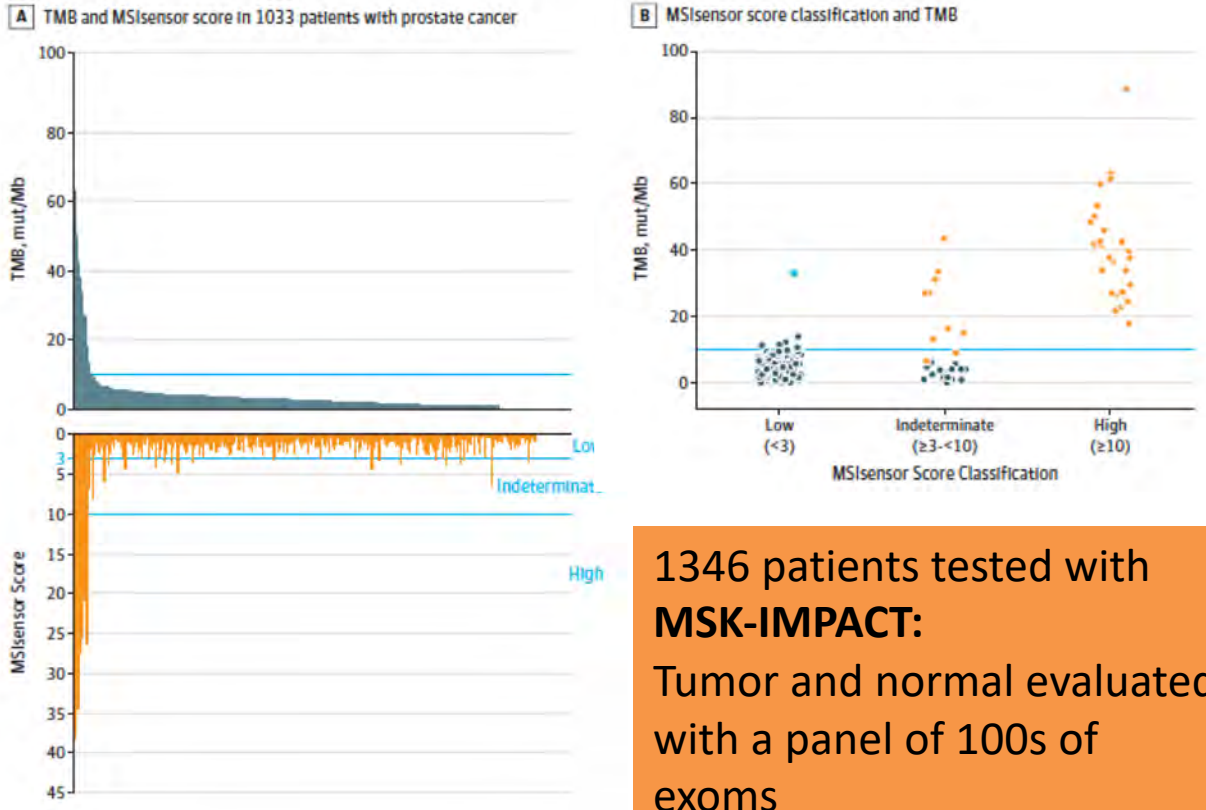
https://www.biorxiv.org/content/10.1101/2020.05.12.092296v1

JAMA Oncology | Original Investigation

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

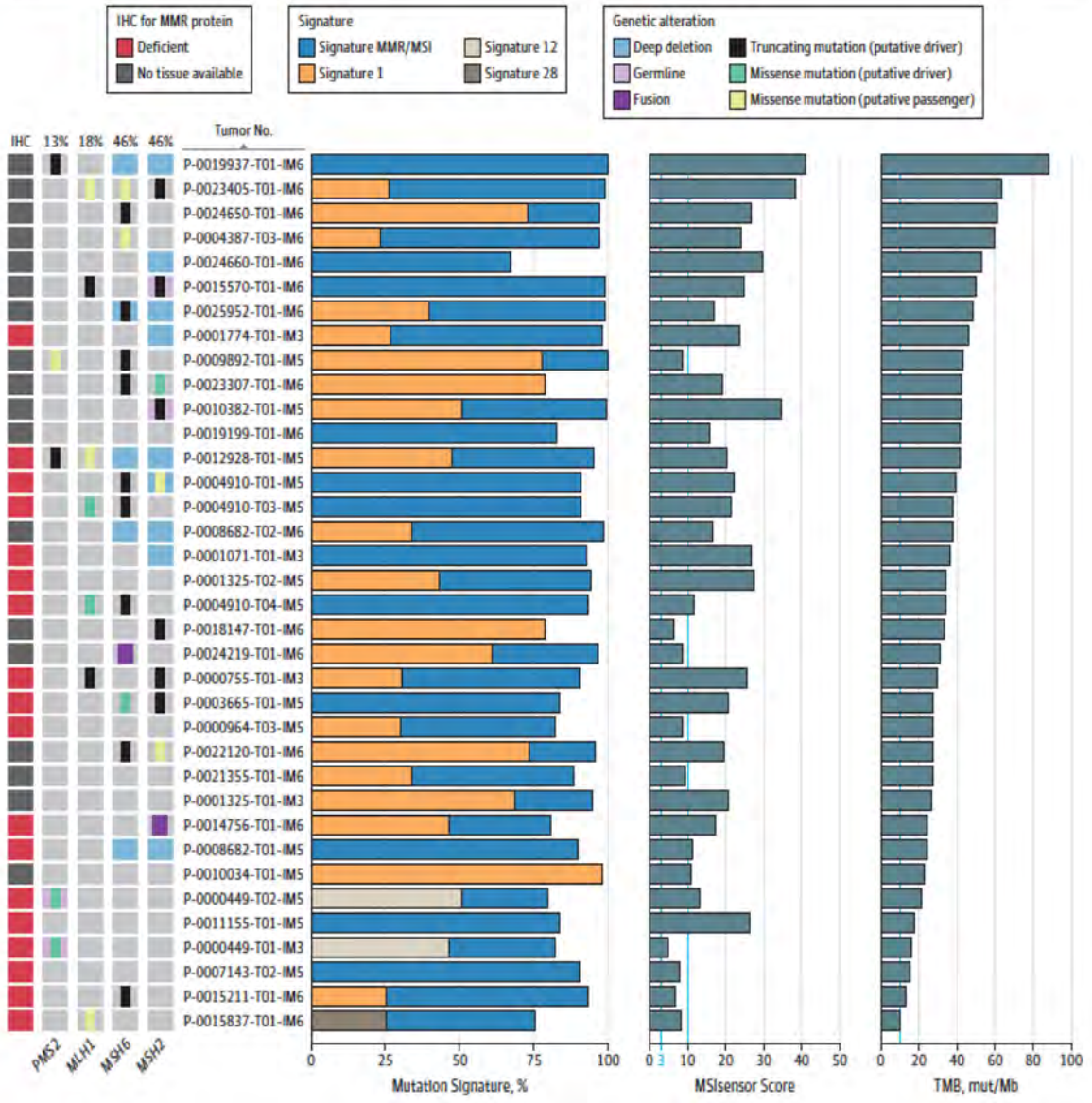
Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman, 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**




1346 patients tested with **MSK-IMPACT:**
Tumor and normal evaluated with a panel of 100s of exoms

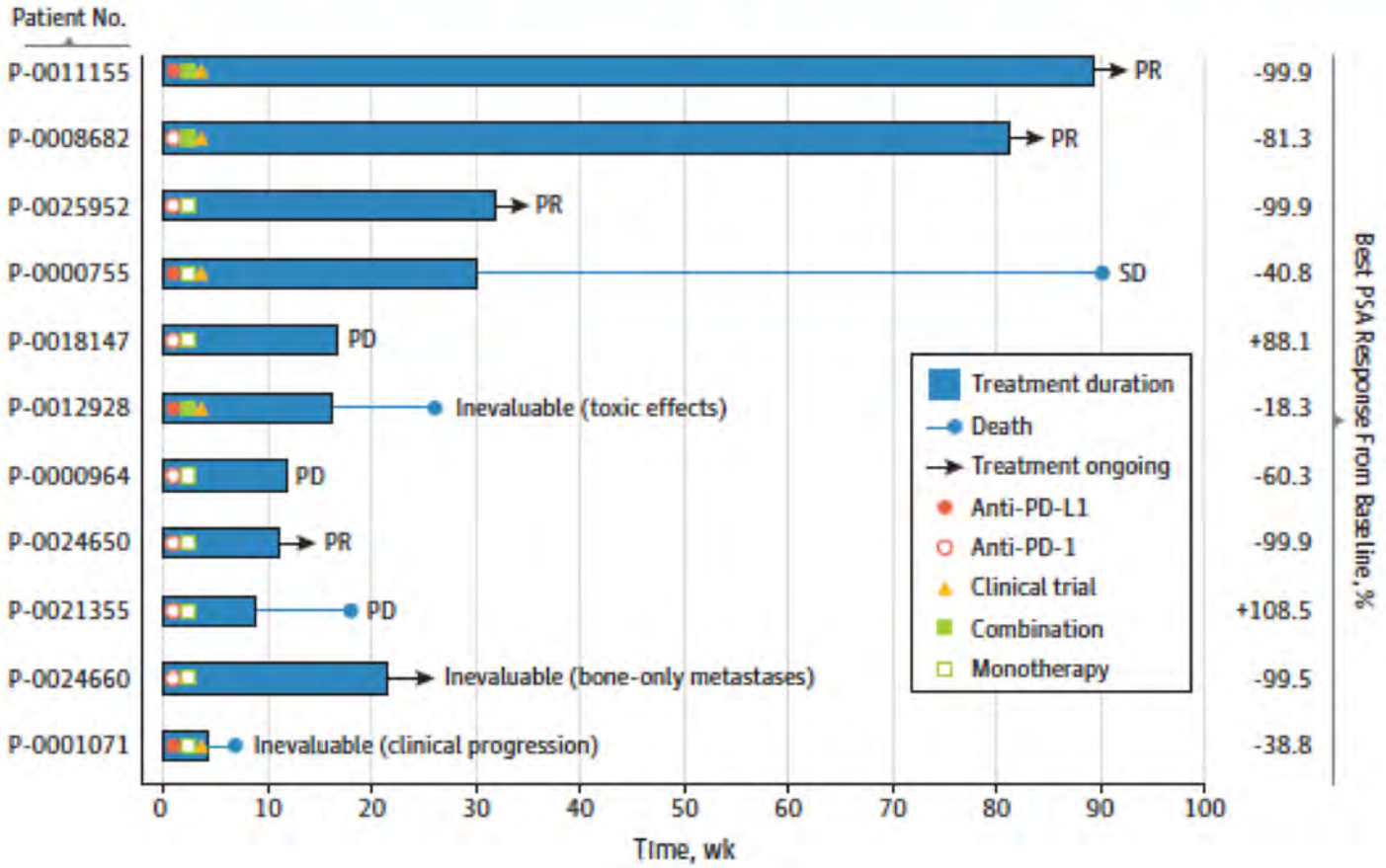
**Figure 2. Integrative Analysis of Microsatellite Instability (MSI), Tumor Mutation Burden (TMB), Mutational Signature Decomposition, and Mismatch Repair (MMR) Gene and Protein Status**






JAMA Oncology Published online December 27, 2018

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



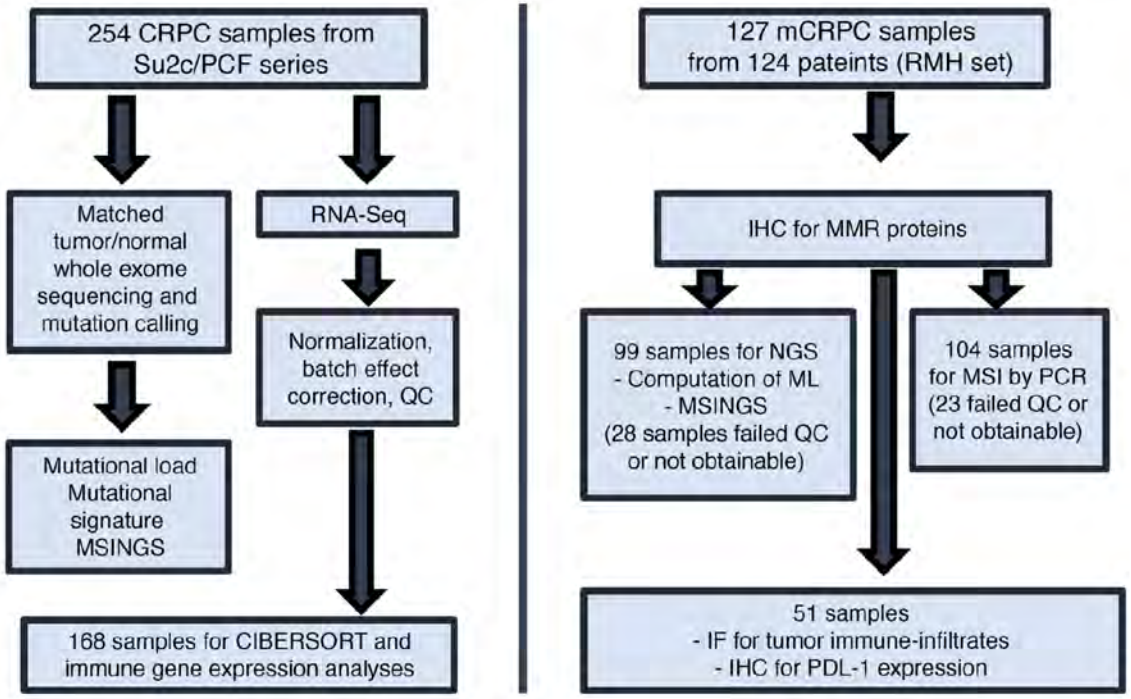


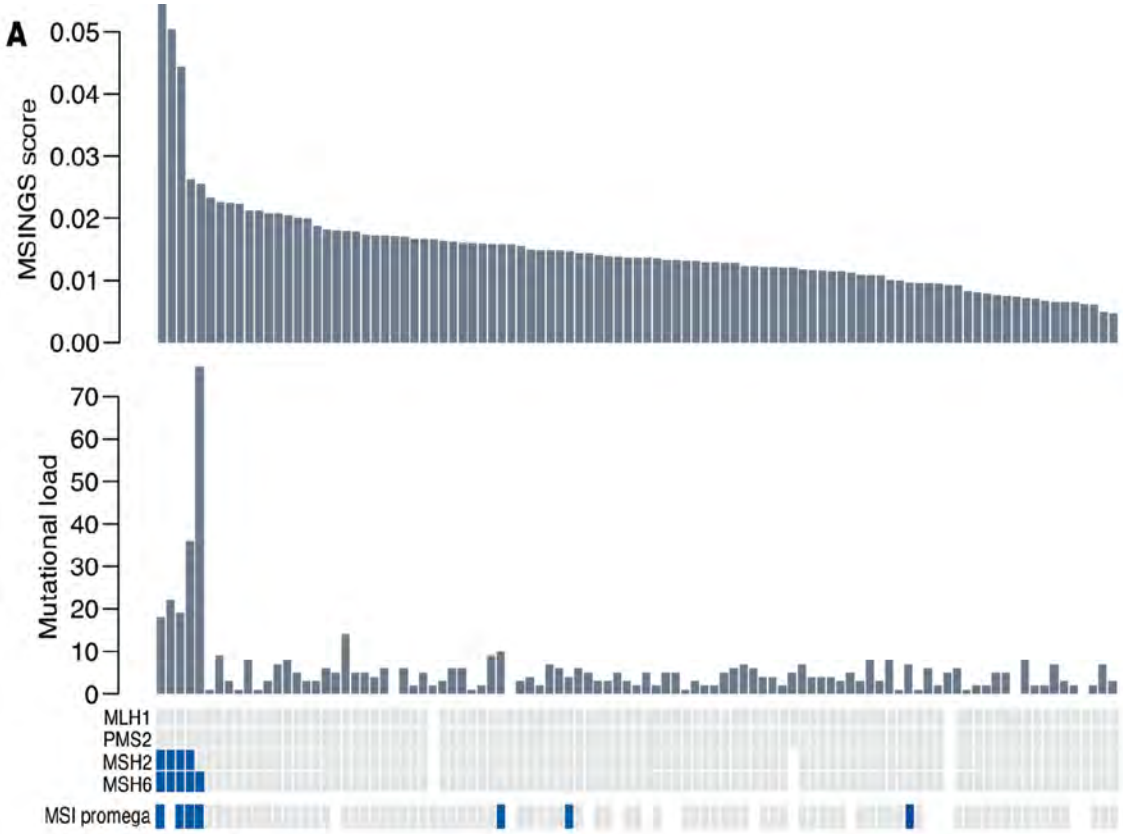

JAMA Oncology Published online December 27, 2018

# Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer

Daniel Nava Rodrigues,[1,2] Pasquale Rescigno,[1,2,3] David Liu,[4,5] Wei Yuan,[1] Suzanne Carreira,[1] Maryou B. Lambros,[1] George Seed,[1] Joaquin Mateo,[1,2] Ruth Riisnaes,[1] Stephanie Mullane,[4,5] Claire Margolis,[4,5] Diana Miao,[4,5] Susana Miranda,[1] David Dolling,[1] Matthew Clarke,[1] Claudia Bertan,[1] Mateus Crespo,[1] Gunther Boysen,[1] Ana Ferreira,[1] Adam Sharp,[1] Ines Figueiredo,[1] Daniel Keliher,[4,5] Saud Aldubayan,[4,5] Kelly P. Burke,[4] Semini Sumanasuriya,[1] Mariane Sousa Fontes,[1,2] Diletta Bianchini,[1,2] Zafeiris Zafeiriou,[1,2] Larissa Sena Teixeira Mendes,[2] Kent Mouw,[4] Michael T. Schweizer,[6,7] Colin C. Pritchard,[6] Stephen Salipante,[6] Mary-Ellen Taplin,[3] Himisha Beltran,[8] Mark A. Rubin,[8] Marcin Cieslik,[9] Dan Robinson,[9] Elizabeth Heath,[10] Nikolaus Schultz,[11] Joshua Armenia,[11] Wassim Abida,[11] Howard Scher,[11] Christopher Lord,[1] Alan D'Andrea,[4] Charles L. Sawyers,[11] Arul M. Chinnaiyan,[9] Andrea Alimonti,[12] Peter S. Nelson,[6,7] Charles G. Drake,[13] Eliezer M. Van Allen,[4,5] and Johann S. de Bono[1,2]

Testing with a targeted NGS panel and WES of Tumor and Normal
Overall, 8.1% had evidence of MMR



color Health Systems Employers Individuals Providers Giving Back Help Activate Kit Sign In


## A new model for data-driven healthcare

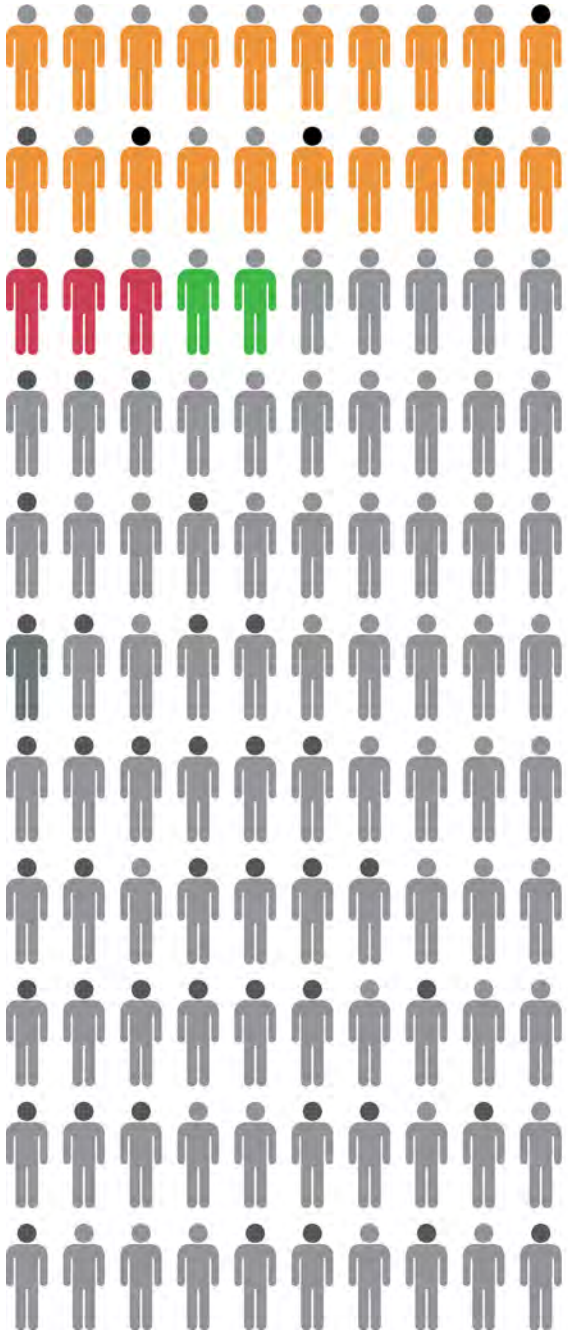
Color helps create an end-to-end delivery model that links precision data to risk, risk to decisions, and decisions to behavior change across populations.

- Quickly engage your population through clinical-grade genetics and digital tools.
- Efficiently collect rich phenotypic and genotypic (whole genome) information across your population and their families while protecting individual privacy.
- Translate precision clinical data into an understanding of risk for individuals, providers, and systems to help inform appropriate health interventions
- Drive behavior changes such as adherence, compliance, and lifestyle choices to impact outcomes.

**Color Extended: The most relevant genes for common hereditary cancers**

| Gene | Breast | Ovarian | Uterine | Colorectal | Melanoma | Pancreatic | Stomach | Prostate* |
|---|---|---|---|---|---|---|---|---|
| BRCA1 | ● | ● | | | | ● | | ● |
| BRCA2 | ● | ● | | | ● | ● | | ● |
| MLH1 | | ● | ● | ● | | ● | ● | ● |
| MSH2 | | ● | ● | ● | | ● | ● | ● |
| MSH6 | | ● | ● | ● | | | ● | ● |
| PMS2*** | | ● | ● | ● | | | | ● |
| EPCAM** | | ● | ● | ● | | ● | ● | ● |
| APC | | | | ● | | ● | ● | |
| MUTYH | | | | ● | | | | |
| MITF** | | | | | ● | | | |
| BAP1 | | | | | ● | | | |
| CDKN2A | | | | | ● | ● | | |
| CDK4** | | | | | ● | | | |
| TP53 | ● | ● | ● | ● | ● | ● | ● | ● |
| PTEN | ● | | ● | ● | ● | | | |
| STK11 | ● | ● | ● | ● | | ● | ● | |
| CDH1 | ● | | | | | | ● | |
| BMPR1A | | | | ● | | ● | ● | |
| SMAD4 | | | | ● | | ● | ● | |
| GREM1** | | | | ● | | | | |
| POLD1** | | | | ● | | | | |
| POLE** | | | | ● | | | | |
| PALB2 | ● | ● | | | | ● | | |
| CHEK2 | ● | | | ● | | | | ● |
| ATM | ● | | | | | ● | | ● |
| NBN | ● | | | | | | | ● |
| BARD1 | ● | | | | | | | |
| BRIP1 | ● | ● | | | | | | |
| RAD51C | | ● | | | | | | |
| RAD51D | | ● | | | | | | |

Many tests available – need test that is designed to address clinically relevant alterations. For advanced PCa, combining somatic and germline will be critical



DNA Repair (BRCA1/2, ATM, etc.) 20%

MMR /MSI 5%

The remaining 75%

# Overview of Tests that are Ready/Promising*

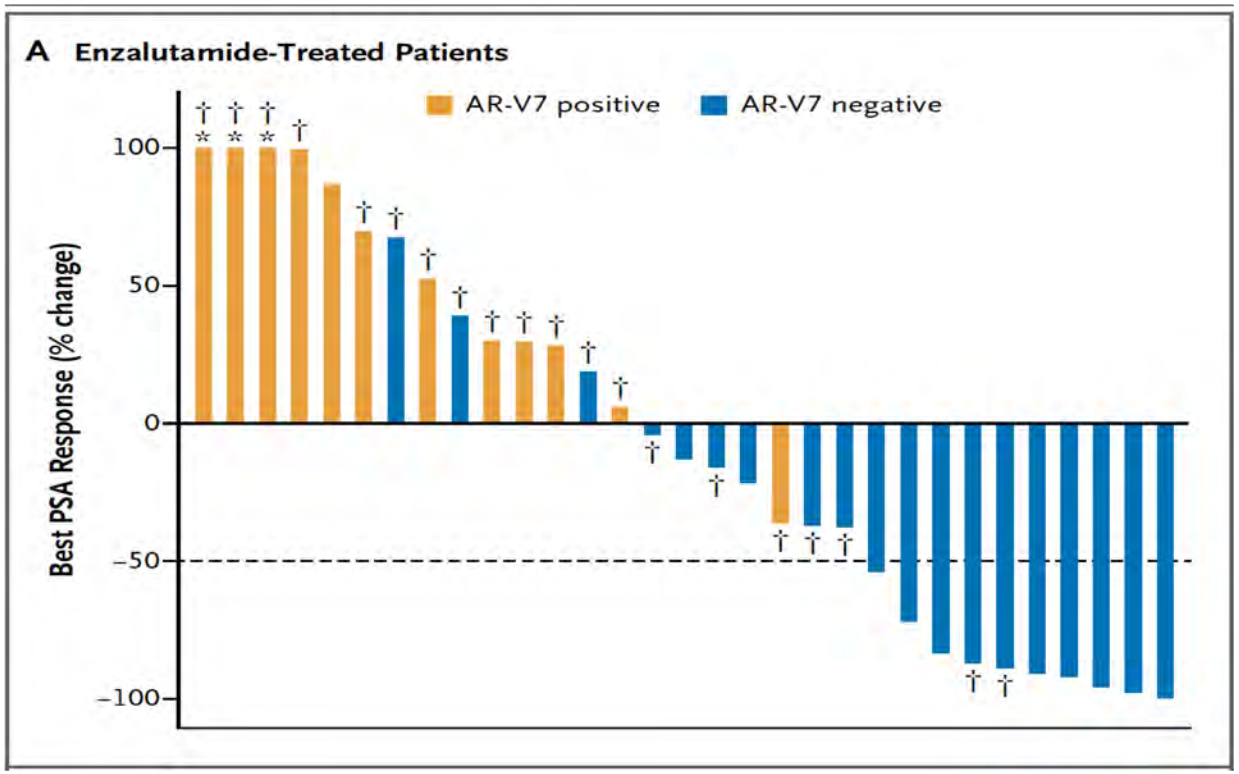
a. **MSI testing**
b. **DNA repair status** ("BRCAness"-assay for BRCA1/2/ATM,PALB2) for mutation/loss or HR signature useful for for platinum therapy or PARPi
c. **Loss of AR** lack of response to AR therapy (AR-V7, mutations)
d. **cfDNA** amount associated with prognosis
e. **PTEN loss** - possibly 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

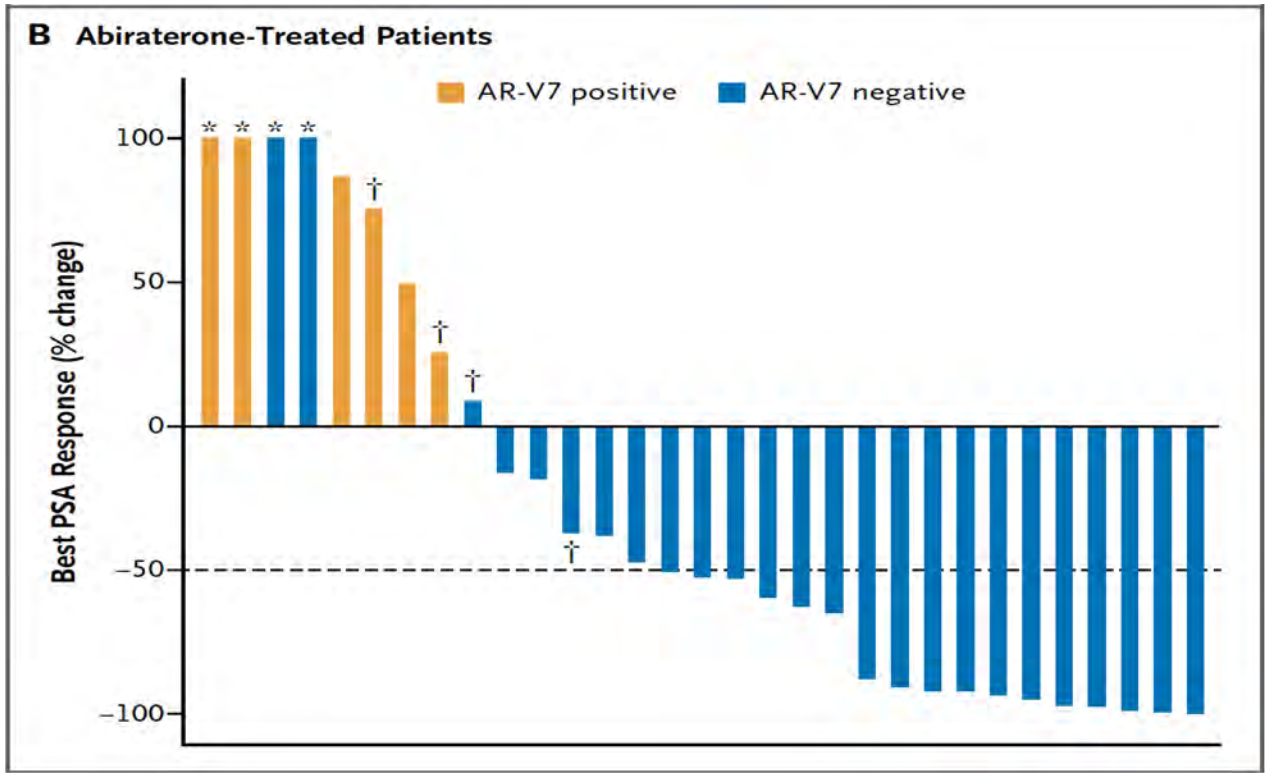
*Thanks Pete Nelson
Always comprehensive!

The NEW ENGLAND JOURNAL of MEDICINE

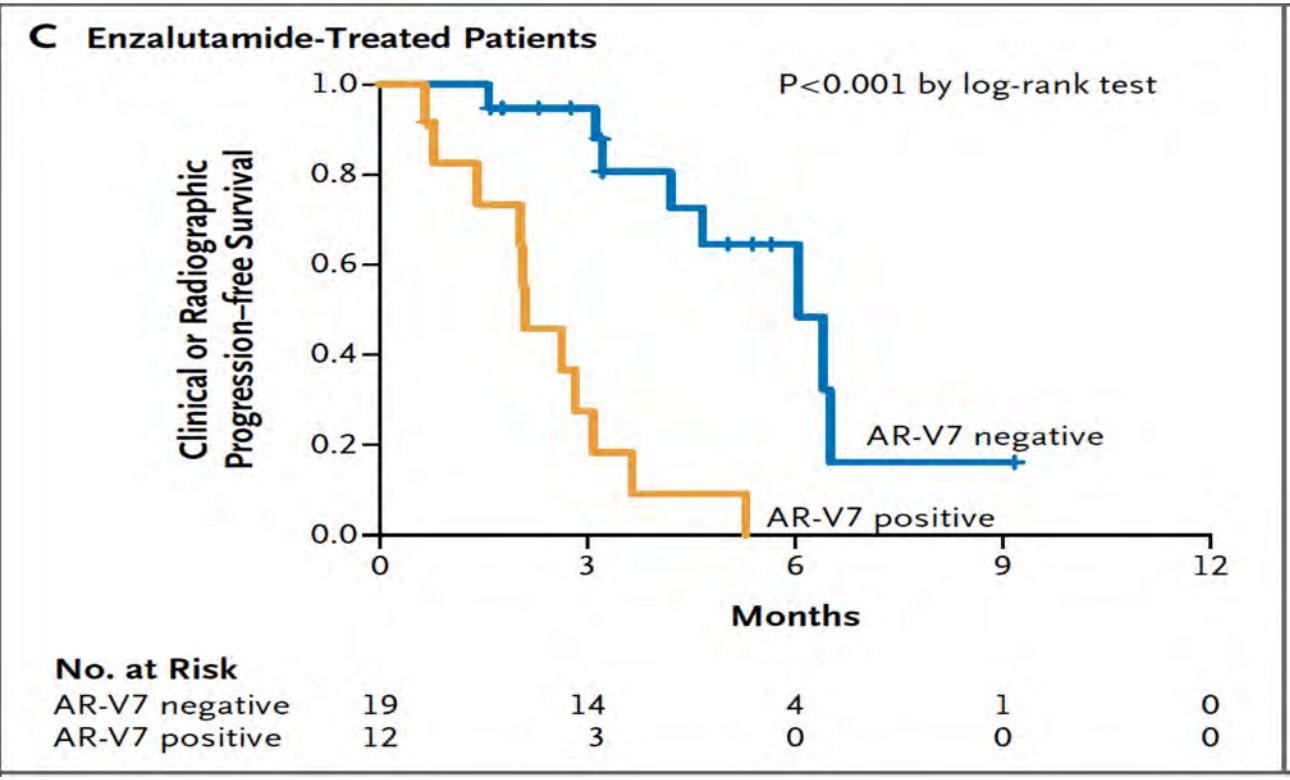
ORIGINAL ARTICLE

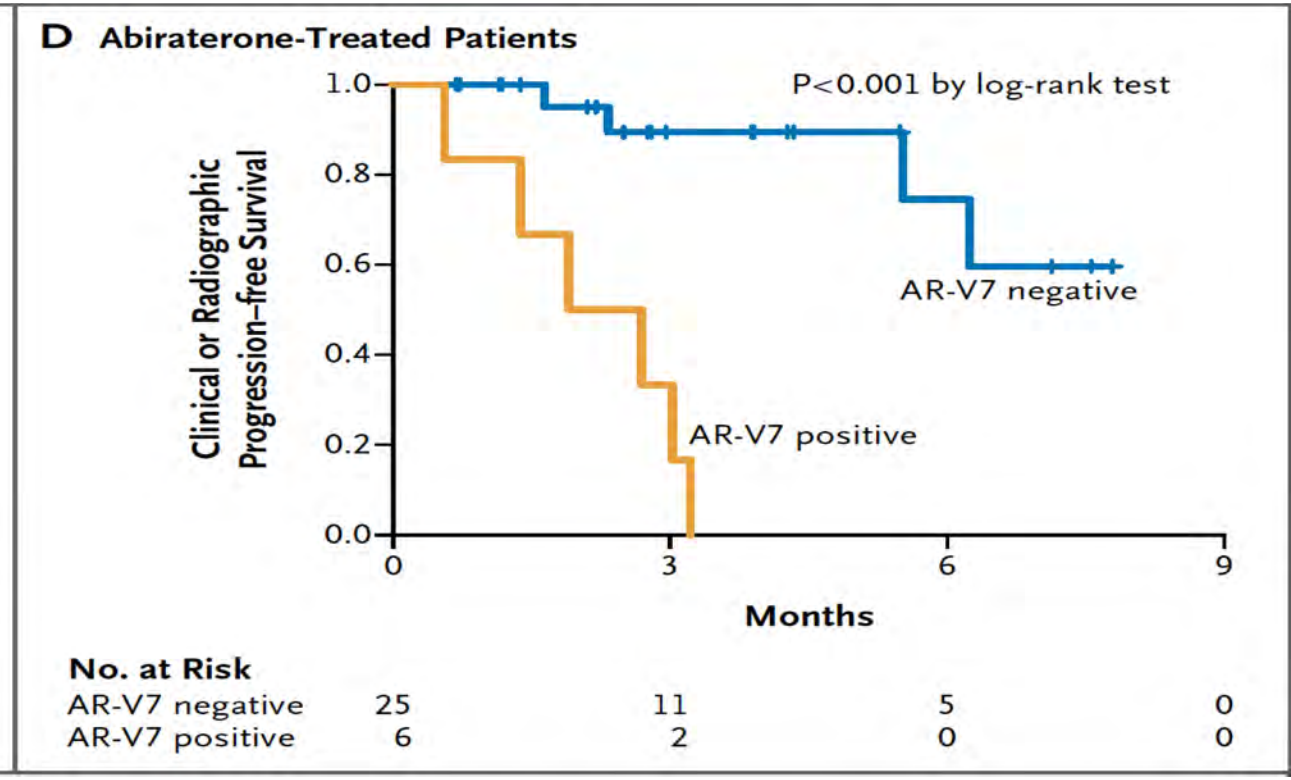
# AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer



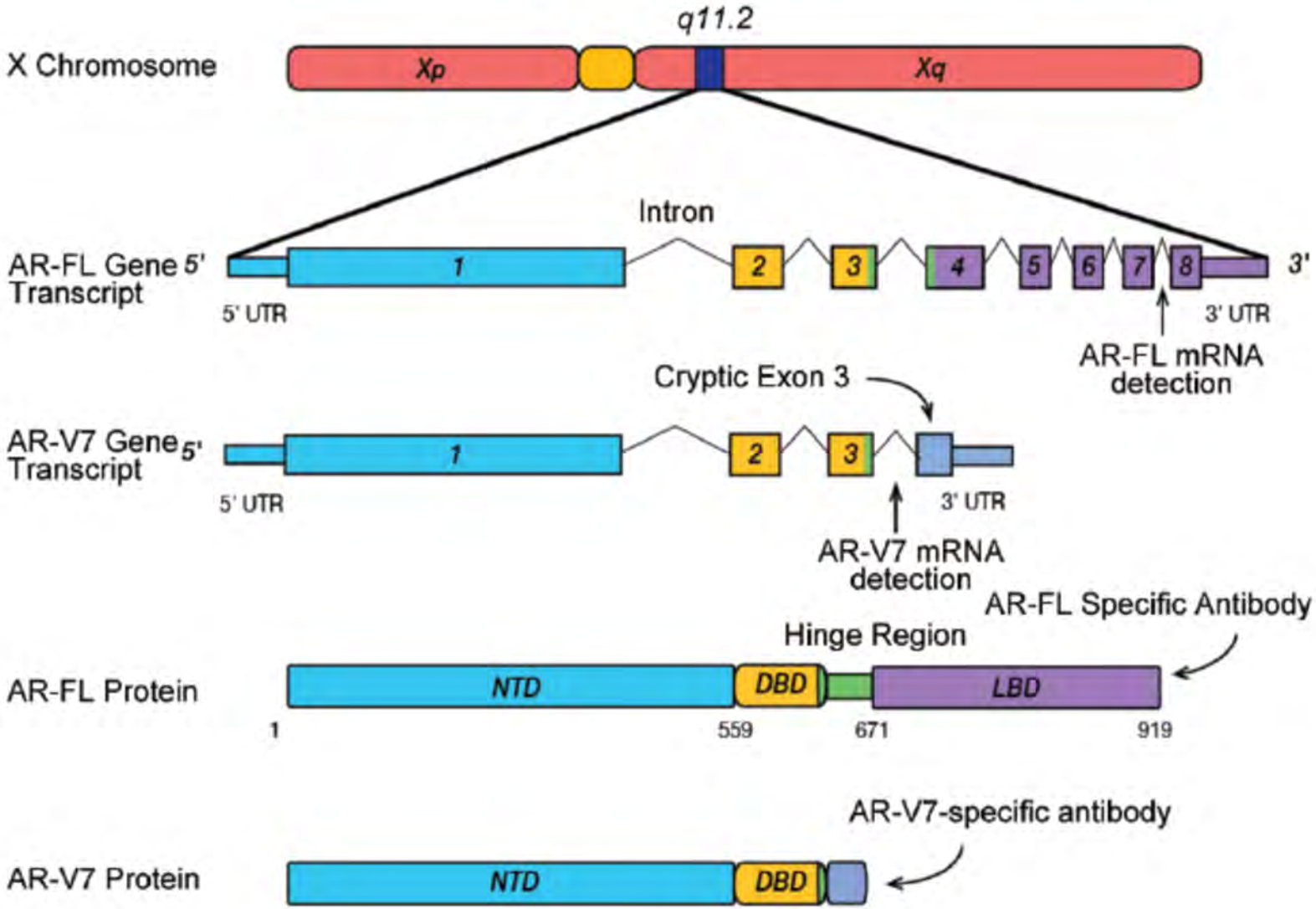

Antonarakis ES et al, NEJM 2014




Antonarakis ES et al, NEJM 2014

# The Androgen Receptor and associated ligand-indepedent variant, AR-V7

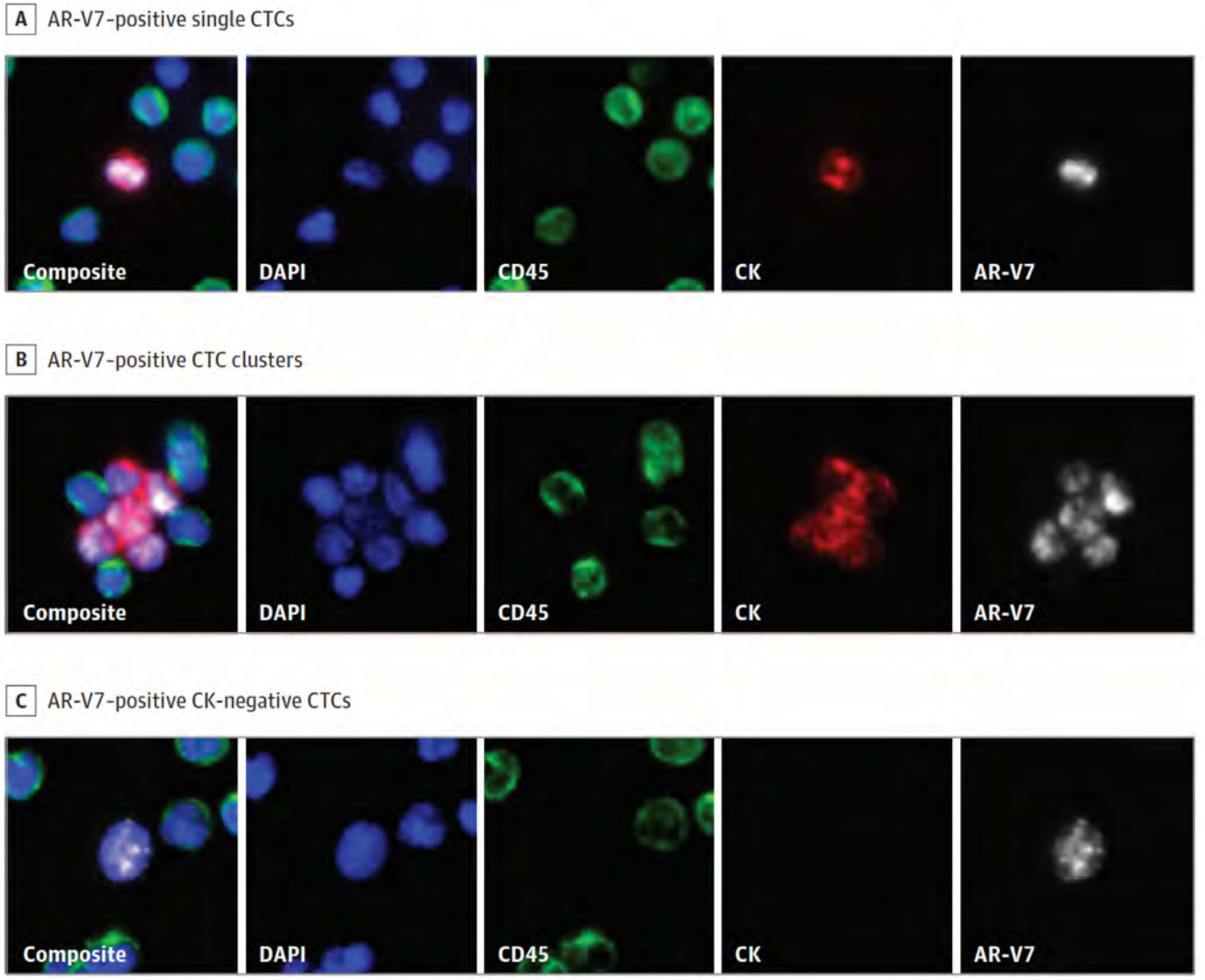


Research

JAMA Oncology | Original Investigation

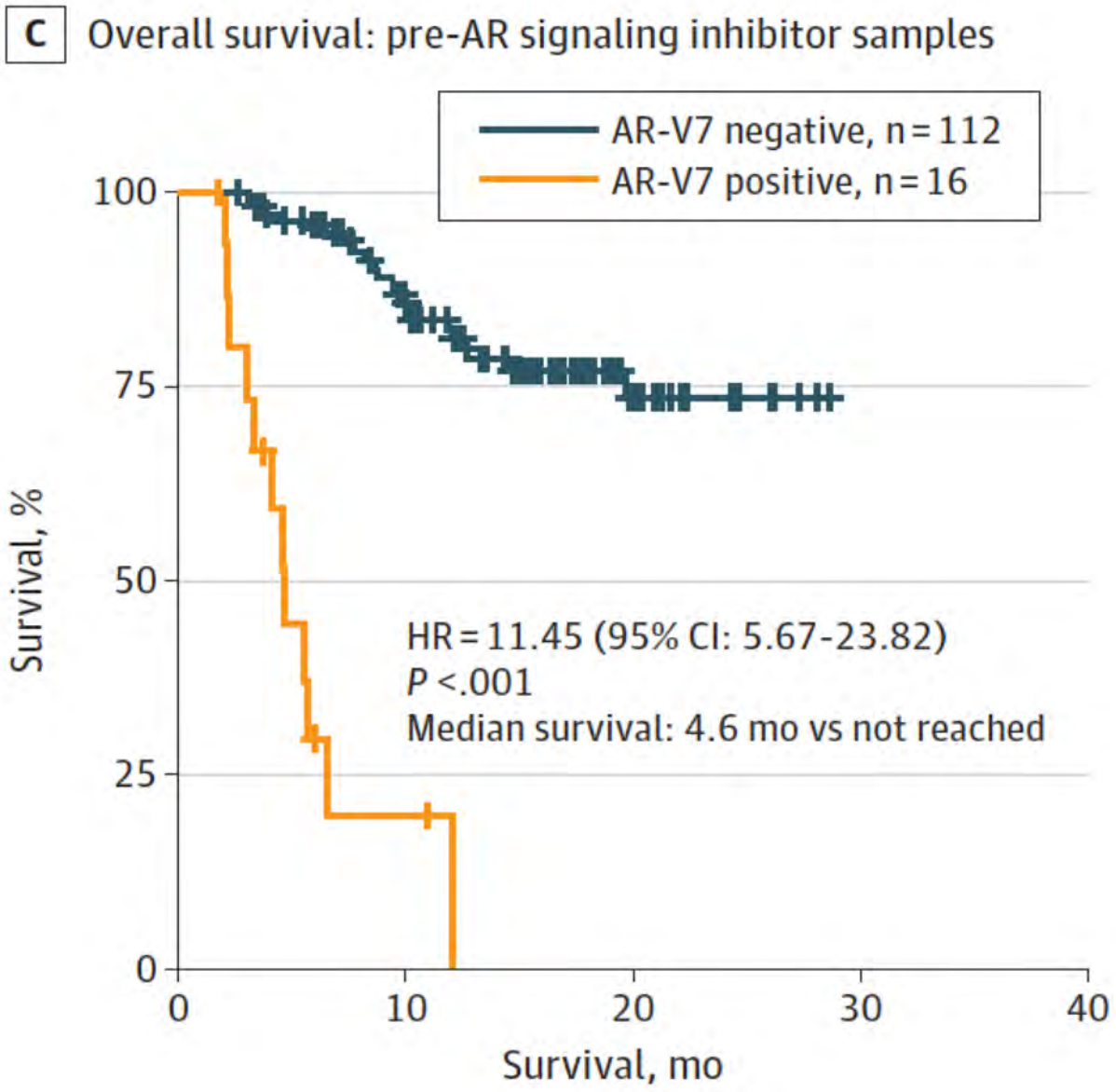
# Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

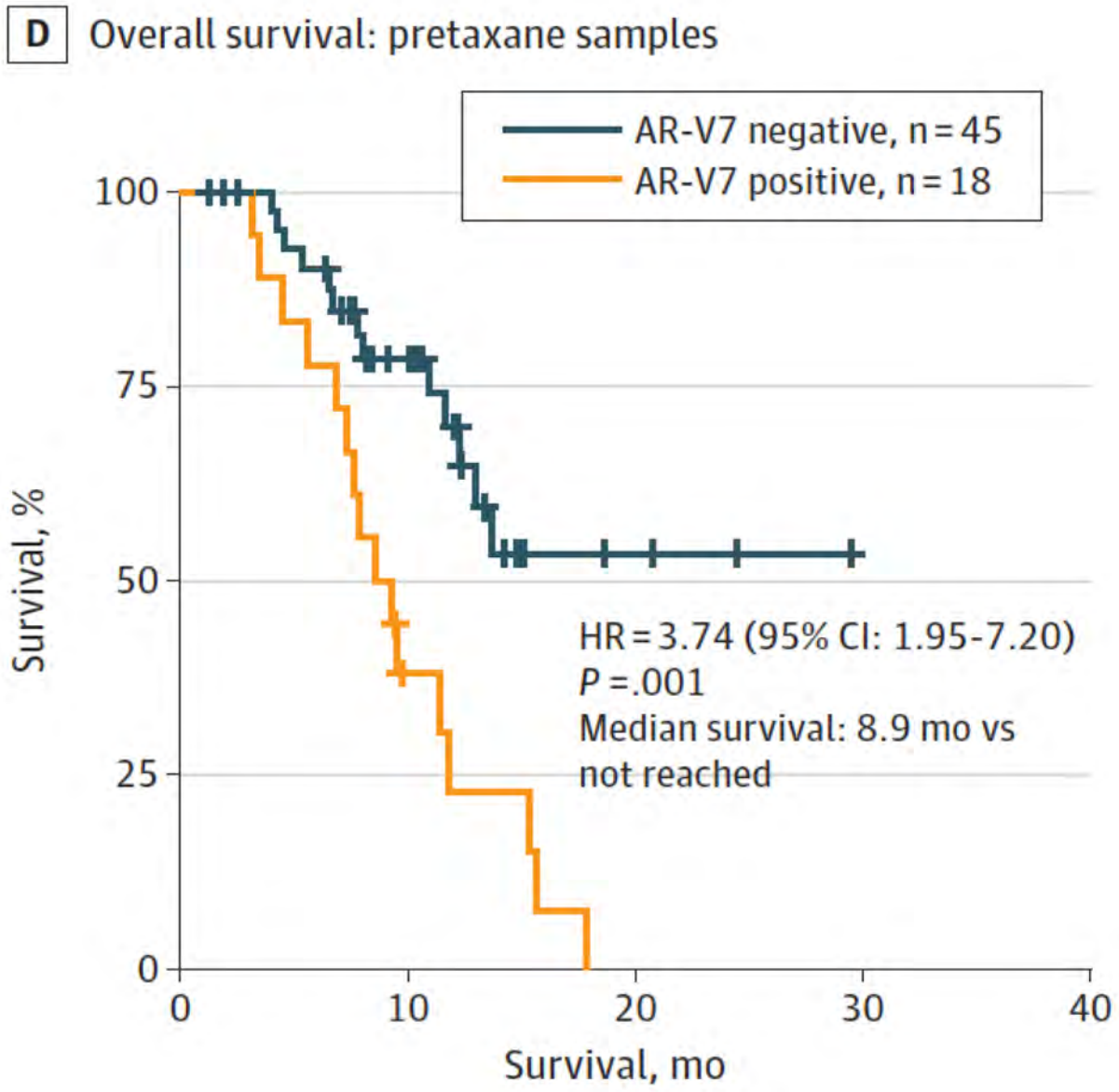
Howard I. Scher, MD; David Lu, PhD; Nicole A. Schreiber, BA; Jessica Louw, BS; Ryon P. Graf, PhD; Hebert A. Vargas, MD; Ann Johnson, MS; Adam Jendrisak, MBA; Richard Bambury, MB, BCh, BAO; Daniel Danila, MD; Brigit McLaughlin, BS; Justin Wahl, BS; Stephanie B. Greene, PhD; Glenn Heller, PhD; Dena Marrinucci, PhD; Martin Fleisher, PhD; Ryan Dittamore, MBA

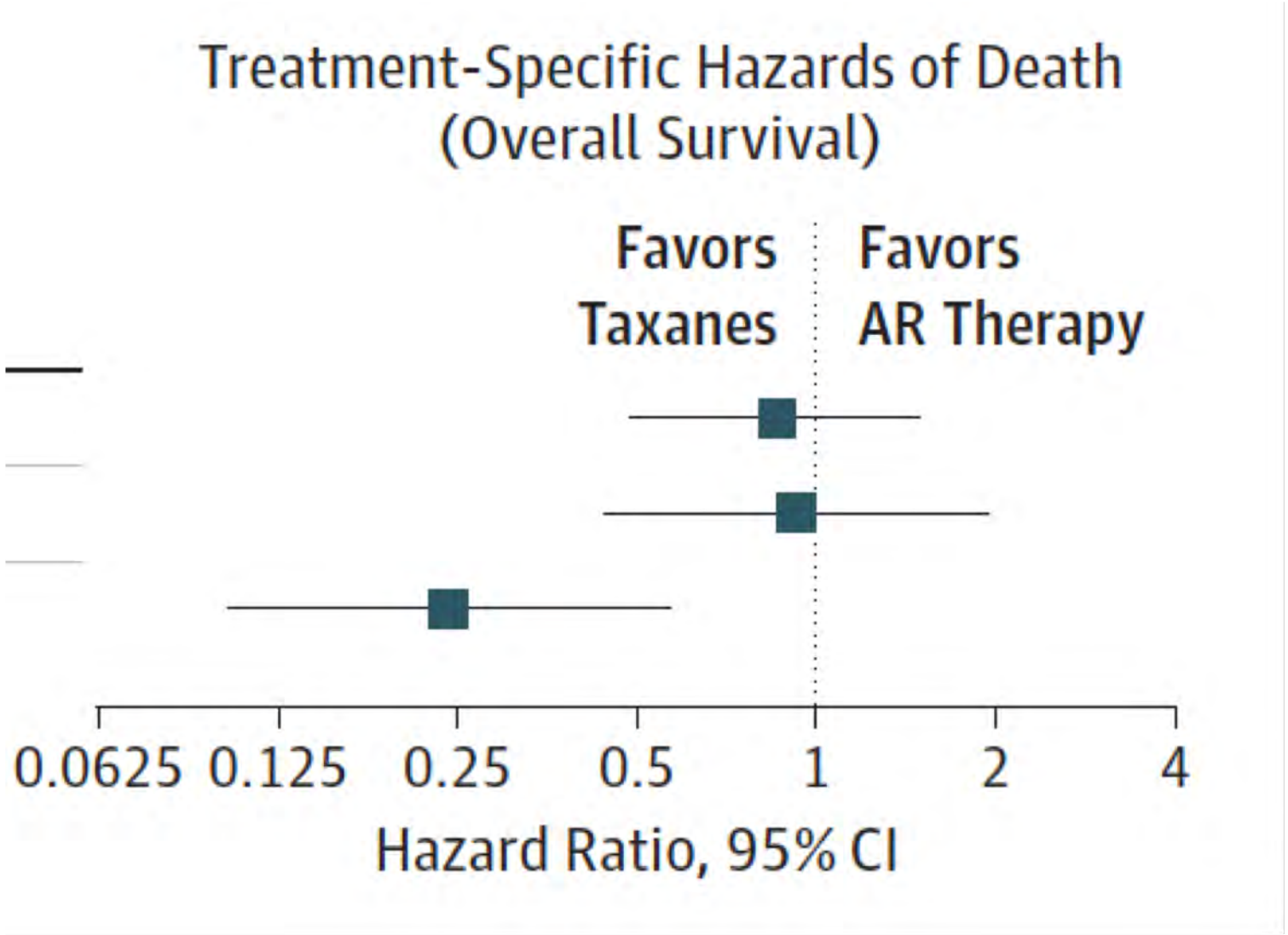





JAMA Oncology November 2016 Volume 2, Number 11







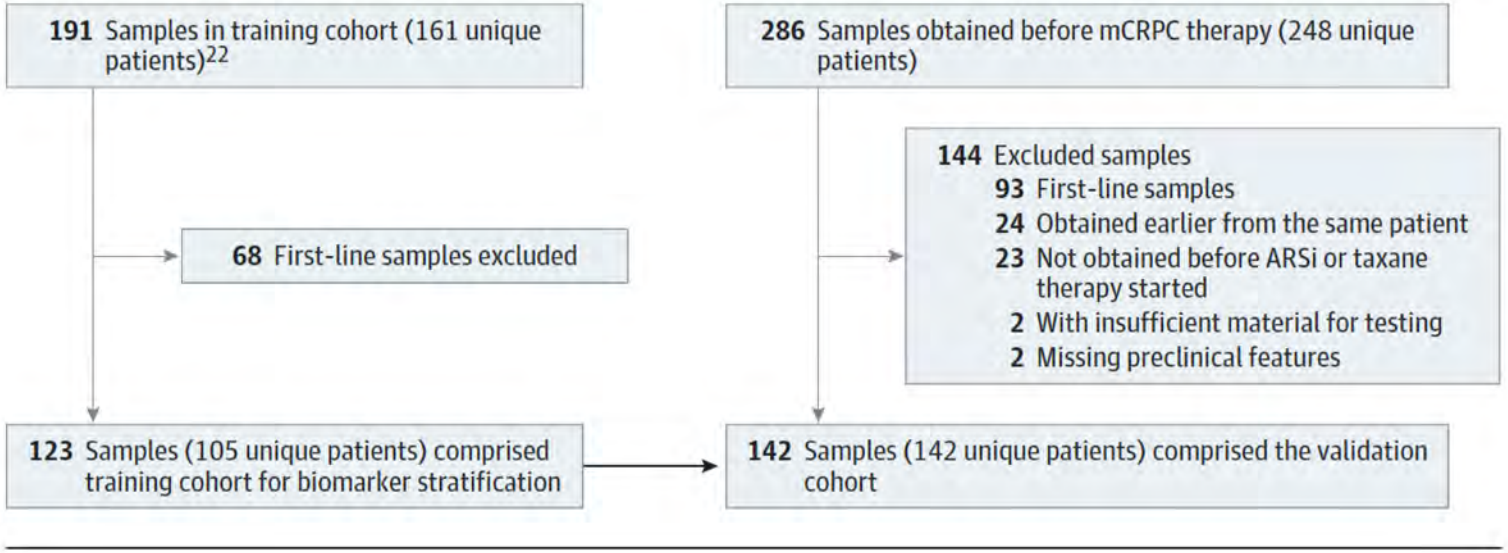

JAMA Oncology November 2016 Volume 2, Number 11

JAMA Oncology | Original Investigation

# Assessment of the Validity of Nuclear-Localized Androgen Receptor Splice Variant 7 in Circulating Tumor Cells as a Predictive Biomarker for Castration-Resistant Prostate Cancer

Howard I. Scher, MD; Ryon P. Graf, PhD; Nicole A. Schreiber, BA; Anuradha Jayaram, MB, BCh; Eric Winquist, MD; Brigit McLaughlin, BS; David Lu, PhD; Martin Fleisher, PhD; Sarah Orr, MS; Lori Lowes, PhD; Amanda Anderson, PhD; Yipeng Wang, MD, PhD; Ryan Dittamore, MBA; Alison L. Allan, PhD; Gerhardt Attard, MD, PhD; Glenn Heller, PhD

## Figure 1. Distribution of Patient Samples in the Training Cohort and Validation Cohort



Invited Commentary

# Nuclear Circulating Tumor Cell Androgen Receptor Variant 7 in Castration-Resistant Prostate Cancer

## The Devil Is in the Detail

Stephen R. Plymate, MD; Adam Sharp, MD, PhD; Johann S. de Bono, MD, PhD

***Concerns regarding the assay…***

1) positivity not continuous but binary (only 1 positive CTC needed)
2) Total CTC counts not reported
3) False-negative rate cannot be interpreted with total CTC count
4) Anti-body to cryptic exon 3 may be non-specific leading to false positivity
5) AR-V7 may be more prognostics of overall survival

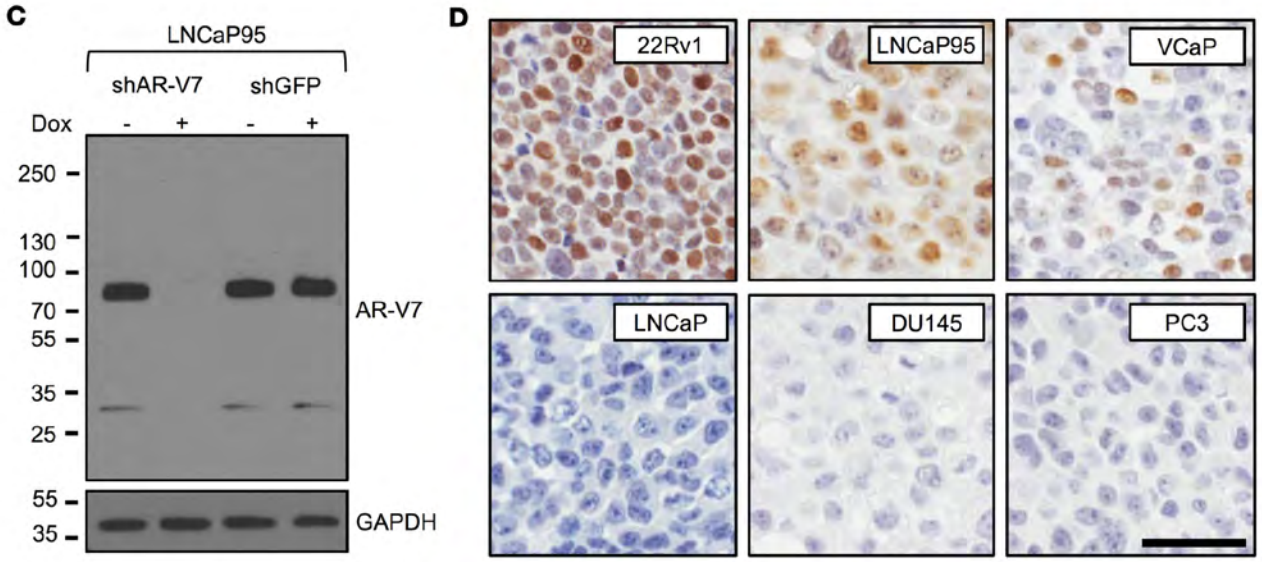


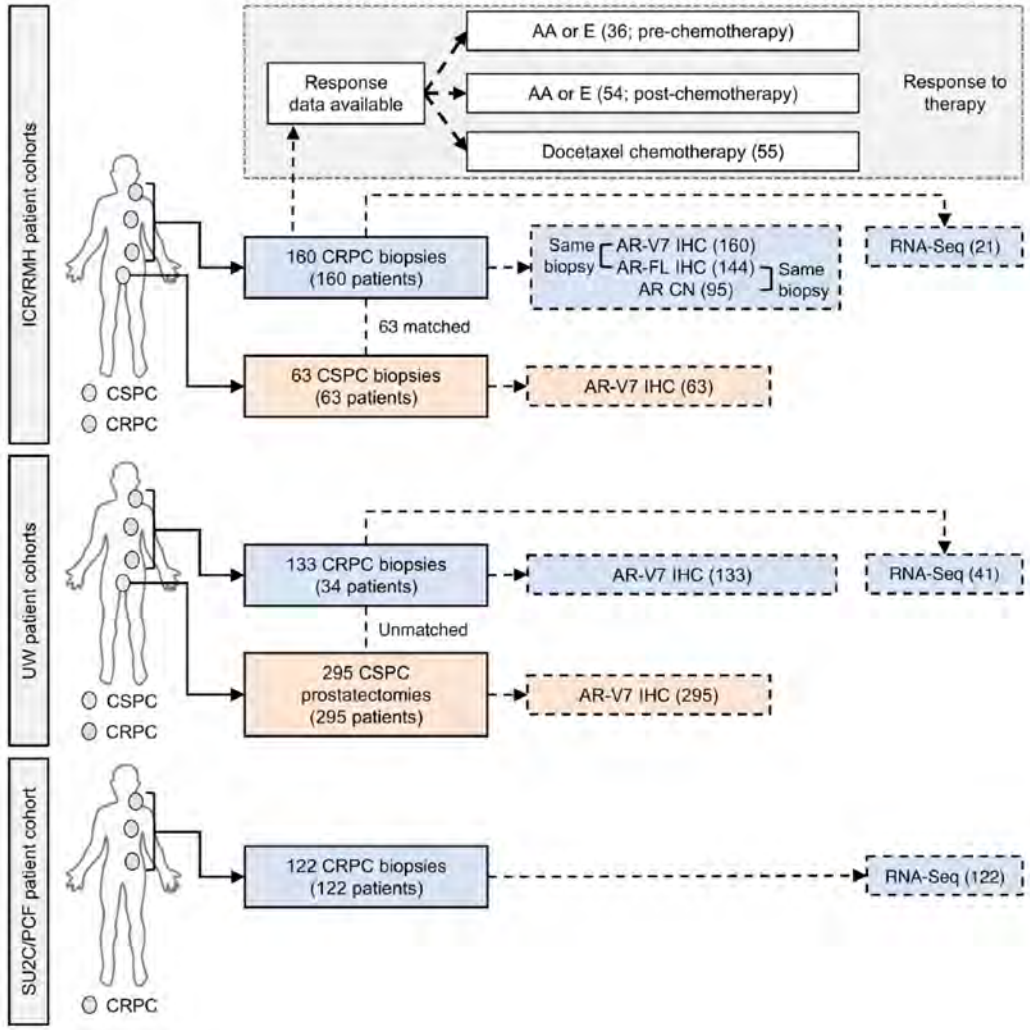
JAMA Oncology September 2018 Volume 4, Number 9

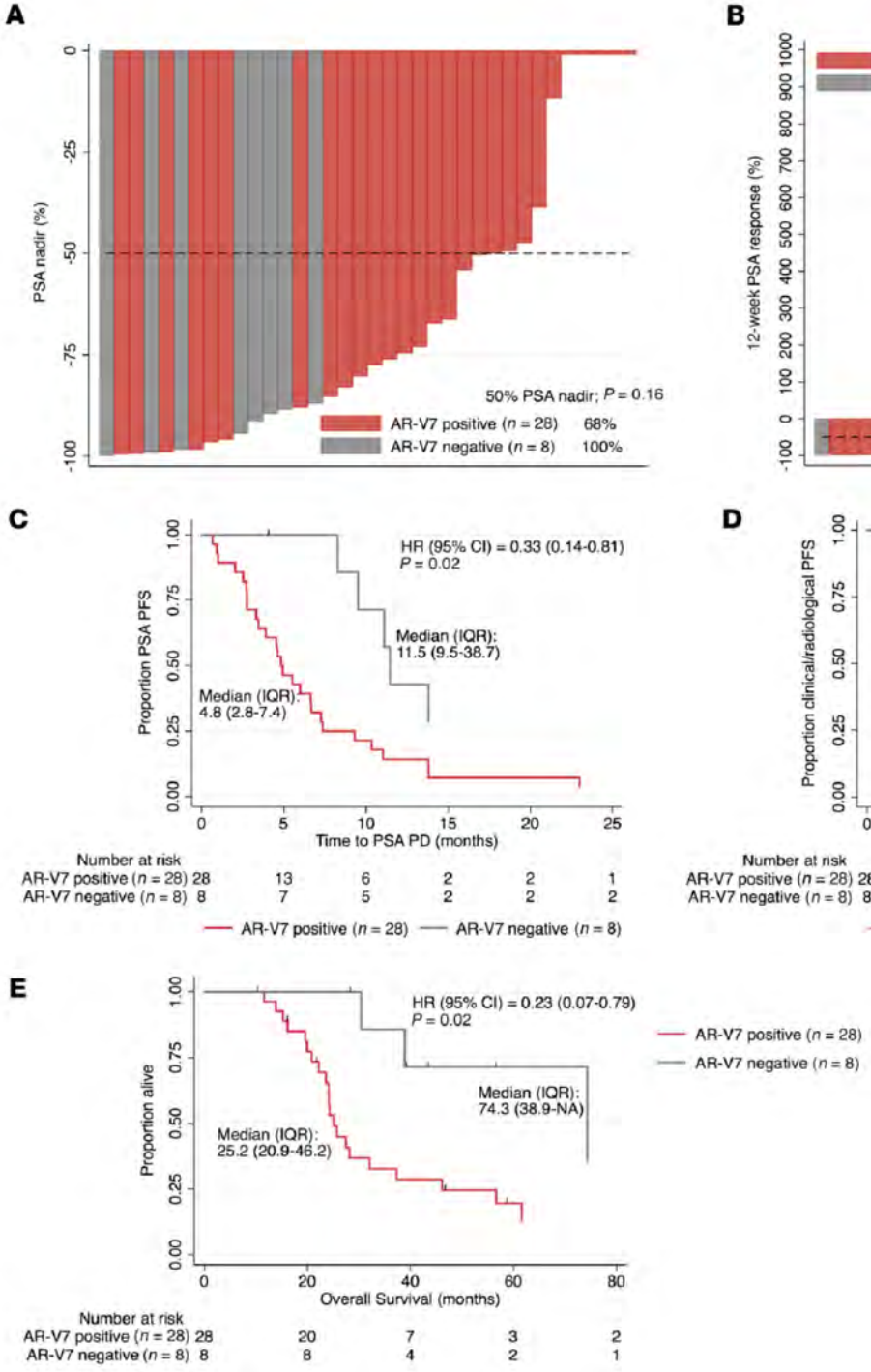
# Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer

Adam Sharp,[1,2] Ilsa Coleman,[3] Wei Yuan,[1] Cynthia Sprenger,[4] David Dolling,[1] Daniel Nava Rodrigues,[1] Joshua W. Russo,[5] Ines Figueiredo,[1] Claudia Bertan,[1] George Seed,[1] Ruth Riisnaes,[1] Takuma Uo,[4] Antje Neeb,[1] Jonathan Welti,[1] Colm Morrissey,[4] Suzanne Carreira,[1] Jun Luo,[6] Peter S. Nelson,[3,4] Steven P. Balk,[5] Lawrence D. True,[4] Johann S. de Bono,[1,2] and Stephen R. Plymate[4,7]

[1]The Institute of Cancer Research, London, United Kingdom. [2]The Royal Marsden, London, United Kingdom. [3]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA. [4]Department of Medicine, University of Washington, Seattle, Washington, USA. [5]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. [6]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [7]Puget Sound VA Health Care System, Geriatric Research Education and Clinical Center (PSVAHCS-GRECC), Seattle, Washington, USA.






## Major Findings

-AR-V7 found in <1% of hormone naïve PCA (therefore not likely a useful biomarker at this stage) and appears only after resistance to ADT

-Differences in prevalence of AR-V7 likely due to different antibodies used (methods)

-AR-V7 expressed in 75% progressing CRPC

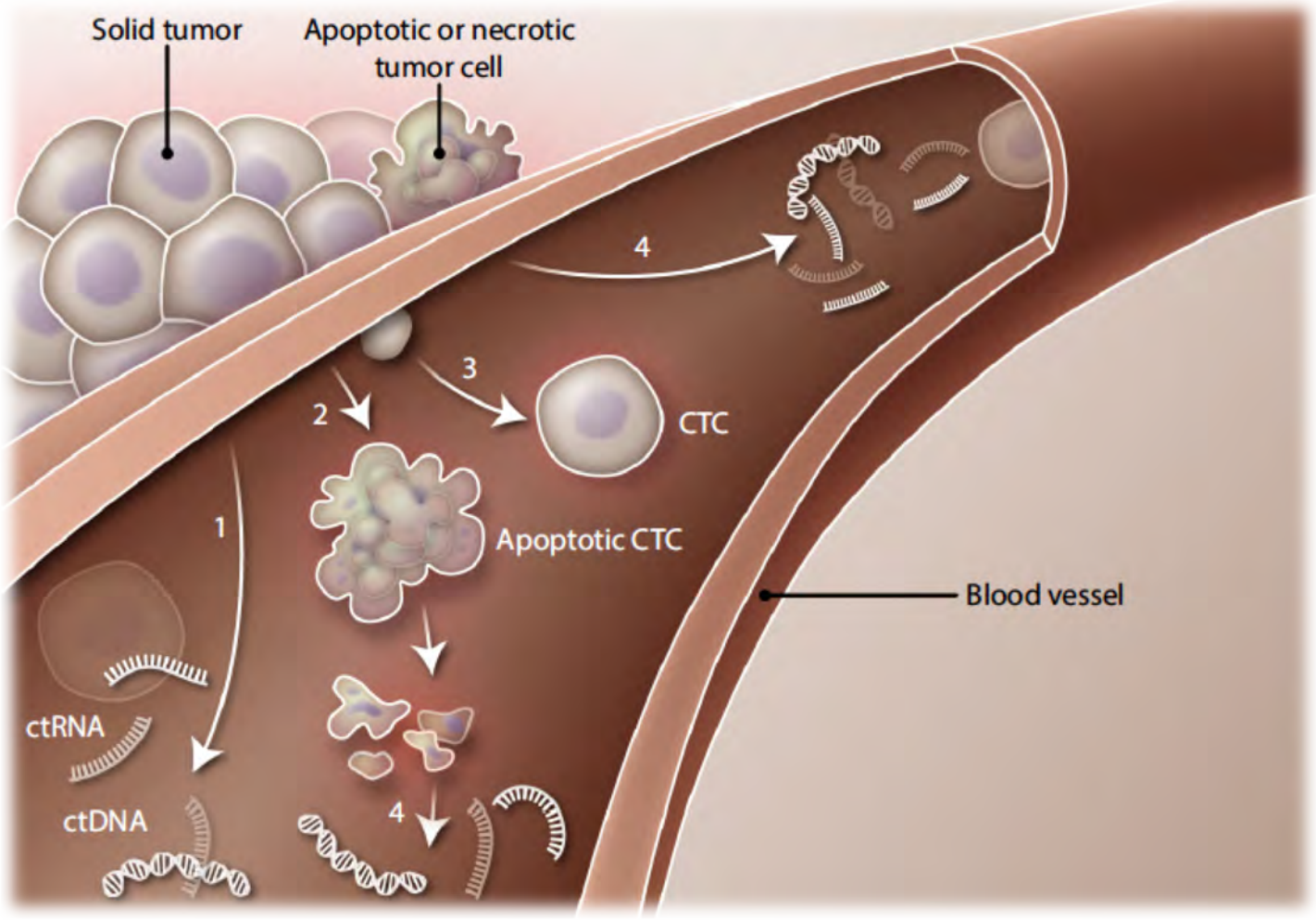
-AR-V7 higher in biopsy as compared to liquid biopsy

-Heterogeneity observed with implications for partial response if some lesions have low AR-V7

-Associated with resistance to AR targeted agents but not taxane

JCI Volume 129 Number 1 January 2019

# What is next for CRPC Diagnostics




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

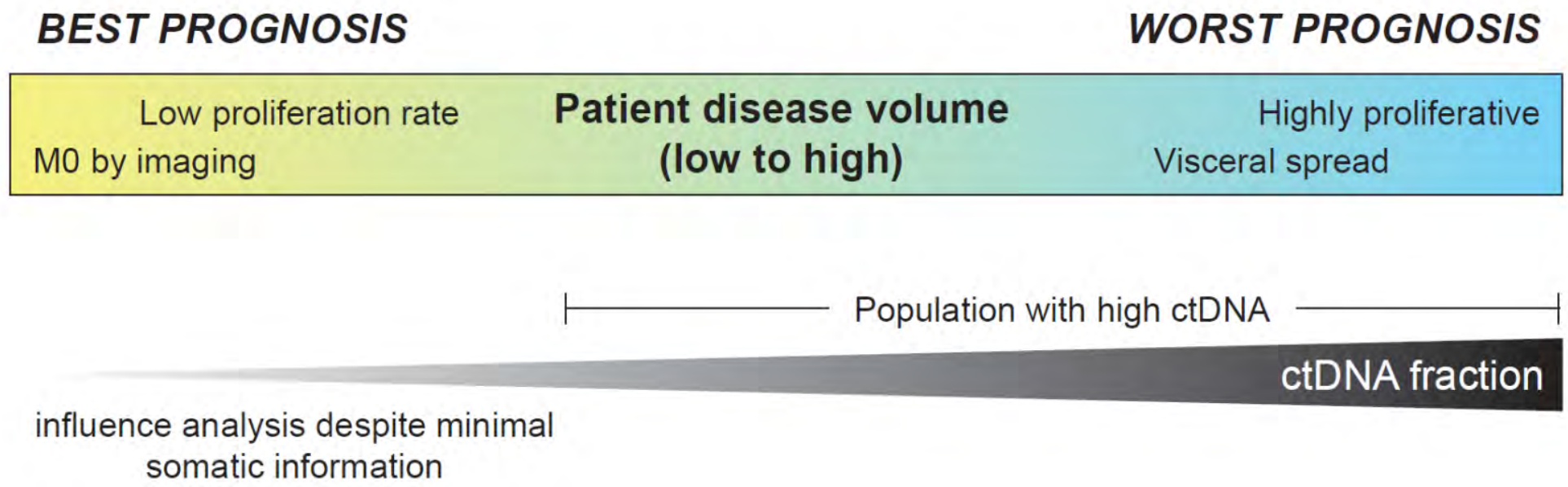
from Schweizer MT and Antonarakis ES, Sci Transl Med. 2015 Nov 4;7(312)

# CIRCULATING BIOMARKERS FOR ADAVANCED 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 |

# Plasma circulating tumour DNA (ctDNA) is abundant in progressing mCRPC patients

- Cell-free DNA (cfDNA) is shed by apoptosing normal and cancer cells
- Putative ctDNA can be identified via somatic alterations in cfDNA
- CtDNA / cfDNA ‘fractions’ are high in mCRPC but very variable

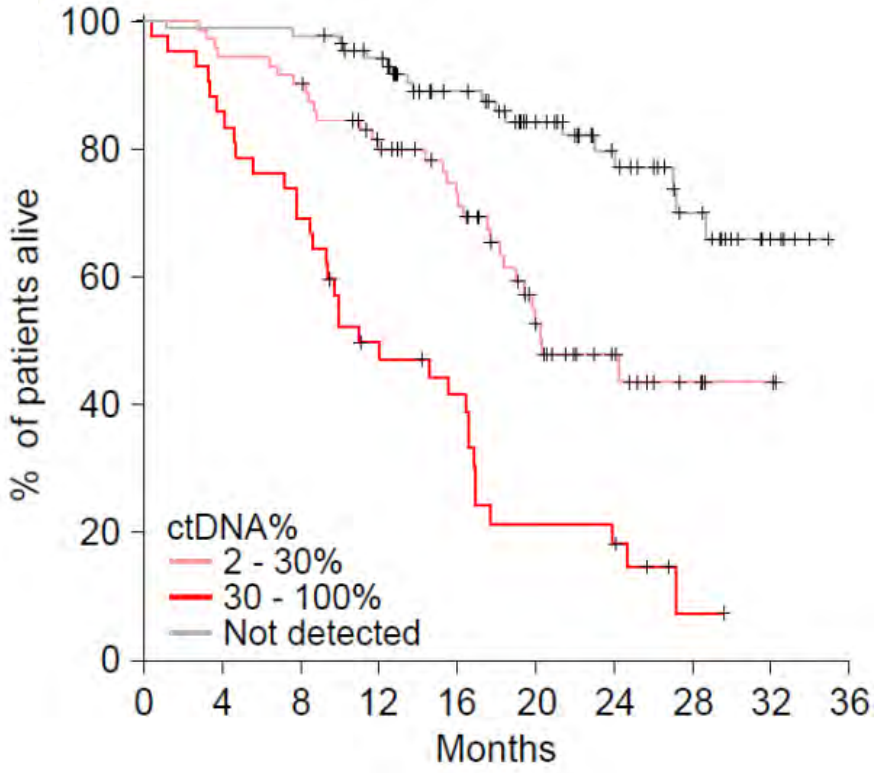



Courtesy of A. Wyatt

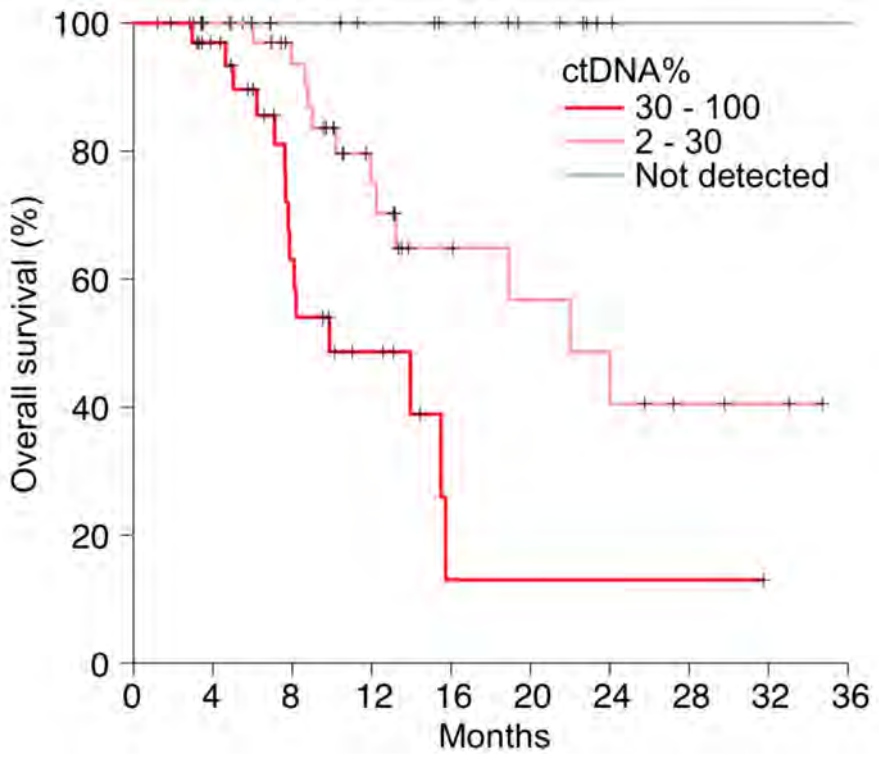
Warner *et al.*, BJUI 2018

# Prognostic effect of ctDNA fraction in mCRPC

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



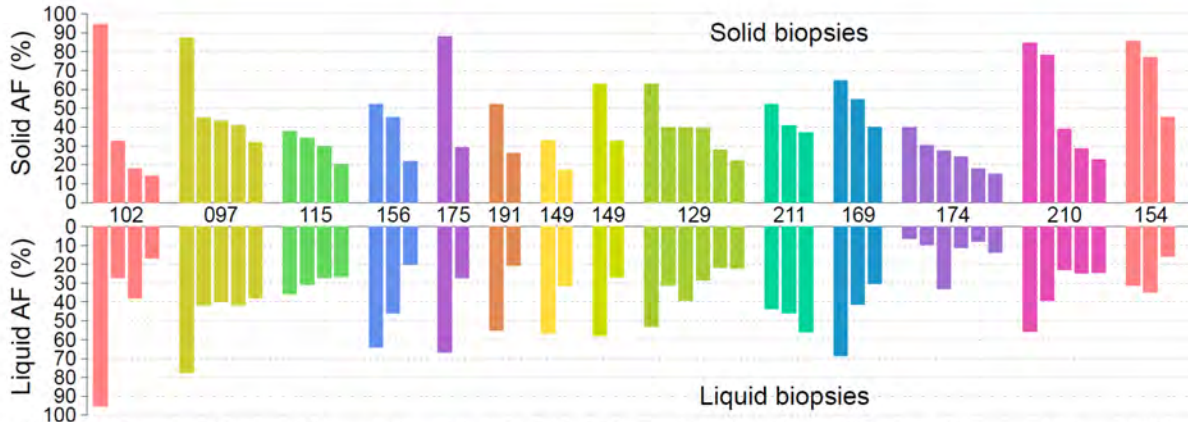

First line mCRPC poor prognosis (n = 95)
Chi et al., ESMO 2018




Courtesy of A. Wyatt

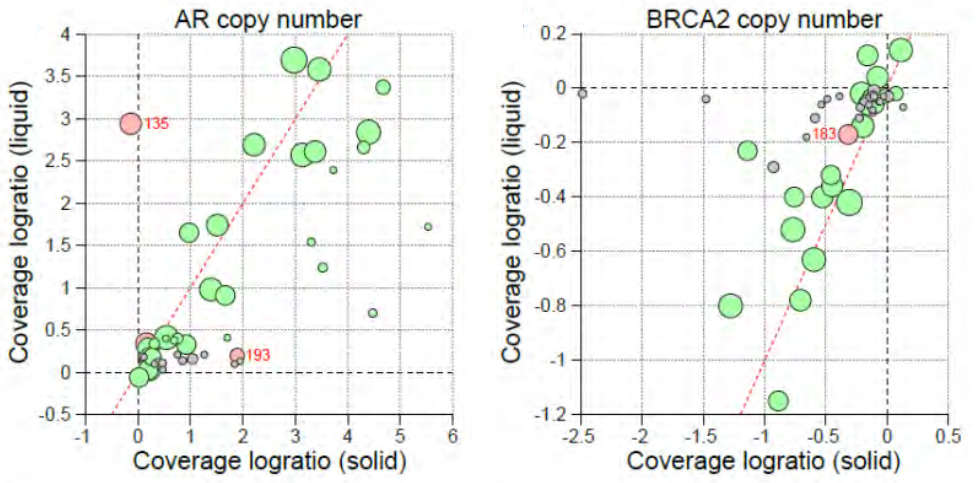
# High concordance between ctDNA and matched metastatic tissue biopsy (in CRPC)

Wyatt et al studied 45 plasma samples collected at time of metastatic tissue biopsy (SU2C / PCF West Coast Dream Team, Eric Small *et al*.)




Similar mutation profiles, ctDNA vs tissue

Similar gene copy numbers, ctDNA vs tissue




See also: Hovelson, Tomlins *et al.* Oncotarget. 2017; 8(52): 89848–89866.

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

available at www.sciencedirect.com
journal homepage: www.europeanurology.com


European Association of Urology

Platinum Priority – Prostate Cancer

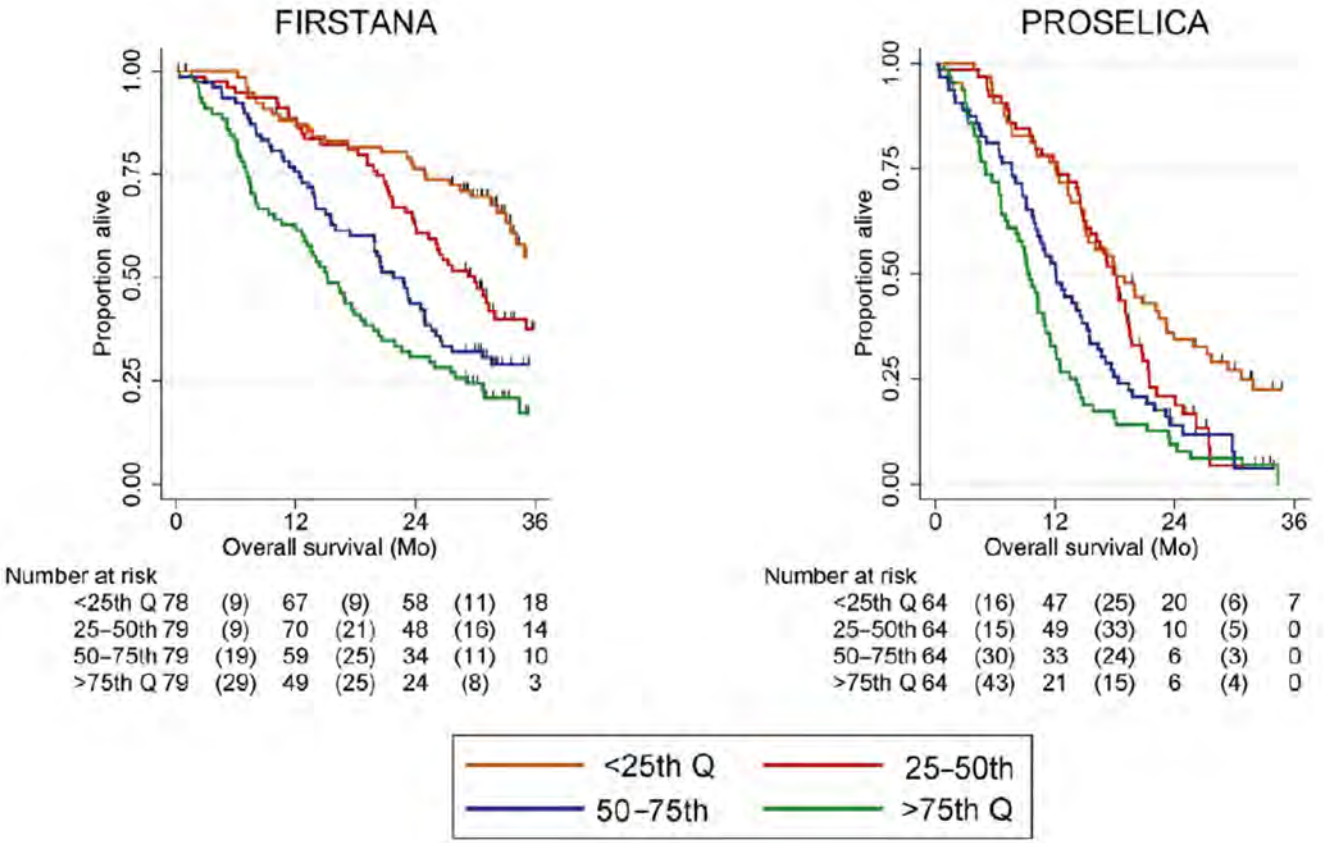
*Editorial by Robert J. van Soest, Bertrand Tombal, Martijn P. Lolkema and Ronald de Wit on pp. 292–293 of this issue*

# Plasma Cell-free DNA Concentration and Outcomes from Taxane Therapy in Metastatic Castration-resistant Prostate Cancer from Two Phase III Trials (FIRSTANA and PROSELICA)

*Niven Mehra[a], David Dolling[b], Semini Sumanasuriya[a], Rossitza Christova[c], Lorna Pope[c], Suzanne Carreira[c], George Seed[c], Wei Yuan[c], Jane Goodall[c], Emma Hall[b], Penny Flohr[c], Gunther Boysen[c], Diletta Bianchini[a], Oliver Sartor[d], Mario A. Eisenberger[e], Karim Fizazi[f], Stephane Oudard[g], Mustapha Chadjaa[h], Sandrine Macé[h], Johann S. de Bono[a,*]*

**Conclusions: We report that changes in cfDNA concentrations correlate with both rPFSand OS in patients receiving first- and second-line taxane therapy, and may serve as independent prognostic biomarkers of response to taxanes.**

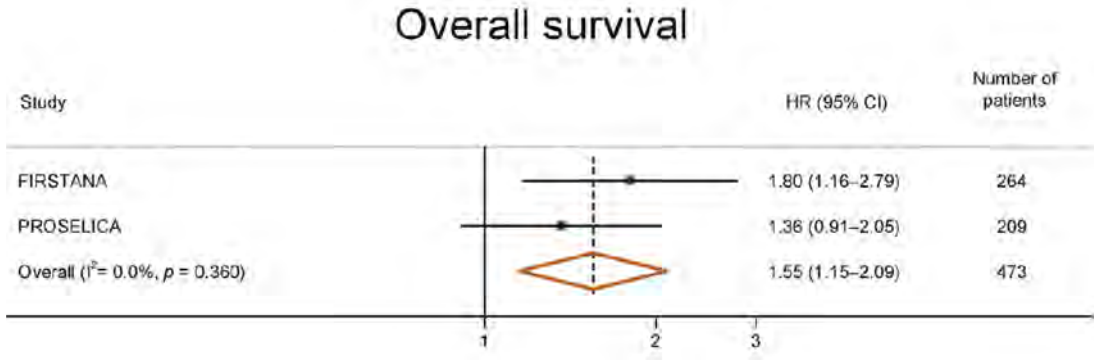
EUR Urol 74 ( 2 0 18 ) 2 8 3 – 2 9 1




*"Our study identifies baseline cfDNA concentration as an independent prognostic biomarker in patients with mCRPC, with higher baseline concentrations associated with shorter rPFS and OS following taxane therapy. A decline in total cfDNA concentration during the first 9 wk of treatment was associated with response to taxane therapy."*

<u>-Two phase III clinical trials</u>

FIRSTANA (NCT01308567) and PROSELICA(NCT01308580)
Patients received docetaxel (75 mg/m2) or cabazitaxel (20 or 25 mg/m2) as first-line chemotherapy (FIRSTANA), and cabazitaxel (20 or 25 mg/m2) as second-line chemotherapy (PROSELICA).



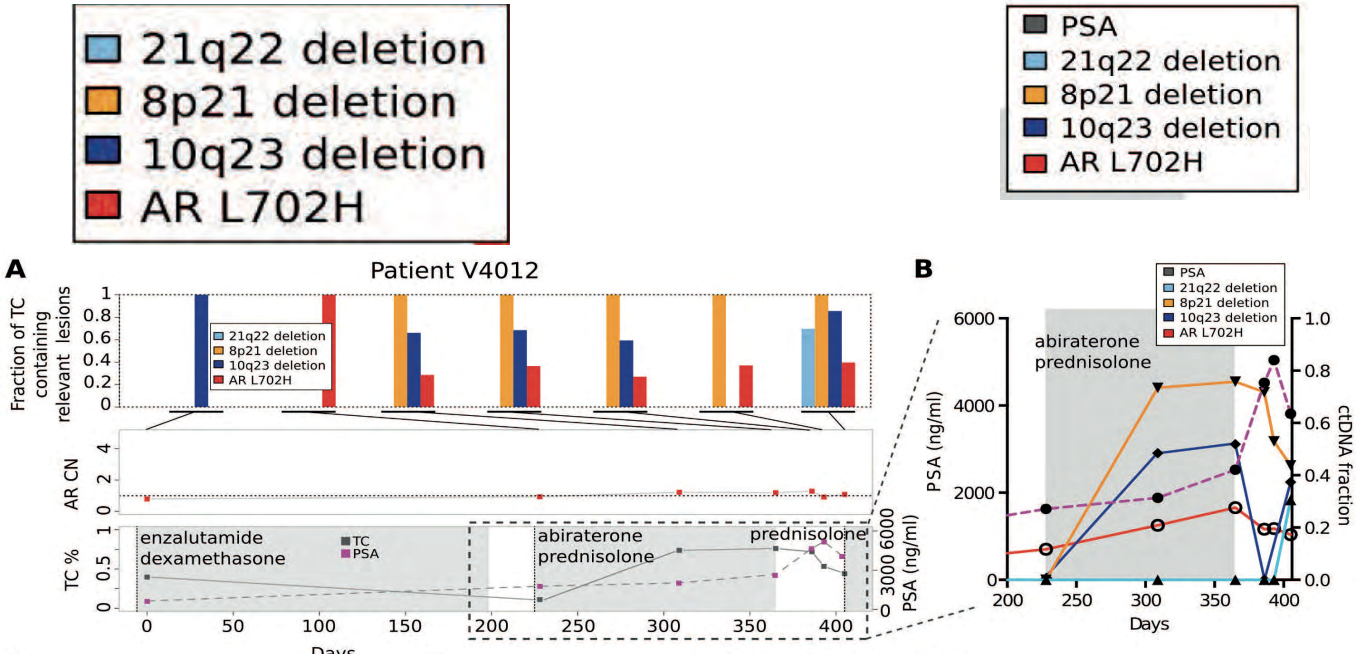

EUR Urol 74 ( 2 0 18 ) 2 8 3 – 2 9 1

RESEARCH ARTICLE

CANCER

# Tumor clone dynamics in lethal prostate cancer

Suzanne Carreira,[1]* Alessandro Romanel,[2]* Jane Goodall,[1]* Emily Grist,[1,3] Roberta Ferraldeschi,[1,3] Susana Miranda,[1] Davide Prandi,[2] David Lorente,[1,3] Jean-Sebastien Frenel,[1] Carmel Pezaro,[1,3] Aurelius Omlin,[1,3] Daniel Nava Rodrigues,[1] Penelope Flohr,[1] Nina Tunariu,[1,3] Johann S. de Bono,[1,3] Francesca Demichelis,[2,4,5†‡] Gerhardt Attard[1,3†‡]




Emergence of *AR-L702H* on treatment

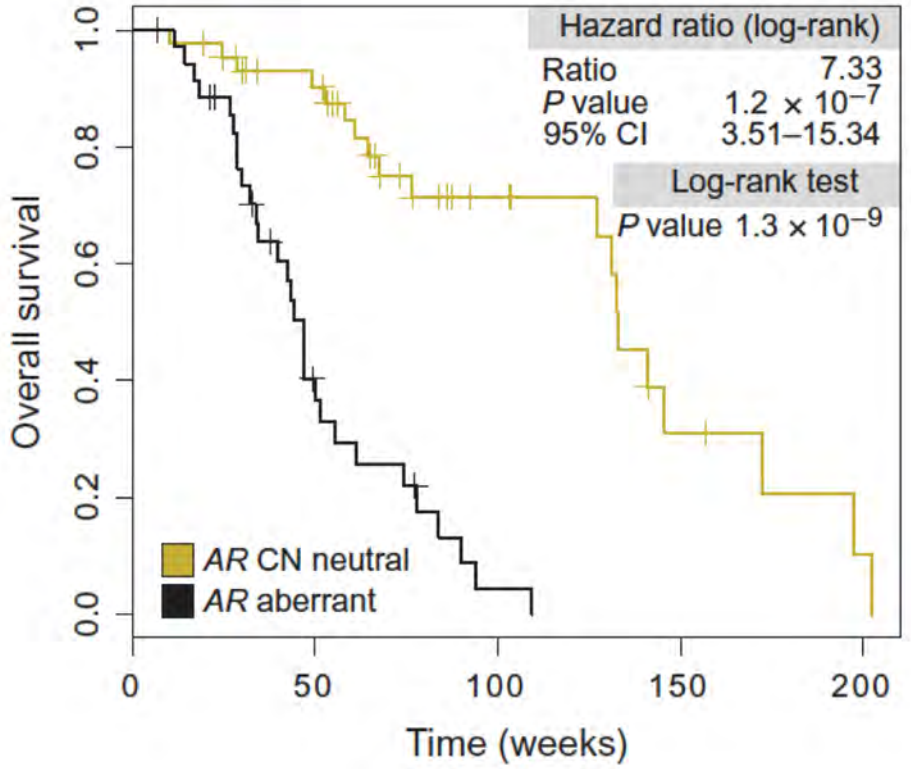
*Sci Transl Med* **6**, *254ra125 (2014)*

REPORT

CANCER

# Plasma *AR* and abiraterone-resistant prostate cancer

Alessandro Romanel,[1]* Delila Gasi Tandefelt,[2]* Vincenza Conteduca,[2,3] Anuradha Jayaram,[2,4] Nicola Casiraghi,[1] Daniel Wetterskog,[2] Samanta Salvi,[3] Dino Amadori,[3] Zafeiris Zafeiriou,[2,4] Pasquale Rescigno,[2,4] Diletta Bianchini,[2,4] Giorgia Gurioli,[3] Valentina Casadio,[3] Suzanne Carreira,[2] Jane Goodall,[2] Anna Wingate,[2,4] Roberta Ferraldeschi,[2,4†] Nina Tunariu,[2,4] Penny Flohr,[2] Ugo De Giorgi,[3] Johann S. de Bono,[2,4] Francesca Demichelis,[1,5,6‡§] Gerhardt Attard[2,4‡§]




Plasma AR and abiraterone-resistant PCa

*Sci Transl Med*, 2015 Vol 7 Issue 312 312re10

JUST ONE OF MANY EXAMPLES

ARTICLE

https://doi.org/10.1038/s41467-020-17673-9 OPEN

Check for updates

# An integrative multi-omics analysis to identify candidate DNA methylation biomarkers related to prostate cancer risk

Lang Wu[1,91]✉, Yaohua Yang[2,91], Xingyi Guo[2], Xiao-Ou Shu[2], Qiuyin Cai[2], Xiang Shu[2], Bingshan Li[3,4], Ran Tao[4,5], Chong Wu[6], Jason B. Nikas[7], Yanfa Sun[1,8], Jingjing Zhu[1], Monique J. Roobol[9], Graham G. Giles[10,11], Hermann Brenner[12,13,14], Esther M. John[15], Judith Clements[16,17], Eli Marie Grindedal[18], Jong Y. Park[19], Janet L. Stanford[20,21], Zsofia Kote-Jarai[22], Christopher A. Haiman[23], Rosalind A. Eeles[22], Wei Zheng[2], Jirong Long[2]✉, The PRACTICAL consortium*, CRUK Consortium*, BPC3 Consortium*, CAPS Consortium* & PEGASUS Consortium*

Nat Communication 2020

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

cfDNA (tumor DNA)

AR-V7

AR gain

AR mutations

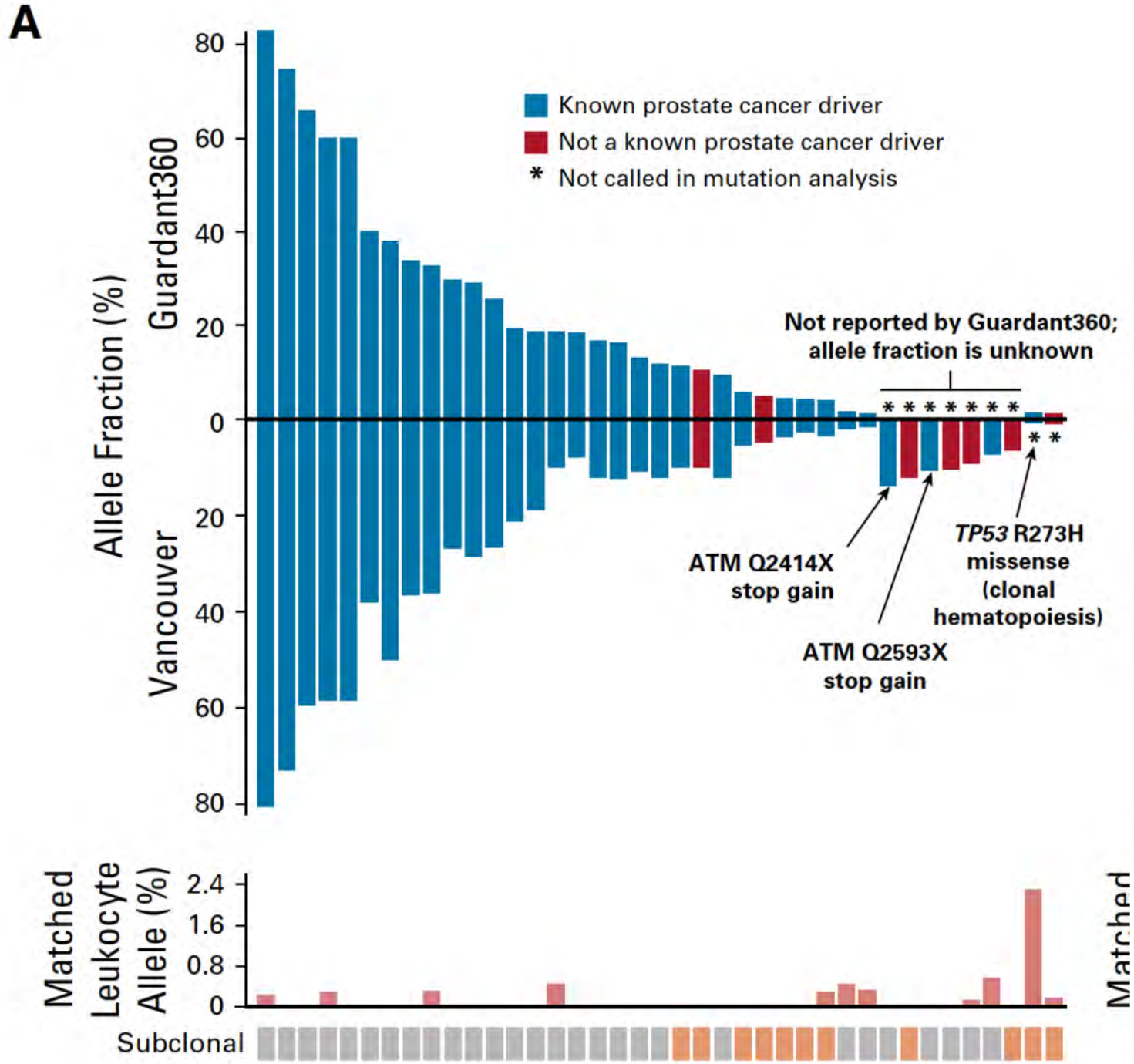
Other (neuroendocrine differentiation)

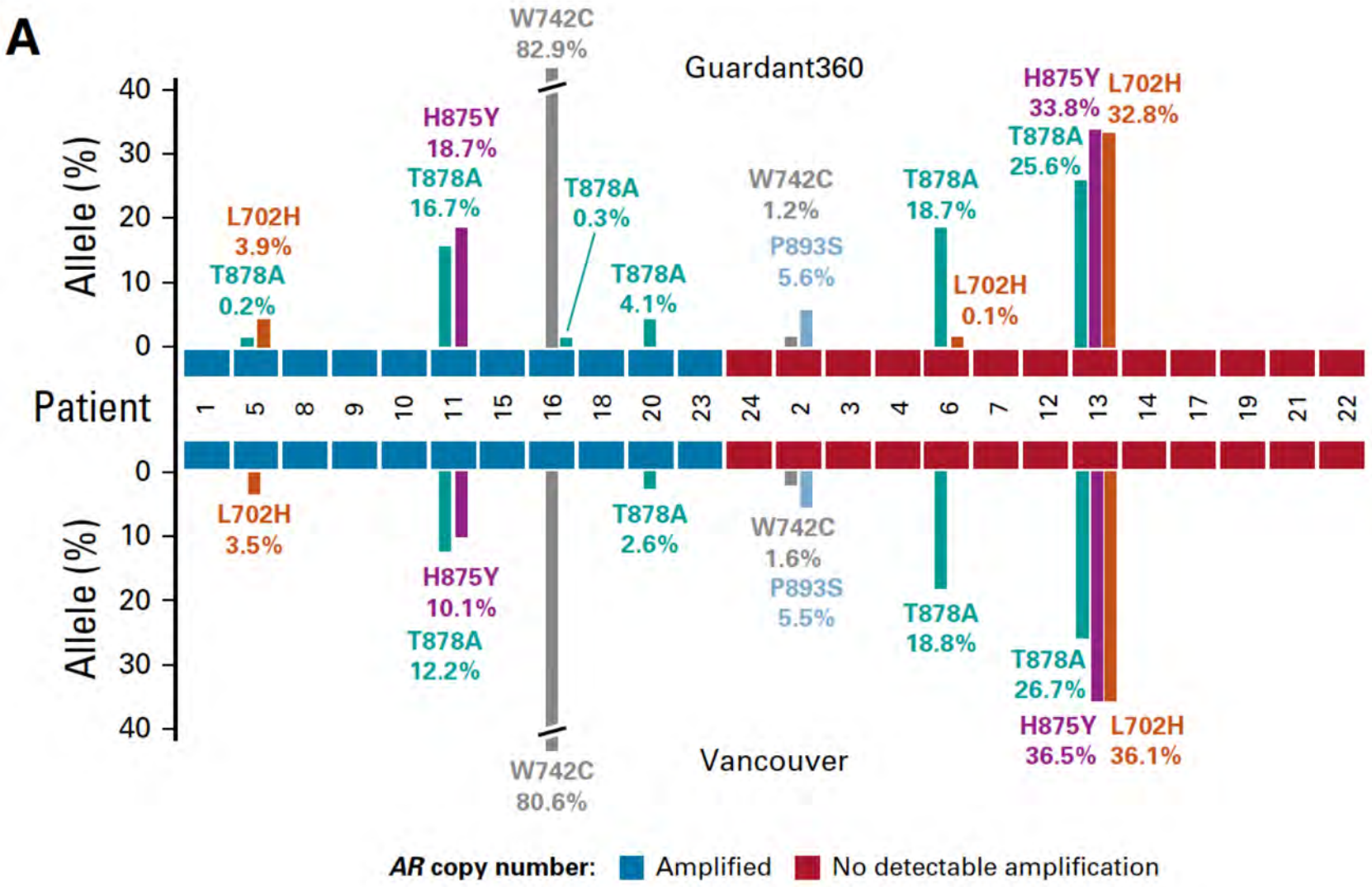
Most studies are not exploring these parameters together

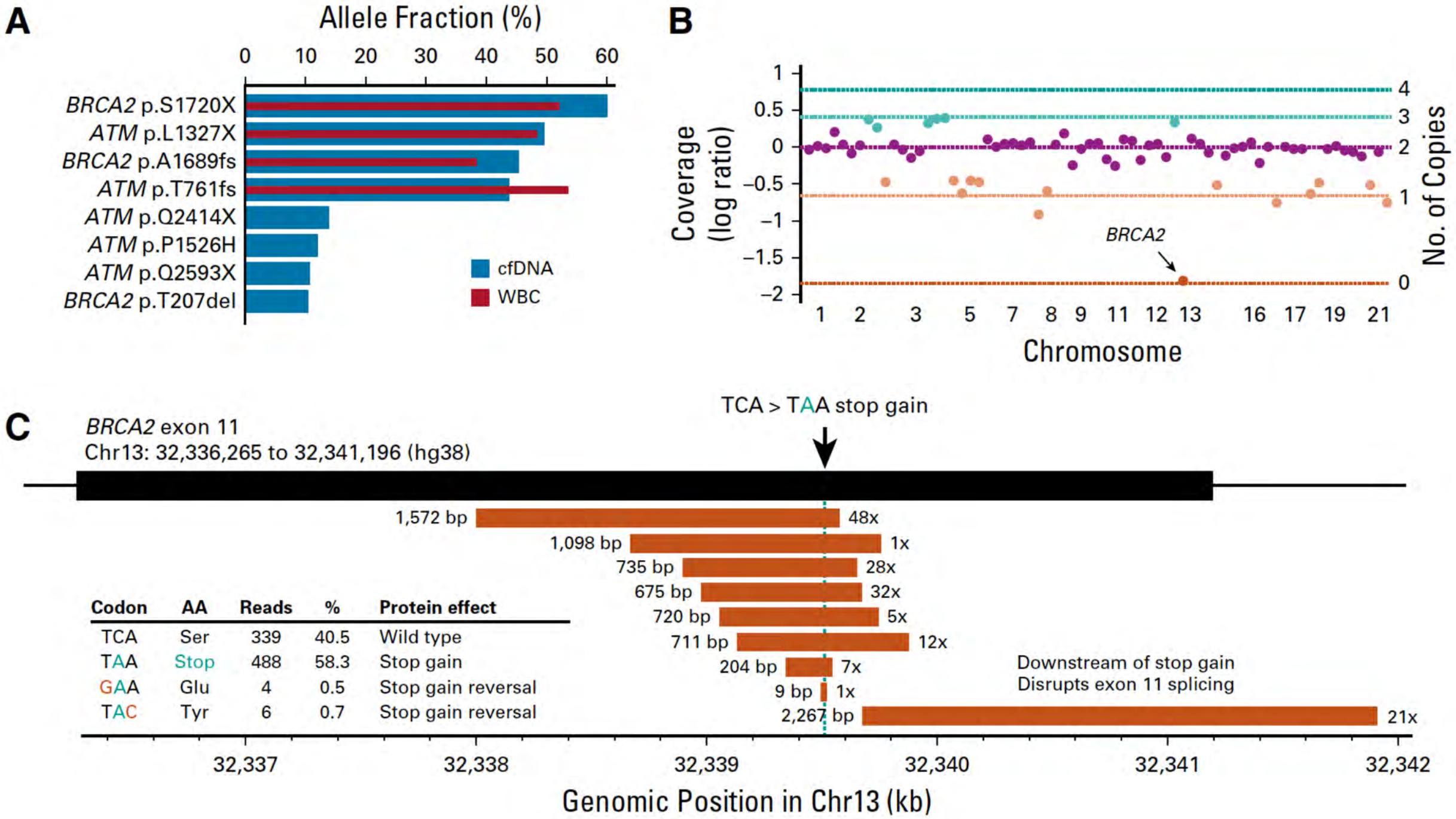
# Evaluation of Commercial Circulating Tumor DNA Test in Metastatic Prostate Cancer

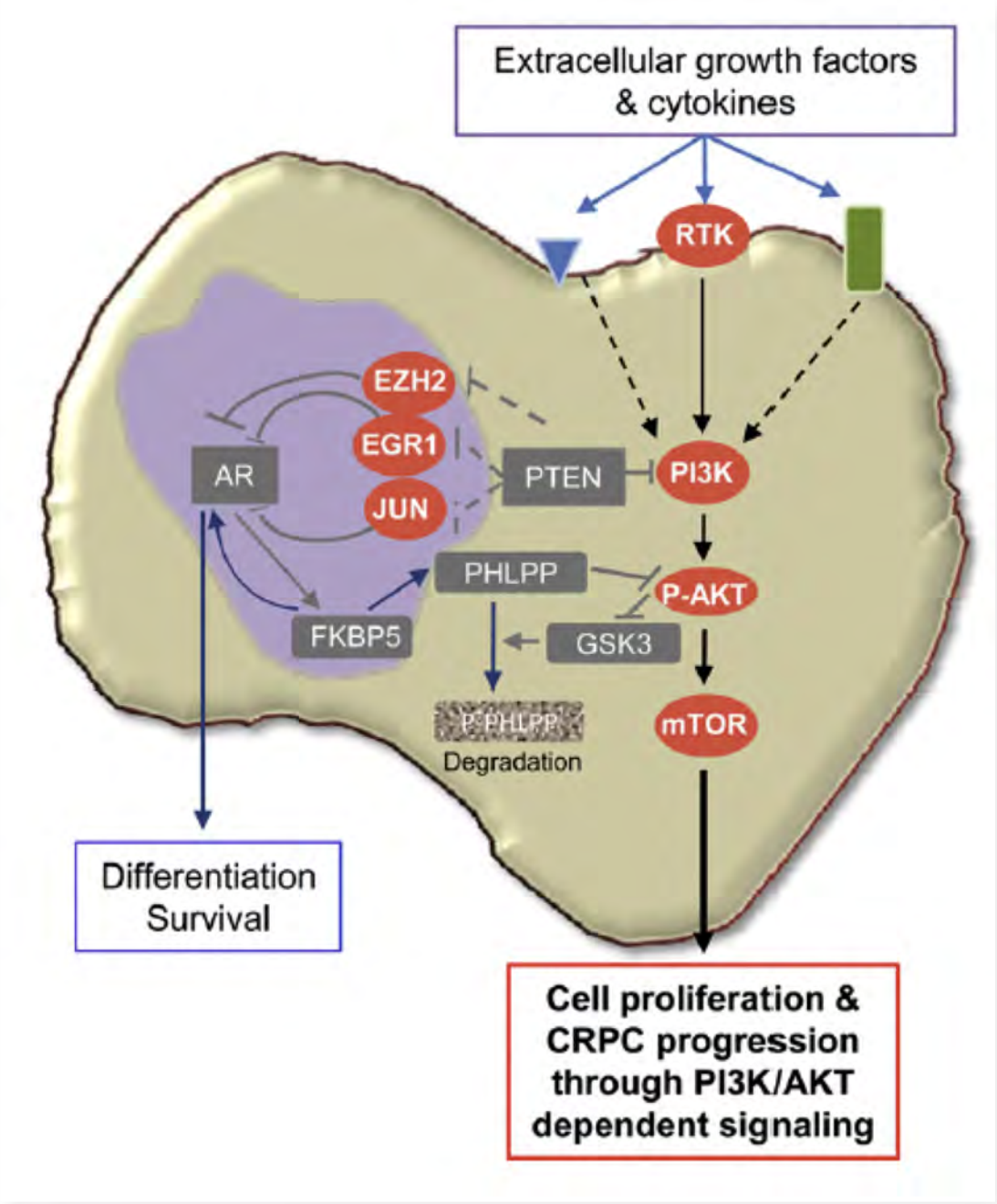
Sinja Taavitsainen, MSc[1,2]; Matti Annala, MSc[1,2]; Elisa Ledet, PhD[3]; Kevin Beja, MSc[1]; Patrick J. Miller, MS, MPH[3]; Marcus Moses, MS[3]; Matti Nykter, PhD[2]; Kim N. Chi, MD[1,4]; Oliver Sartor, MD[3]; and Alexander W. Wyatt, PhD[1]

JCO PO 2019


A
Known prostate cancer driver
Not a known prostate cancer driver
* Not called in mutation analysis
Allele Fraction (%)
Guardant360
Vancouver
80
60
40
20
0
20
40
60
80
Not reported by Guardant360;
allele fraction is unknown
ATM Q2414X
stop gain
ATM Q2593X
stop gain
TP53 R273H
missense
(clonal
hematopoiesis)
Matched
Leukocyte
Allele (%)
2.4
1.6
0.8
0
Subclonal
Matched




A
Allele Fraction (%)
0
10
20
30
40
50
60
BRCA2 p.S1720X
ATM p.L1327X
BRCA2 p.A1689fs
ATM p.T761fs
ATM p.Q2414X
ATM p.P1526H
ATM p.Q2593X
BRCA2 p.T207del
cfDNA
WBC
B
Coverage (log ratio)
1
0.5
0
−0.5
−1
−1.5
−2
4
3
2
1
0
No. of Copies
BRCA2
1
2
3
5
7
8
9
11
12
13
16
17
19
21
Chromosome
C
BRCA2 exon 11
Chr13: 32,336,265 to 32,341,196 (hg38)
TCA > TAA stop gain
1,572 bp
48x
1,098 bp
1x
735 bp
28x
675 bp
32x
720 bp
5x
711 bp
12x
204 bp
7x
9 bp
1x
2,267 bp
21x
Downstream of stop gain
Disrupts exon 11 splicing
Codon AA Reads % Protein effect
TCA Ser 339 40.5 Wild type
TAA Stop 488 58.3 Stop gain
GAA Glu 4 0.5 Stop gain reversal
TAC Tyr 6 0.7 Stop gain reversal
32,337
32,338
32,339
32,340
32,341
32,342
Genomic Position in Chr13 (kb)



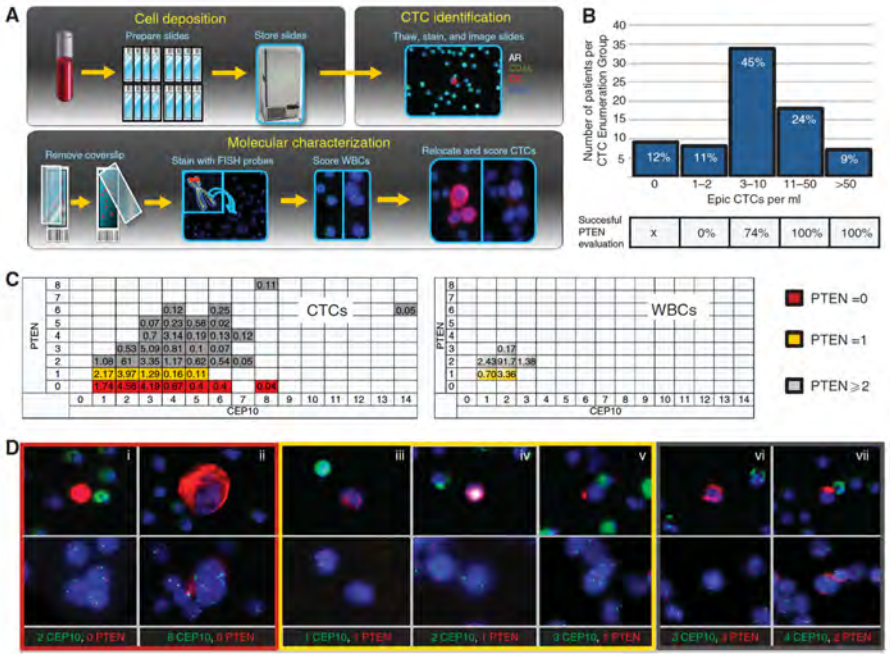



Mulholland et al., Cancer Cell 2011

# PTEN loss in circulating tumour cells correlates with PTEN loss in fresh tumour tissue from castration-resistant prostate cancer patients

Elizabeth A Punnoose[1,6], Roberta Ferraldeschi[2,3,6], Edith Szafer-Glusman[1,6], Eric K Tucker[4], Sankar Mohan[5], Penelope Flohr[3], Ruth Riisnaes[3], Susana Miranda[3], Ines Figueiredo[3], Daniel Nava Rodrigues[2], Aurelius Omlin[2,3], Carmel Pezaro[2,3], Jin Zhu[1], Lukas Amler[1], Premal Patel[1], Yibing Yan[1], Natalee Bales[4], Shannon L Werner[4], Jessica Louw[4], Ajay Pandita[5], Dena Marrinucci[4], Gerhardt Attard[3] and Johann de Bono*[,3]

[1]*Genentech Inc., South San Francisco, CA, USA;* [2]*The Royal Marsden National Health Service (NHS) Foundation Trust, Sutton, Surrey, UK;* [3]*The Institute of Cancer Research, London, UK;* [4]*Epic Sciences Inc., San Diego, CA, USA and* [5]*Core Diagnostics, Palo Alto, CA, USA*

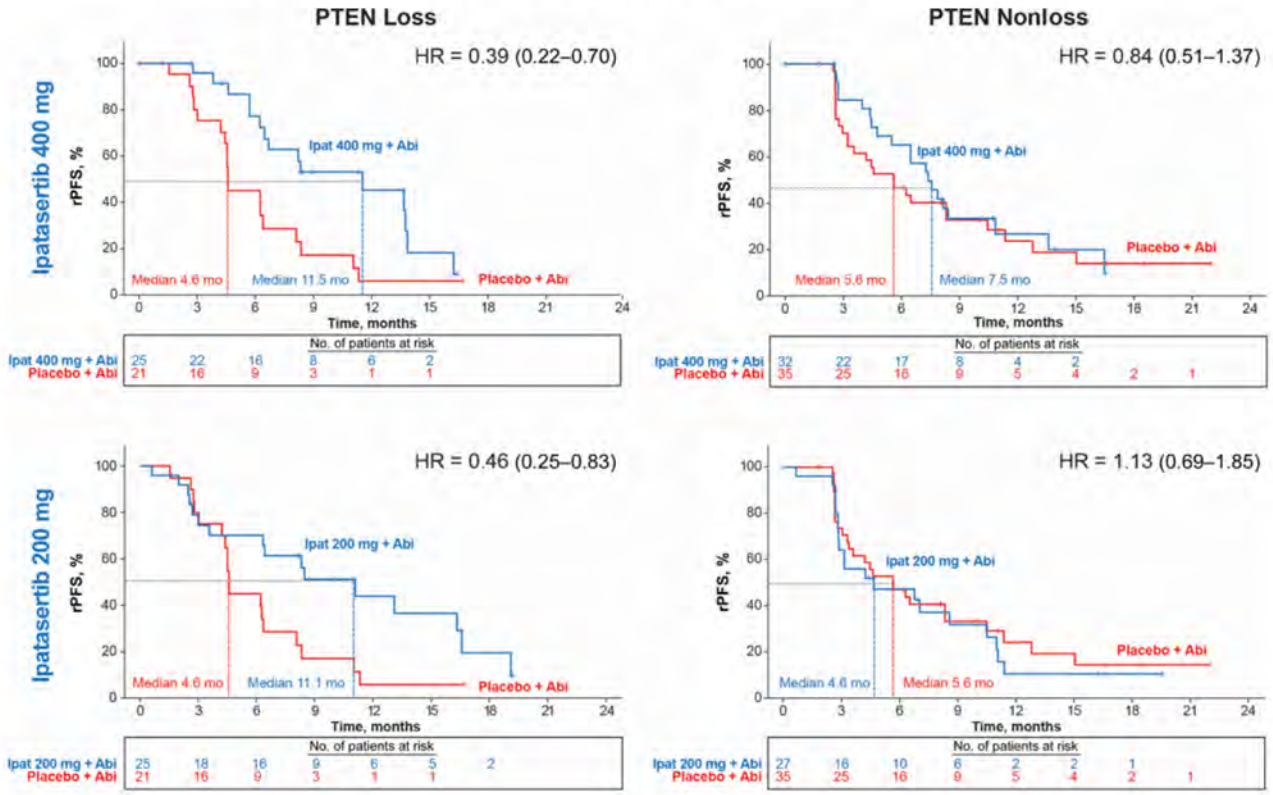



www.bjcancer.com | DOI:10.1038/bjc.2015.332



# Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss

Johann S. de Bono[1], Ugo De Giorgi[2], Daniel Nava Rodrigues[1], Christophe Massard[3], Sergio Bracarda[4], Albert Font[5], Jose Angel Arranz Arija[6], Kent C. Shih[7], George Daniel Radavoi[8], Na Xu[9], Wai Y. Chan[9], Han Ma[9], Steven Gendreau[9], Ruth Riisnaes[1], Premal H. Patel[9], Daniel J. Maslyar[9], and Viorel Jinga[8]



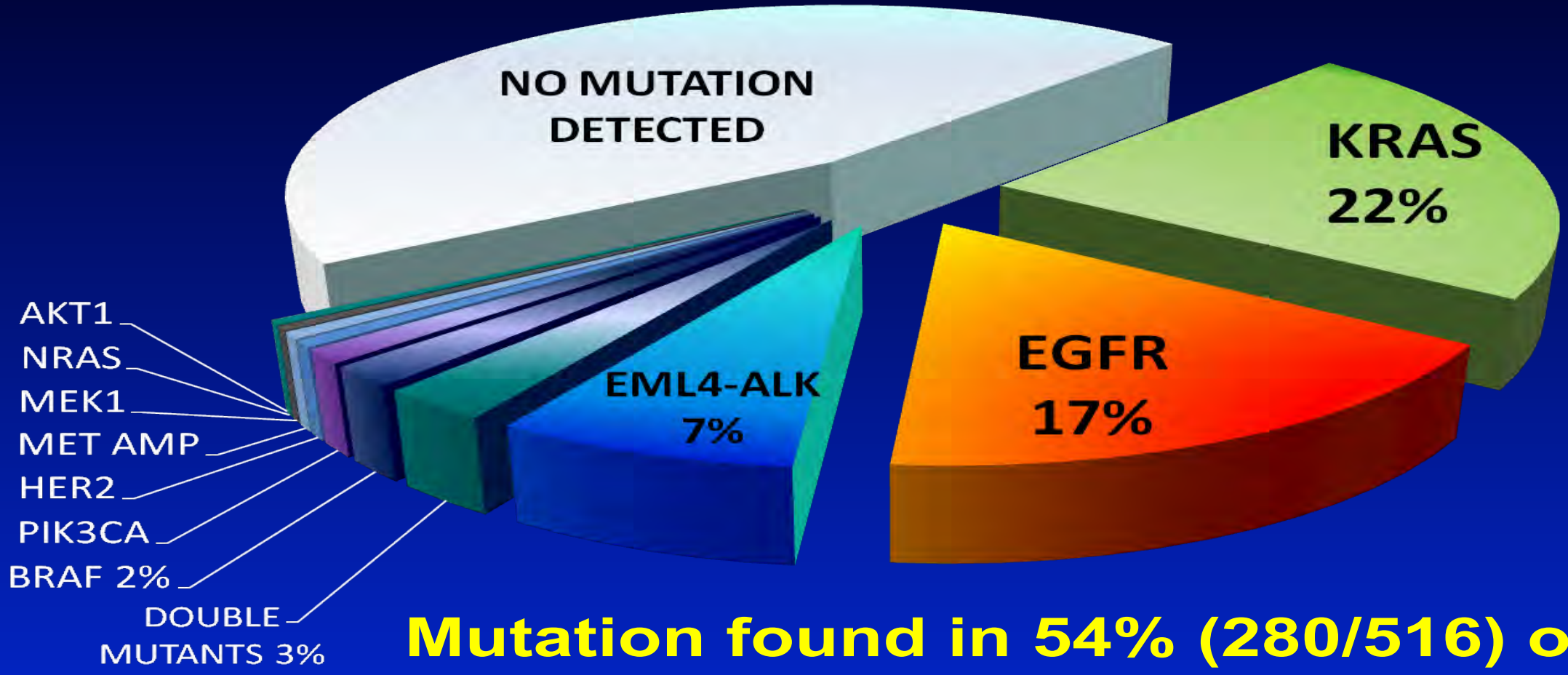



Clin Cancer Res; 25(3) February 1, 2019

Lung Cancer Mutation Consortium

# Incidence of Single Driver Mutations

5/13/11 data cut




**Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)**

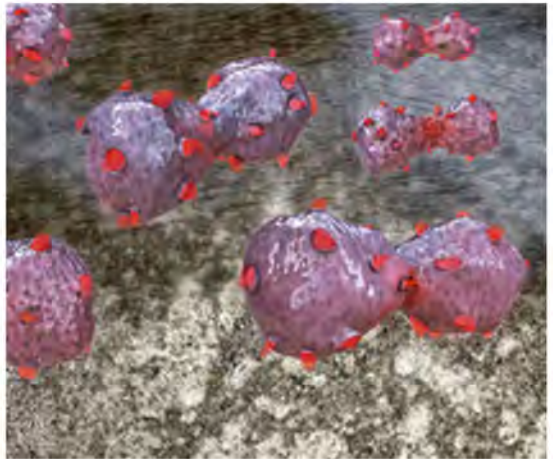
CANCER RESEARCH

The Official Blog of the American Association for Cancer Research

# FDA Approves First Liquid Biopsy Test for Lung Cancer Patients

Posted on June 6, 2016 by Srivani Ravoori, PhD

On June 1, the U.S. Food and Drug Administration (FDA) approved a liquid biopsy test, a companion diagnostic test called cobas EGFR Mutation Test v2. The test uses plasma samples to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with the EGFR-targeted therapeutic erlotinib (Tarceva).

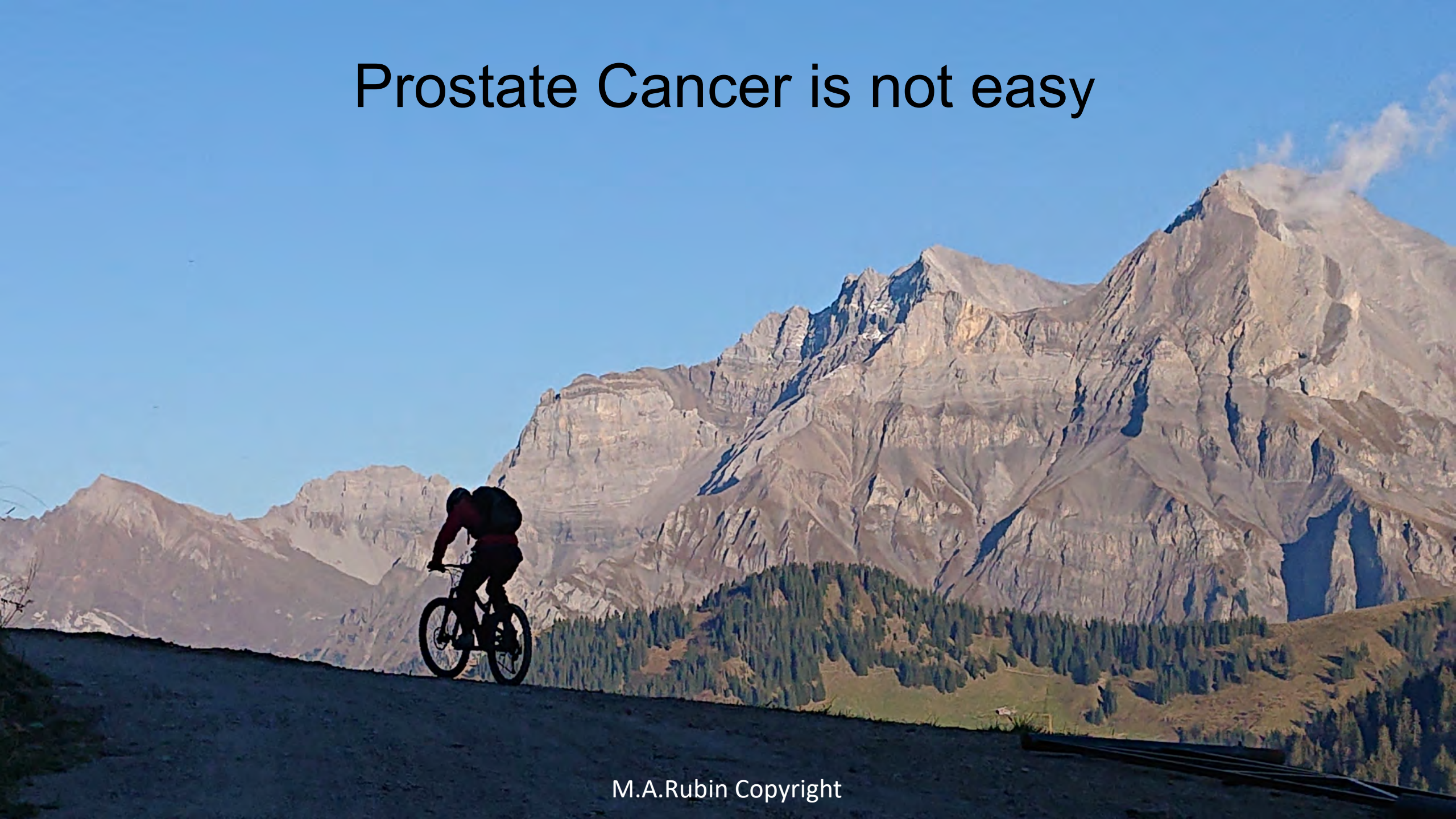


**Becoming the new standard of care**

In an interview to forecast cancer research and treatment advances in 2016, a precision medicine expert at Memorial Sloan Kettering Cancer Center, David Solit, MD, said, "The use of circulating free DNA collected from blood [liquid biopsy] to determine which treatment a cancer patient should receive is already a reality, and will begin to change the way we diagnose and treat patients in 2016. In 2016 and 2017, we will likely see liquid biopsies becoming a standard of care for some cancer types."

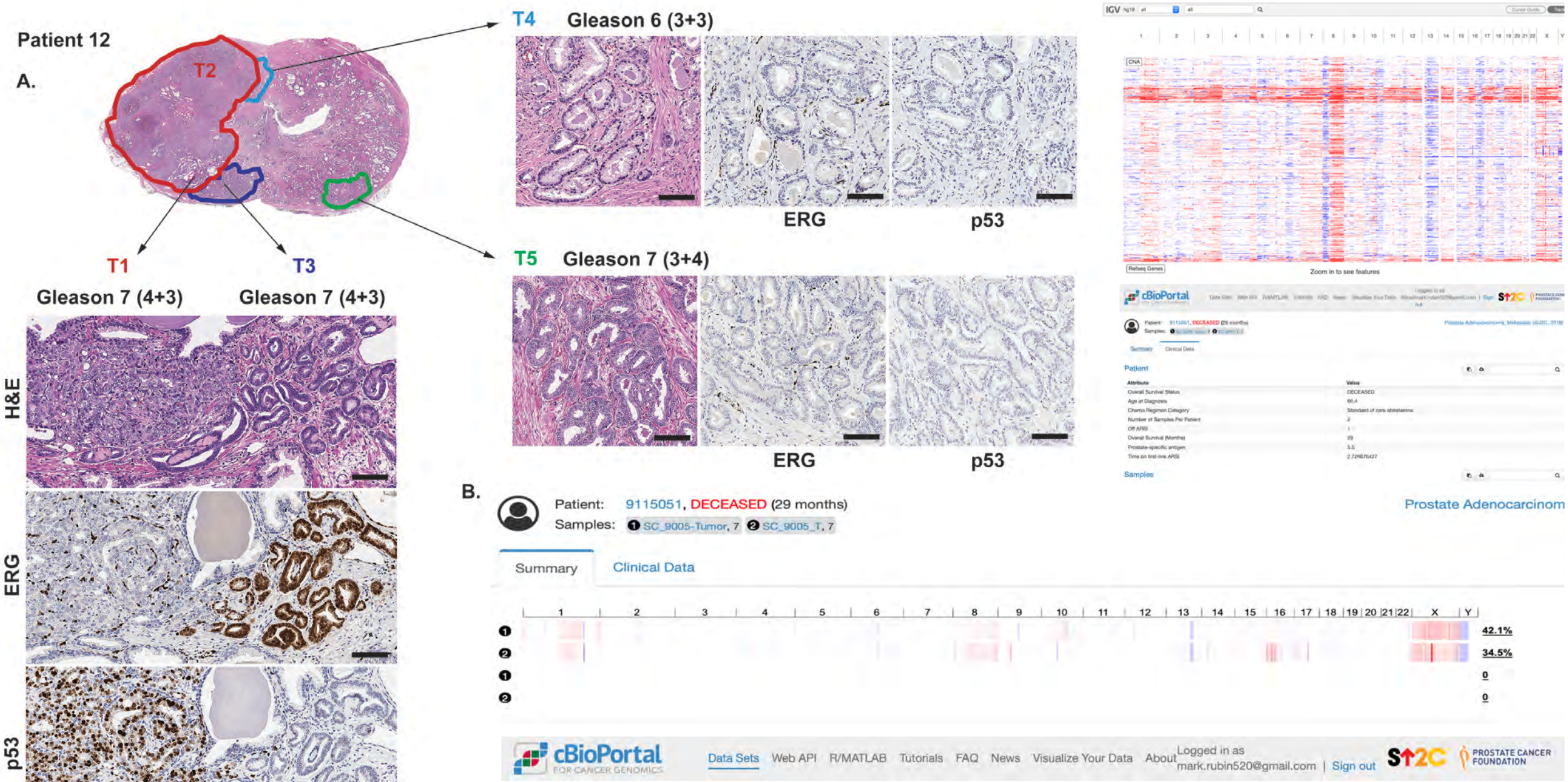
**DA Approves Foundation Medicine's FoundationOne®Liquid CDx For PARP therapy evaluation in Pca—BRCA1/2 (Oct 2020)**

# Prostate Cancer is not easy



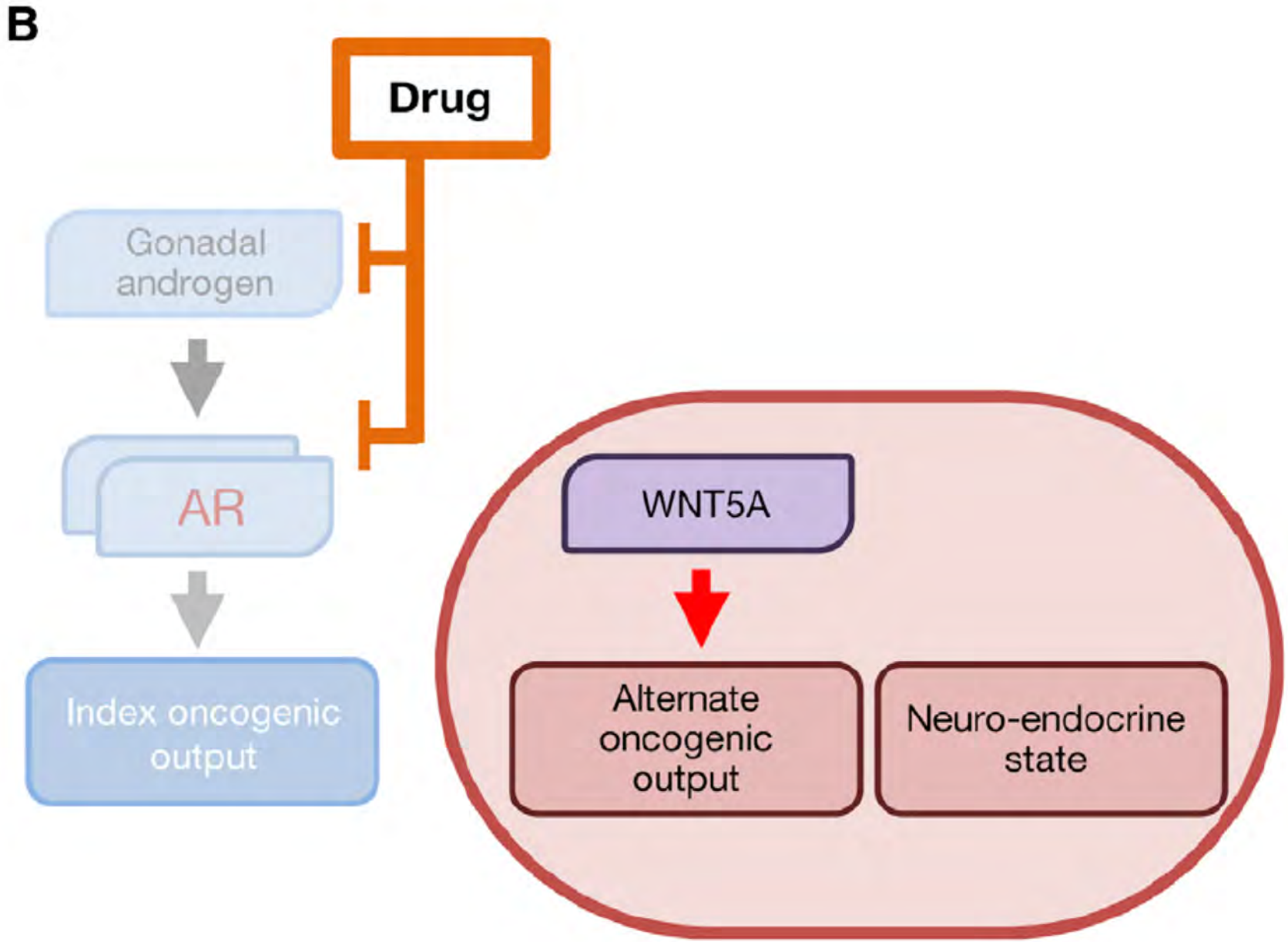
# What is Needed Next?

# Overcome Heterogeneity



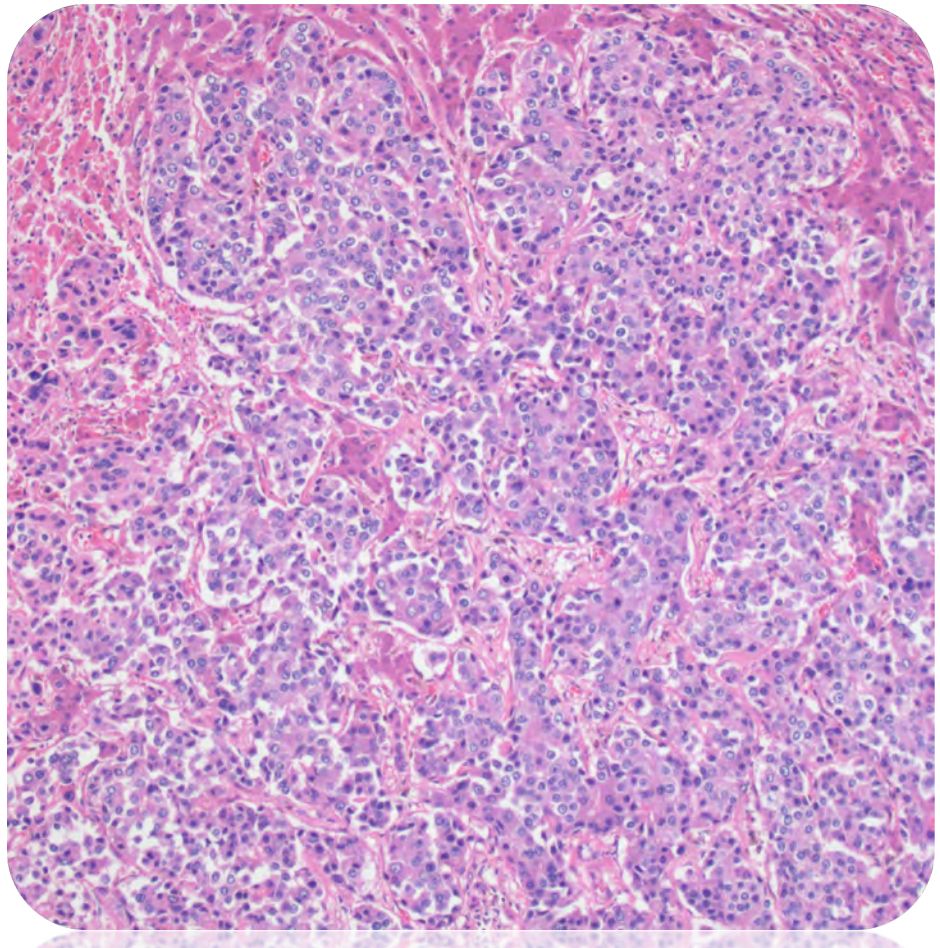

Case Contributed by Peter Nelson, MD
U of Washington / Fred Hutchinson Cancer Research Center

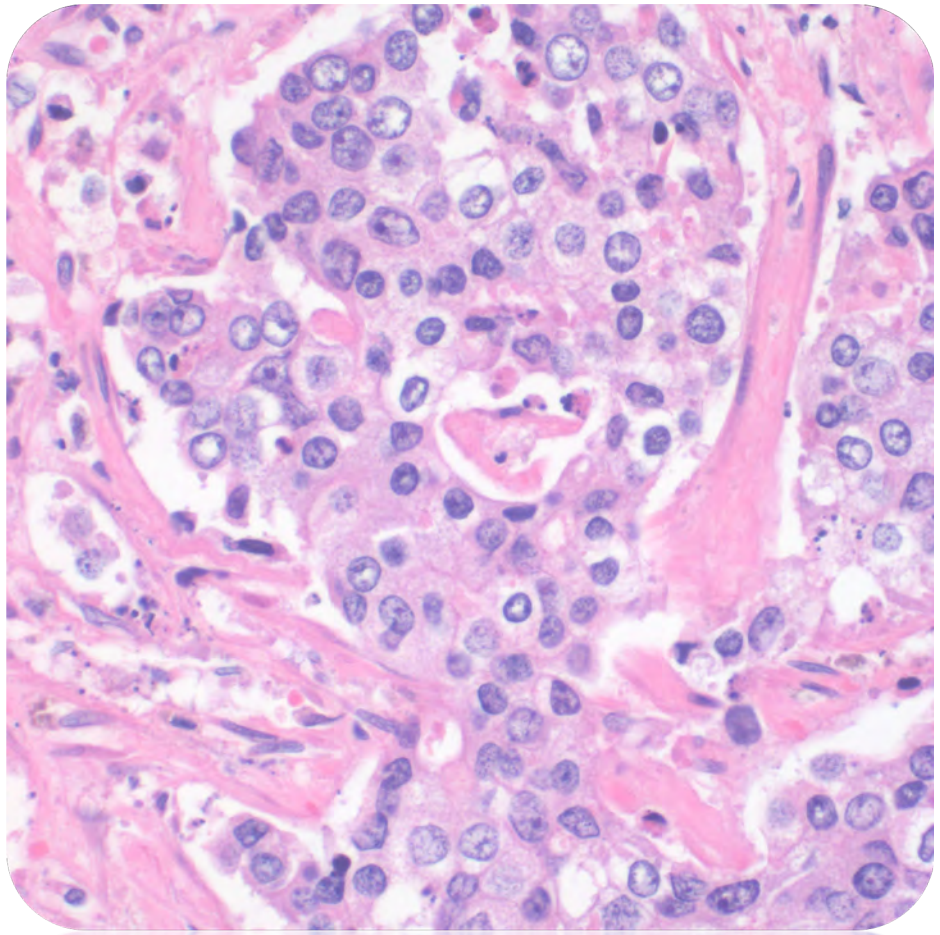
Cyrta, Prandi, et al., in preparation



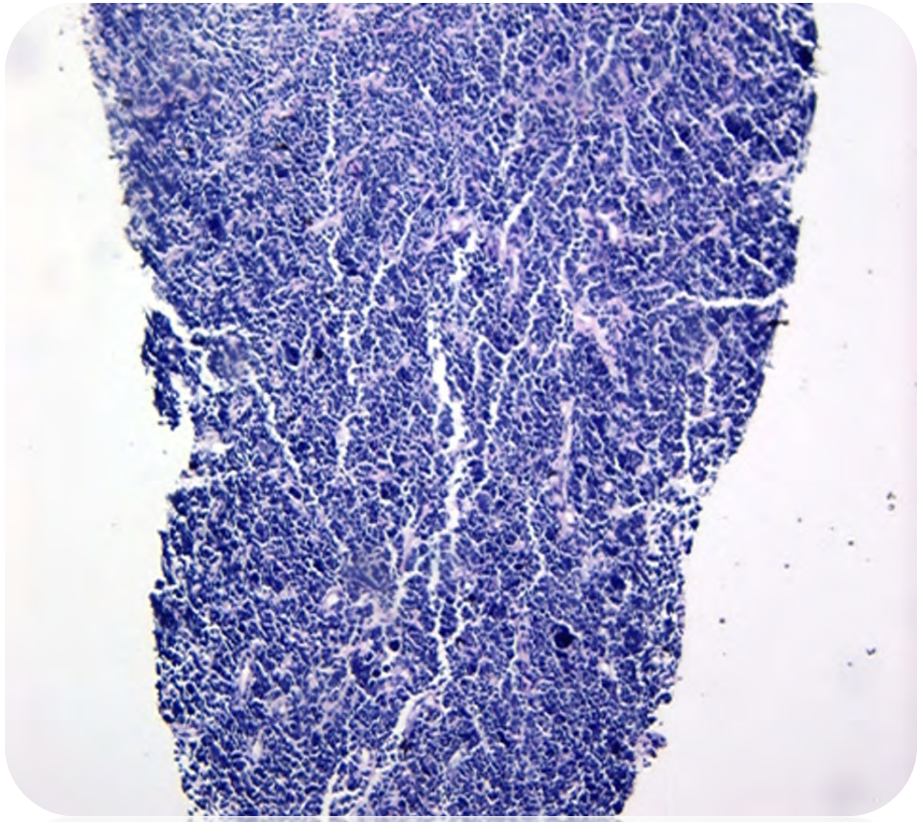

Konieczkowski et al, Cancer Cell 2018

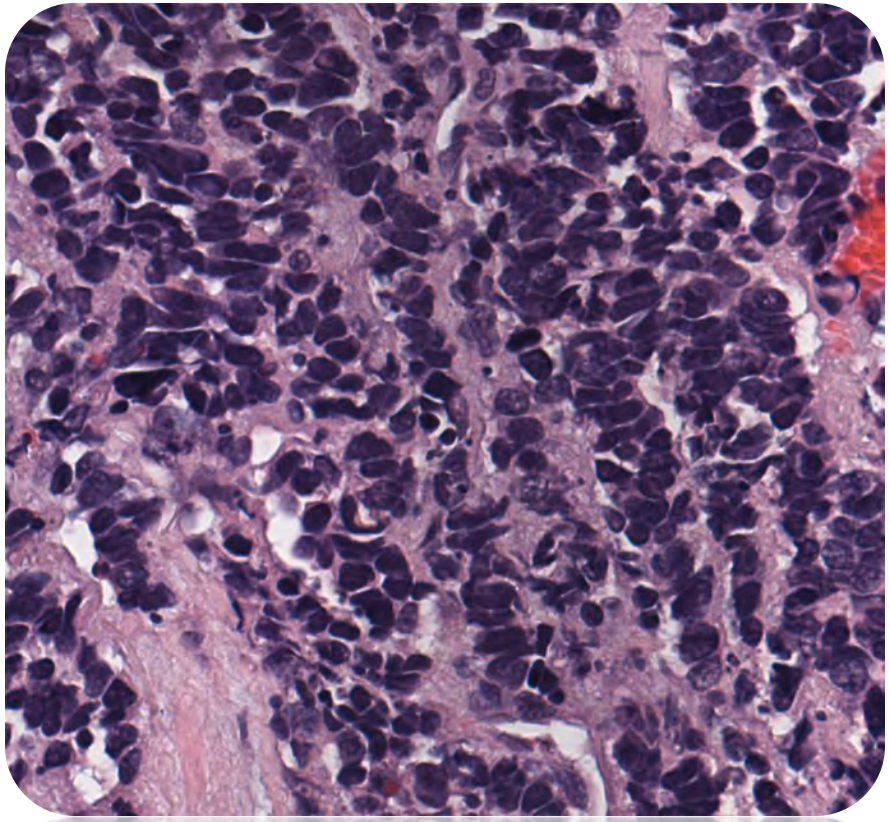
# Diagnosis: Prostate Cancer, adenocarcinoma



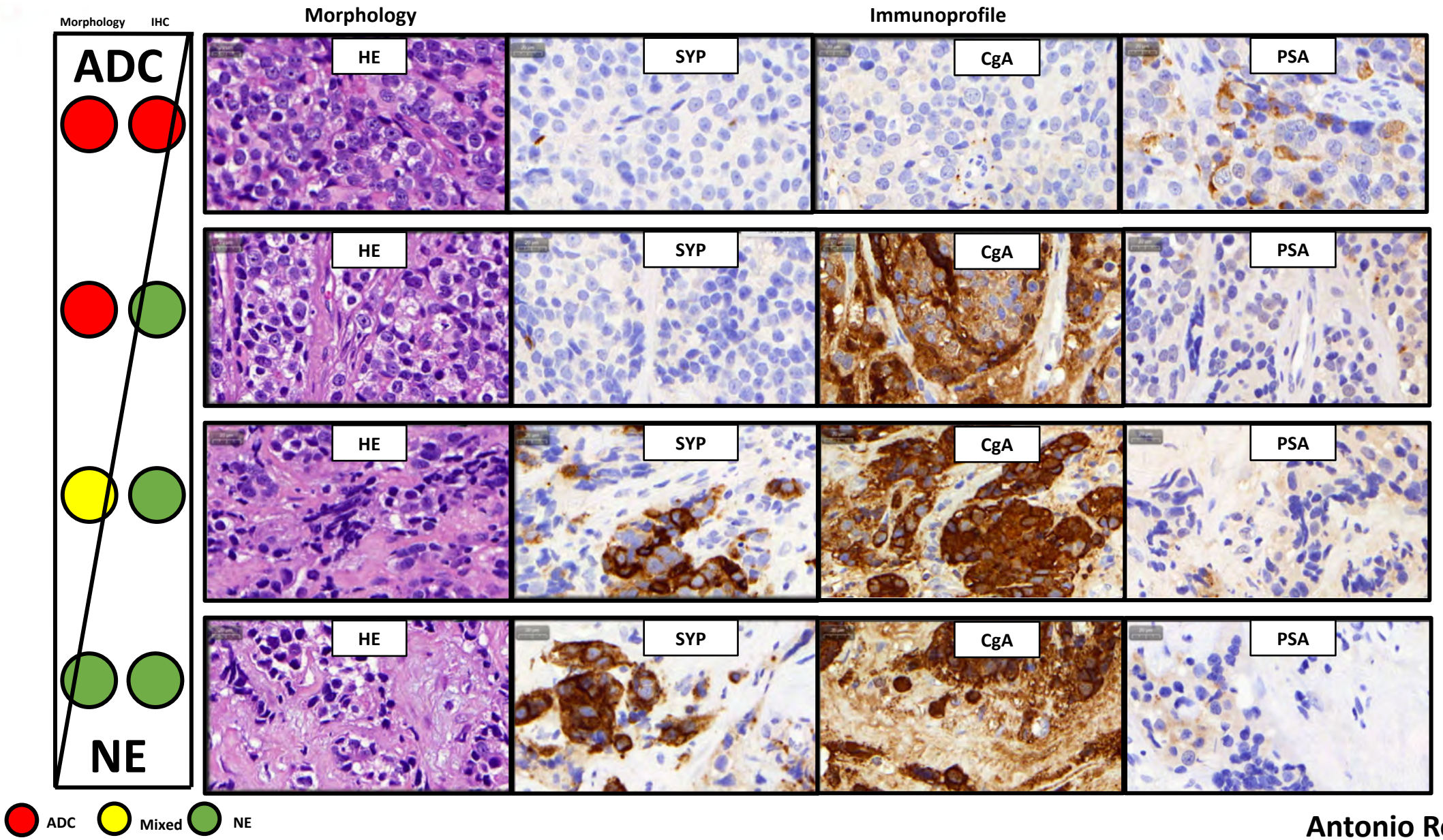


# Diagnosis: Small Cell/Neuroendocrine Prostate Cancer





# Sample: Spectrum adenocarcinoma-NE differentiation




Antonio Rodríguez

# In conclusion:

## What is "*actionable*" or ready for clinical use?

**Need prospective validation**

--CTC for AR v7 (Available via CTC Episciences)
-Metastatic biopsy - AR gain (multiple tests)
-cfDNA for DNA fraction, AR, others

**Approved by FDA/EMA**

-Blood/biopsy/cfDNA DNA repair BRCA1/2, ATM (multiple clinical tests)
-MSI/MMR (multiple tests)-clinical ready/FDA indication broad

# Thanks for your input on this presentation

All Slides available @ Rubinlab.unibe.ch *or* @MarkARubin1

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