Practical Application of Genomic Assays in Clinical Decision-Making

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DISCLOSURES

FUNDING:

NCI, EDRN,PCF, SU2C/PCF, Starr Cancer Consortium, DOD, SNF, Krebsliga, SPHN
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.

Practical Application of Genomic Assays in Clinical Decision-Making

Focus on advanced prostate cancer

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

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

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

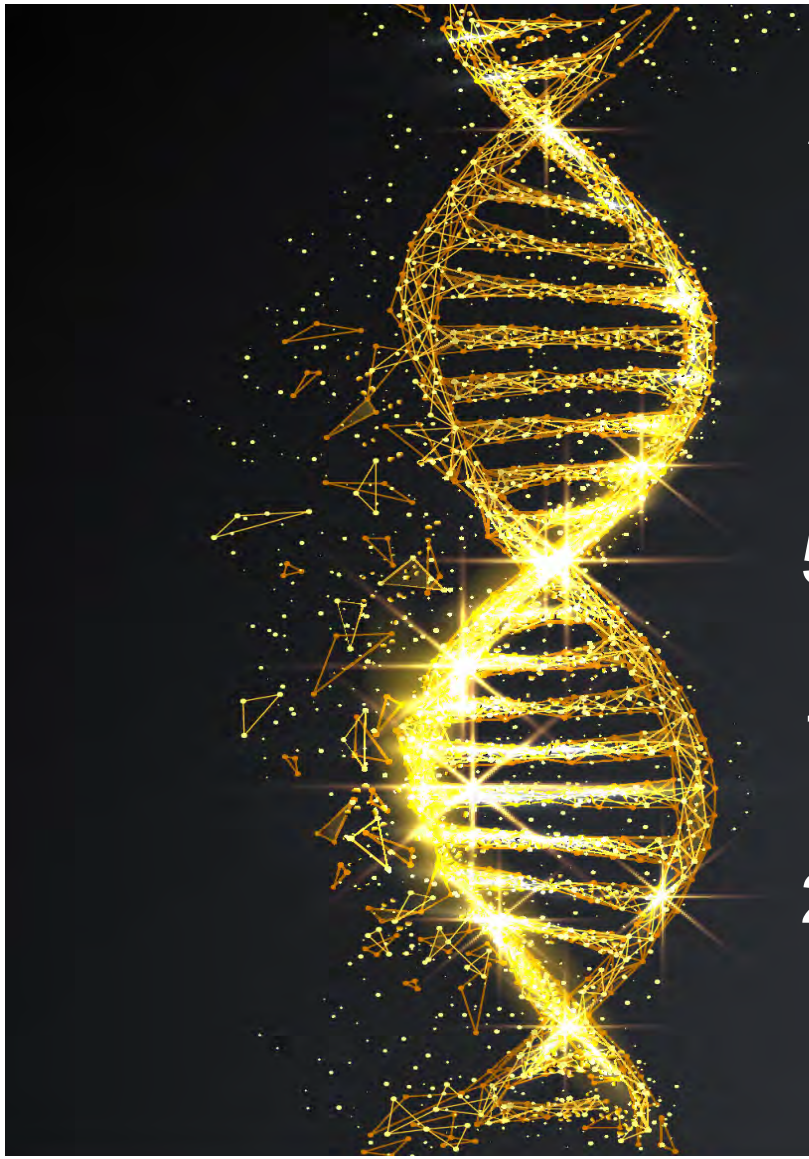
Dan L. Longo, M.D., *Editor*

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



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: What we count

Genetic Testing- counting germline sequence
Genomic Testing-counting tumor (somatic) seq context germline
Molecular Imagining-measuring protein expression

Numerous types of tests available for localized prostate cancer (e.g., Genomic Health, Myriad-CCP, Decipher, PCA3). These are usually predicting some outcome or assessing risk of disease progression.

Focus today will be on assessing advanced prostate cancer prognosis, and/or prediction

Definitions

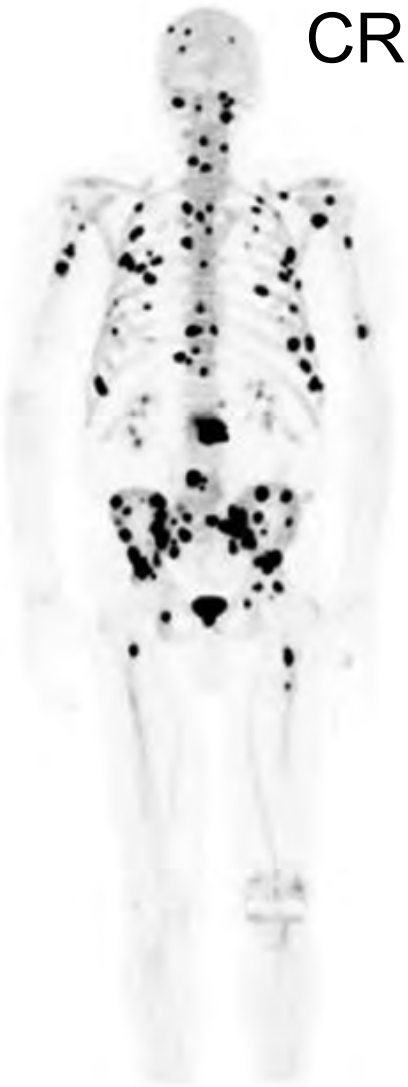
A **prognostic biomarker** is one that indicates an increased (or decreased) likelihood of a future clinical event, disease recurrence or progression in an identified population. Prognostic biomarkers are measured at a defined baseline, which may include a background treatment

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

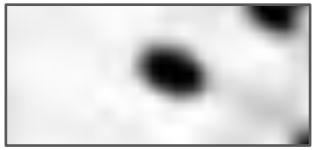
CRPC Patient and acquisition of samples for testing



Buccal sample

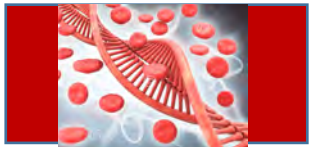
Germline DNA
Genetic testing (e.g., BRCA1/2)
Control normal sample for genomics

Tumor sample



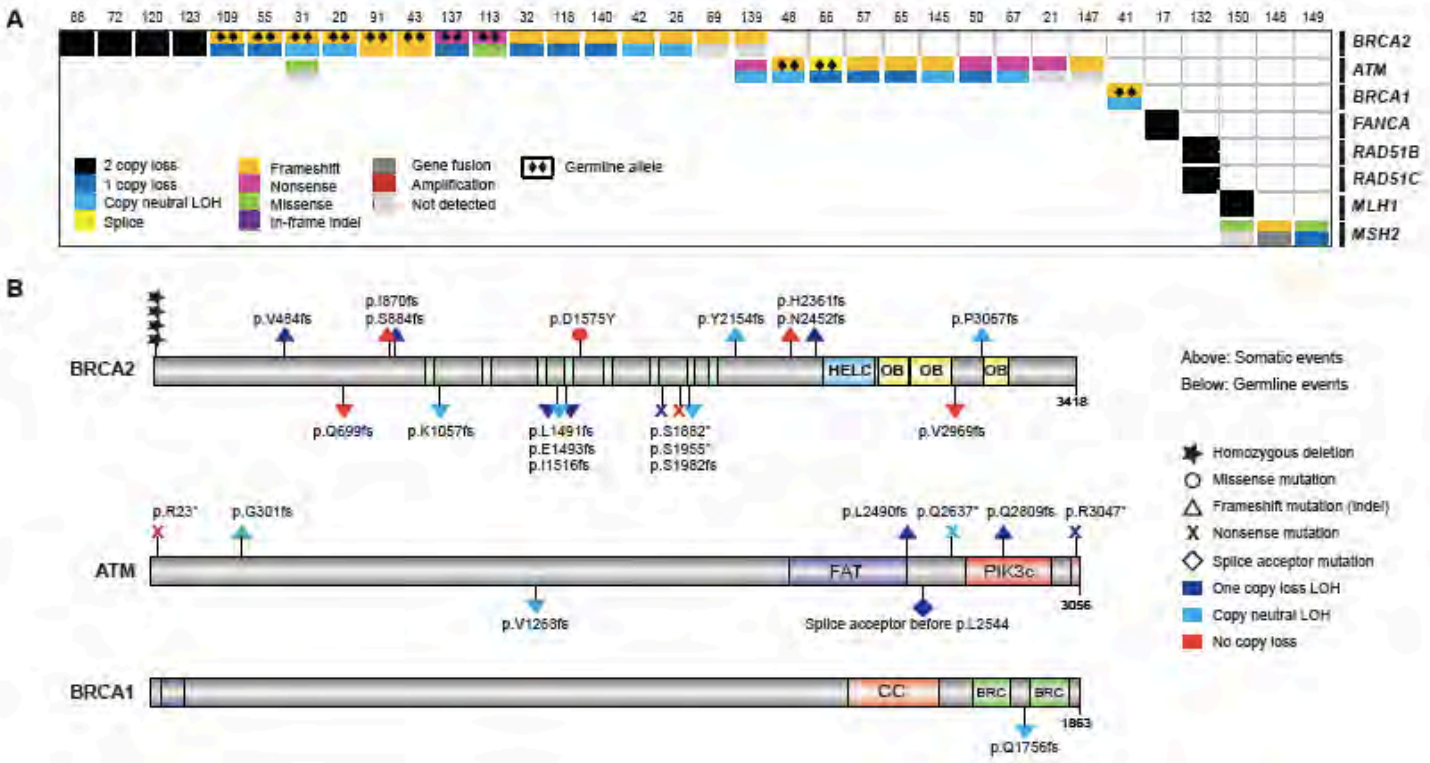
Tumor DNA/RNA/Protein
For genomic sequencing, transcriptomic sequencing, etc.

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

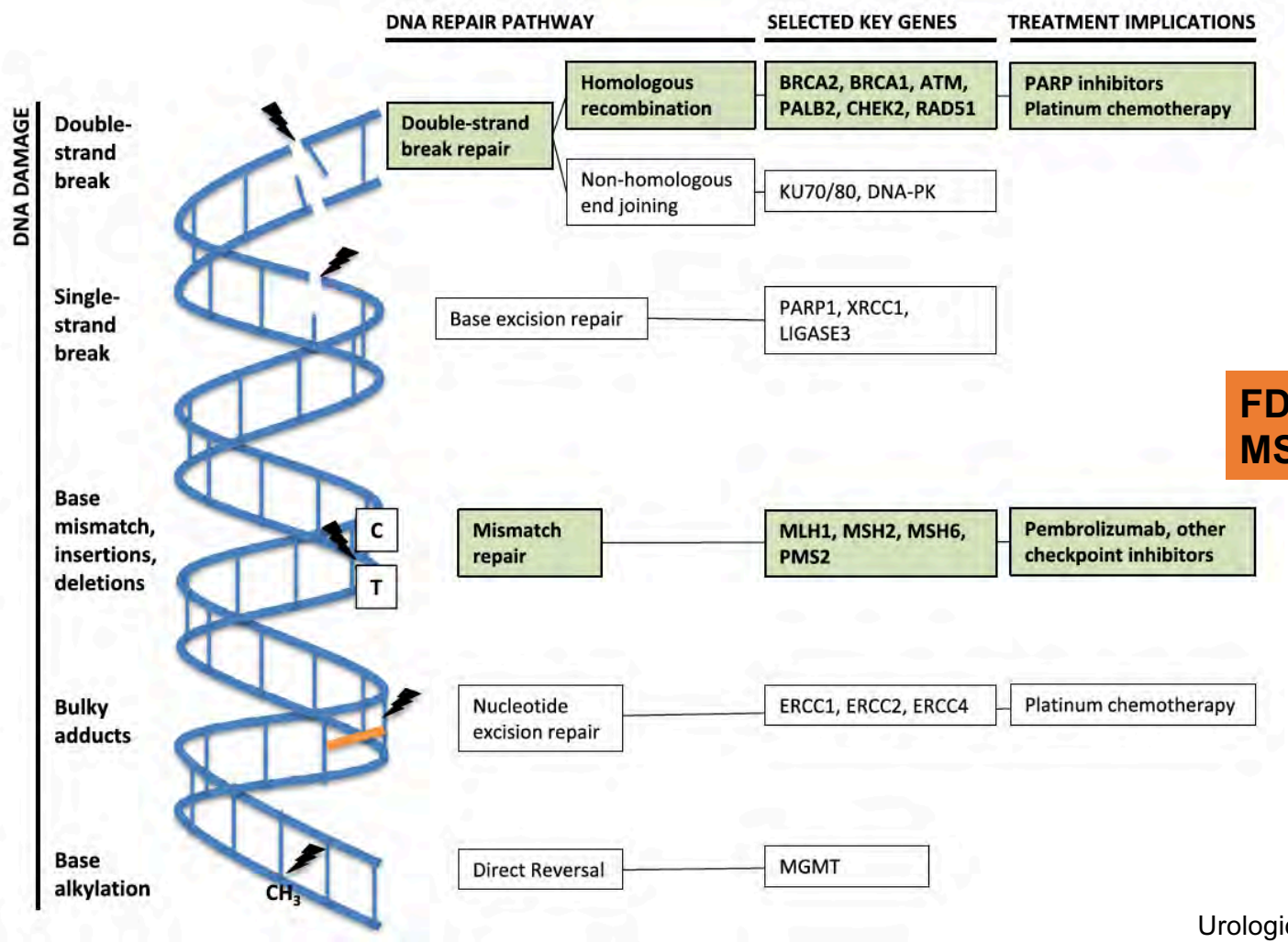
The resounding effect of DNA repair deficiency in prostate cancer

Heather H. Cheng, M.D., Ph.D.[a,b,*]

[a] *Division of Medical Oncology, University of Washington, Seattle, WA*

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

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



20%

FDA (May 2017) approval for MSI and MMR deficiency

5%

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

VOLUME 31 · NUMBER 14 · MAY 10 2013

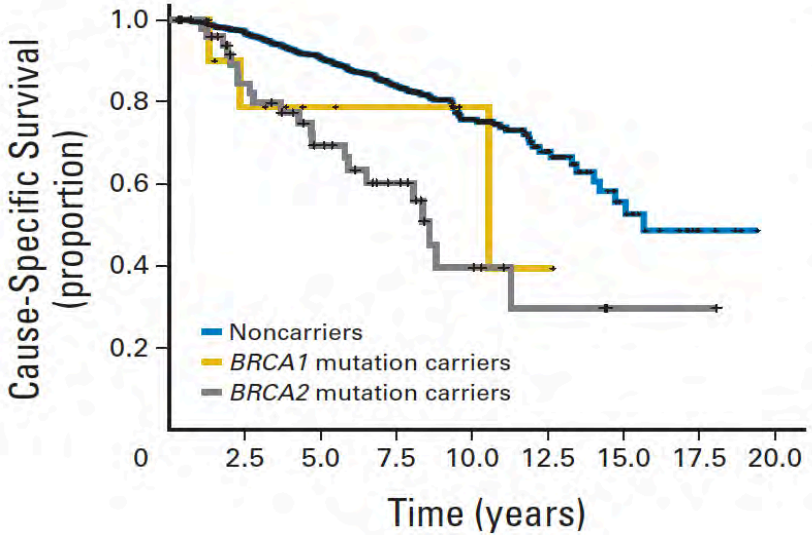
JOURNAL OF CLINICAL ONCOLOGY

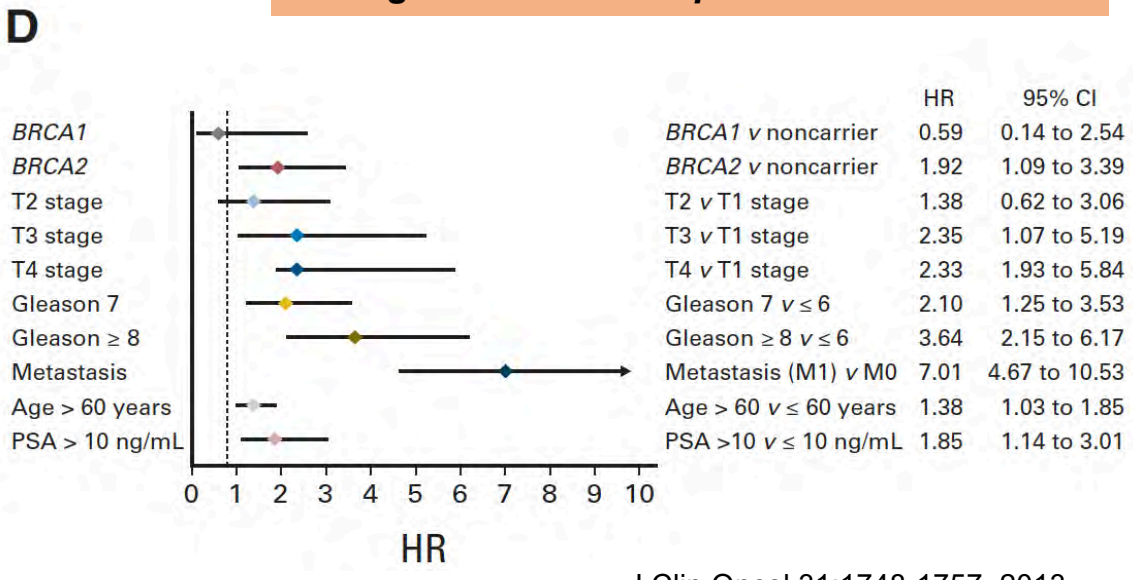
ORIGINAL REPORT

Germline *BRCA* Mutations Are Associated With Higher Risk of Nodal Involvement, Distant Metastasis, and Poor Survival Outcomes in Prostate Cancer

Elena Castro, Chee Goh, David Olmos, Ed Saunders, Daniel Leongamornlert, Malgorzata Tymrakiewicz, Nadiya Mahmud, Tokhir Dadaev, Koveela Govindasami, Michelle Guy, Emma Sawyer, Rosemary Wilkinson, Audrey Ardern-Jones, Steve Ellis, Debra Frost, Susan Peock, D. Gareth Evans, Marc Tischkowitz, Trevor Cole, Rosemarie Davidson, Diana Eccles, Carole Brewer, Fiona Douglas, Mary E. Porteous, Alan Donaldson, Huw Dorkins, Louise Izatt, Jackie Cook, Shirley Hodgson, M. John Kennedy, Lucy E. Side, Jacqueline Eason, Alex Murray, Antonis C. Antoniou, Douglas F. Easton, Zsofia Kote-Jarai, and Rosalind Eeles

BRCA1/2 mutations confer a more aggressive PCa phenotype with a higher probability of nodal involvement and distant metastasis. BRCA mutations are associated with poor survival outcomes and this should be considered for tailoring clinical management of these patients.





J Clin Oncol 31:1748-1757. 2013

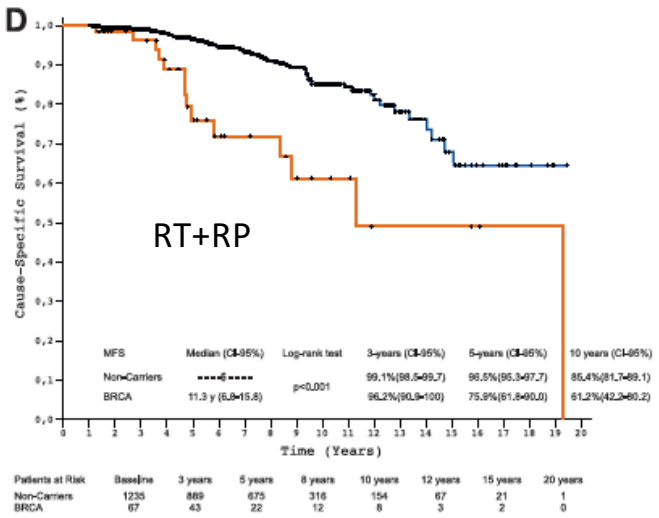
Platinum Priority – Prostate Cancer

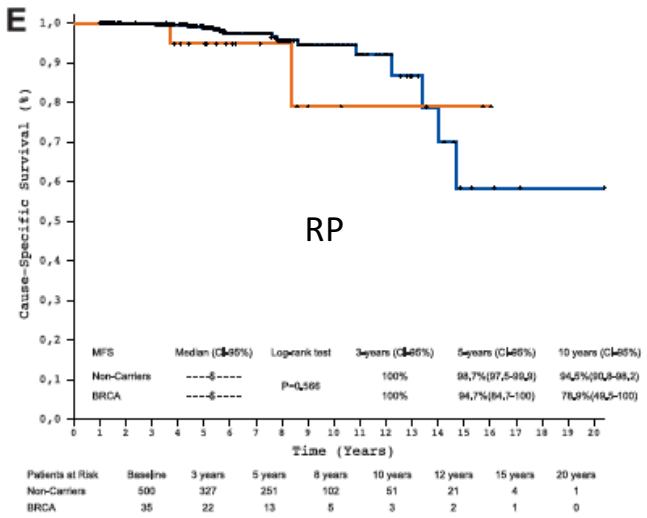
Editorial by Ola Bratt and Niklas Loman on pp. 194–195 of this issue

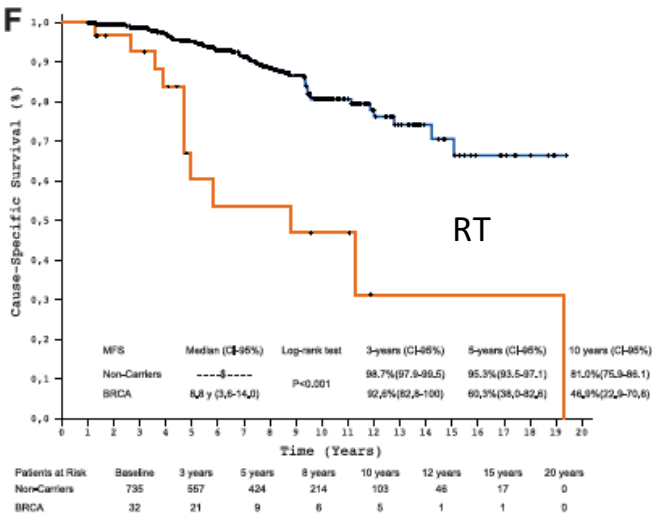
Effect of *BRCA* Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer

Elena Castro[a,b,], Chee Goh[b], Daniel Leongamornlert[b], Ed Saunders[b], Malgorzata Tymrakiewicz[b], Tokhir Dadaev[b], Koveela Govindasami[b], Michelle Guy[b], Steve Ellis[c], Debra Frost[c], Elizabeth Bancroft[b], Trevor Cole[d], Marc Tischkowitz[e], M. John Kennedy[f], Jacqueline Eason[g], Carole Brewer[h], D. Gareth Evans[i], Rosemarie Davidson[j], Diana Eccles[k], Mary E. Porteous[l], Fiona Douglas[m], Julian Adlard[n], Alan Donaldson[o], Antonis C. Antoniou[c], Zsofia Kote-Jarai[b], Douglas F. Easton[c], David Olmos[a,*,†], Rosalind Eeles[b,†]*

"Our study demonstrates that BRCA carriers treated for localized PCa have worse outcomes than noncarriers because they relapse and progress earlier to lethal metastatic disease."







EUROPEAN UROLOGY 6 8 (2 01 5) 1 8 6 – 1 9 3

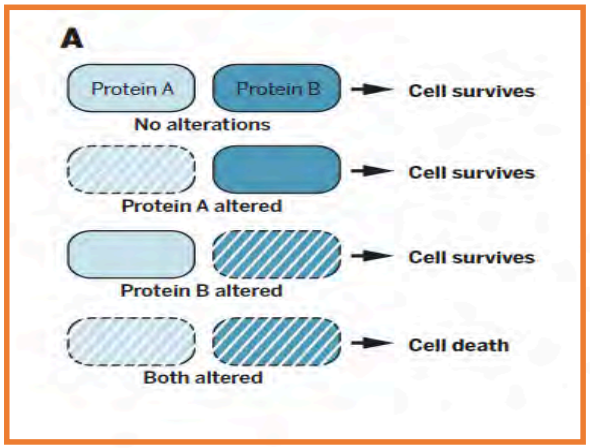
Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

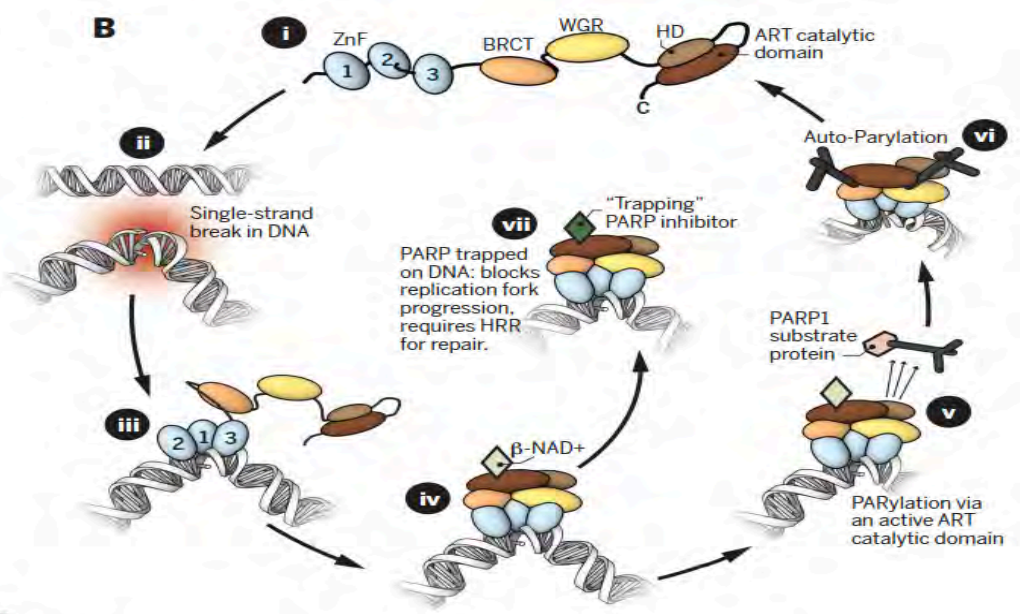
Hannah Farmer[1,2]*, Nuala McCabe[1,2]*, Christopher J. Lord[2]*, Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2]†, Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]

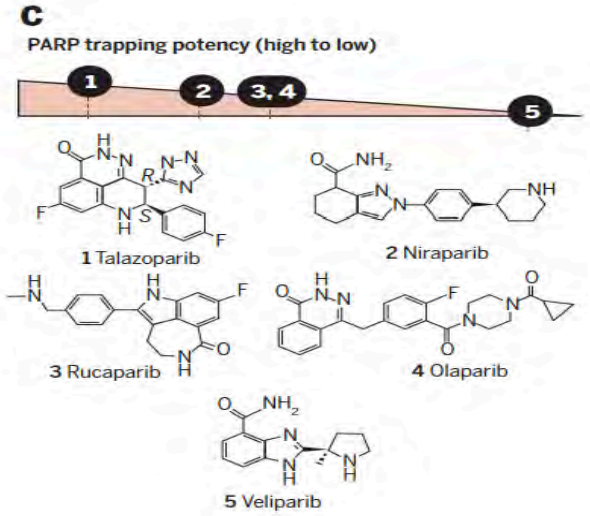
[1]*Cancer Research UK Gene Function and Regulation Group and* [2]*The Breakthrough Breast Cancer Research Centre Institute of Cancer Research, Fulham Road, London SW3 6JB, UK*
[3]*Guy's Hospital, St Thomas' Street, London SE1 9RT, UK*
[4]*KuDOS Pharmaceuticals Ltd, Cambridge Science Park, Cambridge CB4 0WG, UK*
[5]*Wellcome Trust and Cancer Research UK, Gurdon Institute of Cancer and Developmental Biology, and Department of Zoology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QN, UK*

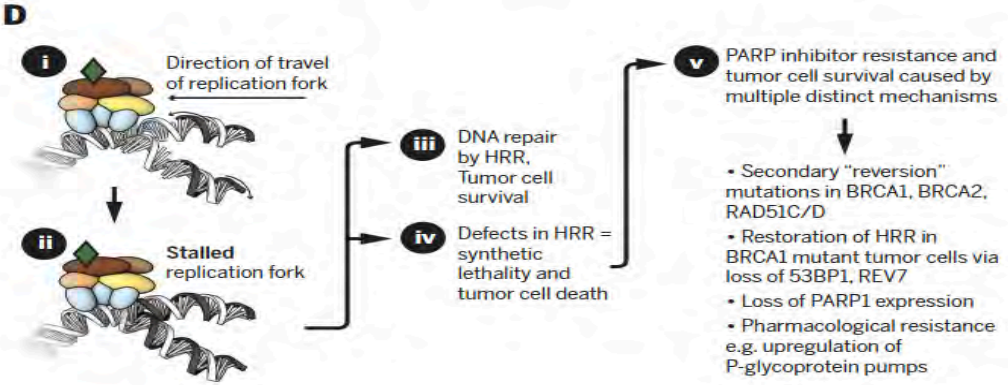
* These authors contributed equally to this work
† Present address: Division of Experimental Oncology 1, CRO-IRCCS, Aviano 33081 PN, Italy

NATURE |VOL 434 | 14 APRIL 2005









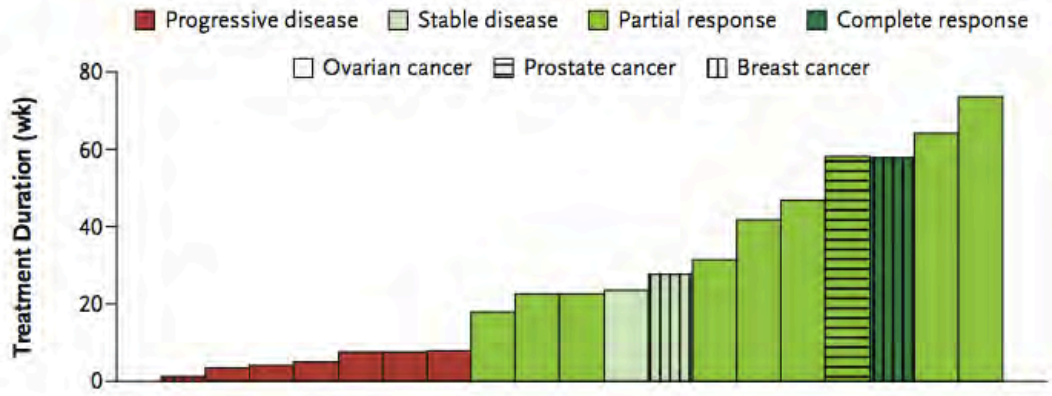
Lord and Ashworth, Science 355, 1152–1158 (2017)

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.



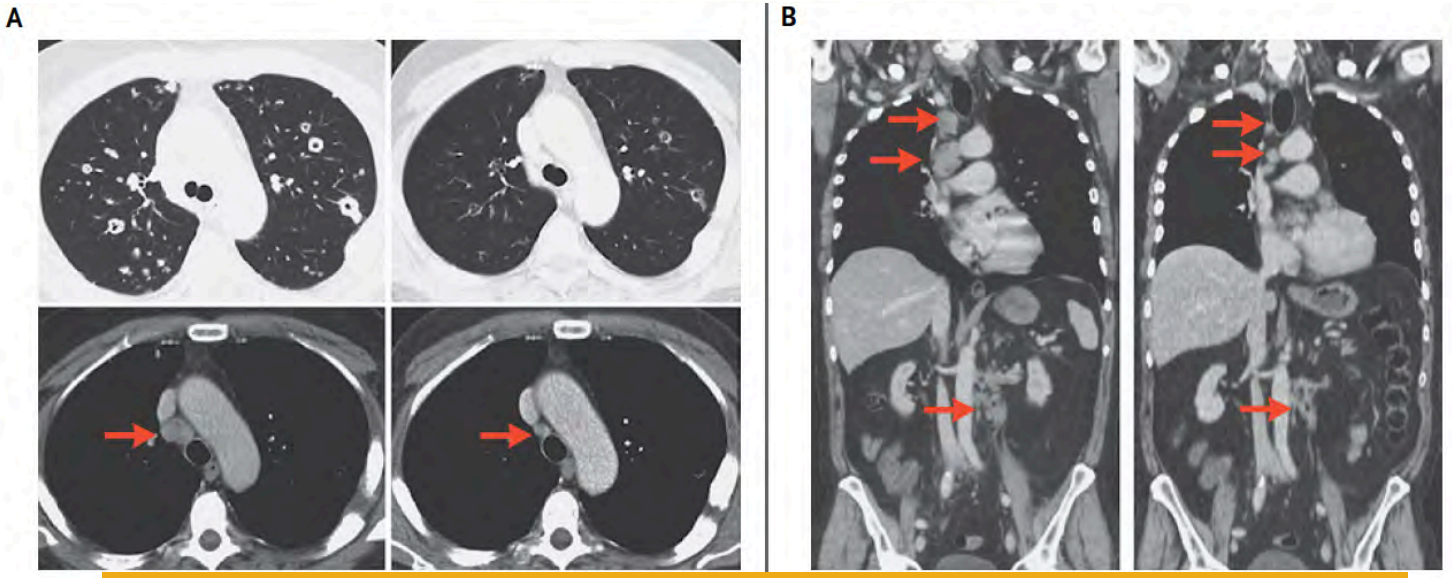
19 BRCA mutated

The NEW ENGLAND JOURNAL of MEDICINE

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

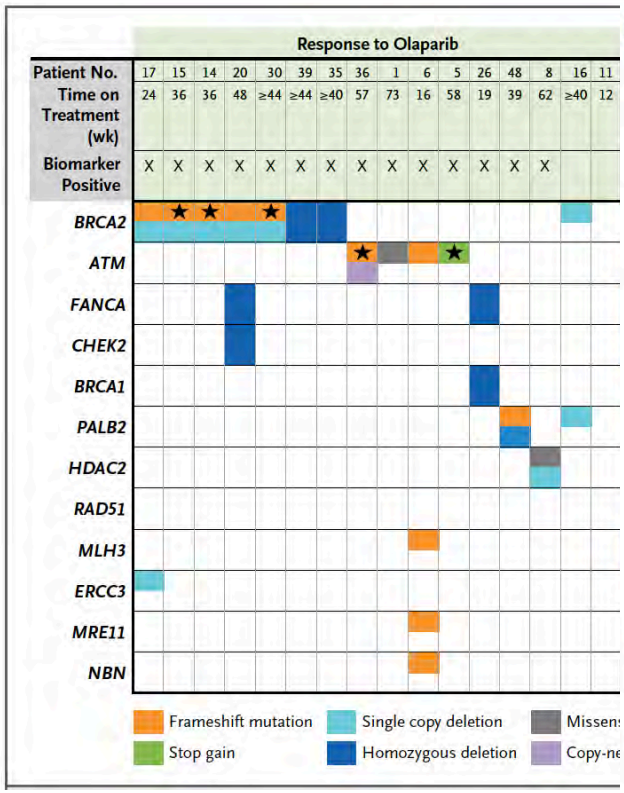
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

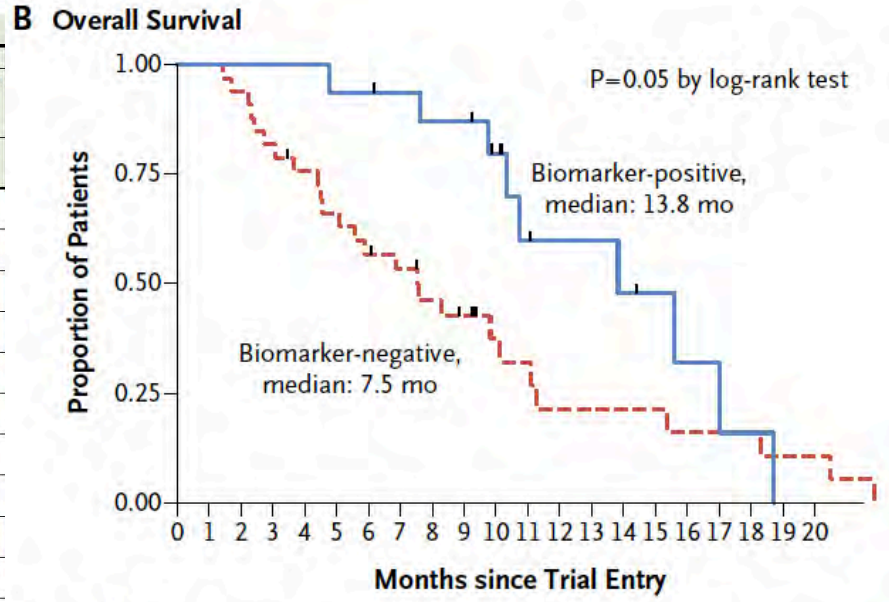
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, 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





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	–

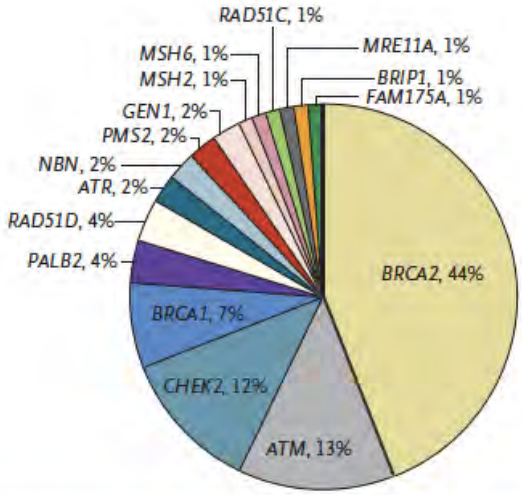
The NEW ENGLAND JOURNAL of MEDICINE

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)

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

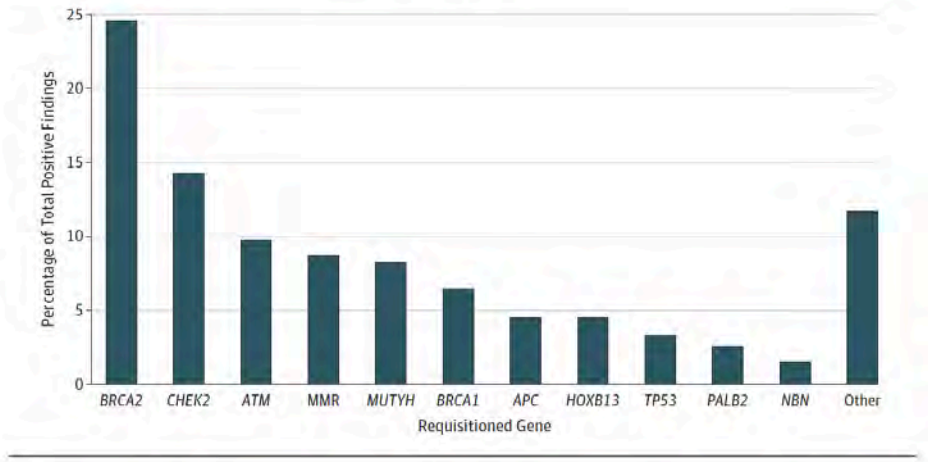
Cross-sectional study of data from 3607 men with a personal history of prostate cancer who underwent germline genetic testing between 2013 and 2018 and were unselected for family history, stage of disease, or age at diagnosis.

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

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

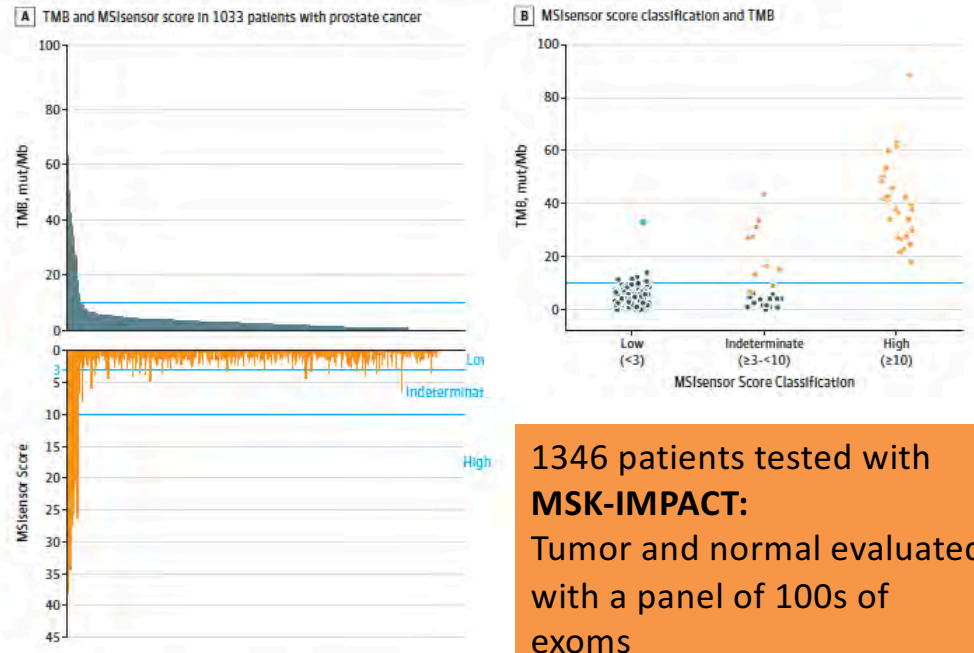
JAMA Oncology Published online February 7, 2019

JAMA Oncology | Original Investigation

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

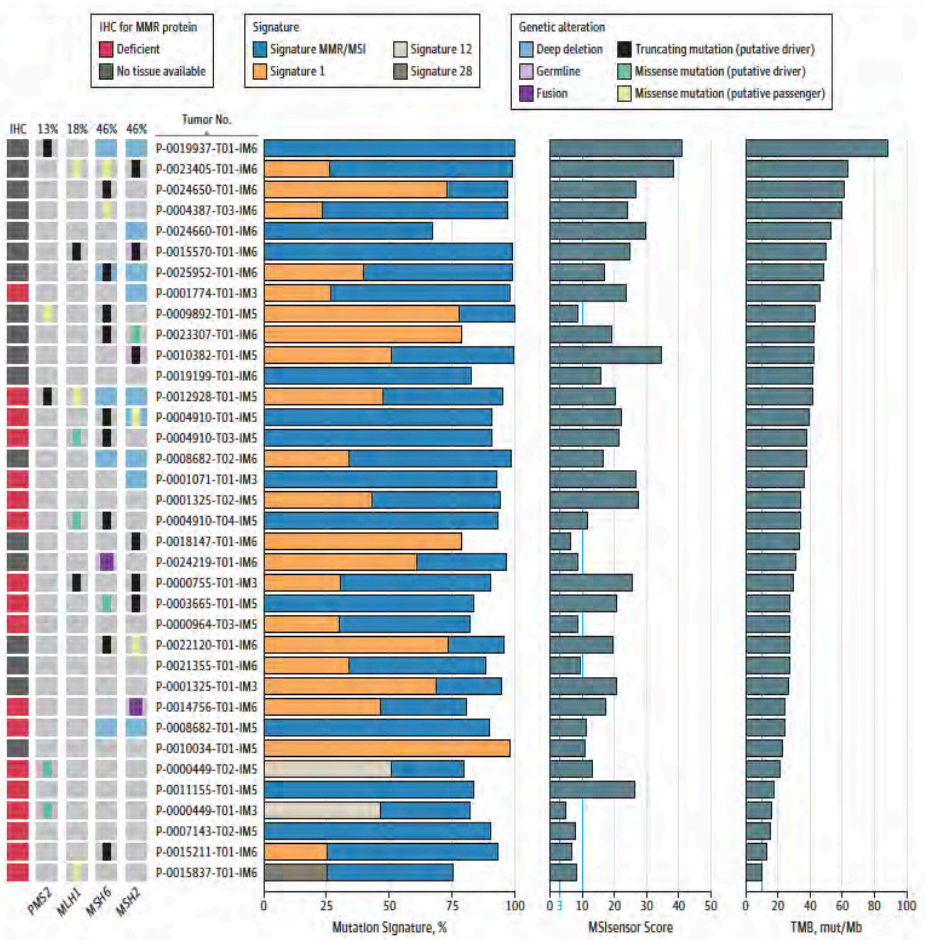
Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman,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



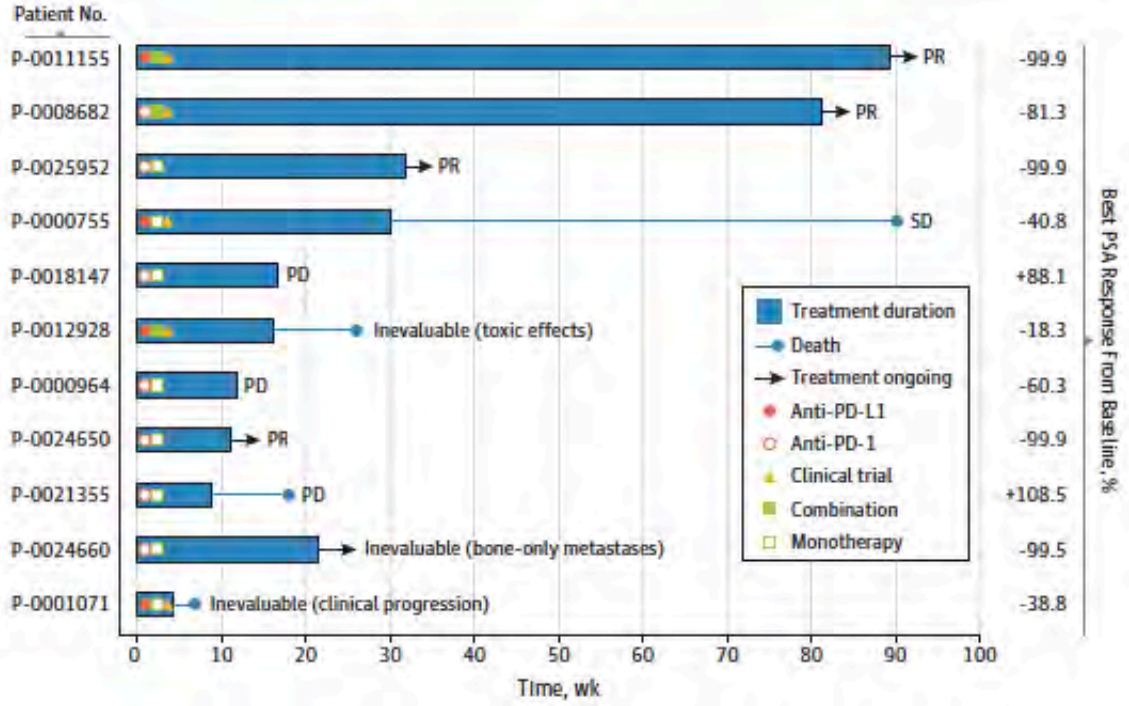
1346 patients tested with **MSK-IMPACT:**
Tumor and normal evaluated with a panel of 100s of exoms

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



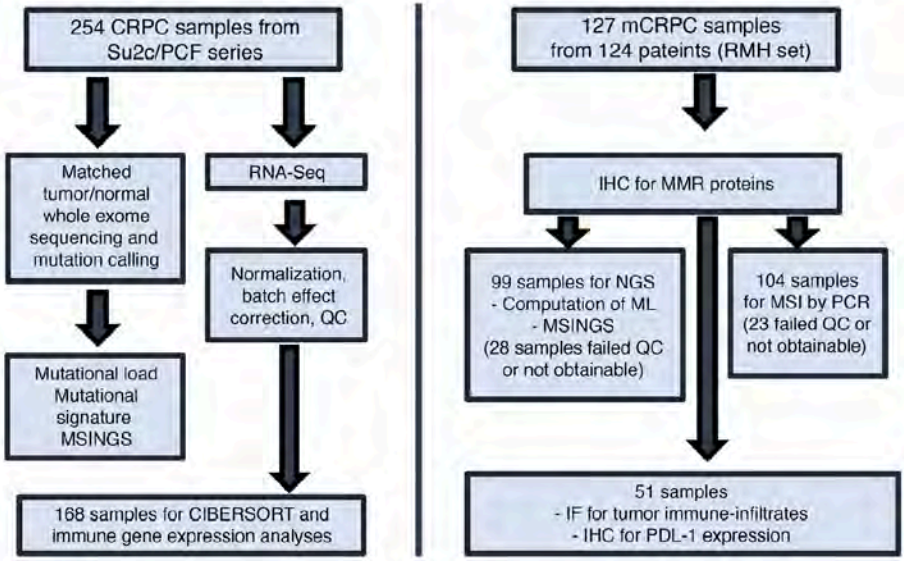
JAMA Oncology Published online December 27, 2018

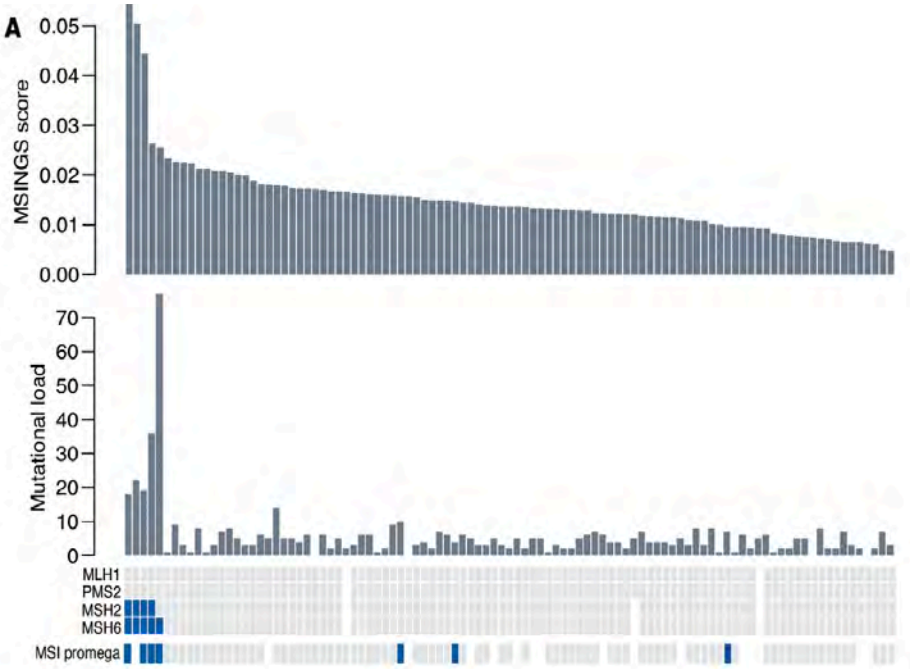
The Journal of Clinical Investigation CLINICAL MEDICINE

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

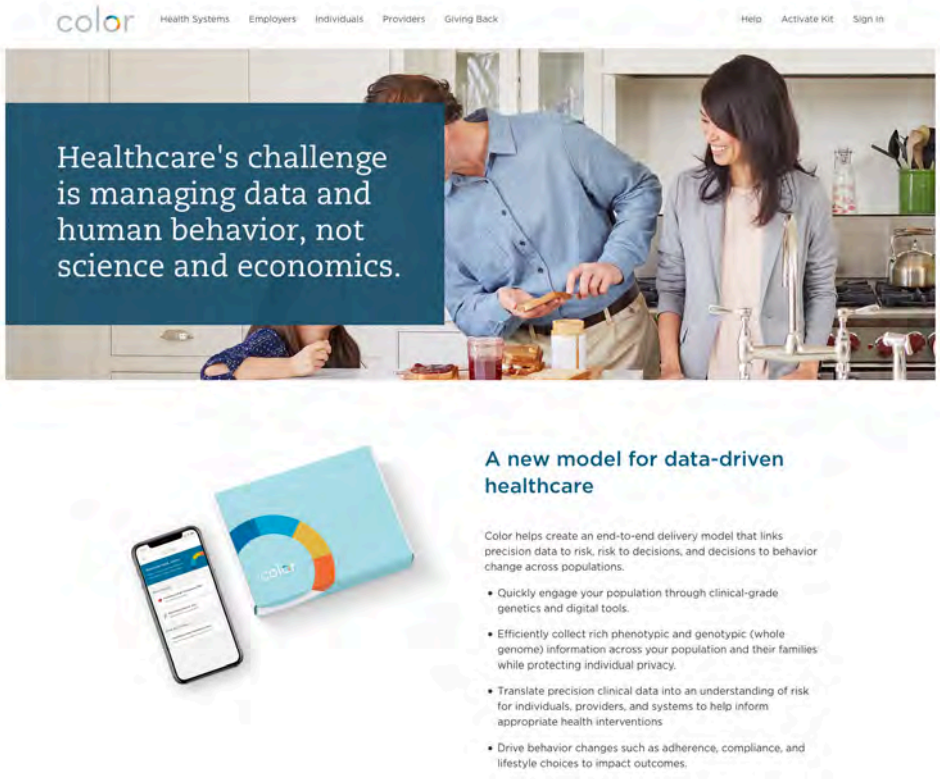
Daniel Nava Rodrigues,[1,2] Pasquale Rescigno,[1,2,3] David Liu,[4,5] Wei Yuan,[1] Suzanne Carreira,[1] Maryou B. Lambros,[1] George Seed,[1] Joaquin Mateo,[1,2] Ruth Riisnaes,[1] Stephanie Mullane,[4,5] Claire Margolis,[4,5] Diana Miao,[4,5] Susana Miranda,[1] David Dolling,[1] Matthew Clarke,[1] Claudia 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





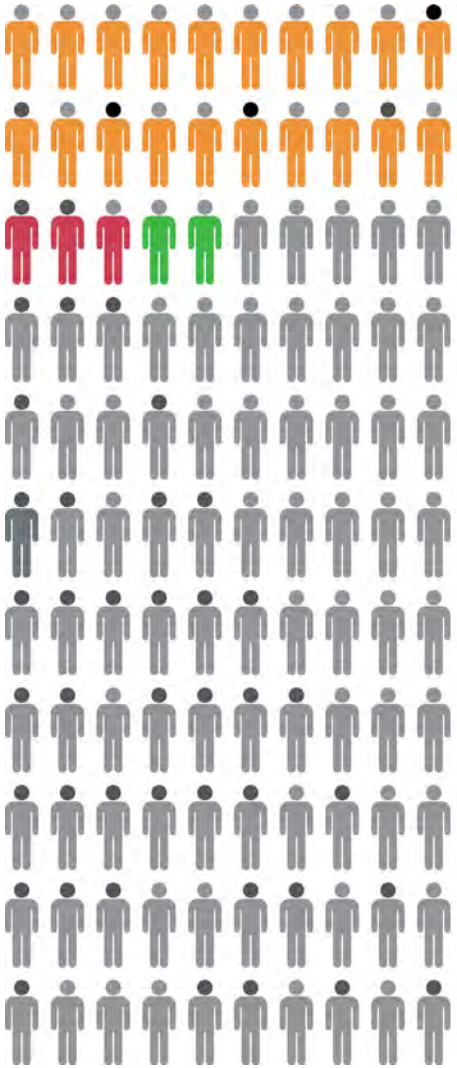
JCI Volume 128 Number 10 October 2018



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*

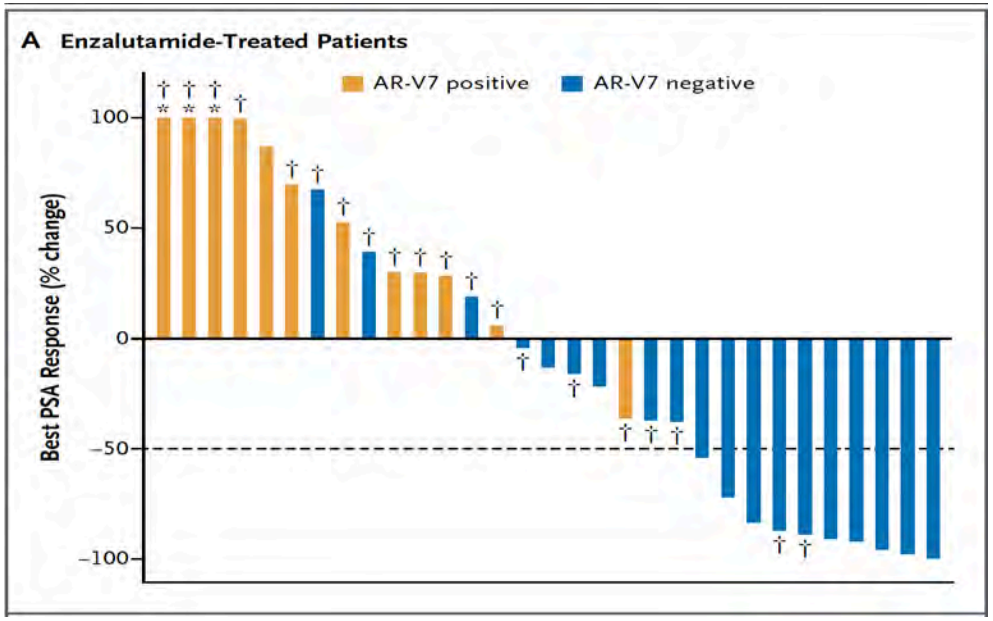
a. **MSI testing**
b. **DNA repair status** ("BRCAness"-assay for BRCA1/2/ATM,PALB2) for mutation/loss or HR signature useful for for platinum therapy or PARPi
c. **Loss of AR** lack of response to AR therapy (AR-V7, mutations)
d. **cfDNA** amount associated with prognosis
e. **PTEN loss** - possibly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

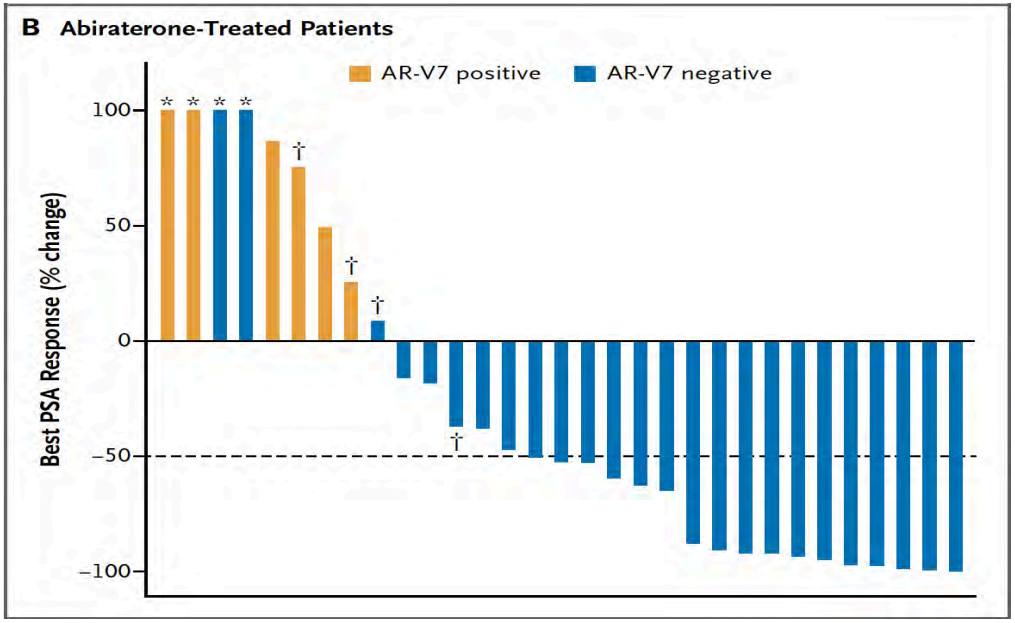
*Thanks Pete Nelson
Always comprehensive!

The NEW ENGLAND JOURNAL of MEDICINE

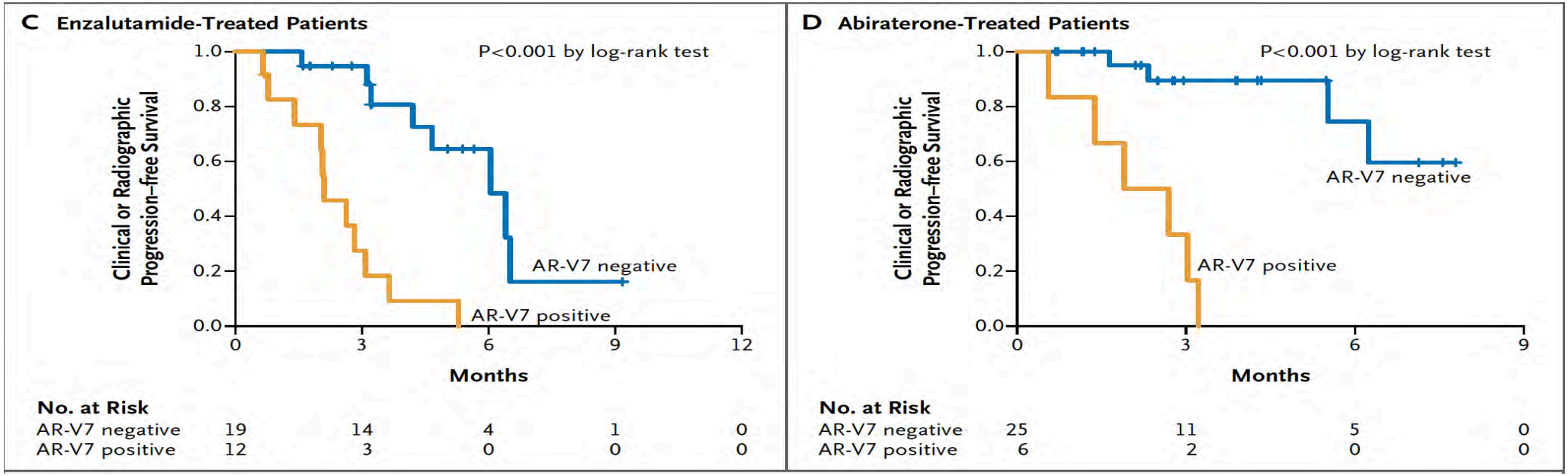
ORIGINAL ARTICLE

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

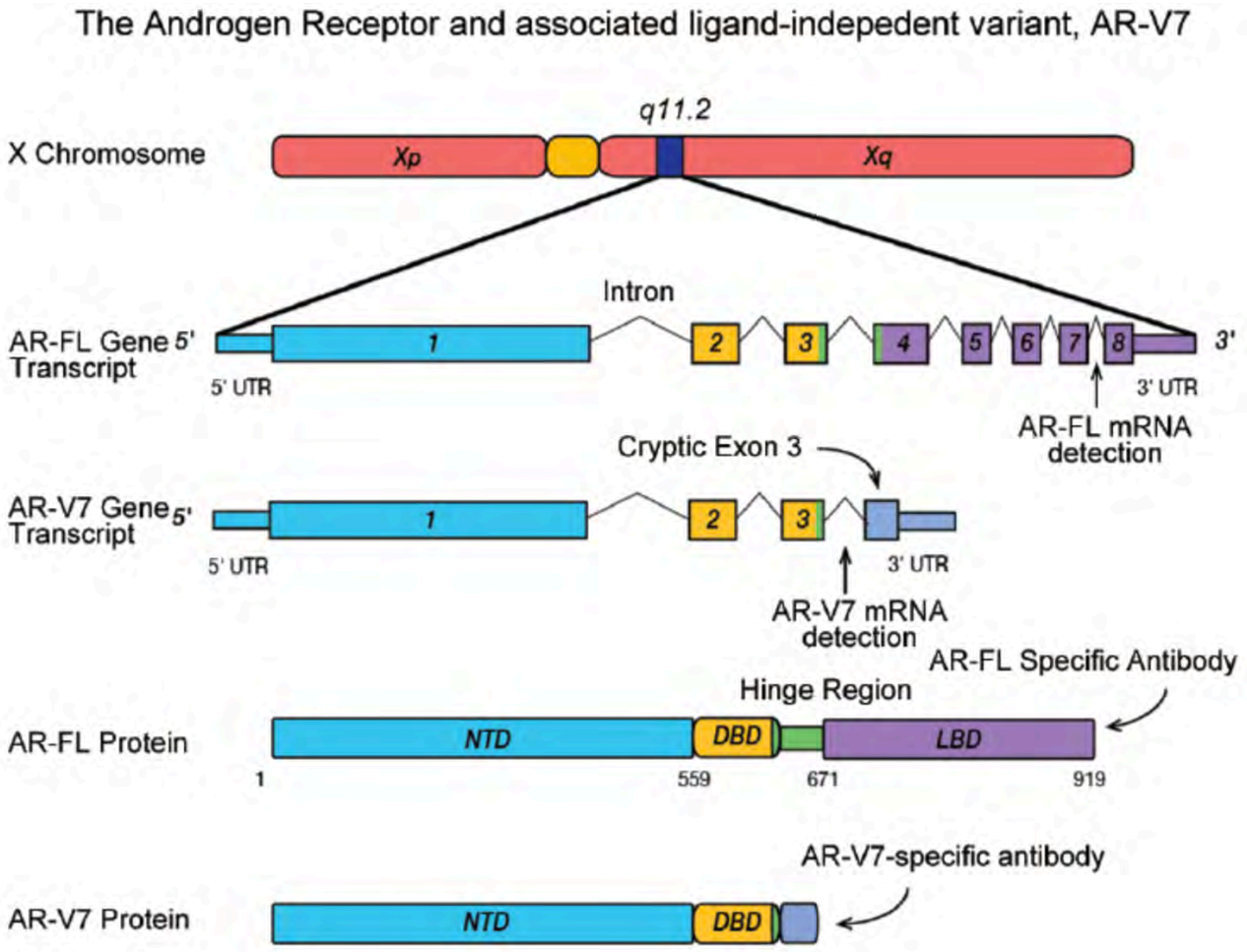




Antonarakis ES et al, NEJM 2014



Antonarakis ES et al, NEJM 2014

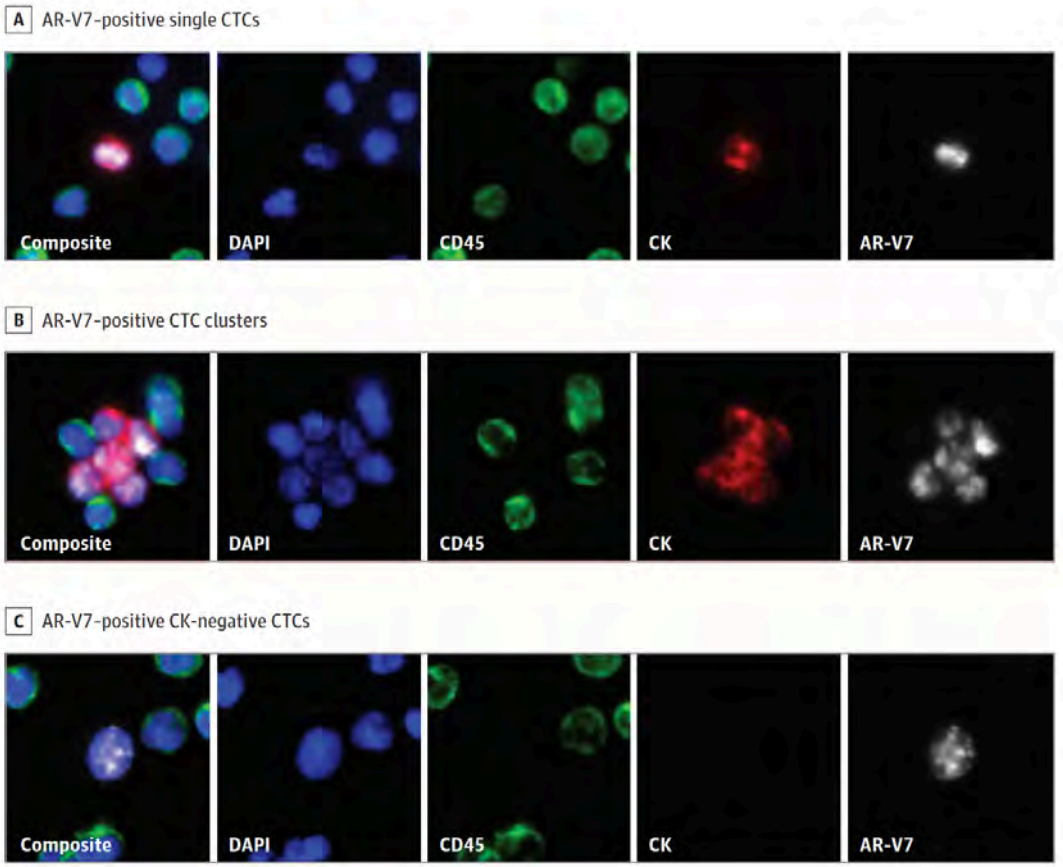

The Androgen Receptor and associated ligand-indepedent variant, AR-V7
q11.2
X Chromosome
Xp
Xq
Intron
AR-FL Gene Transcript
5'
3'
1
2
3
4
5
6
7
8
5' UTR
3' UTR
AR-FL mRNA detection
Cryptic Exon 3
AR-V7 Gene Transcript
5'
1
2
3
5' UTR
3' UTR
AR-V7 mRNA detection
AR-FL Specific Antibody
Hinge Region
AR-FL Protein
NTD
DBD
LBD
1
559
671
919
AR-V7-specific antibody
AR-V7 Protein
NTD
DBD

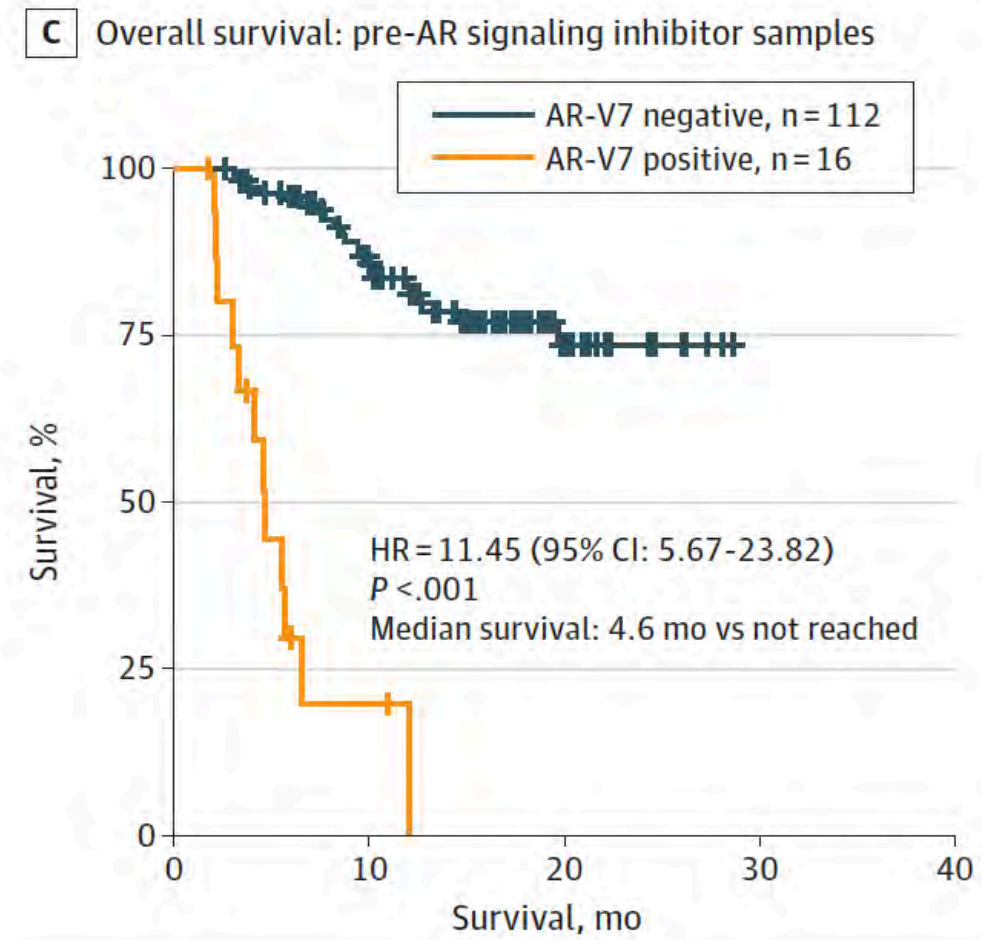
Research

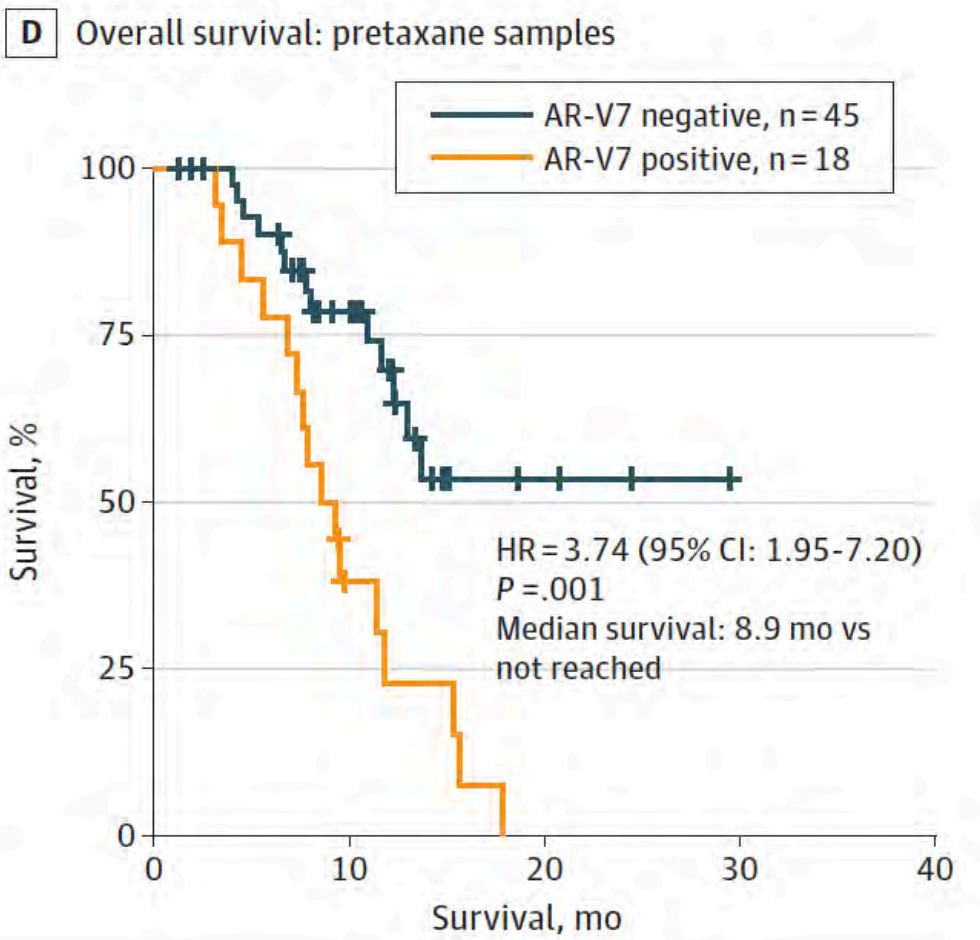
JAMA Oncology | Original Investigation

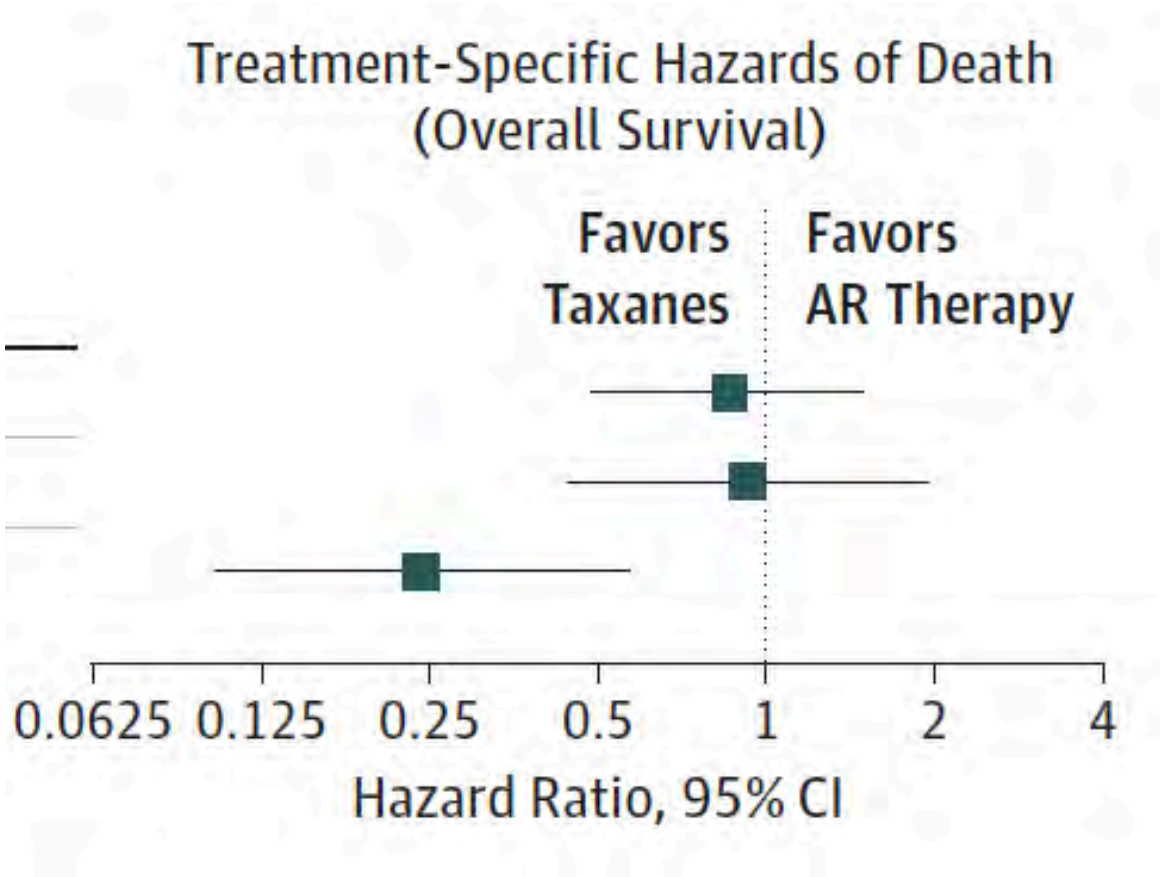
Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

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

Research

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

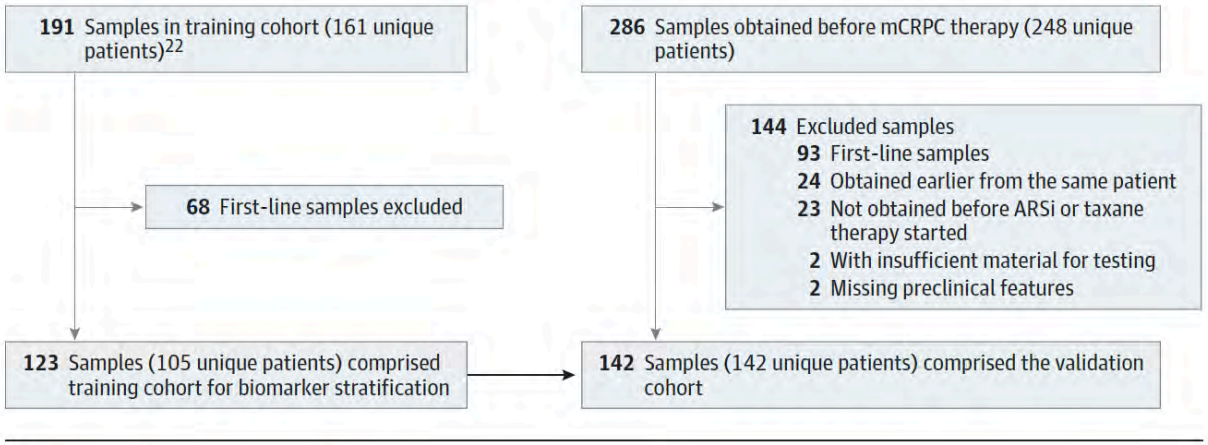
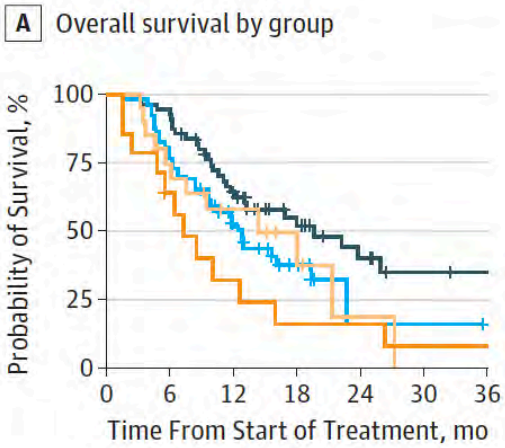
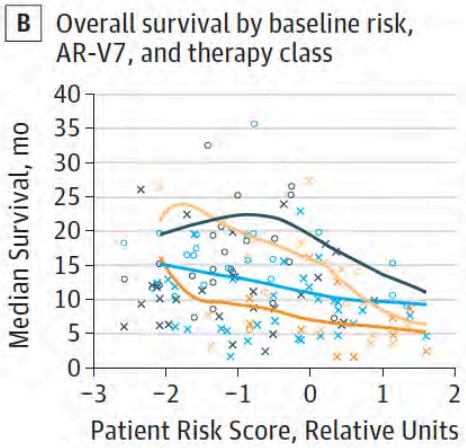
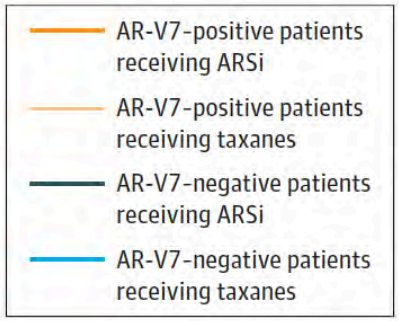


Figure 2. Association Between Patient Risk, Androgen Receptor Splice Variant 7 (AR-V7) Status, and Therapy

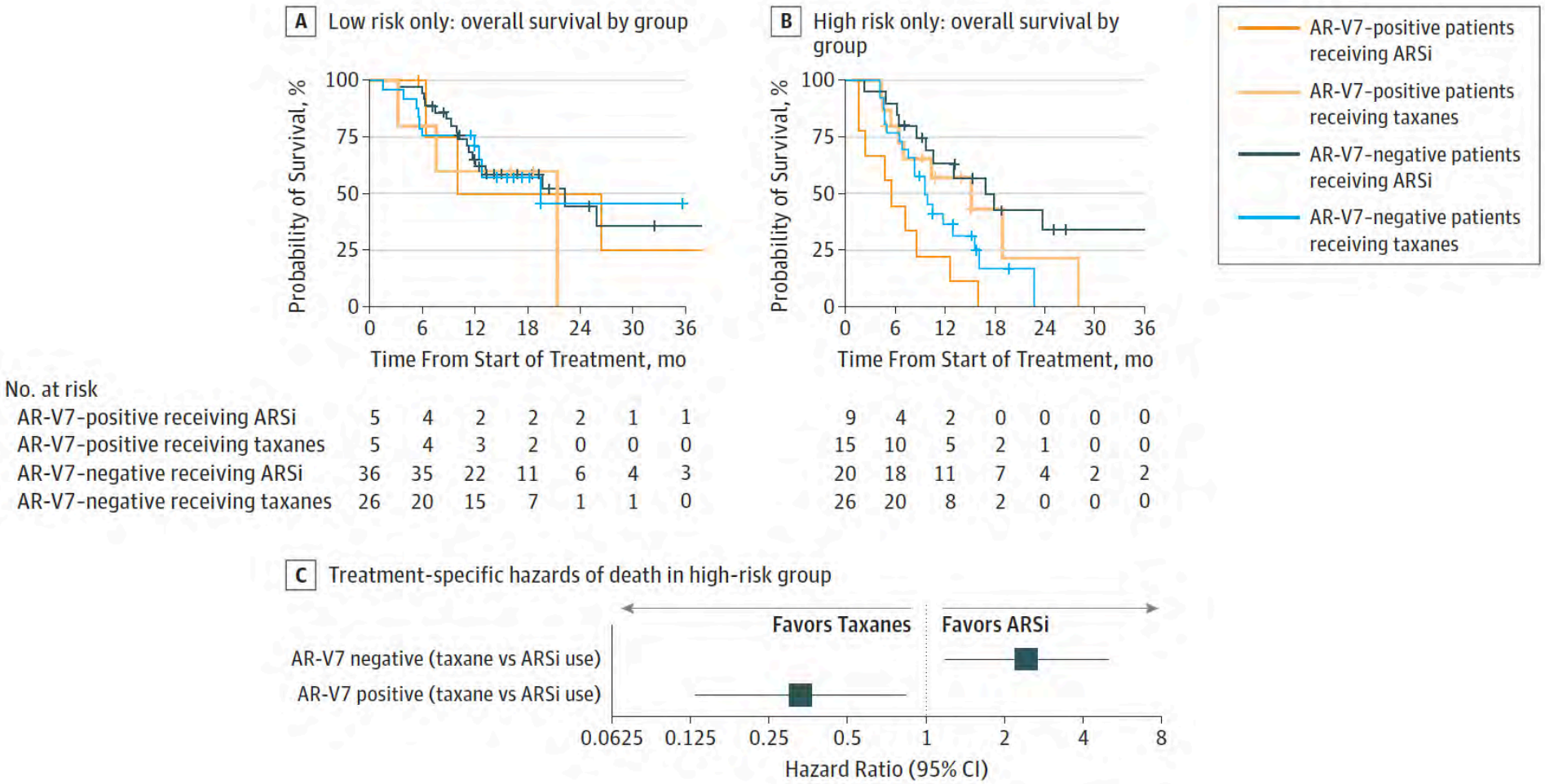






No. at risk

AR-V7-positive receiving ARSi	14	8	4	2	2	1	1
AR-V7-positive receiving taxanes	20	14	8	4	1	0	0
AR-V7-negative receiving ARSi	56	53	33	18	10	6	5
AR-V7-negative receiving taxanes	52	40	23	9	1	1	0



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…

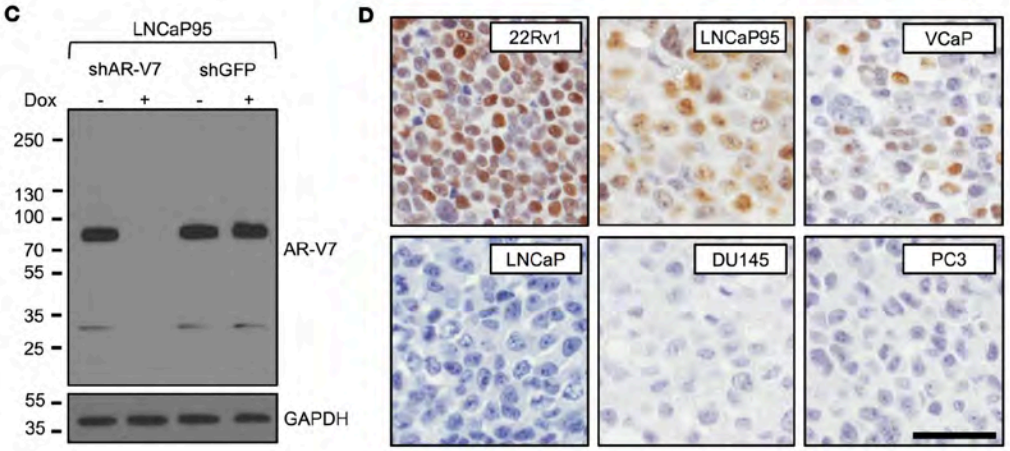
1) positivity not continuous but binary (only 1 positive CTC needed)
2) Total CTC counts not reported
3) False-negative rate cannot be interpreted with total CTC count
4) Anti-body to cryptic exon 3 may be non-specific leading to false positivity
5) AR-V7 may be more prognostics of overall survival

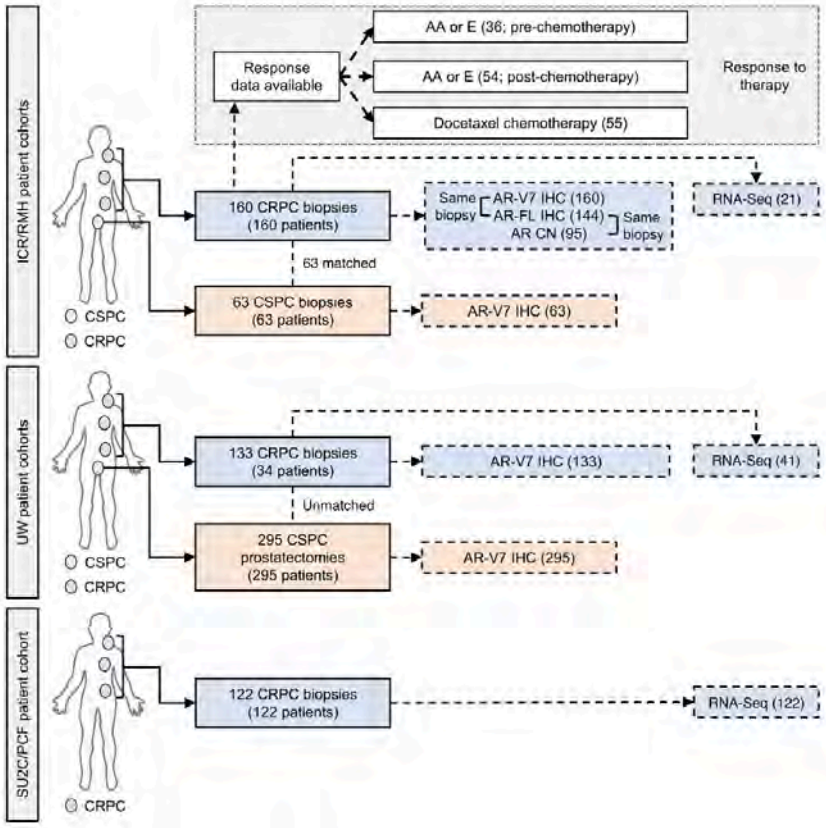
JAMA Oncology September 2018 Volume 4, Number 9

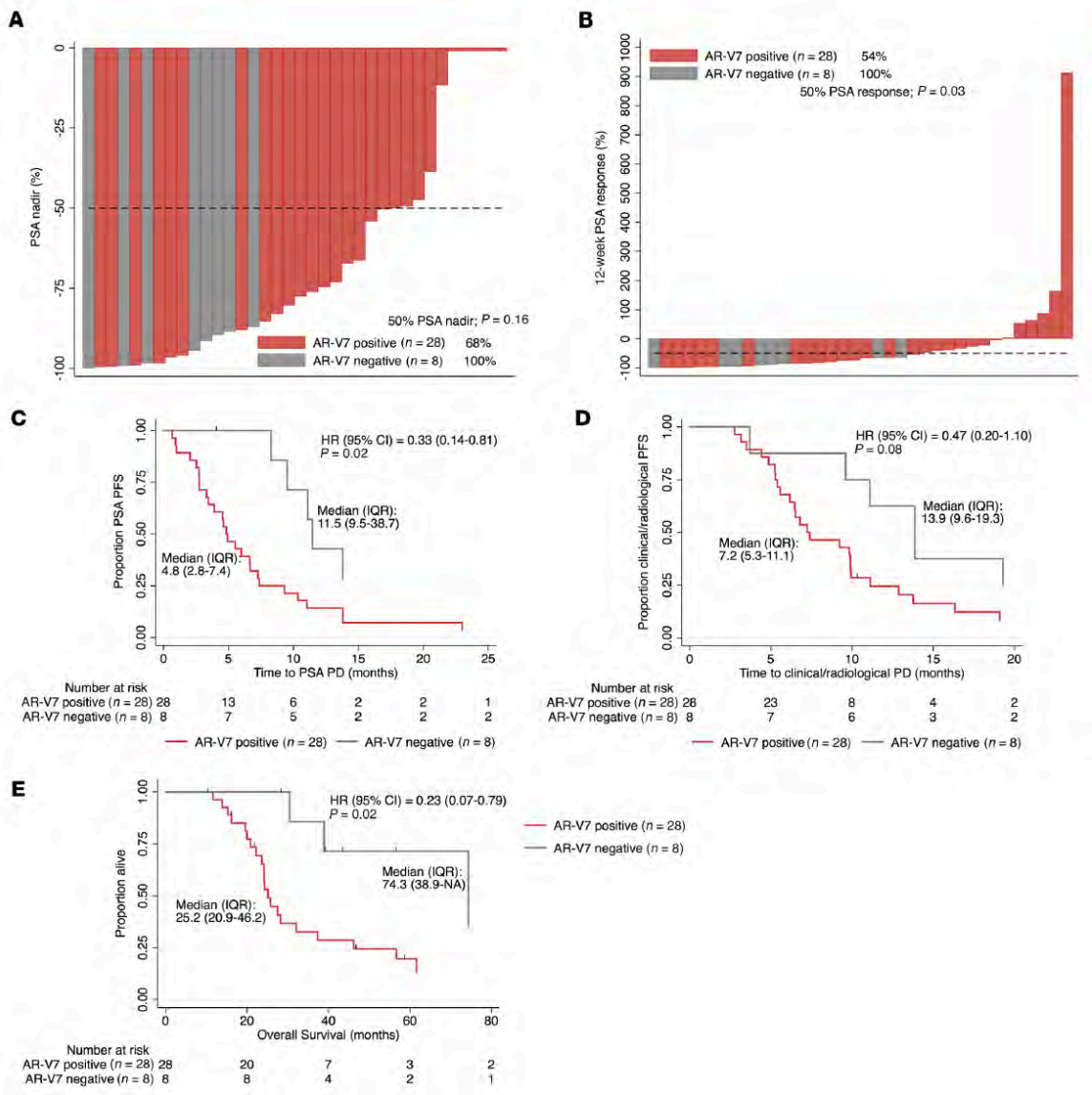
Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer

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

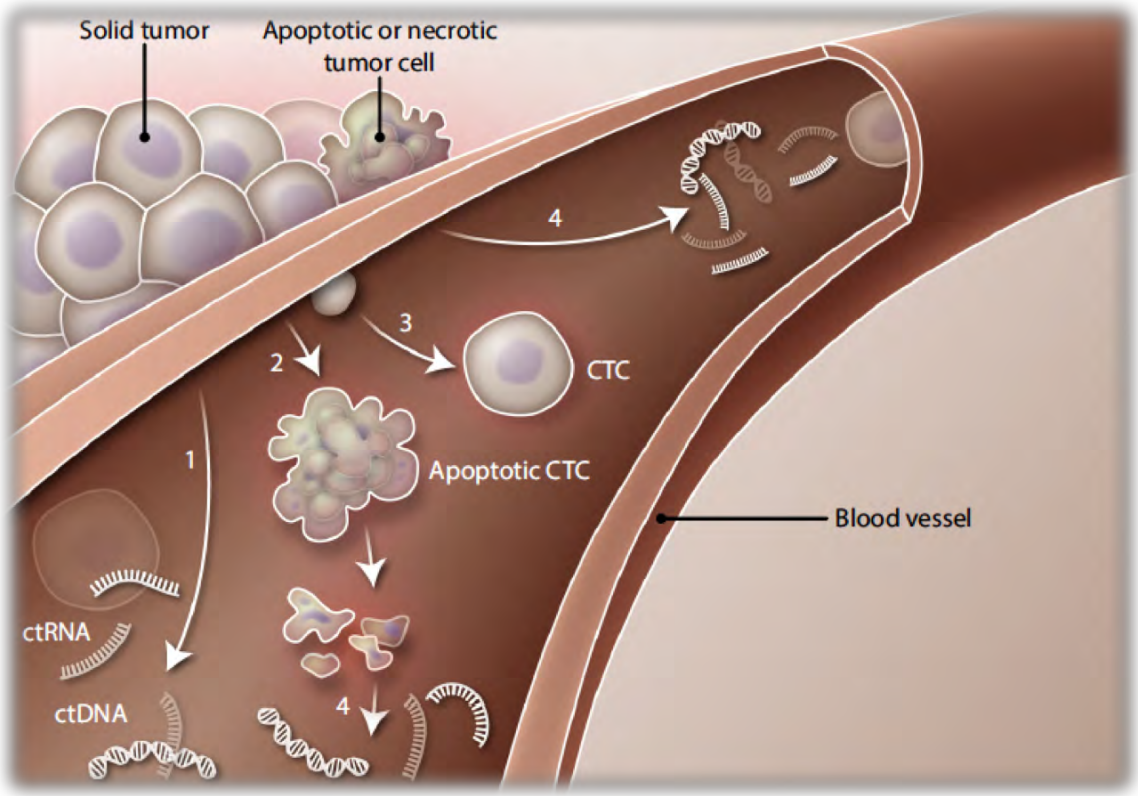
-AR-V7 higher in biopsy as compared to liquid biopsy

-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

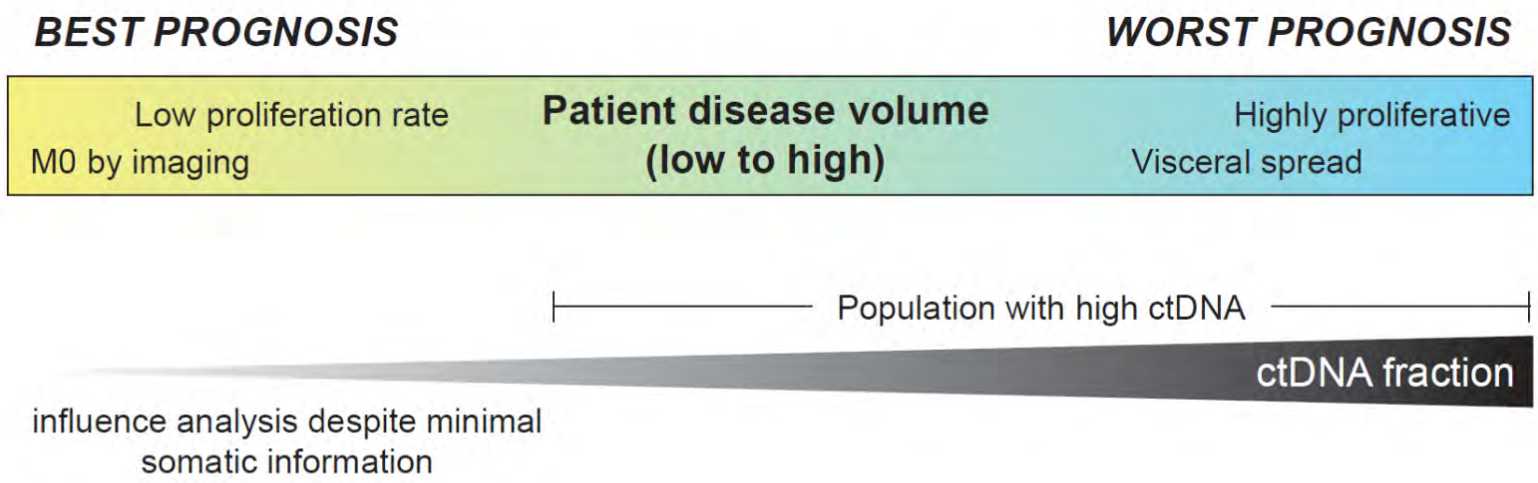
from Schweizer MT and Antonarakis ES, Sci Transl Med. 2015 Nov 4;7(312)

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

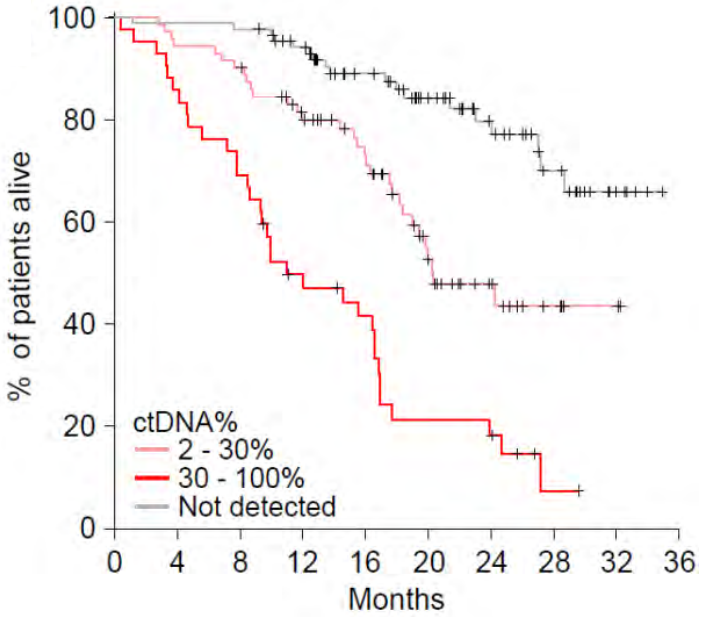


Courtesy of A. Wyatt

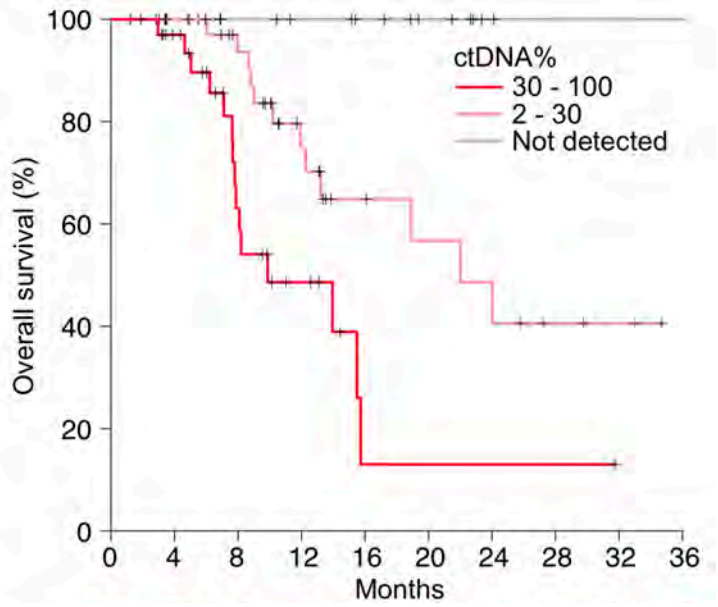
Warner *et al*., BJUI 2018

Prognostic effect of ctDNA fraction in mCRPC

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



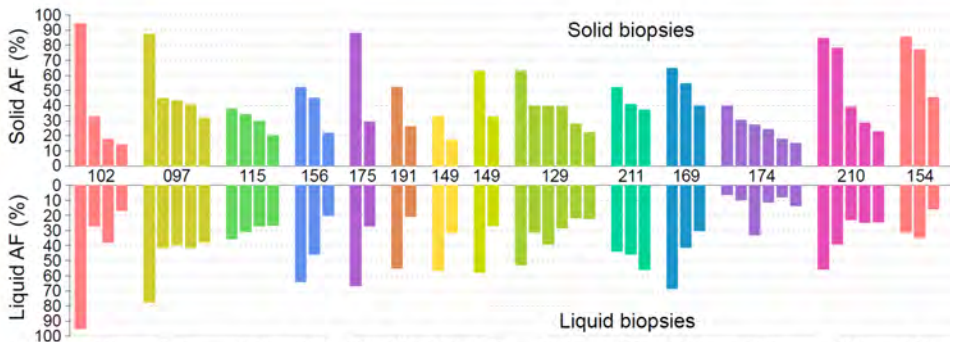
First line mCRPC poor prognosis (n = 95)
Chi et al., ESMO 2018



Courtesy of A. Wyatt

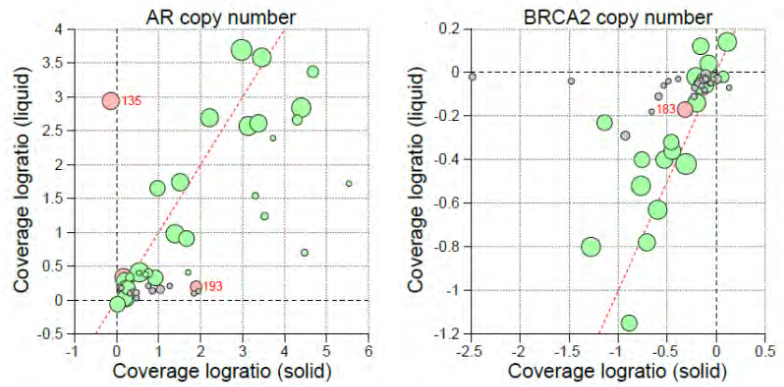
High concordance between ctDNA and matched metastatic tissue biopsy (in CRPC)

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

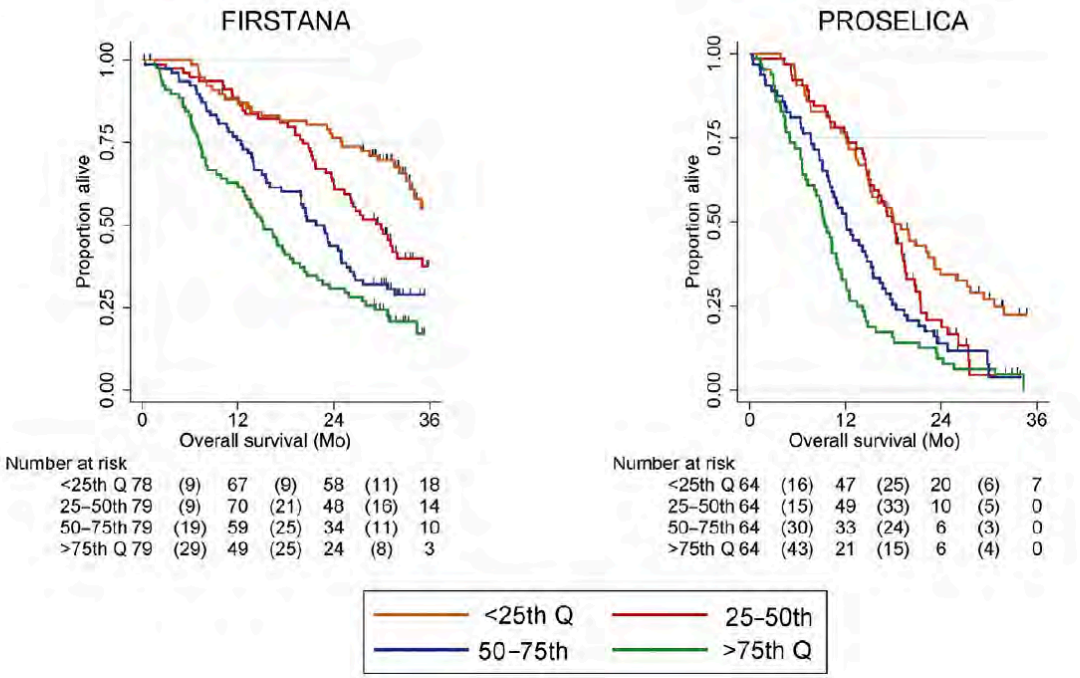
Editorial by Robert J. van Soest, Bertrand Tombal, Martijn P. Lolkema and Ronald de Wit on pp. 292–293 of this issue

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.

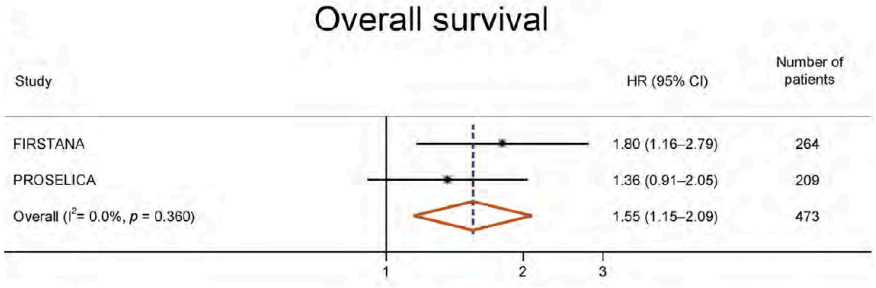
EUR Urol 74 (2 0 18) 2 8 3 – 2 9 1



"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."

-Two phase III clinical trials

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).



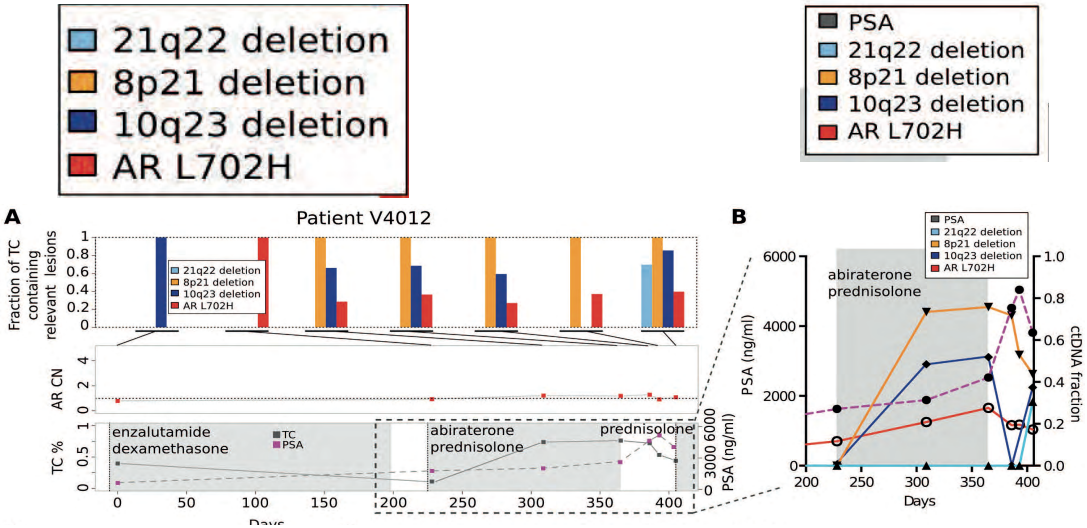
EUR Urol 74 (2 0 18) 2 8 3 – 2 9 1

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

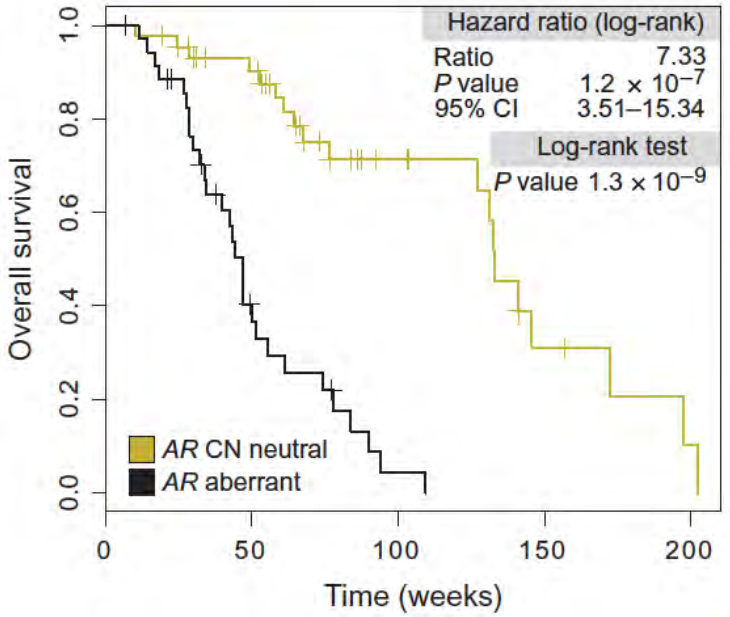
Sci Transl Med **6**, 254ra125 (2014)

REPORT

CANCER

Plasma *AR* and abiraterone-resistant prostate cancer

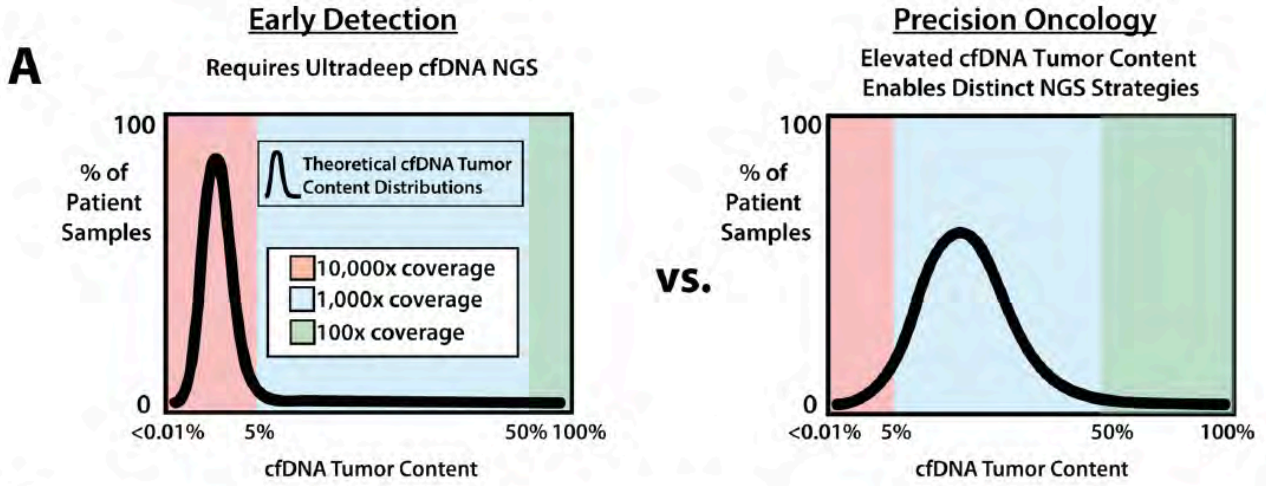
Alessandro Romanel,[1]* Delila Gasi Tandefelt,[2]* Vincenza Conteduca,[2,3] Anuradha Jayaram,[2,4] Nicola Casiraghi,[1] Daniel Wetterskog,[2] Samanta Salvi,[3] Dino Amadori,[3] Zafeiris Zafeiriou,[2,4] Pasquale Rescigno,[2,4] Diletta Bianchini,[2,4] Giorgia Gurioli,[3] Valentina Casadio,[3] Suzanne Carreira,[2] 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

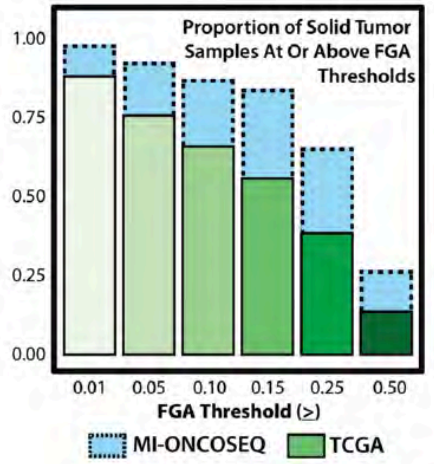
Need to address evolution as a time course with cfDNA, scSeq, molecular imaging, etc.



Research Paper

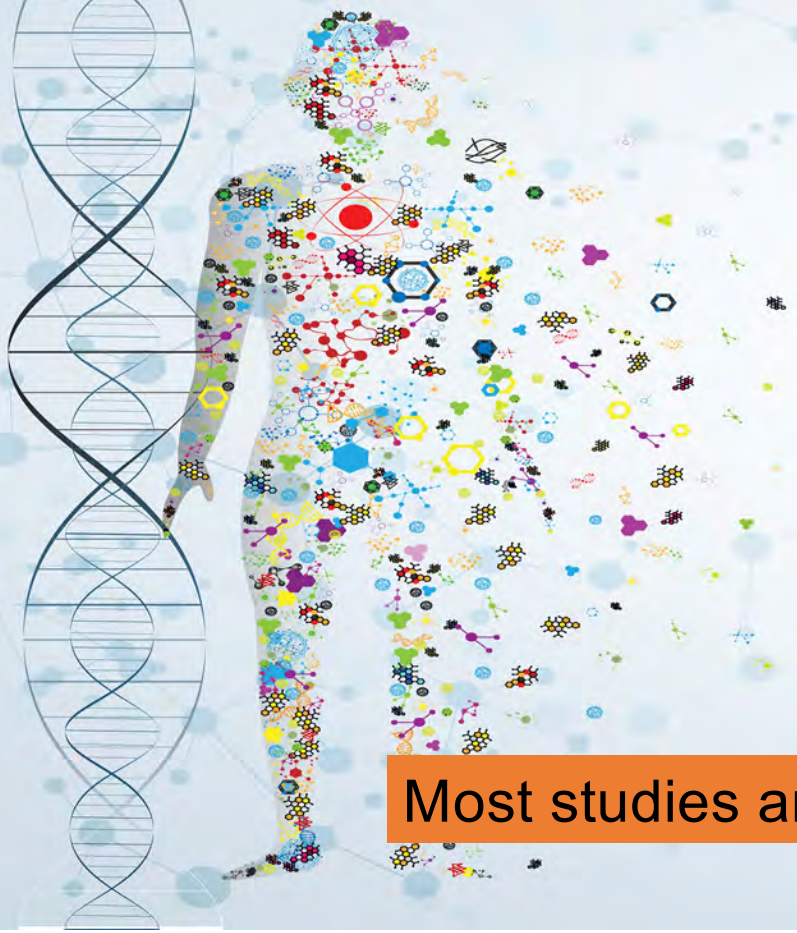
Rapid, ultra low coverage copy number profiling of cell-free DNA as a precision oncology screening strategy

Daniel H. Hovelson[1,2], Chia-Jen Liu[1,3], Yugang Wang[4], Qing Kang[5], James Henderson[4], Amy Gursky[4], Scott Brockman[1], Nithya Ramnath[5], John C. Krauss[5], Moshe Talpaz[5], Malathi Kandarpa[5], Rashmi Chugh[5], Missy Tuck[5], Kirk Herman[5], Catherine S. Grasso[10,11], Michael J. Quist[10,11], Felix Y. Feng[12], Christine Haakenson[13], John Langmore[13], Emmanuel Kamberov[13], Tim Tesmer[13], Hatim Husain[14], Robert J. Lonigro[1,3], Dan Robinson[1,3,8], David C. Smith[5,8], Ajjai S. Alva[5,8], Maha H. Hussain[5,8,15], Arul M. Chinnaiyan[1,3,8,10], Muneesh Tewari[2,5,6,7,8,9], Ryan E. Mills[2,7], Todd M. Morgan[1,4,8,*] and Scott A. Tomlins[1,3,4,8,*]



Oncotarget 2017

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



cfDNA (tumor DNA)

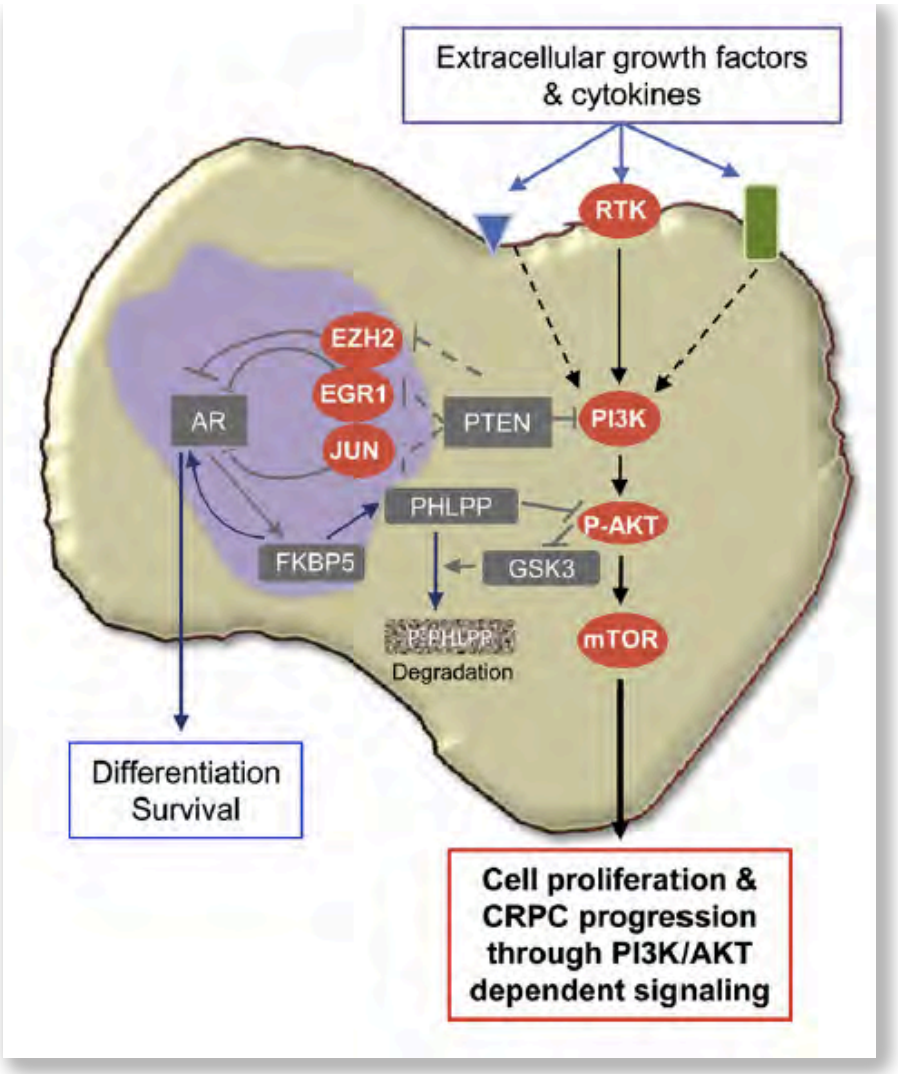
AR-V7

AR gain

AR mutations

Other (neuroendocrine differentiation)

Most studies are not exploring these parameters together

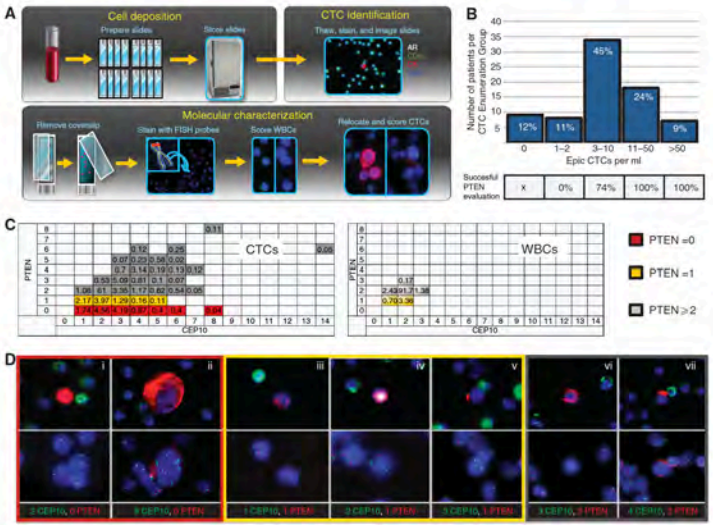


Mulholland et al., Cancer Cell 2011

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]

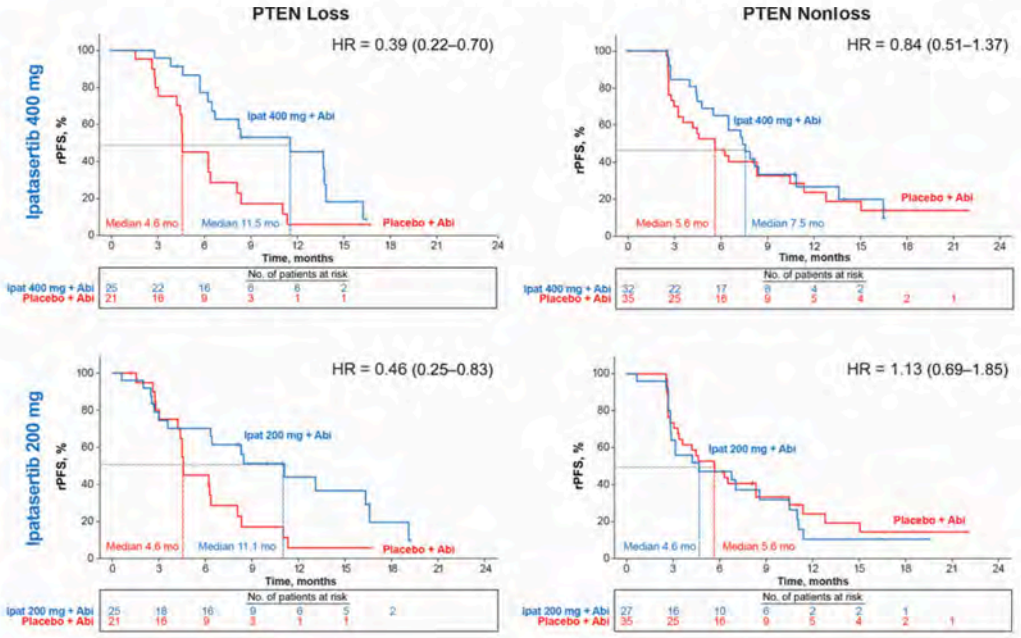
[1]Genentech Inc., South San Francisco, CA, USA; [2]The Royal Marsden National Health Service (NHS) Foundation Trust, Sutton, Surrey, UK; [3]The Institute of Cancer Research, London, UK; [4]Epic Sciences Inc., San Diego, CA, USA and [5]Core Diagnostics, Palo Alto, CA, USA



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]

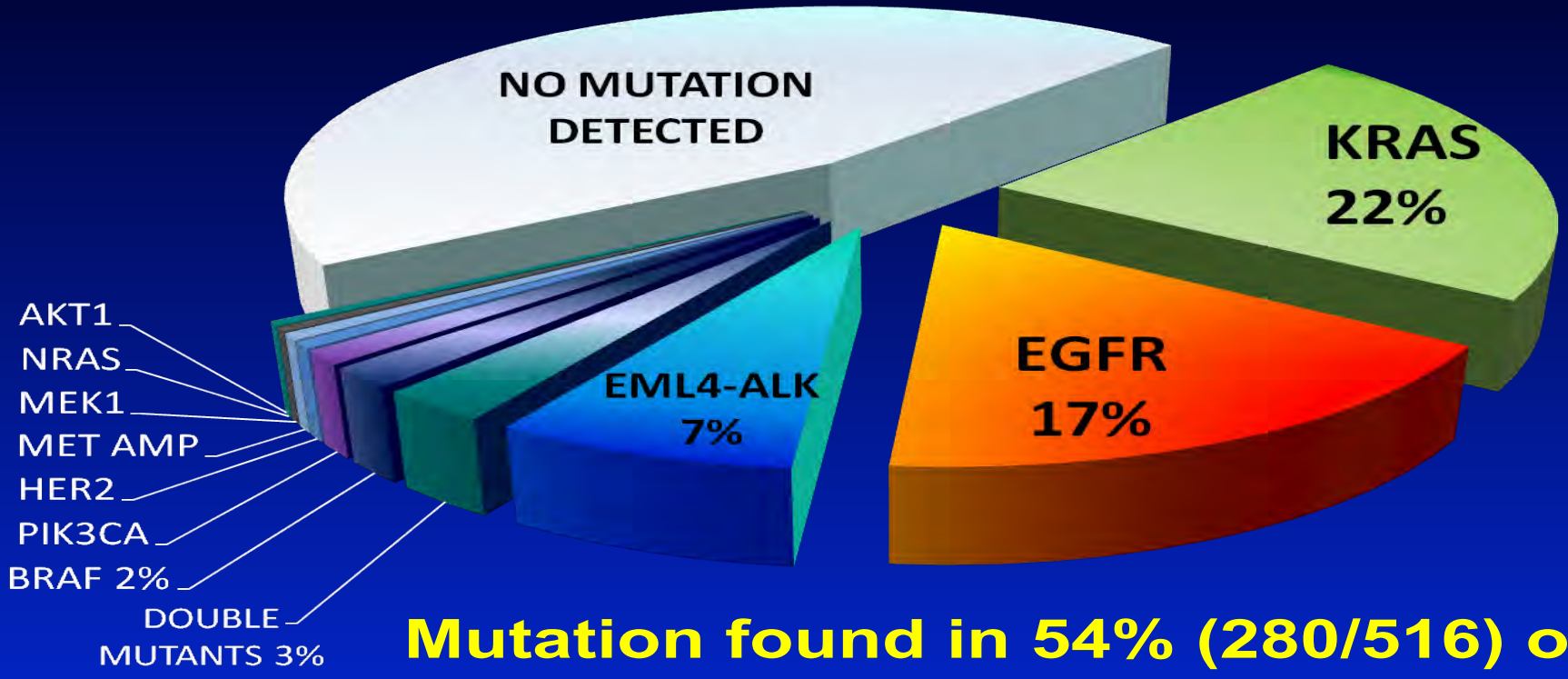


Clin Cancer Res; 25(3) February 1, 2019

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%)

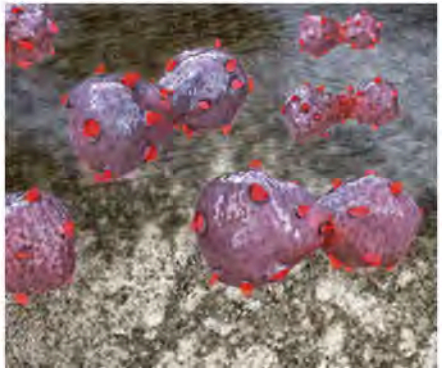
CANCER RESEARCH

The Official Blog of the American Association for Cancer Research

FDA Approves First Liquid Biopsy Test for Lung Cancer Patients

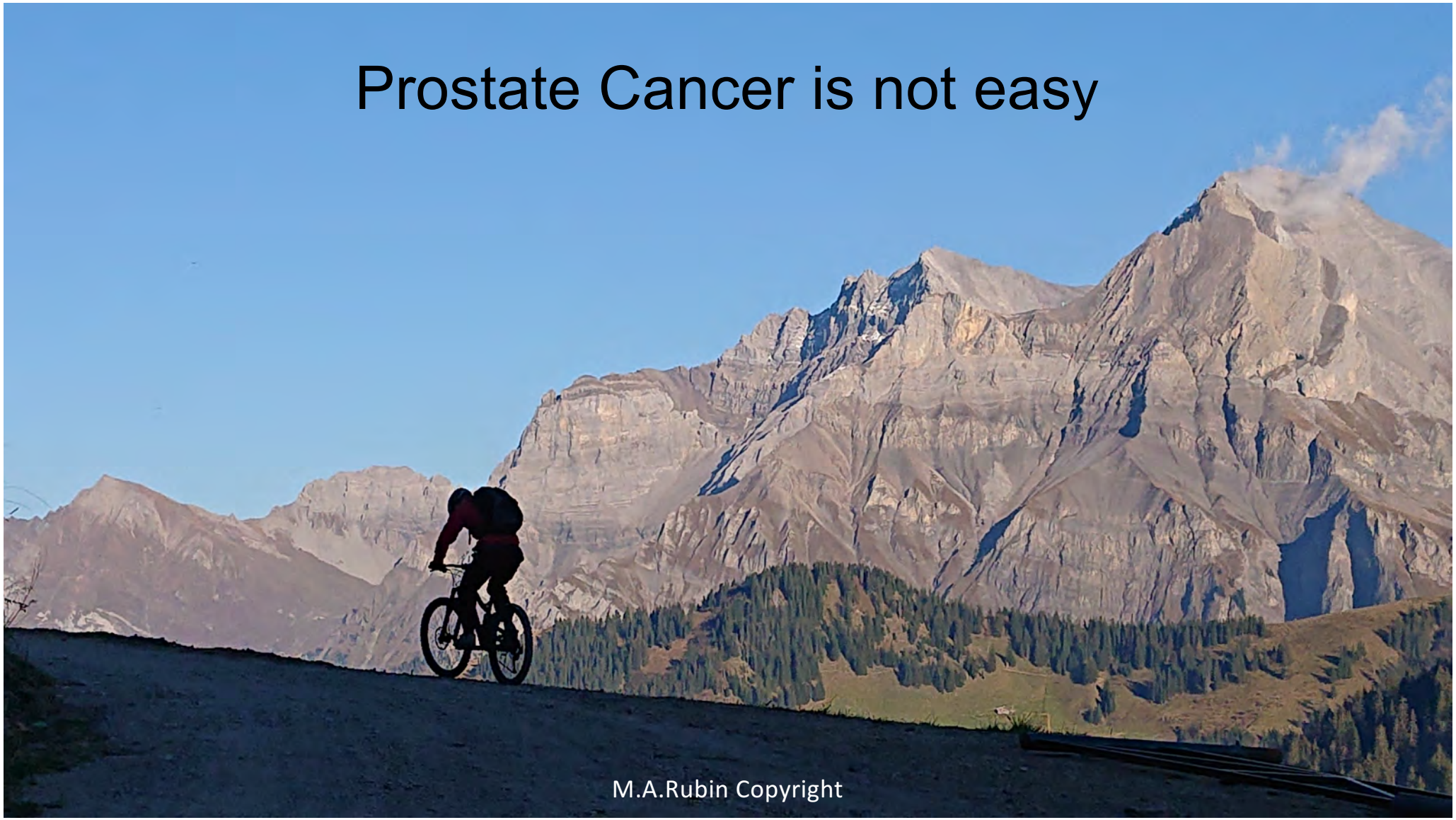
Posted on June 6, 2016 by Srivani Ravoori, PhD

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."


Prostate Cancer is not easy
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In conclusion:

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

Need prospective validation

-Blood/biopsy/cfDNA DNA repair BRCA1/2, ATM (multiple clinical tests)
-CTC for AR v7 (Available via CTC Episciences)
-Metastatic biopsy - AR gain (multiple tests)
-cfDNA for DNA fraction, AR, others

Approved by FDA (Not Prostate Specific)

-MSI/MMR (multiple tests)-clinical ready/FDA indication broad


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Thanks for your input on this presentation

Alex Wyatt
Gert Attard
Pete Nelson
Johann de Bono
Colin Pritchard

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