Homogenising genomic reports: What clinicians need to know

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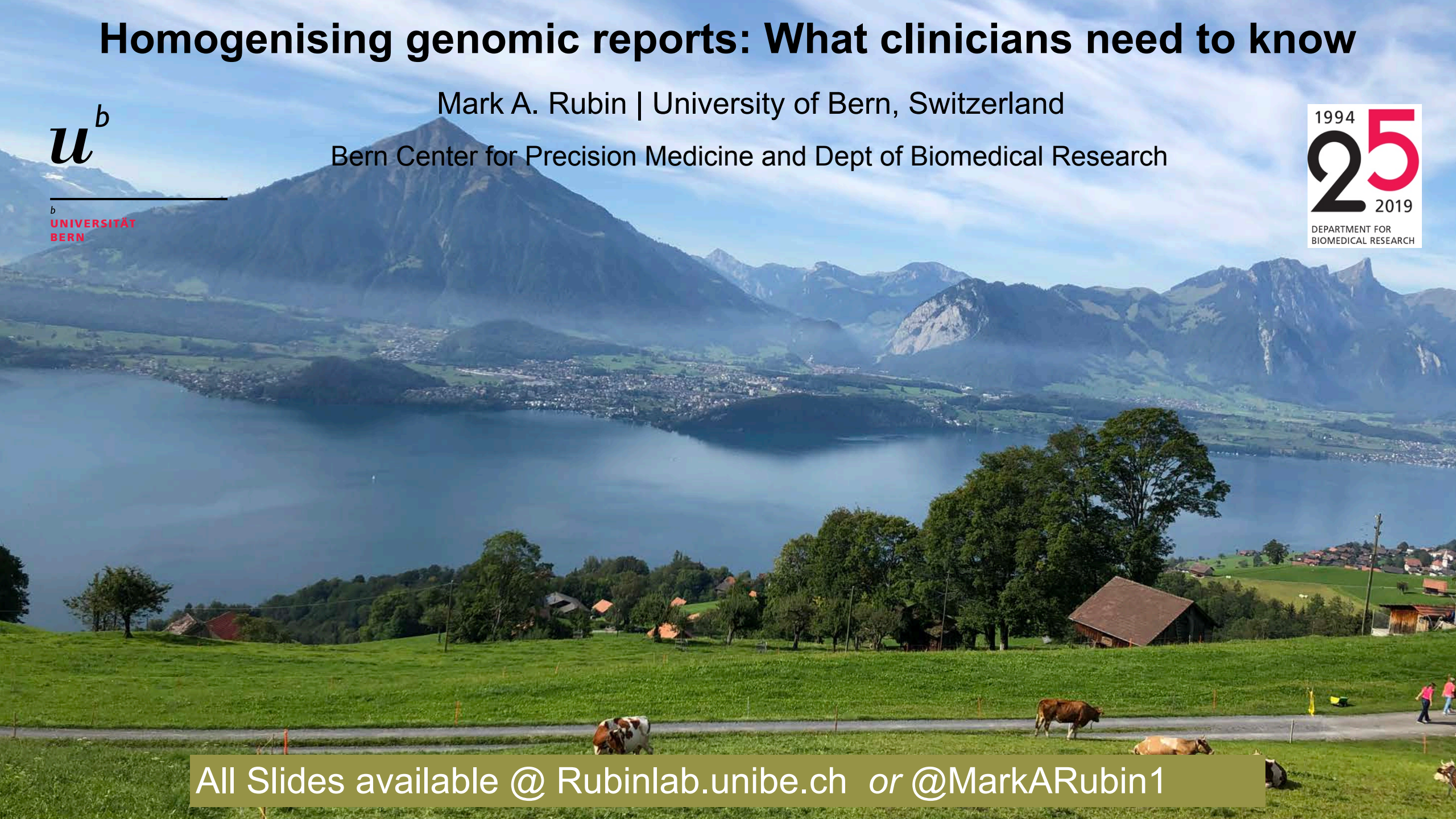


All Slides available @ Rubinlab.unibe.ch *or* @MarkARubin1

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.

Overview of what will be covered

- Definitions of types of tests (predictive vs prognostic)
- Critical types of materials and diagnostics tests
- Setting (early or late disease states)
- What type of information is needed (example of MSKCC system)
- What do reports look like (Two examples)
- Germline Testing (Covered separately)
- Liquid Biopsies

Germline testing is covered separately

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

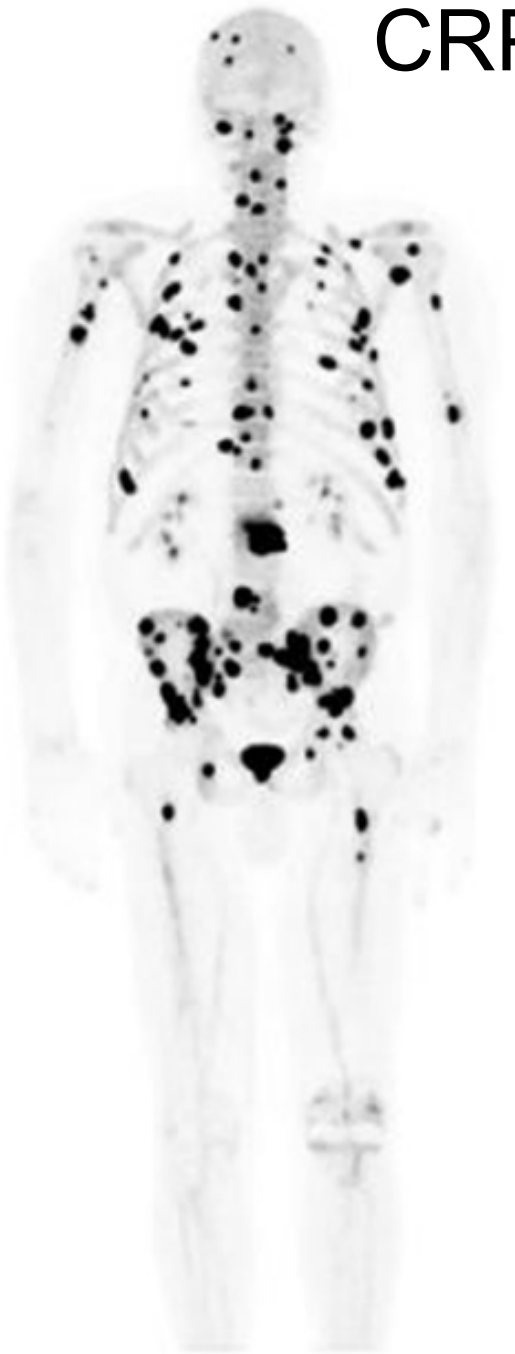
Definitions

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

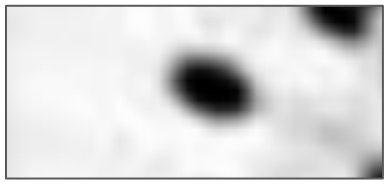


CRPC Patient and acquisition of samples for testing

Buccal sample

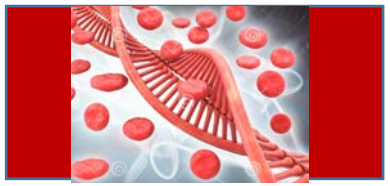
Germline DNA
Genetic testing (e.g., BRCA1/2)
Control normal sample for genomics

Tumor sample



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

Blood sample



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

OncoKB: A Precision Oncology Knowledge Base

Chakravarty et al., JCO PO 2017

OncoKB

Precision Oncology Knowledge Base

642	4932	45	89
Genes	Alterations	Tumor Types	Drugs

Search Gene / Alteration / Drug

Level 1	Level 2	Level 3	Level 4	Level R1	Level R2
FDA-approved	Standard care	Clinical evidence	Biological evidence	Standard care	Clinical evidence
25 Genes	13 Genes	30 Genes	20 Genes	5 Genes	6 Genes

When using OncoKB, please cite: Chakravarty et al., JCO PO 2017.

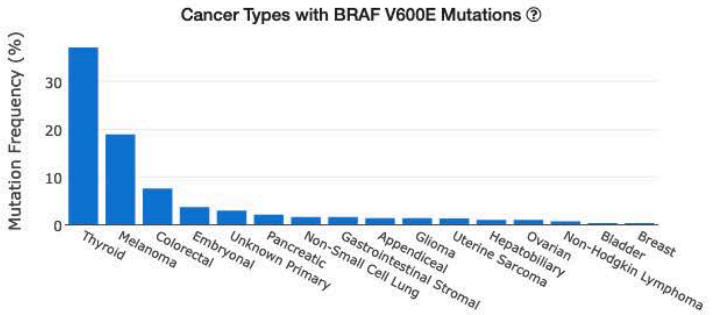
Chakravarty et al., JCO PO 2017

BRAF V600E

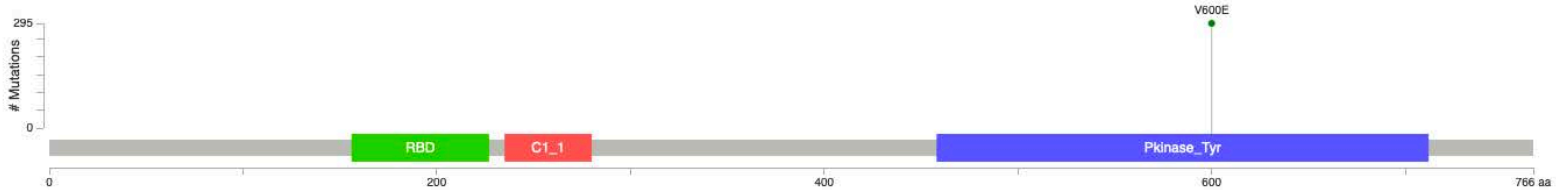
Oncogenic · Gain-of-function , Level 1

BRAF, an intracellular kinase, is frequently mutated in melanoma, thyroid and lung cancers among others. The BRAF V600E mutation is known to be oncogenic.

See additional BRAF information



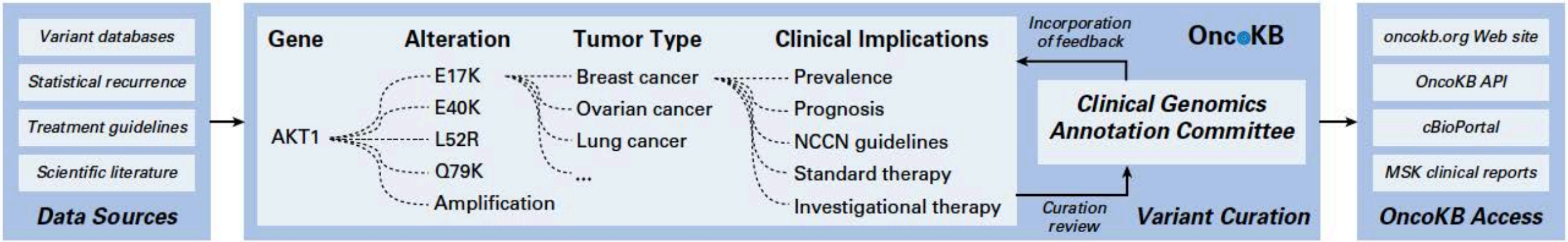
Annotated Mutation Distribution in MSK-IMPACT Clinical Sequencing Cohort (Zehir et al., Nature Medicine, 2017)



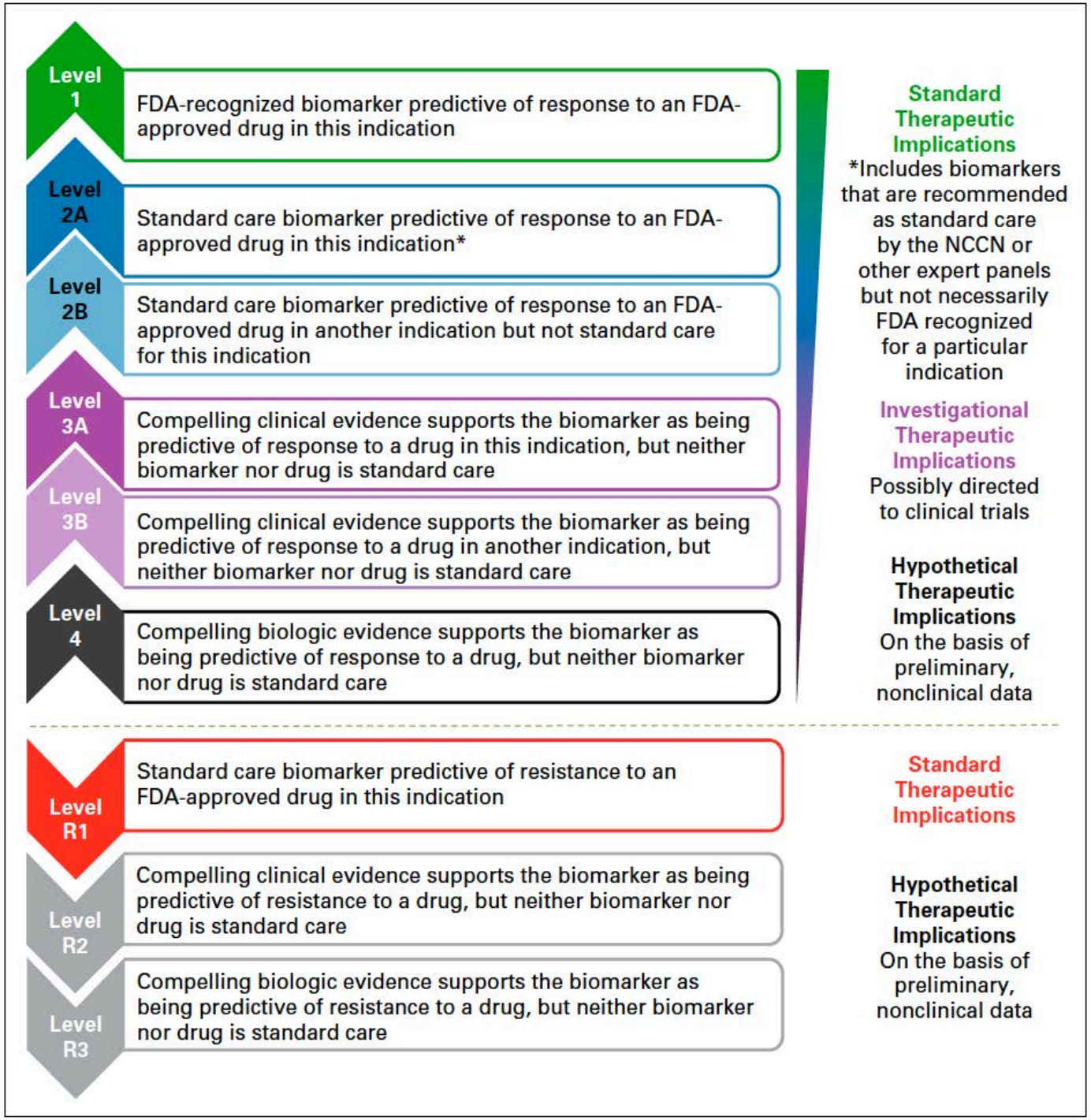
Search:

▲ Alteration	Cancer Type	Drug(s)	▼ Level	Citations
Oncogenic Mutations	Histiocytosis	Cobimetinib	3A	2 references
V600E	Anaplastic Thyroid Cancer	Dabrafenib + Trametinib	1	1 reference
V600E	Melanoma	Vemurafenib Dabrafenib Dabrafenib + Trametinib Vemurafenib + Cobimetinib Trametinib Encorafenib + Binimetinib	1	16 references
V600E	Non-Small Cell Lung Cancer	Dabrafenib + Trametinib	1	2 references
V600E	Hairy Cell Leukemia	Vemurafenib	2A	1 reference
V600E	Colorectal Cancer	Encorafenib + Binimetinib + Cetuximab Panitumumab + Dabrafenib + Trametinib	2A	2 references
V600K	Melanoma	Dabrafenib + Trametinib Vemurafenib + Cobimetinib Trametinib Encorafenib + Binimetinib	1	11 references
V600	Erdheim-Chester Disease	Vemurafenib	1	2 references
		Vemurafenib + Panitumumab		

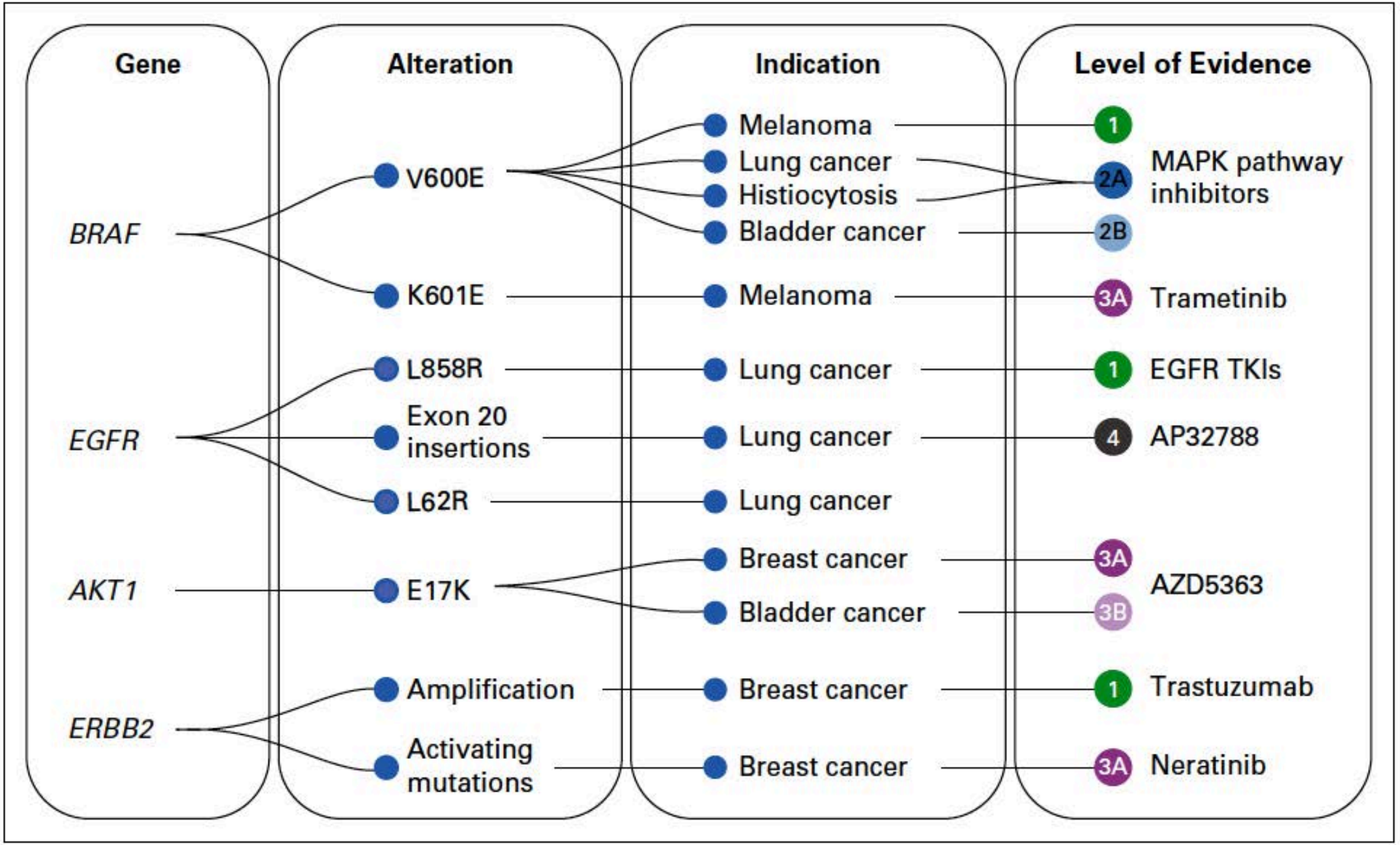
Chakravarty et al., JCO PO 2017



Chakravarty et al., JCO PO 2017

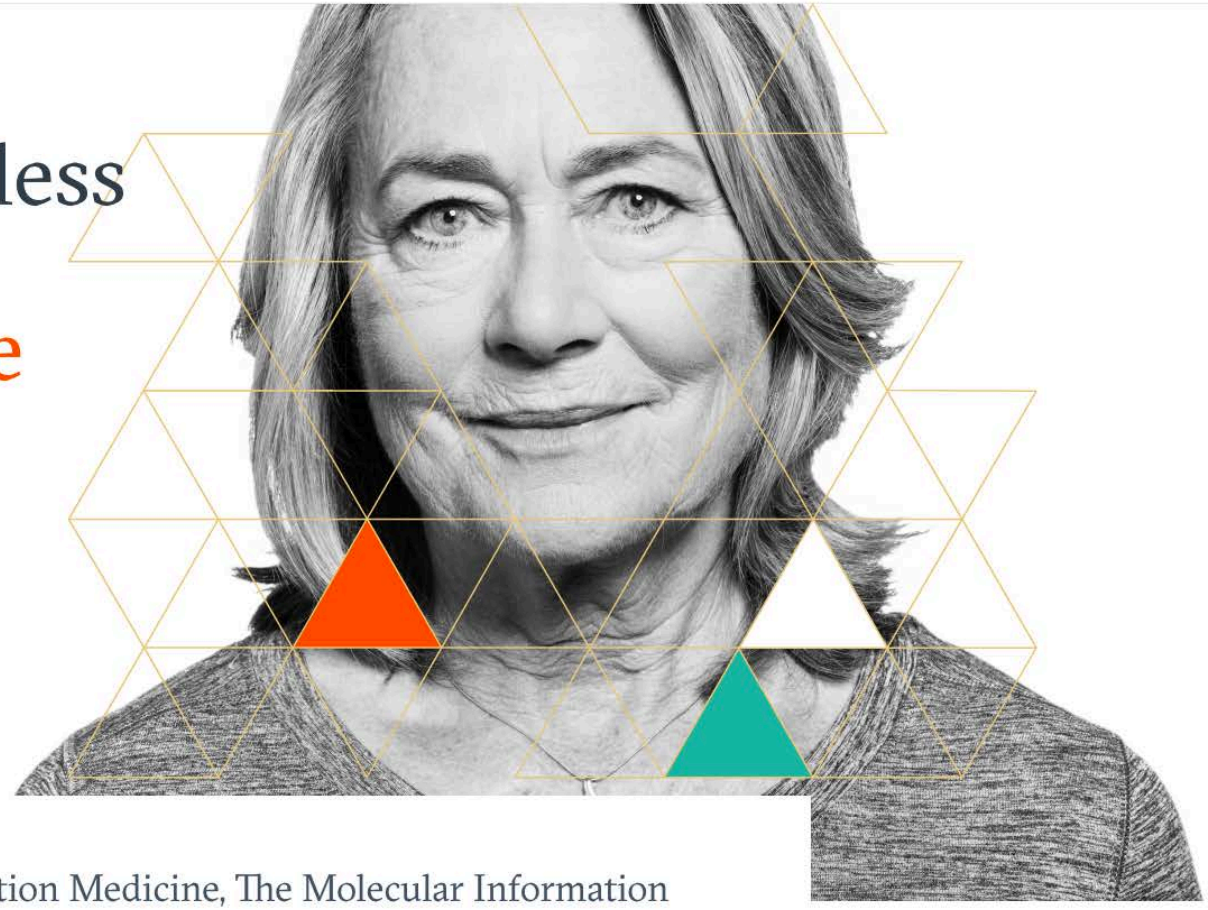


Chakravarty et al., JCO PO 2017



Chakravarty et al., JCO PO 2017

The Relentless Pursuit of Better Care



WE NEVER GIVE UP. We strive to do more for cancer patients - through richer science, deeper insights, and stronger partnerships - providing better cancer care today, and fueling better cancer care tomorrow.

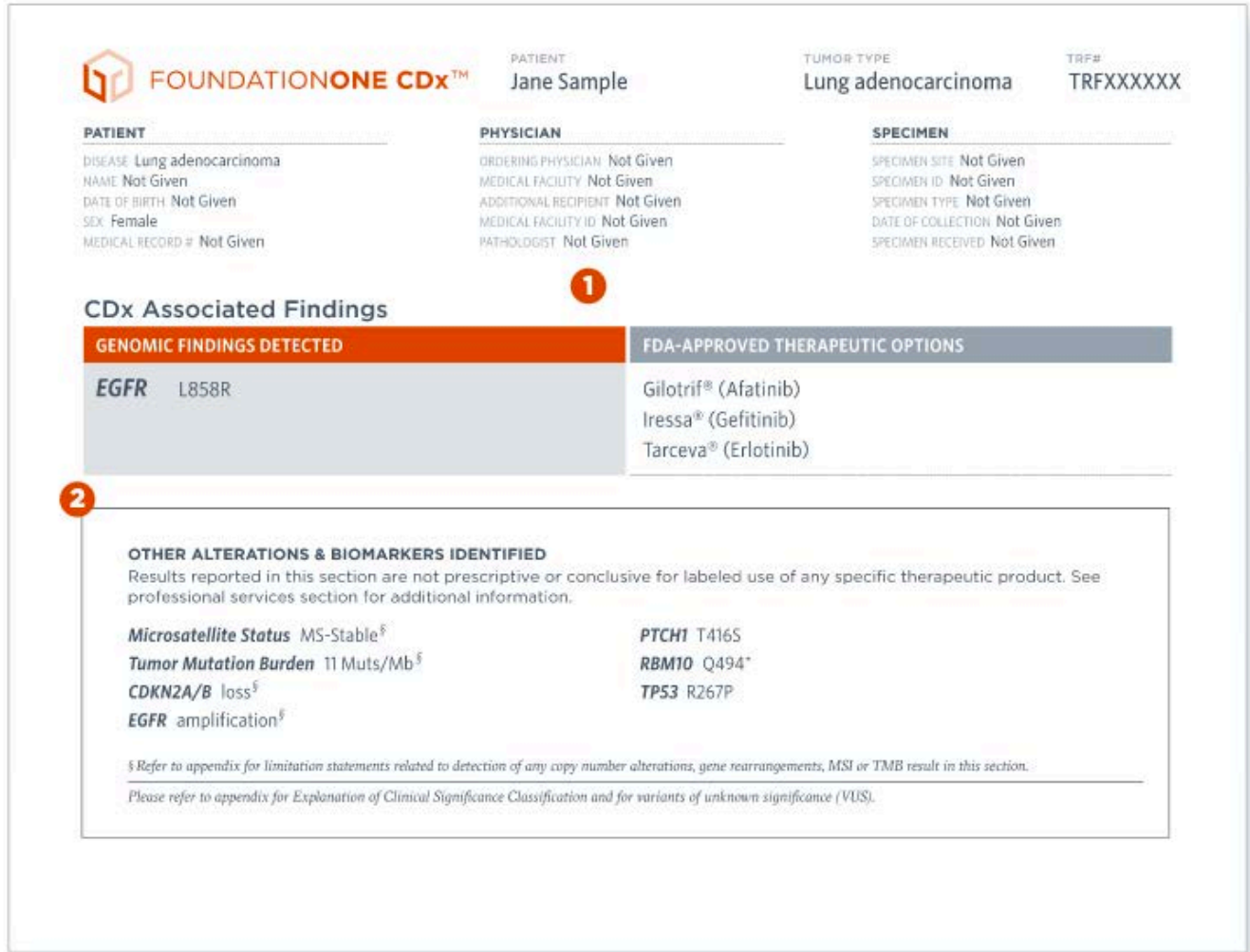
PATIENT INFORMATION HERE ▸

Foundation Medicine, The Molecular Information Company, is connecting physicians and their patients to the latest cancer treatment approaches and making precision medicine a reality for thousands.

Better Care Today

FDA-Approved Content

Report Section 1



FOUNDATIONONE CDx™

PATIENT Jane Sample

TUMOR TYPE Lung adenocarcinoma

TRF# TRFXXXXXX

PATIENT
DISEASE Lung adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Female
MEDICAL RECORD # Not Given

PHYSICIAN
ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN
SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

1

CDx Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR L858R	Gilotrif® (Afatinib) Iressa® (Gefitinib) Tarceva® (Erlotinib)

2

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED
Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for additional information.

Microsatellite Status MS-Stable§
Tumor Mutation Burden 11 Muts/Mb§
CDKN2A/B loss§
EGFR amplification§
PTCH1 T416S
RBM10 Q494*
TP53 R267P

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

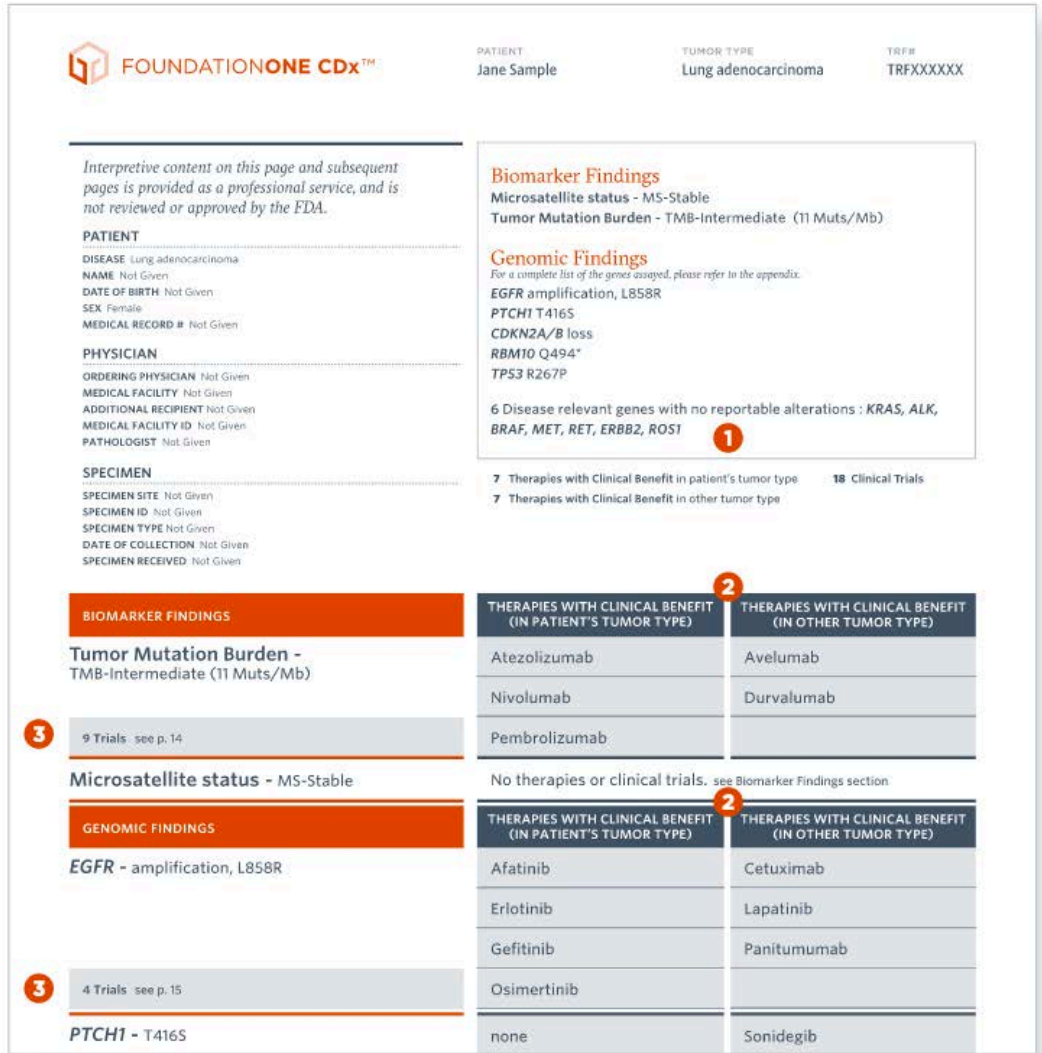
Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

1 **FDA-Approved Therapies**
List of FDA-approved companion diagnostics to identify patients who may benefit from associated therapies

2 **All Other Biomarkers**
All other biomarkers, including tumor mutational burden (TMB) and microsatellite instability (MSI), without companion diagnostic claims

Professional Services

Report Section 2



FOUNDATIONONE CDx™

PATIENT Jane Sample | TUMOR TYPE Lung adenocarcinoma | TRF# TRFXXXXXX

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT
DISEASE Lung adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Female
MEDICAL RECORD # Not Given

PHYSICIAN
ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN
SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Biomarker Findings
Microsatellite status - MS-Stable
Tumor Mutation Burden - TMB-Intermediate (11 Muts/Mb)

Genomic Findings
For a complete list of the genes assayed, please refer to the appendix.
EGFR amplification, L858R
PTCH1 T416S
CDKN2A/B loss
RBM10 Q494*
TP53 R267P

6 Disease relevant genes with no reportable alterations : ***KRAS, ALK, BRAF, MET, RET, ERBB2, ROS1*** (1)

7 Therapies with Clinical Benefit in patient's tumor type
7 Therapies with Clinical Benefit in other tumor type
18 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) (2)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutation Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab	Avelumab
	Nivolumab	Durvalumab
(3) 9 Trials see p. 14	Pembrolizumab	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) (2)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
EGFR - amplification, L858R	Afatinib	Cetuximab
	Erlotinib	Lapatinib
	Gefitinib	Panitumumab
(3) 4 Trials see p. 15	Osimertinib	
PTCH1 - T416S	none	Sonidegib

(1) **Pertinent Negatives**
Identifies important negative results that can be used for patient management

(2) **Therapies with Clinical Benefit**
Interpretive content that can be used for patient management according to professional guidelines in oncology

(3) **Clinical Trials**
Identifies trials based on patients' unique genomic profile with page number for quick reference

Genomic Prostate Score® (GPS™) Report

oncotype DX® Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **19-Apr-1961** Gender: **Male** Report Number: **OR000123456-01** Report Date: **23-May-2019**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

GPS + NCCN®[1] : Very Low Risk

Clinical Interpretation	Clinical Endpoints	Individualized Risk (95% Confidence Interval [CI])
The combination of GPS and clinical features predicts that this patient's risk is consistent with **NCCN Very Low Risk** disease.‡ In a clinical validation study including patients with NCCN Very Low, Low, and Intermediate Risk, **no patient with a GPS result <20 had metastasis or died** from prostate cancer within 10 years.†	**Prostate Cancer Death Within 10 Years**†	<1% (95% CI: <1% - <1%)
	Metastasis Within 10 Years†§	1% (95% CI: <1% - 4%)
	Adverse Pathology† (Gleason ≥ 4+3 and/or pT3+)	16% (95% CI: 12% - 21%)

NCCN Risk Group‖ **: Low**

Physician-Provided Information¶ **:**

Gleason Score: **3+3**	Prostate Volume (cc): **23**
PSA (ng/mL): **5.0**	PSA Density (ng/mL/cc): **0.22**
Clinical Stage: **T1c**	Number of cores positive: **4**
Max. % of tumor involvement in any core: **≤ 50%**	Number of cores collected: **12**

Leverage adverse pathology to assess tumor aggressiveness and inform immediate treatment decisions[1,2]

Adverse pathology is the presence of high-grade (Gleason Score >4 + 3) and/or non-organ-confined disease (pT3+). It provides an immediate snapshot of the **risk of aggressive disease** at the time of biopsy.

Biopsy alone often misses patients with high risk of adverse pathology.

Predicts BOTH clinical risk and tumor aggressiveness

The Oncotype DX Genomic Prostate Score test provides a comprehensive risk profile for personalized information to guide treatment decisions.

Oncotype DX GPS assay is proven to be an independent predictor of:

Genomic Prostate Score® (GPS™) Report

oncotype DX®
Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **19-Apr-1961** Gender: **Male** Report Number: **OR000123456-01** Report Date: **23-May-2019**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

Medical Record/Patient #: **1234567-01**

Specimen Source/ID: **Prostate/SP-16_0123456**

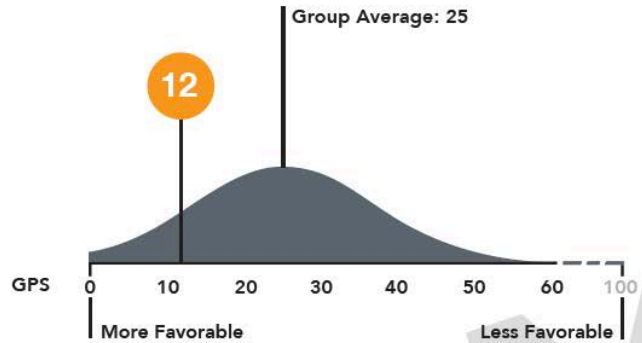
Date of Collection: **29-Apr-2019**

Specimen Received: **1-May-2019**

Additional Recipient: **Dr. First-Name I. Recipient-Physician-Last-Name**

Pathologist: **Dr. First-Name I. Pathologist-Last-Name**

GPS Distribution in NCCN® Low Risk[2,3,5]

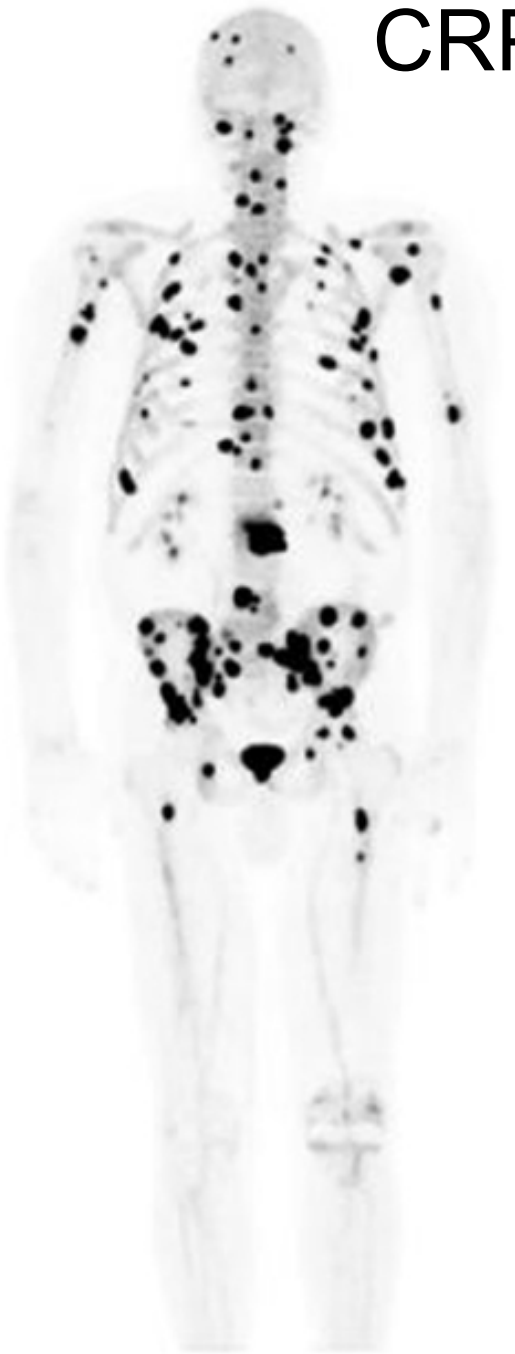


Pathology Endpoints**	Individualized Risk (95% Confidence Interval [CI])
High-Grade Disease (Gleason ≥4+3)	9% (95% CI: 6% - 13%)
Non-Organ-Confined Disease (pT3+)	10% (95% CI: 7% - 15%)

This patient has a GPS result that is **lower than the average GPS result** for NCCN Low Risk.

The Oncotype DX Genomic Prostate Score (GPS) test is a continuous scale (0-100) that quantifies expression of 17 genes in tumor tissue as assessed by RT-PCR. The GPS test has been validated in three prospectively designed studies (N=1056) of biopsy tissue from patients with localized prostate cancer.[2,3,5]

Adverse pathology refers to the finding of an aggressive tumor (high grade) or cancer spread outside of the prostate (non-organ confined). Tumors with a low risk of adverse pathology are less likely to be aggressive and spread.

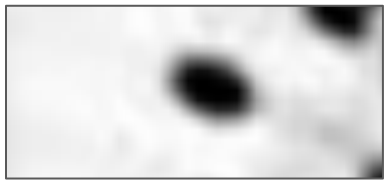


CRPC Patient and acquisition of samples for testing

Buccal sample

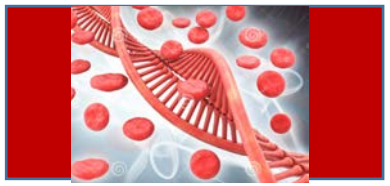
Germline DNA
Genetic testing (e.g., BRCA1/2)
Control normal sample for genomics

Tumor sample



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

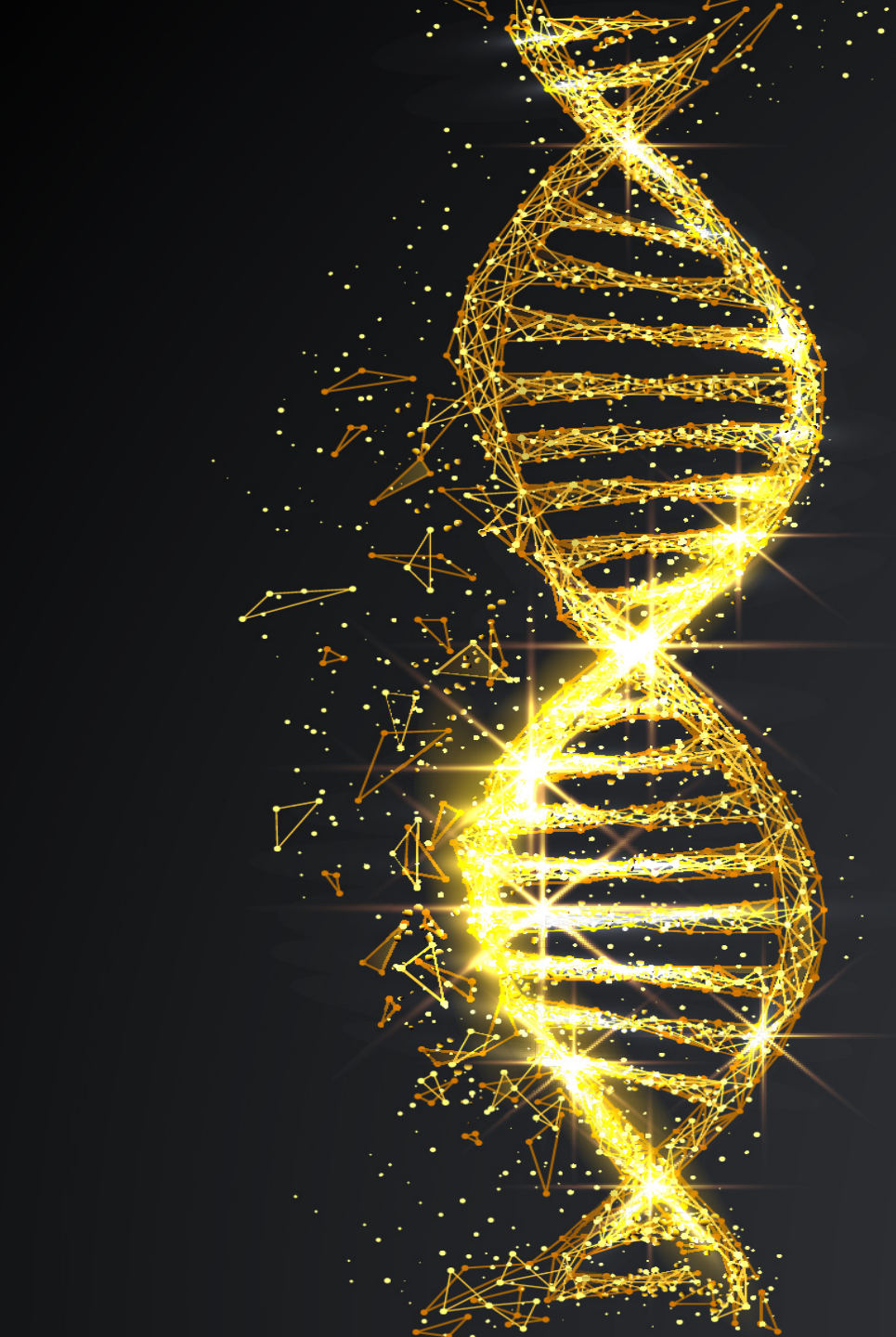
Blood sample



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

Advanced Prostate Cancer

5%, 10%, and 20%



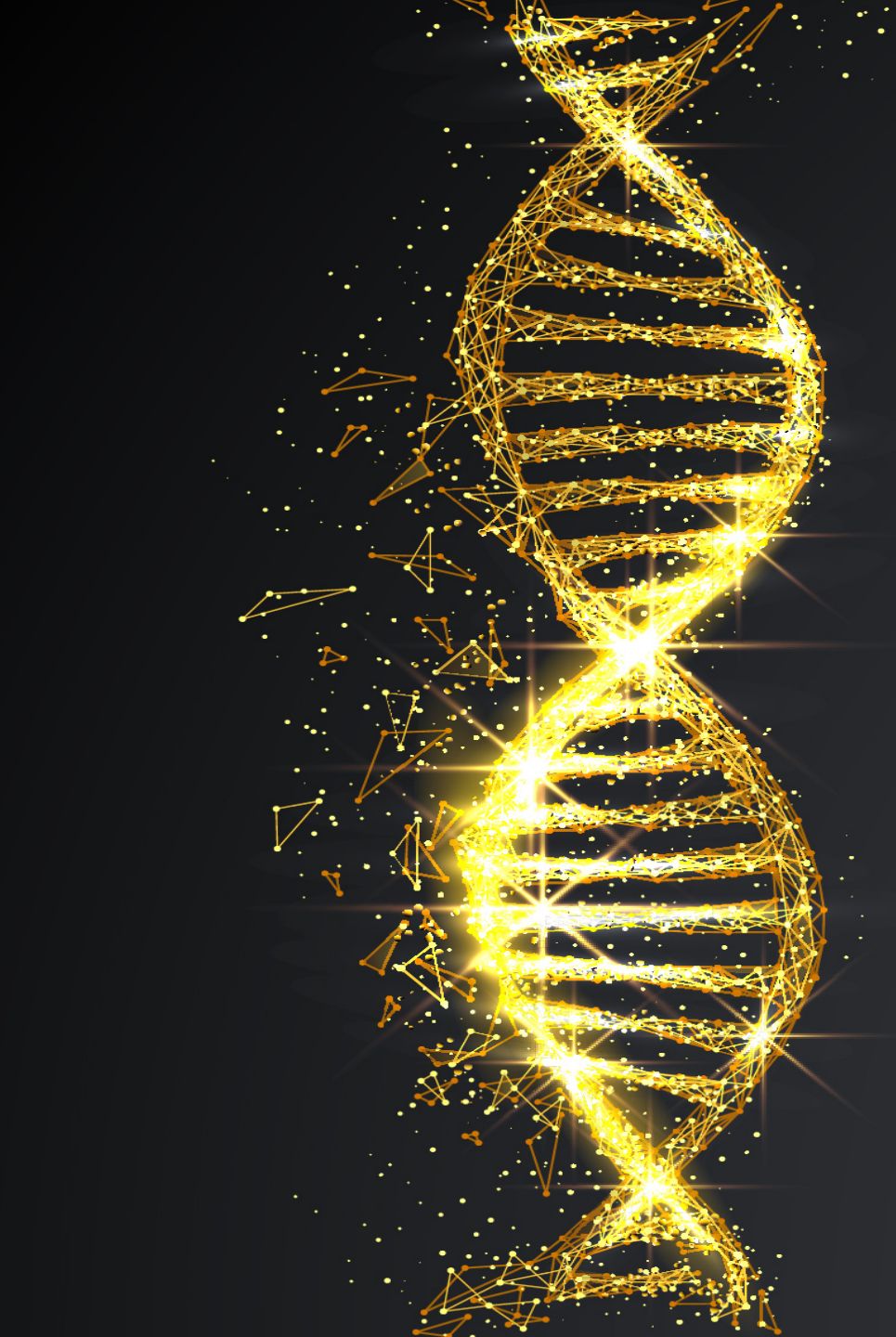
Advanced Prostate Cancer

5%, 10%, and 20%

5% have MSI or MMR alterations

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

20% have DRM somatic-germline



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

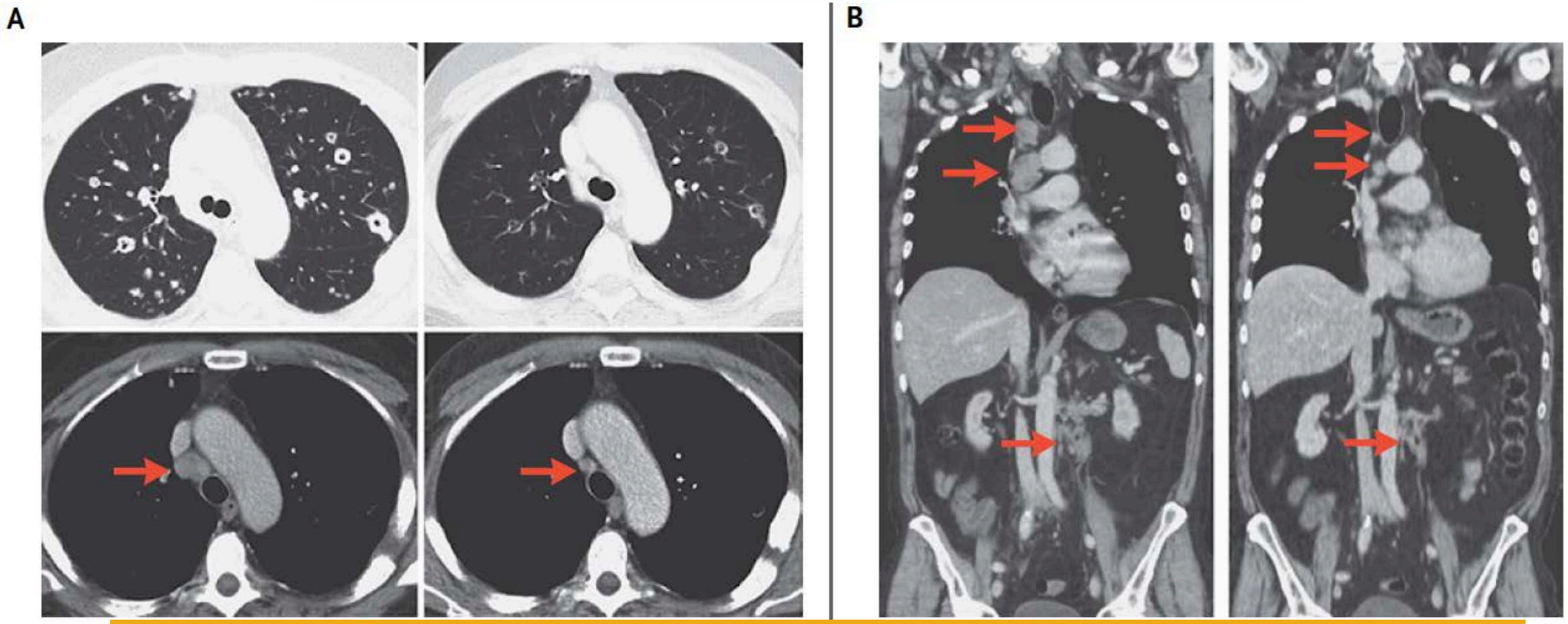
PARPi or Platinum-based Tx

The NEW ENGLAND JOURNAL of MEDICINE

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

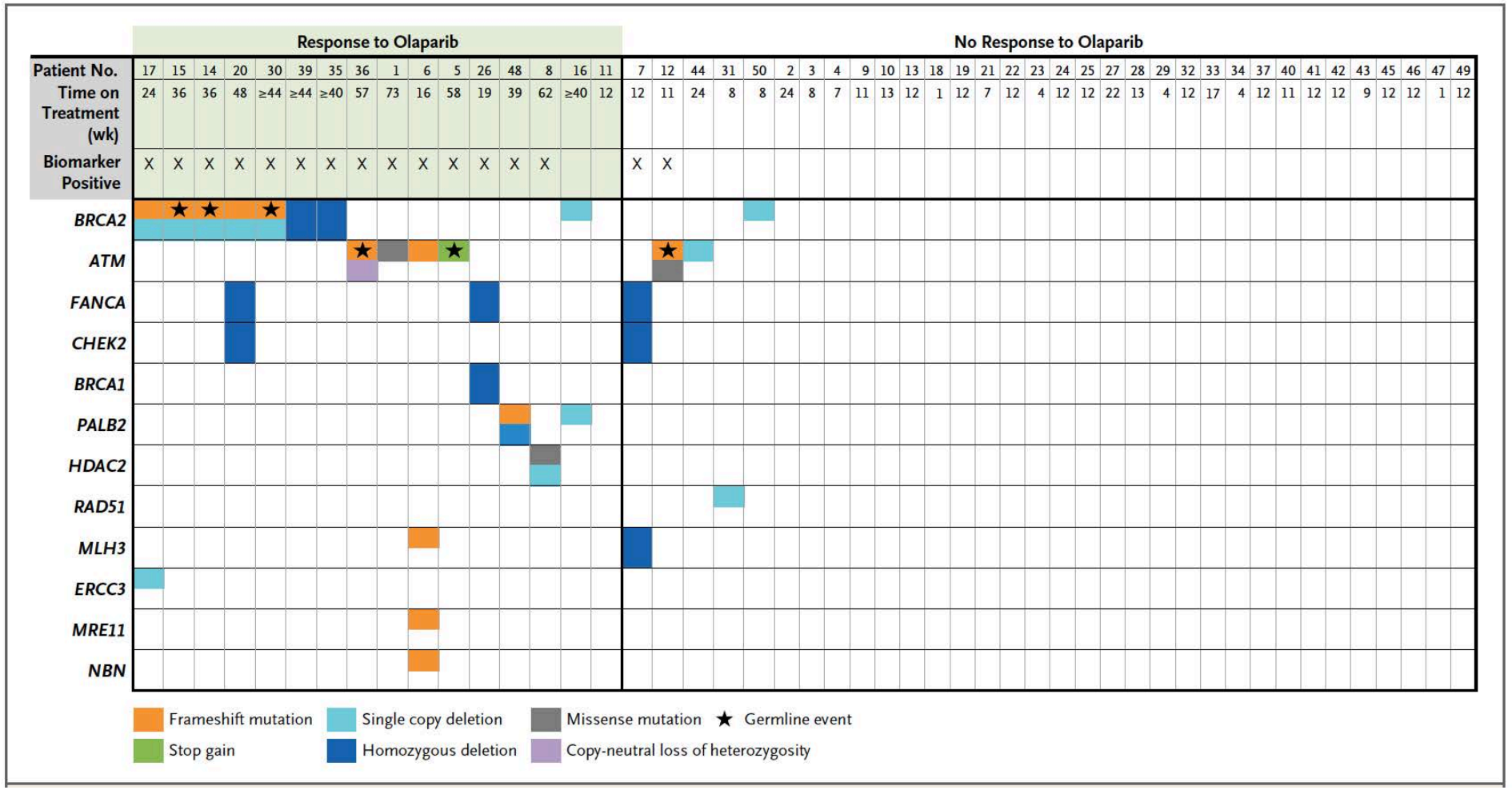
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

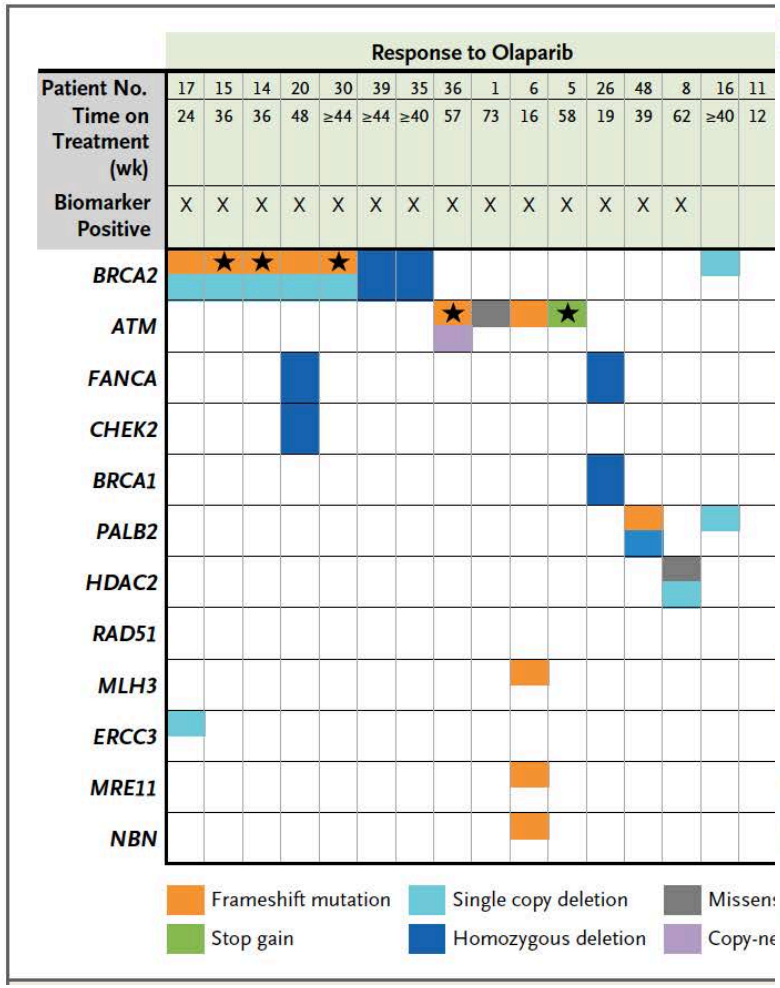
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini,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

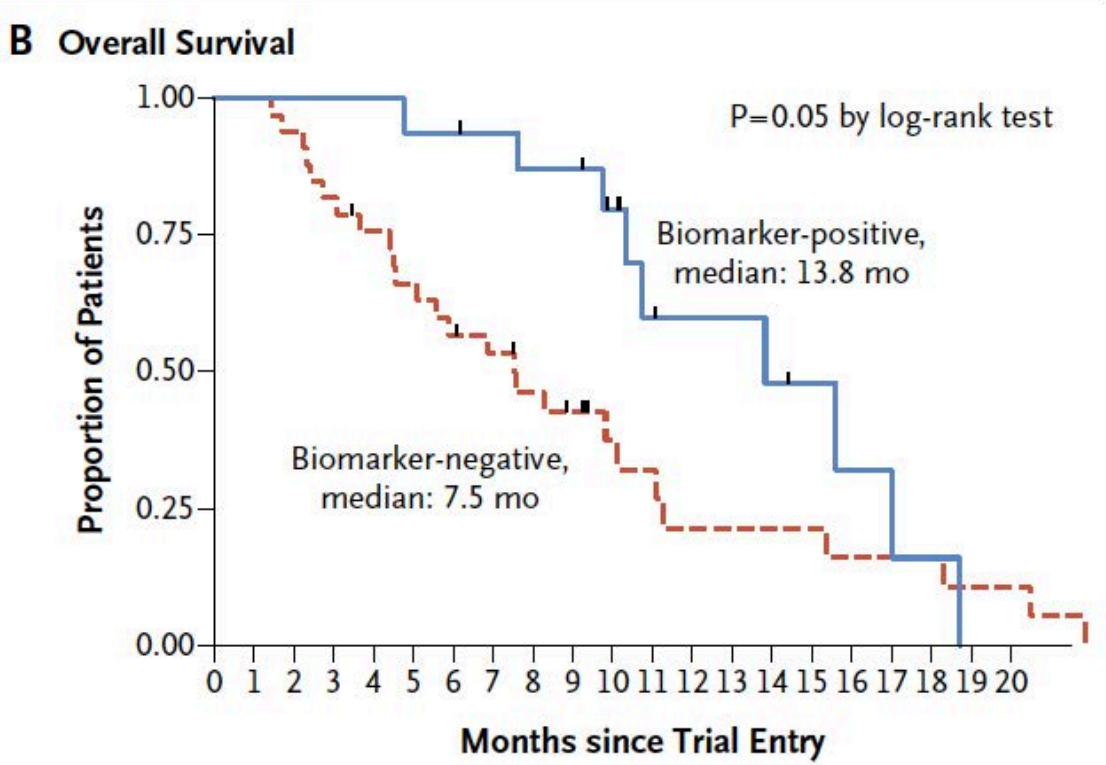


TOPARP Trial shows 30% Long Term Responders

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	–

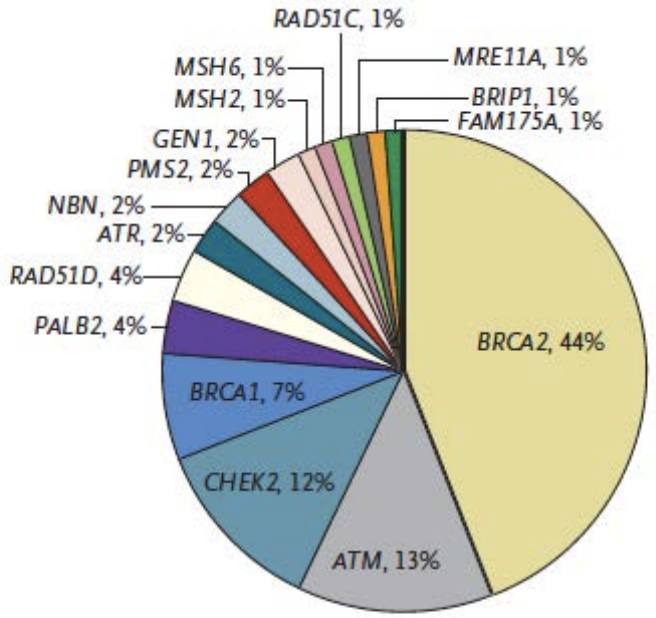
The NEW ENGLAND JOURNAL of MEDICINE

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

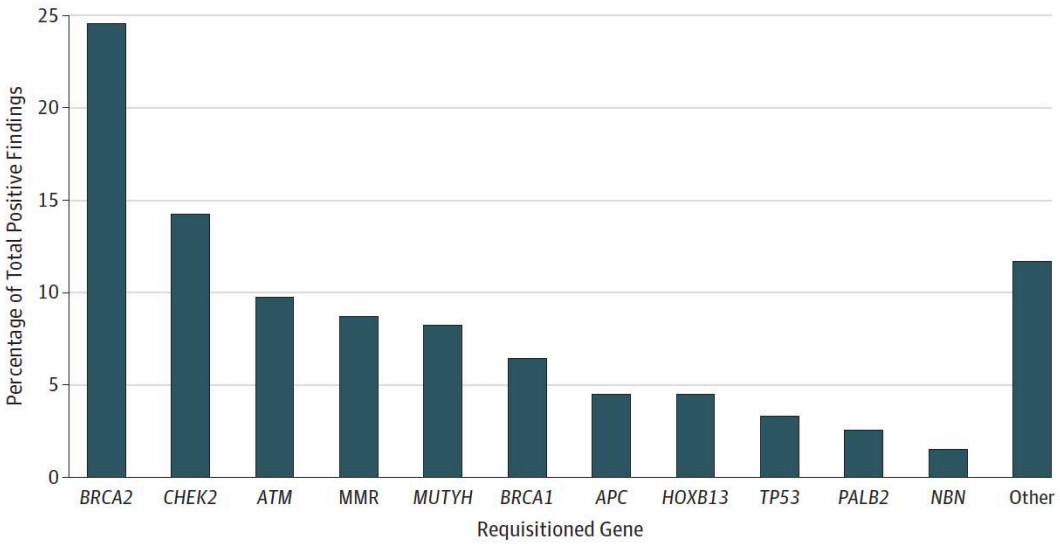
Cross-sectional study of data from 3607 men with a personal history of prostate cancer who underwent germline genetic testing between 2013 and 2018 and were unselected for family history, stage of disease, or age at diagnosis.

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

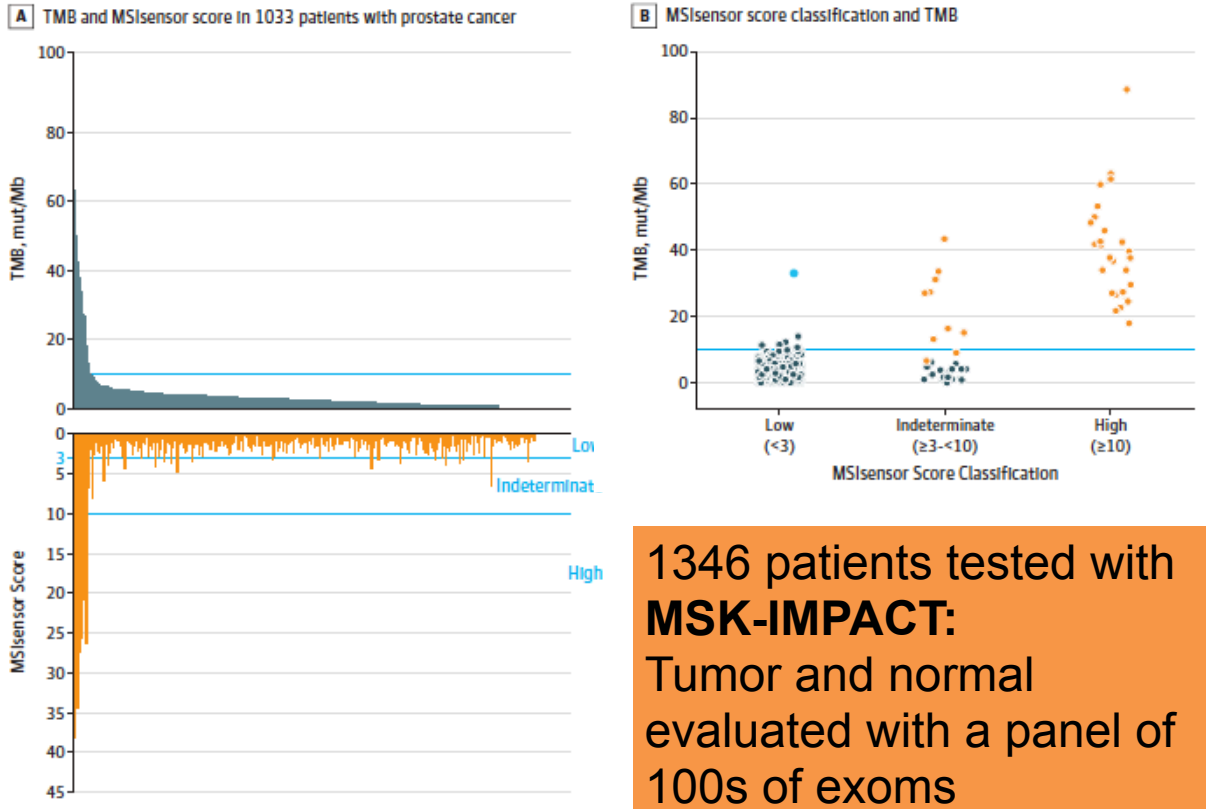
JAMA Oncology Published online February 7, 2019

JAMA Oncology | Original Investigation

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

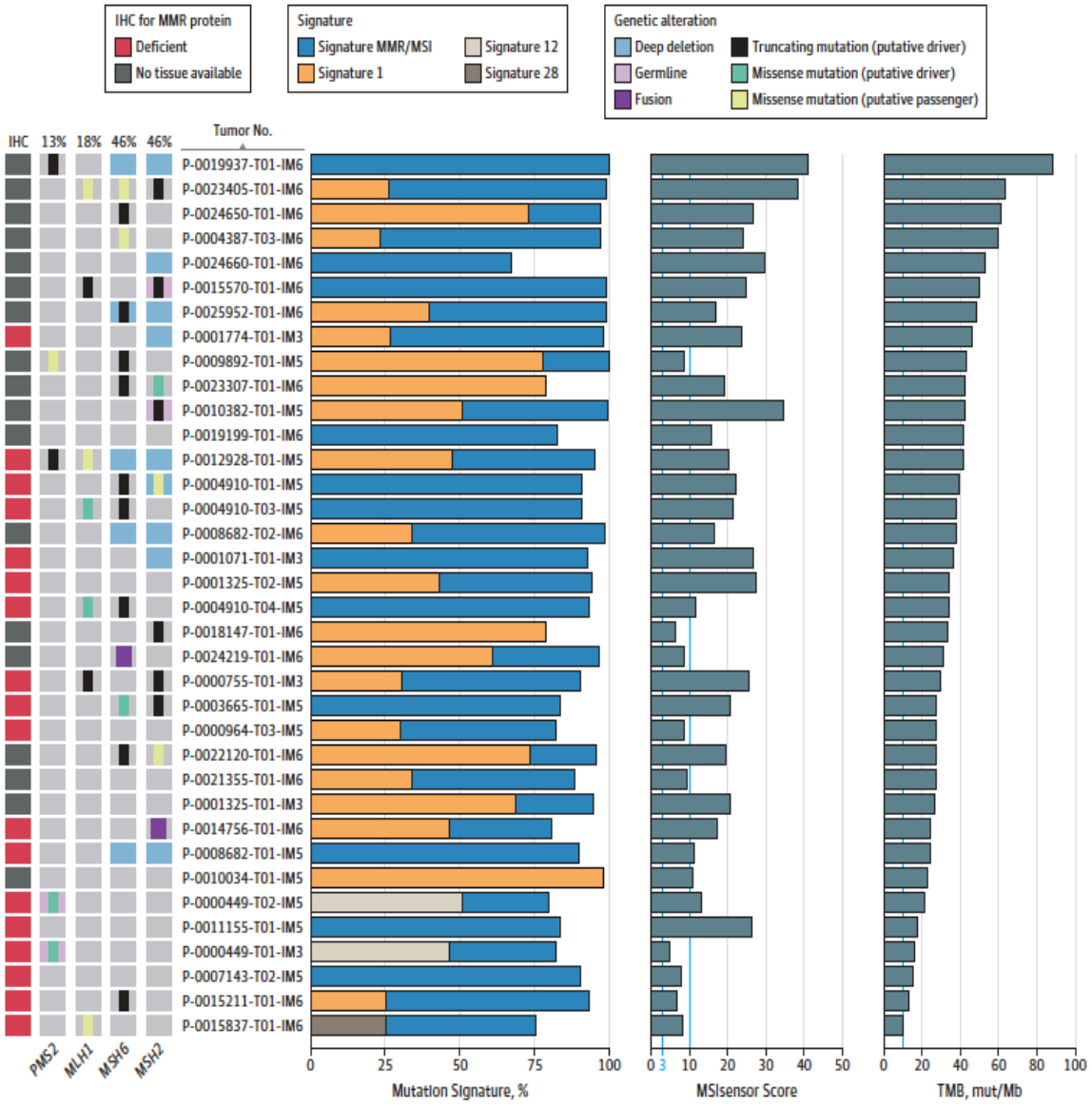
Wassim Abida, MD, PhD; Michael L. Cheng, MD; Joshua Armenia, PhD; Sumit Middha, PhD; Karen A. Autio, MD; Hebert Alberto Vargas, MD; Dana Rathkopf, MD; Michael J. Morris, MD; Daniel C. Danila, MD; Susan F. Slovin, MD, PhD; Emily Carbone, BA; Ethan S. Barnett, MS; Melanie Hullings, BA; Jaclyn F. Hechtman,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



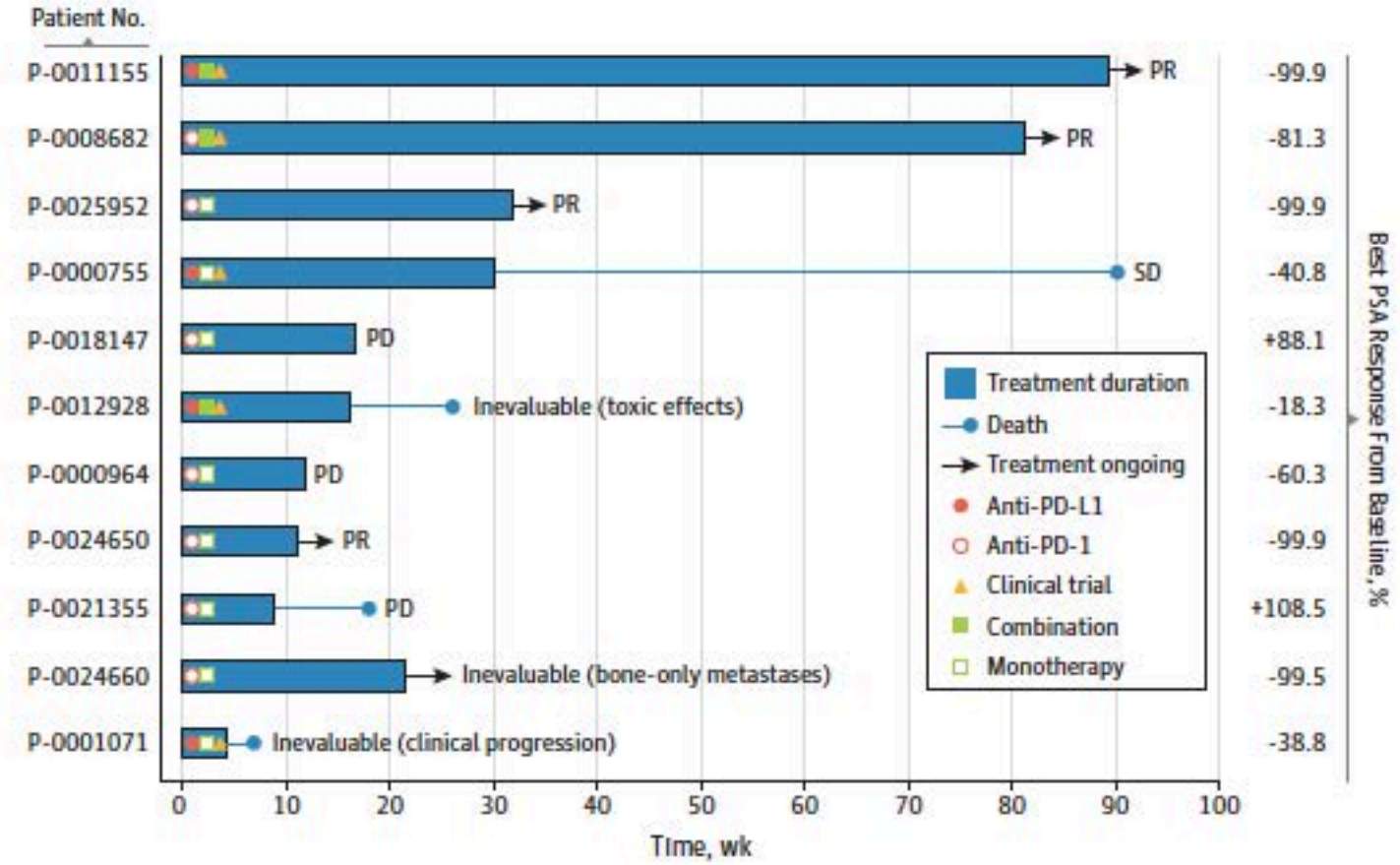
1346 patients tested with **MSK-IMPACT:**
Tumor and normal evaluated with a panel of 100s of exoms

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

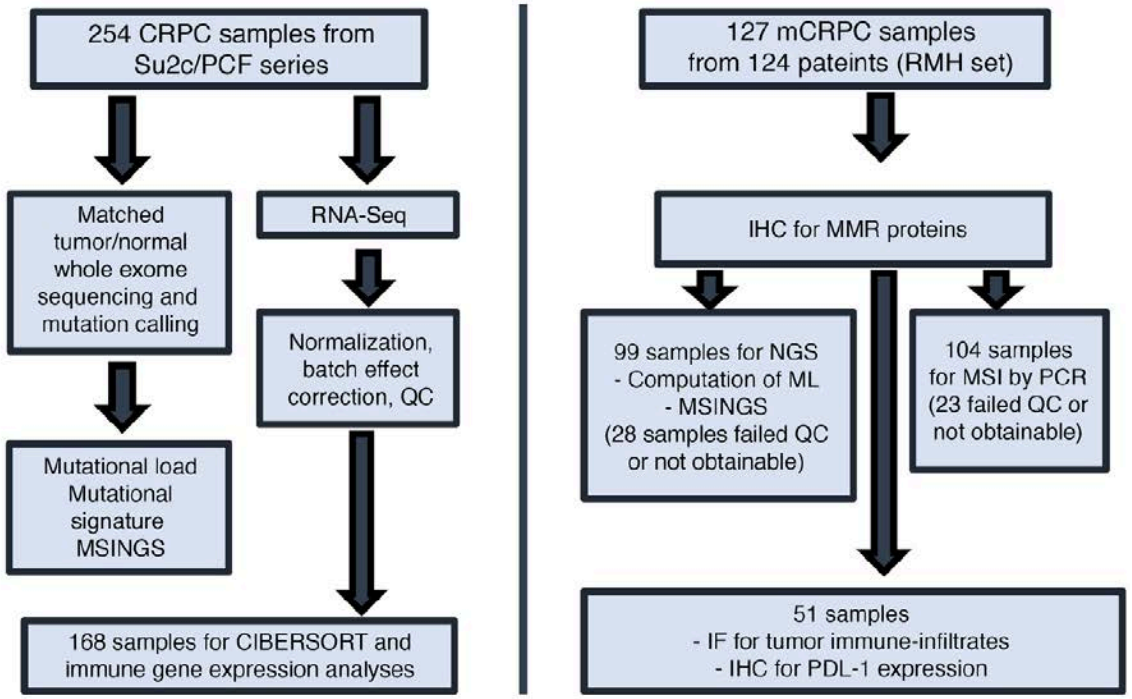


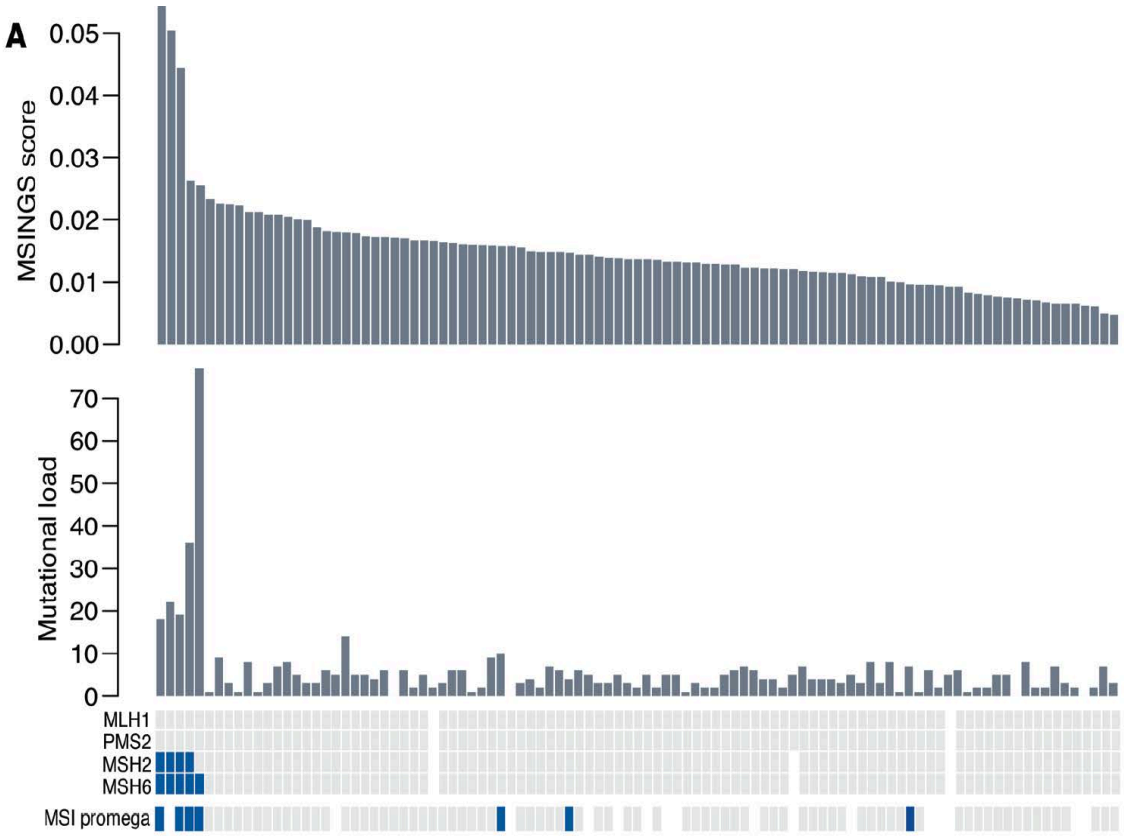
JAMA Oncology Published online December 27, 2018

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

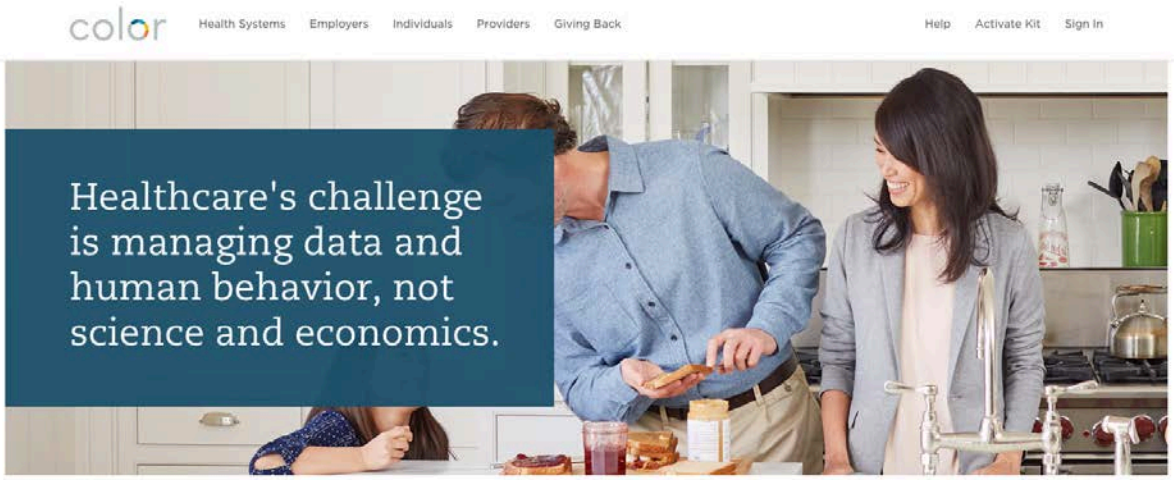
Daniel Nava Rodrigues,[1,2] Pasquale Rescigno,[1,2,3] David Liu,[4,5] Wei Yuan,[1] Suzanne Carreira,[1] Maryou B. Lambros,[1] George Seed,[1] Joaquin Mateo,[1,2] Ruth Riisnaes,[1] Stephanie Mullane,[4,5] Claire Margolis,[4,5] Diana Miao,[4,5] Susana Miranda,[1] David Dolling,[1] Matthew Clarke,[1] Claudia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



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.

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

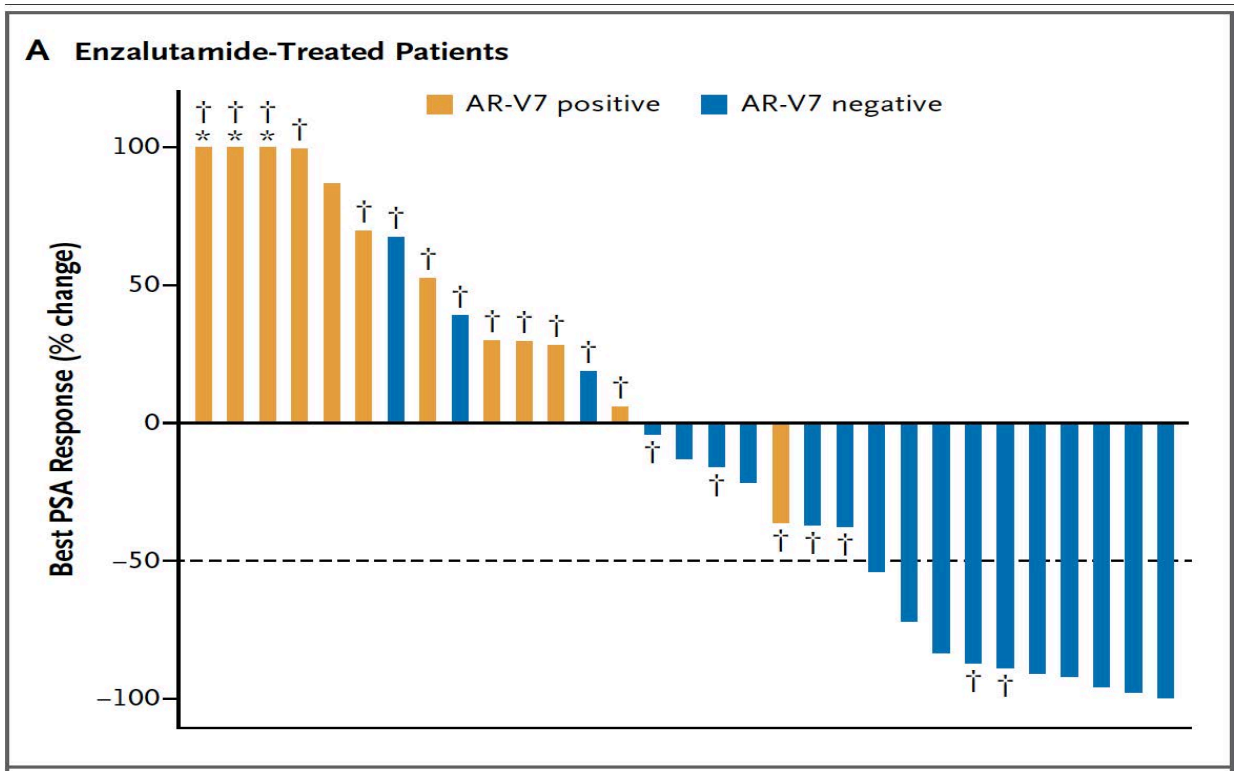
Color Extended: The most relevant genes for common hereditary cancers

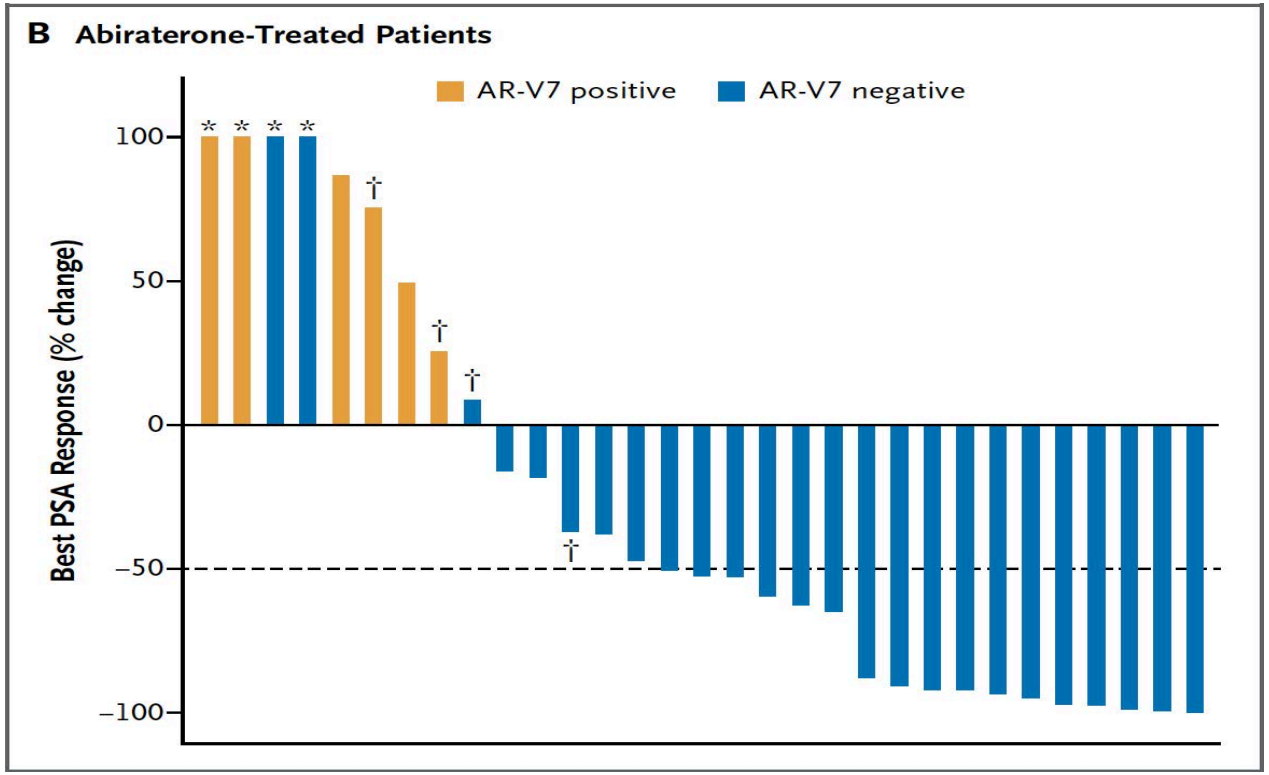
Gene	Breast	Ovarian	Uterine	Colorectal	Melanoma	Pancreatic	Stomach	Prostate*
BRCA1	●	●				●		●
BRCA2	●	●			●	●		●
MLH1		●	●	●		●	●	●
MSH2		●	●	●		●	●	●
MSH6		●	●	●			●	●
PMS2***		●	●	●				●
EPCAM**		●	●	●		●	●	●
APC				●		●	●	
MUTYH				●				
MITF**					●			
BAP1					●			
CDKN2A					●	●		
CDK4**					●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

The NEW ENGLAND JOURNAL of MEDICINE

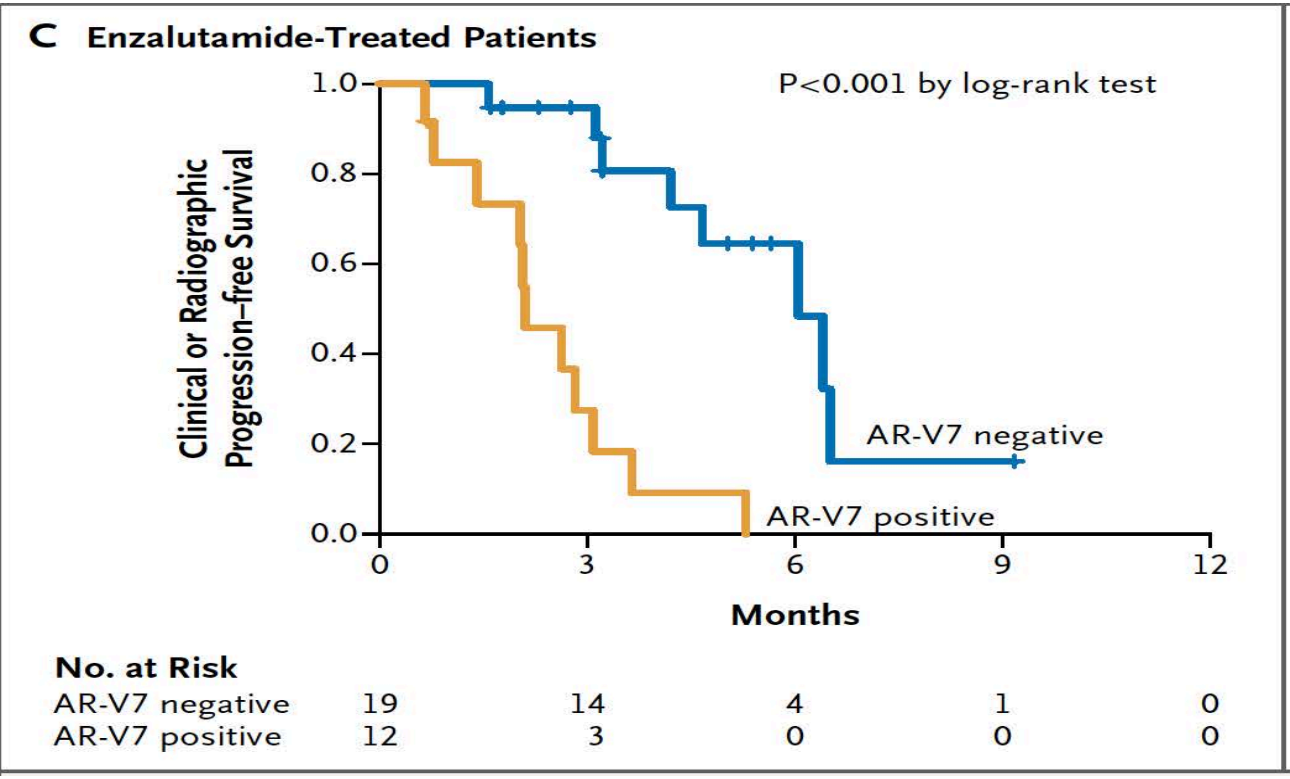
ORIGINAL ARTICLE

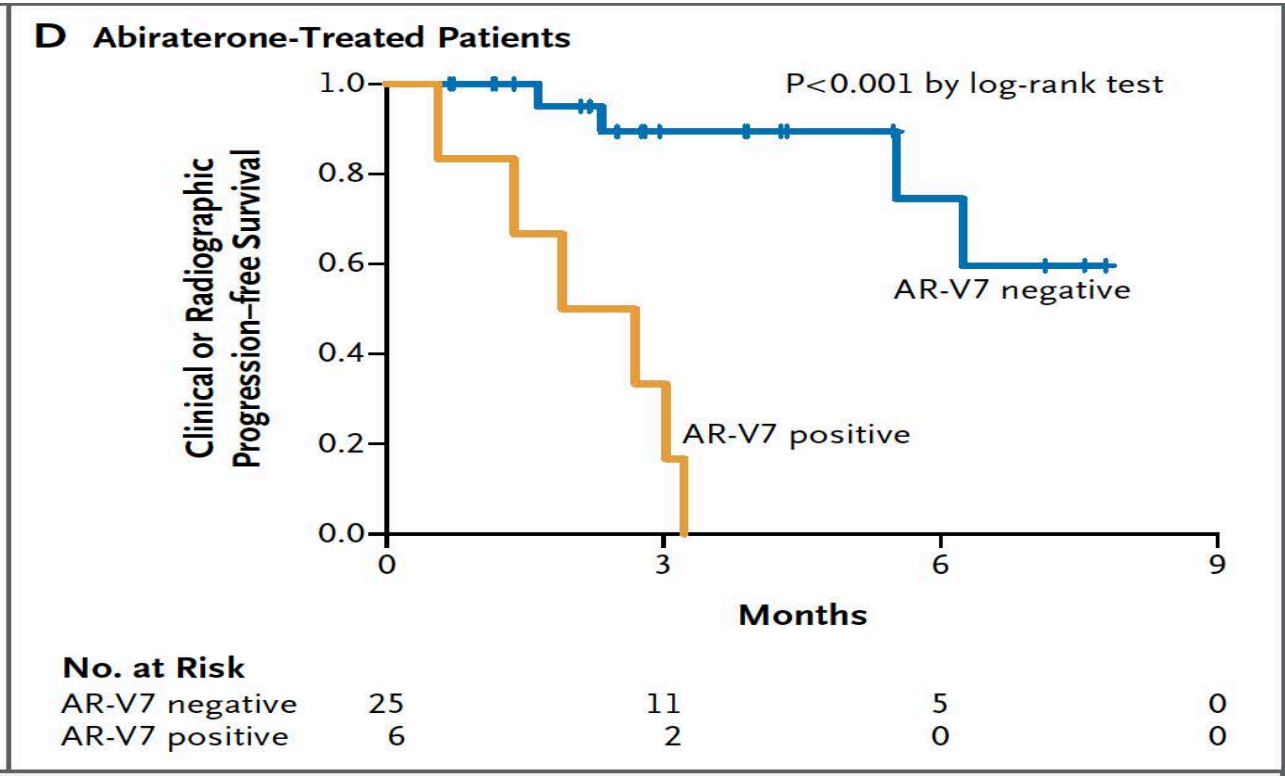
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer





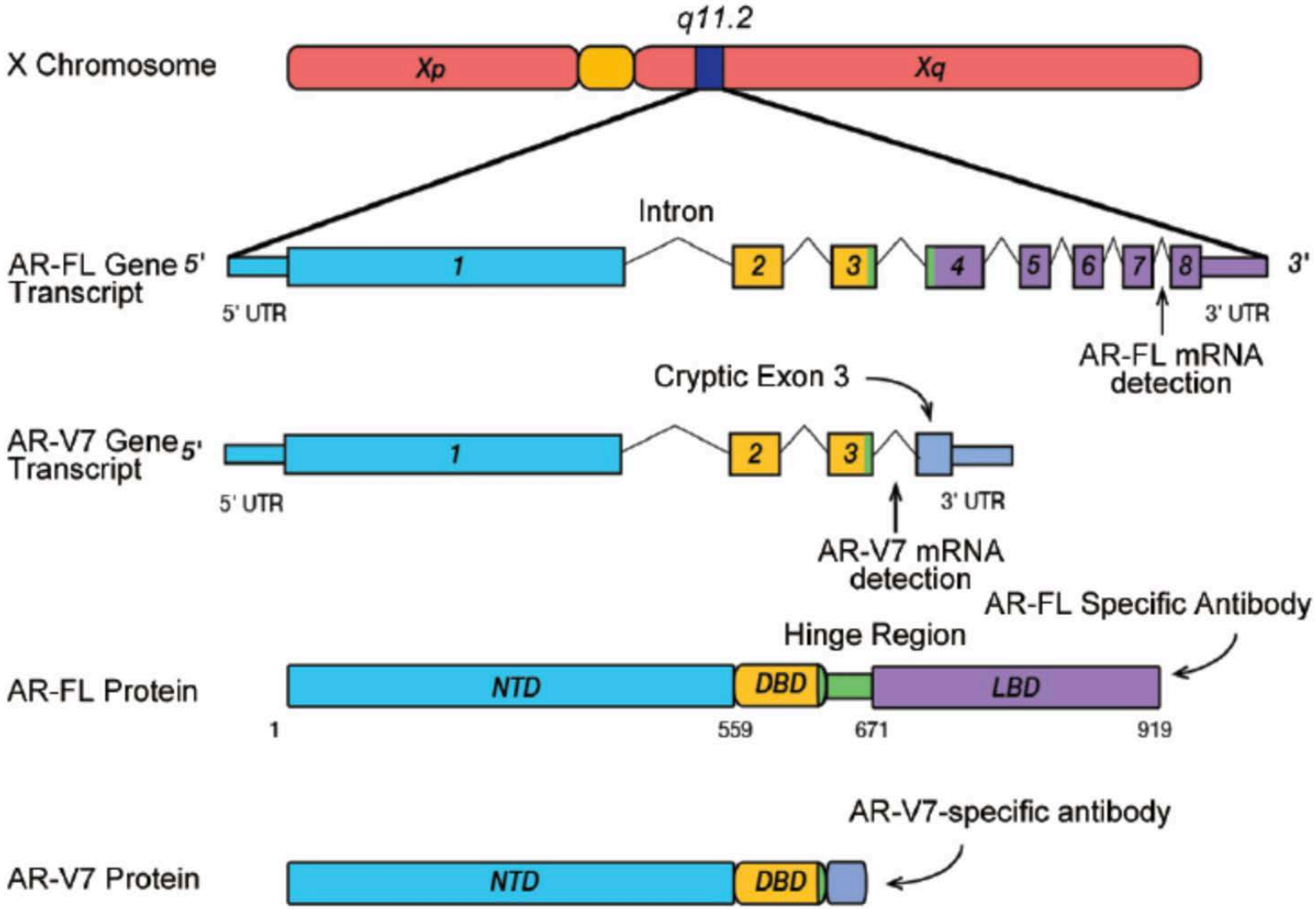
Antonarakis ES et al, NEJM 2014



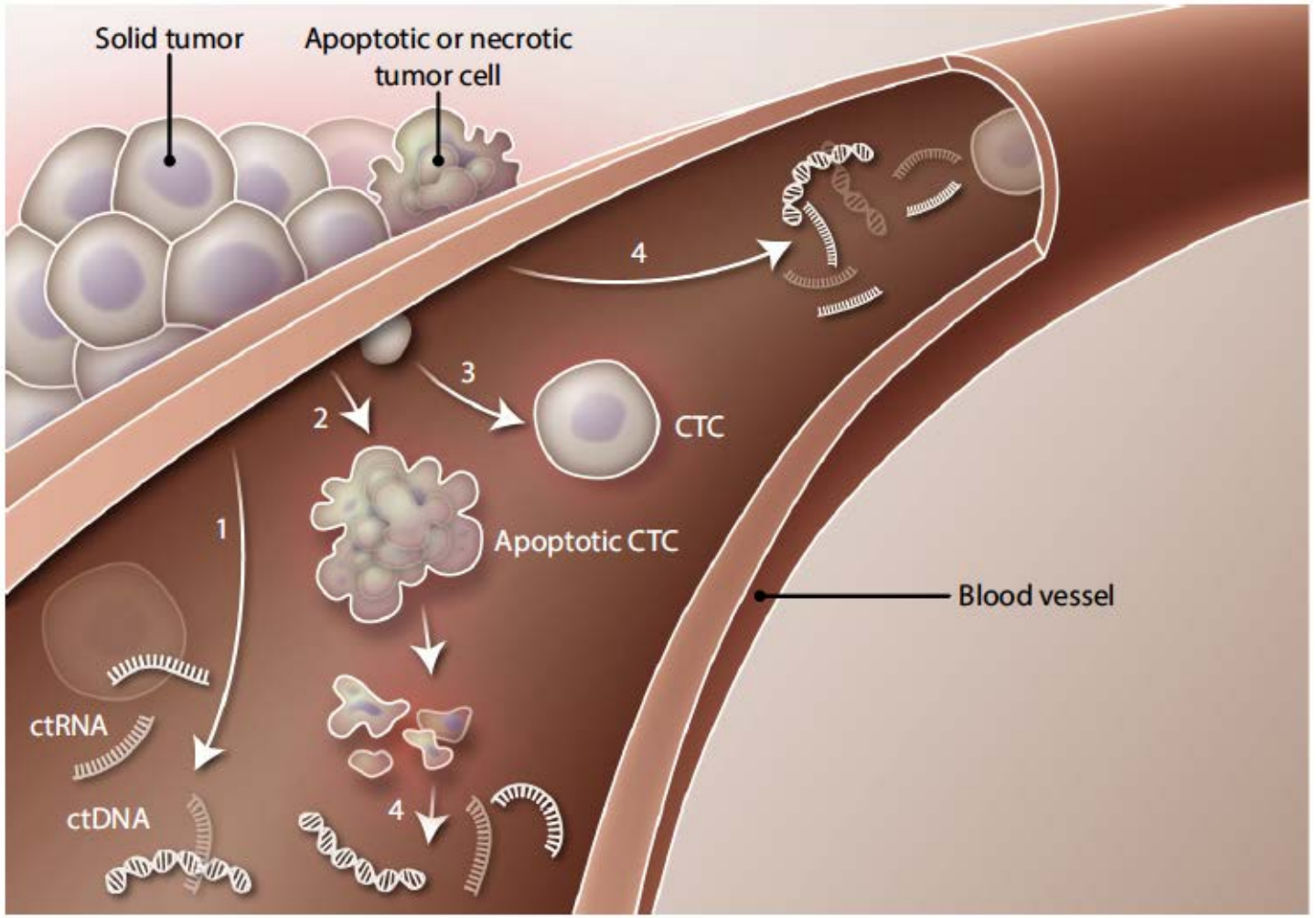


Antonarakis ES et al, NEJM 2014

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



What is next for CRPC Diagnostics



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

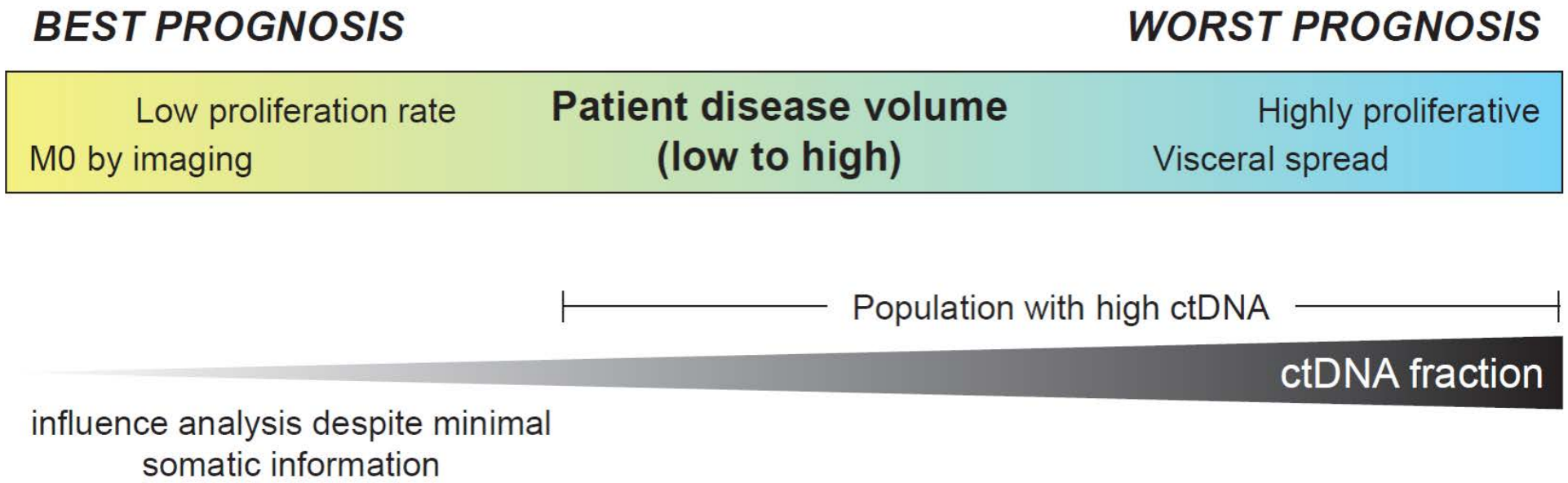
from Schweizer MT and Antonarakis ES, Sci Transl Med. 2015 Nov 4;7(312)

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

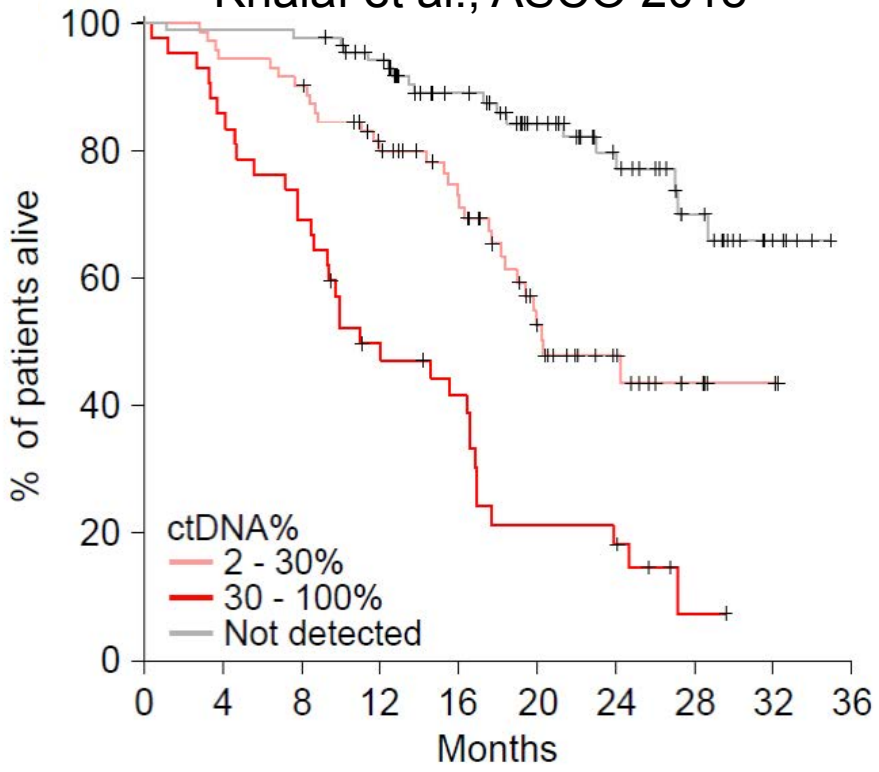


Courtesy of A. Wyatt

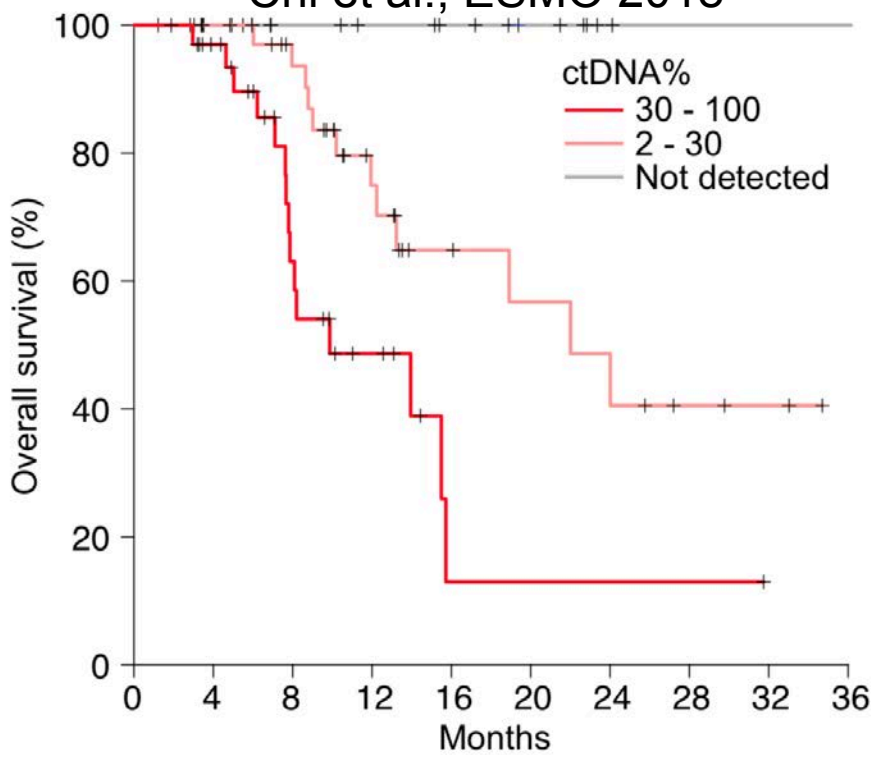
Warner *et al.*, BJUI 2018

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

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

European Association of Urology

Platinum Priority – Prostate Cancer

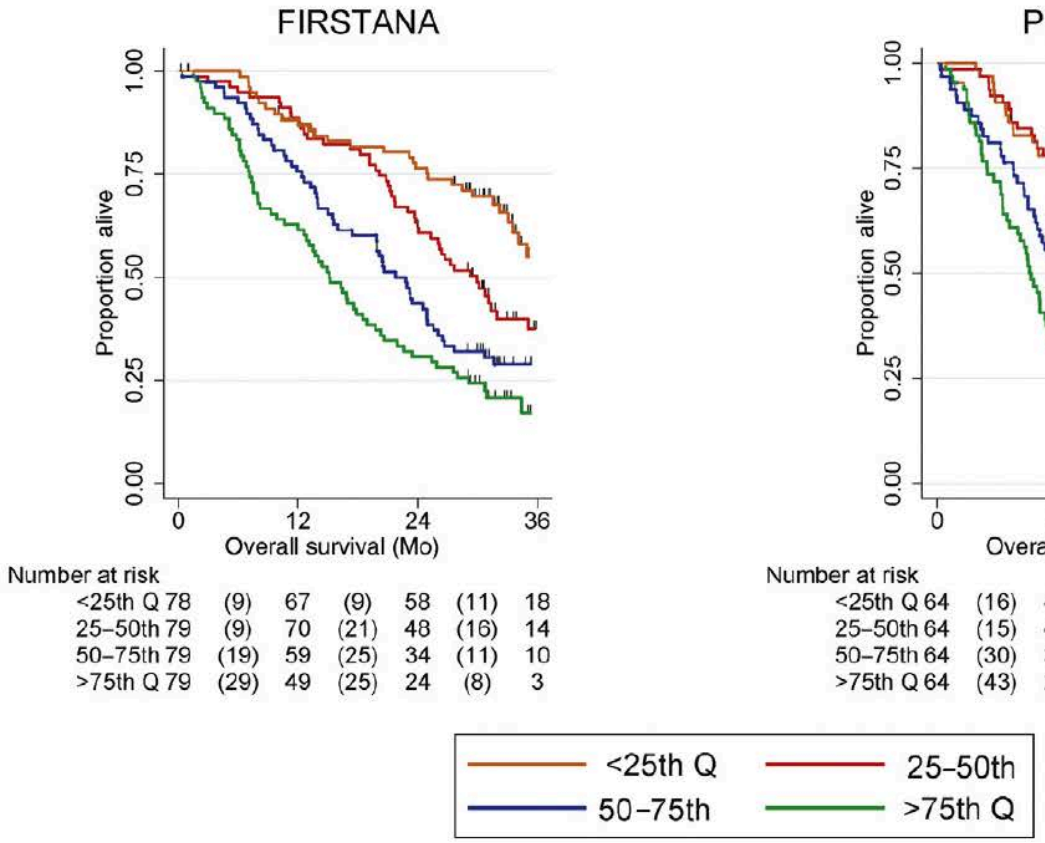
Editorial by Robert J. van Soest, Bertrand Tombal, Martijn P. Lolkema and Ronald de Wit on pp. 292–293 of this issue

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

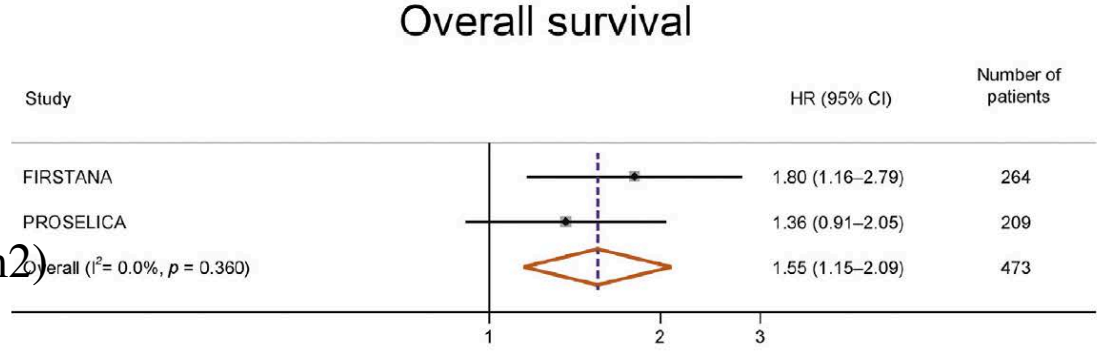


"Our study identifies baseline cfDNA concentration as an independent prognostic biomarker in patients with mCRPC, with higher baseline concentrations associated with shorter rPFS and OS following taxane therapy. A decline in total cfDNA concentration during the first 9 wk of treatment was associated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



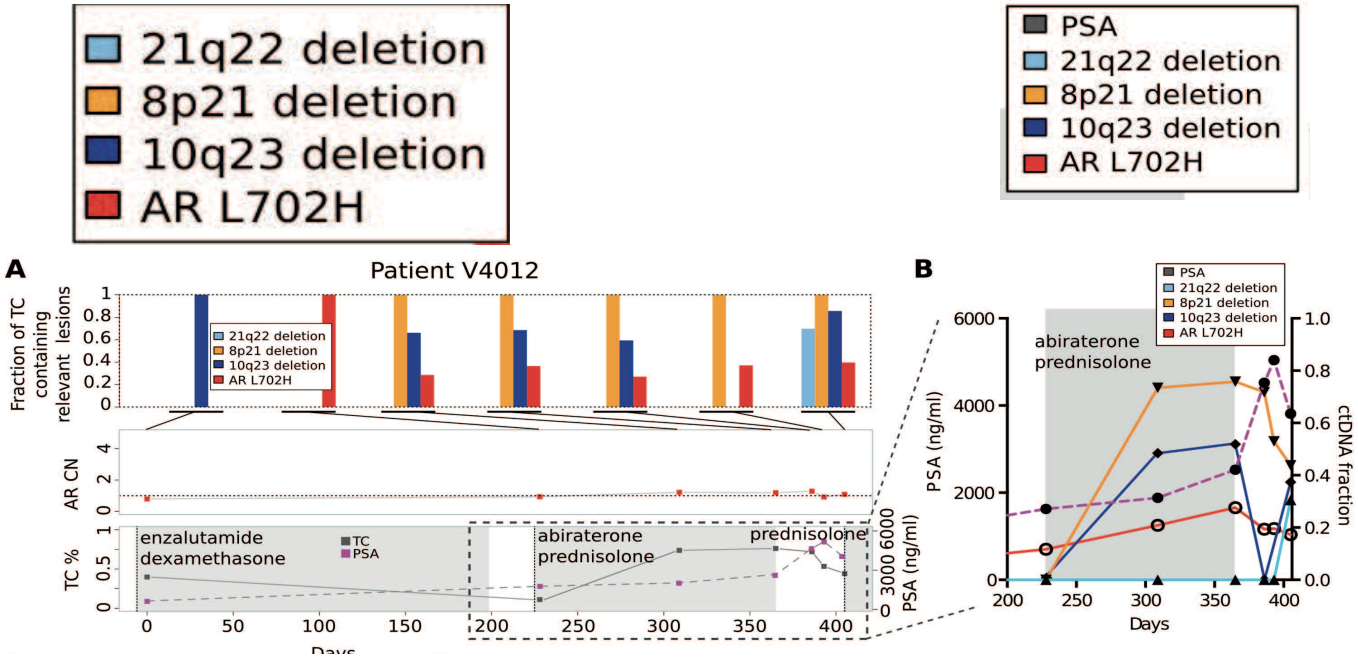
EUR Urol 74 (2 0 18) 2 8 3 – 2 9 1

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

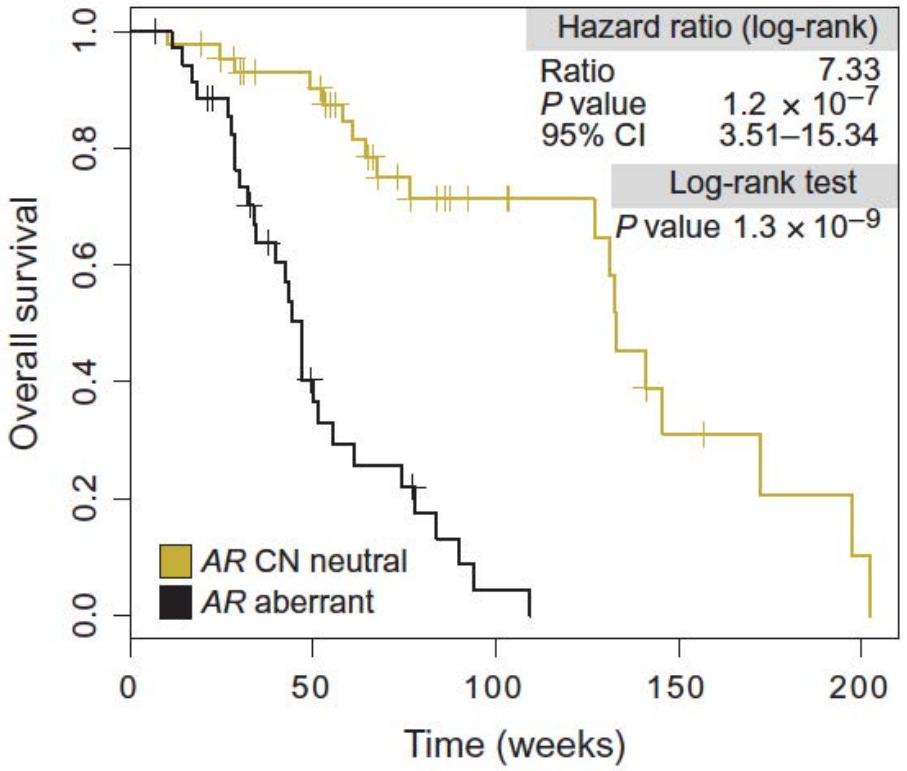
Sci Transl Med **6**, *254ra125 (2014)*

REPORT

CANCER

Plasma *AR* and abiraterone-resistant prostate cancer

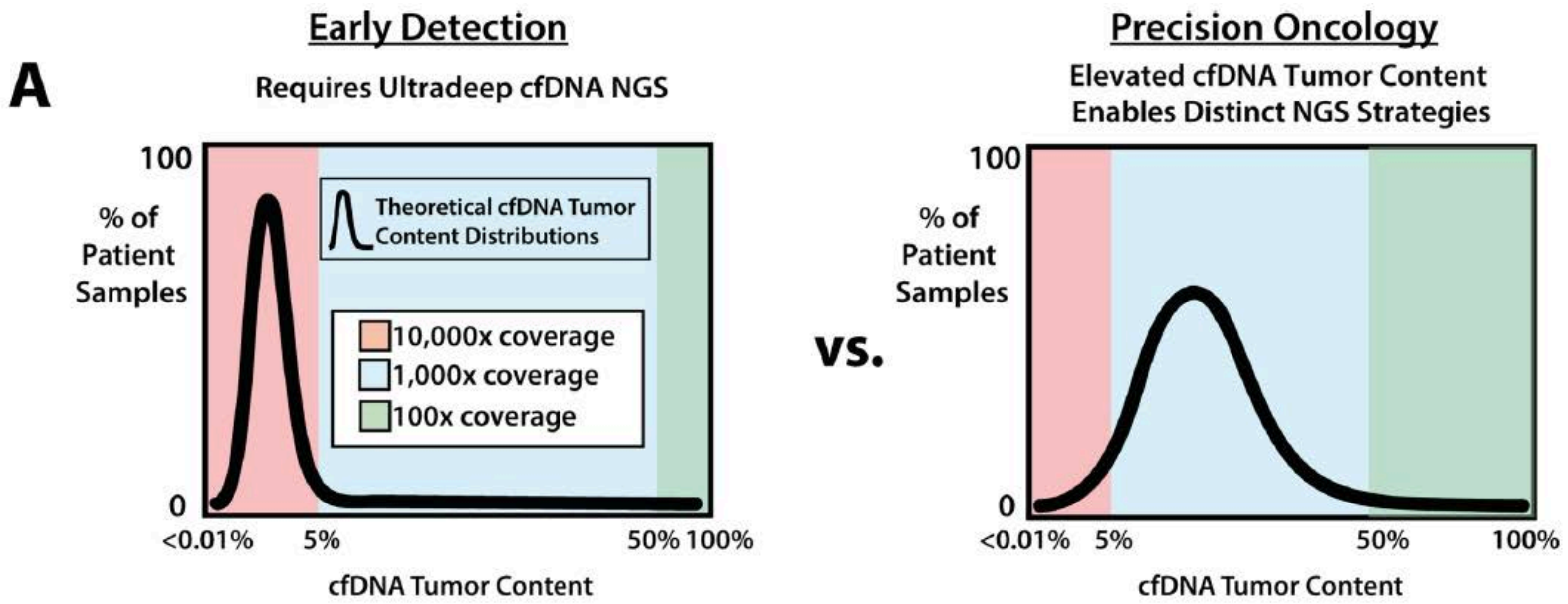
Alessandro Romanel,[1]* Delila Gasi Tandefelt,[2]* Vincenza Conteduca,[2,3] Anuradha Jayaram,[2,4] Nicola Casiraghi,[1] Daniel Wetterskog,[2] Samanta Salvi,[3] Dino Amadori,[3] Zafeiris Zafeiriou,[2,4] Pasquale Rescigno,[2,4] Diletta Bianchini,[2,4] Giorgia Gurioli,[3] Valentina Casadio,[3] Suzanne Carreira,[2]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

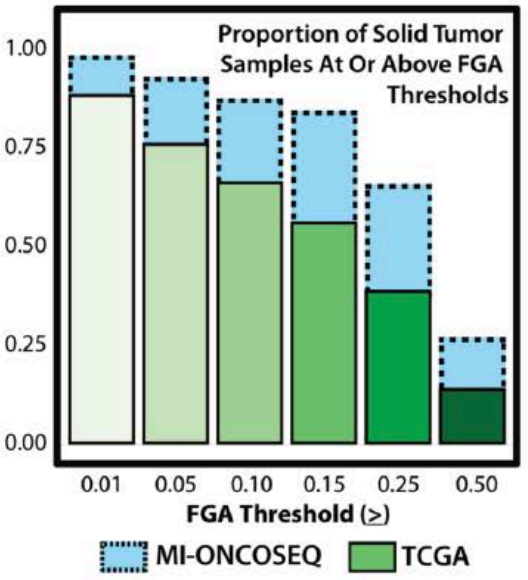
Need to address evolution as a time course with cfDNA, scSeq, molecular imaging, etc.



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,*]



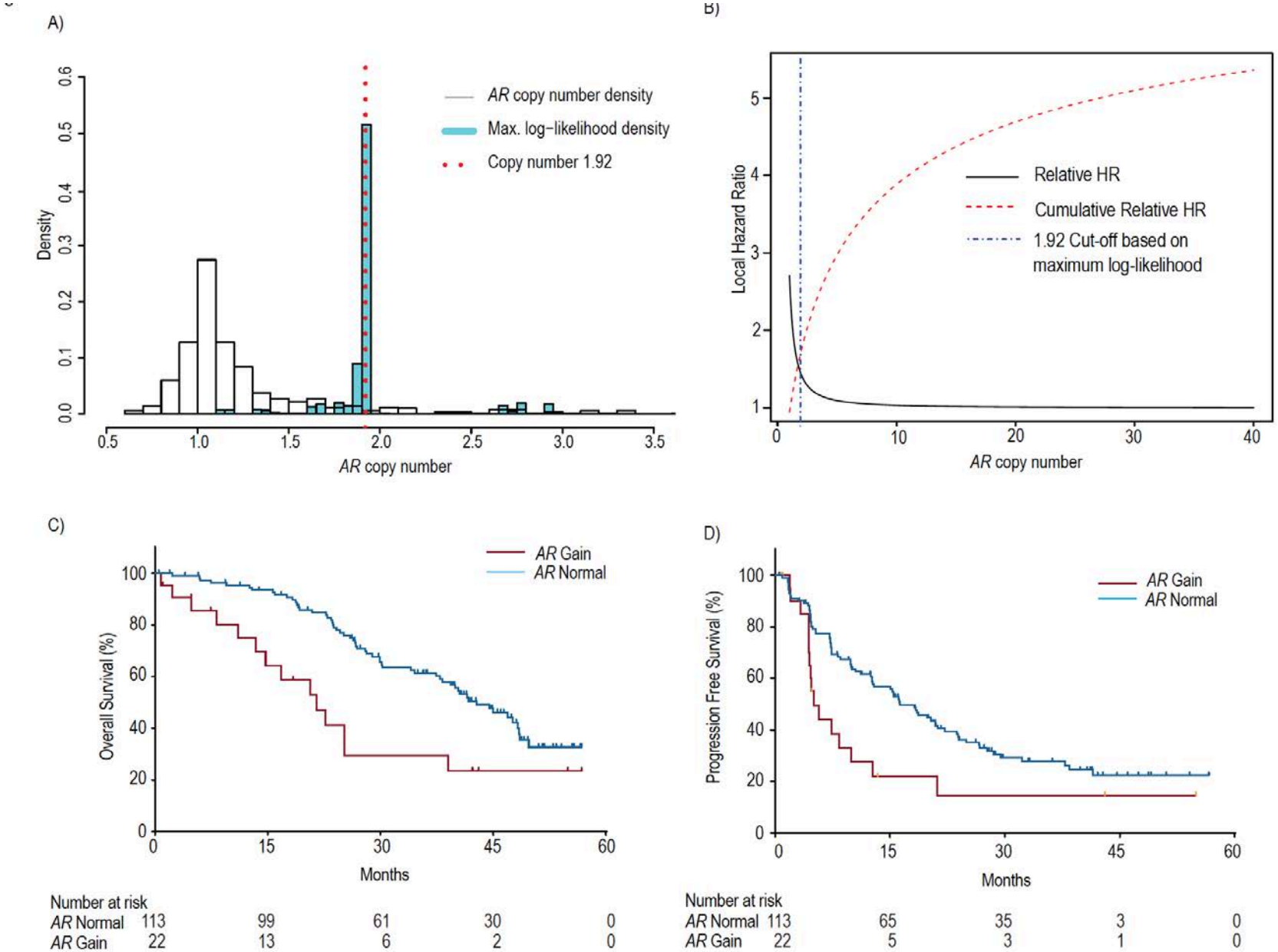
Oncotarget 2017

original report

Plasma Androgen Receptor Copy Number Status at Emergence of Metastatic Castration-Resistant Prostate Cancer: A Pooled Multicohort Analysis

Anuradha Jayaram, MD[1]; Anna Wingate, MSc[1]; Daniel Wetterskog, PhD[1]; Vincenza Conteduca, MD, PhD[2]; Daniel Khalaf, MD[3]; Mansour Taghavi Azar Sharabiani, PhD[4]; Fabio Calabrò, MD[5]; Lorraine Barwell, MD[6]; Susan Feyerabend, MD[7]; Enrique Grande, MD[8]; Alberto Martinez-Carrasco, MsC[9]; Albert Font, MD, PhD[10]; Alfredo Berruti, MD[11]; Cora N. Sternberg, MD[12]; Rob Jones, MA, MD, PhD[6]; Florence Lefresne, MD[13]; Marjolein Lahaye, MSc[13]; Shibu Thomas, PhD[14]; Shilpy Joshi, PhD[15]; Dong Shen, MD, PhD[14]; Deborah Ricci, PhD[14]; Michael Gormley, PhD[14]; Axel S. Merseburger, MD[16]; Bertrand Tombal, MD, PhD[17]; Matti Annala, MSc[3,18]; Kim N. Chi, MD[3,19]; Ugo De Giorgi, MD, PhD[2]; Enrique Gonzalez-Billalabeitia, MD, PhD[9]; Alexander W. Wyatt, MD, PhD[3]; and Gerhardt Attard, MD, PhD[1]

Jayaram et al., JCO Precision Oncology 2019



Jayaram et al., JCO Precision Oncology 2019

AR Copy Number Testing

- Can be determined in both low and high volume disease
- May capture the heterogeneity of the disease state
- Cut point (1.9) could be used as a predictive biomarker (needs additional validation)

Jayaram et al., JCO Precision Oncology 2019

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

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cfDNA (tumor DNA)

AR-V7

AR gain—-***PROMISING (Editorial)***

AR mutations

Other (neuroendocrine differentiation)

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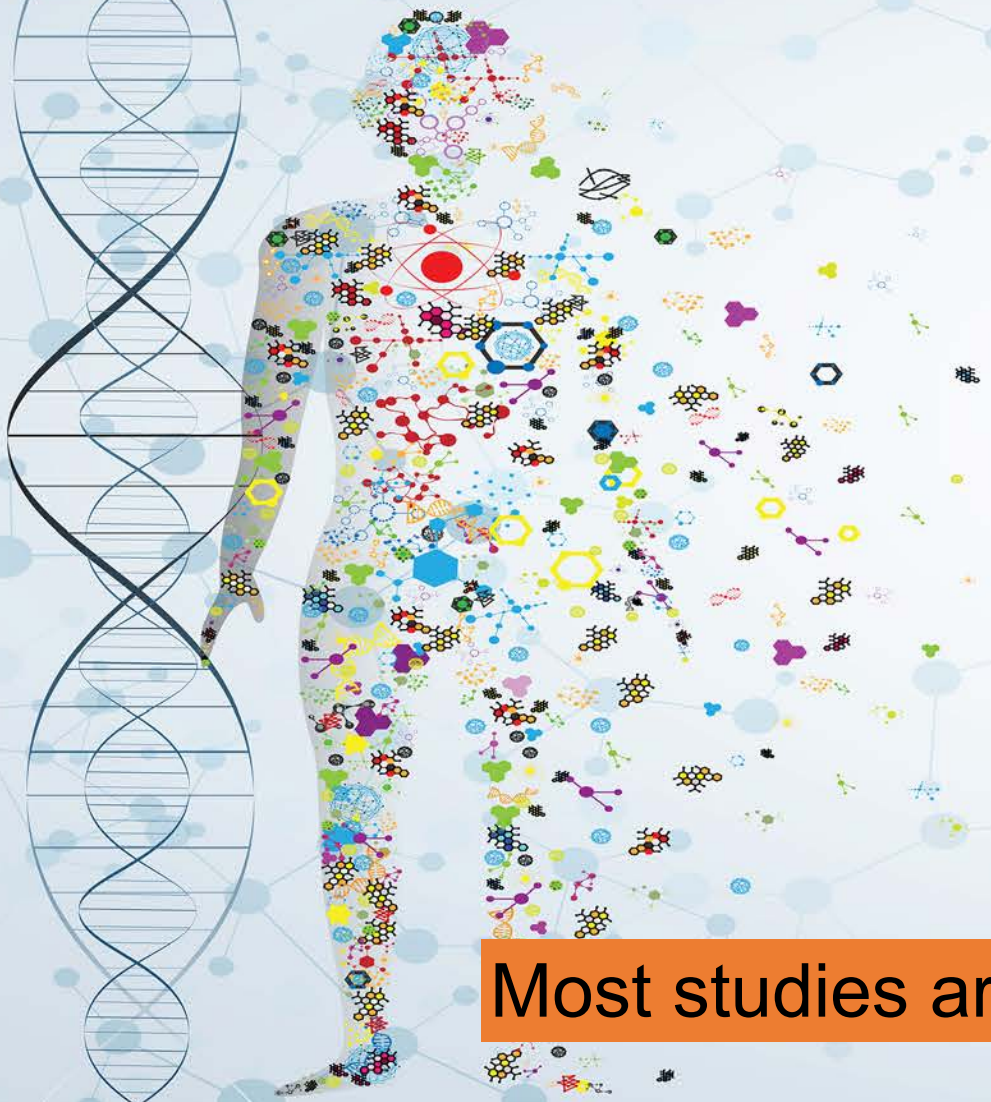
What is predictive? Prognostics? Reproducible?



cfDNA (tumor DNA)

AR-V7

AR gain—-***PROMISING (Editorial)***

AR mutations

Other (neuroendocrine differentiation)

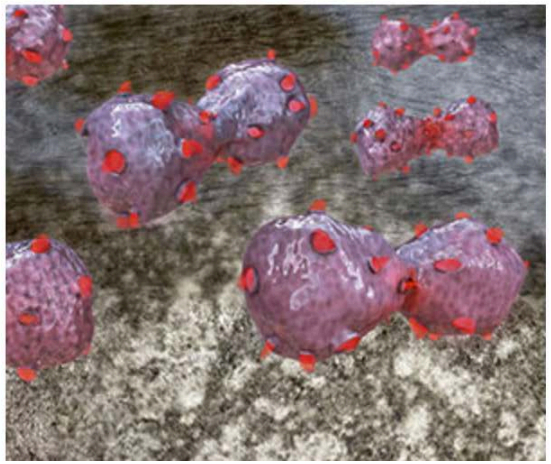
Most studies are not exploring these parameters together

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."

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!

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, needs validation)
-cfDNA for DNA fraction, AR, others
-Tissue testing assays for localised and advanced PCa (many)

Approved by FDA (Not Prostate Specific)

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


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