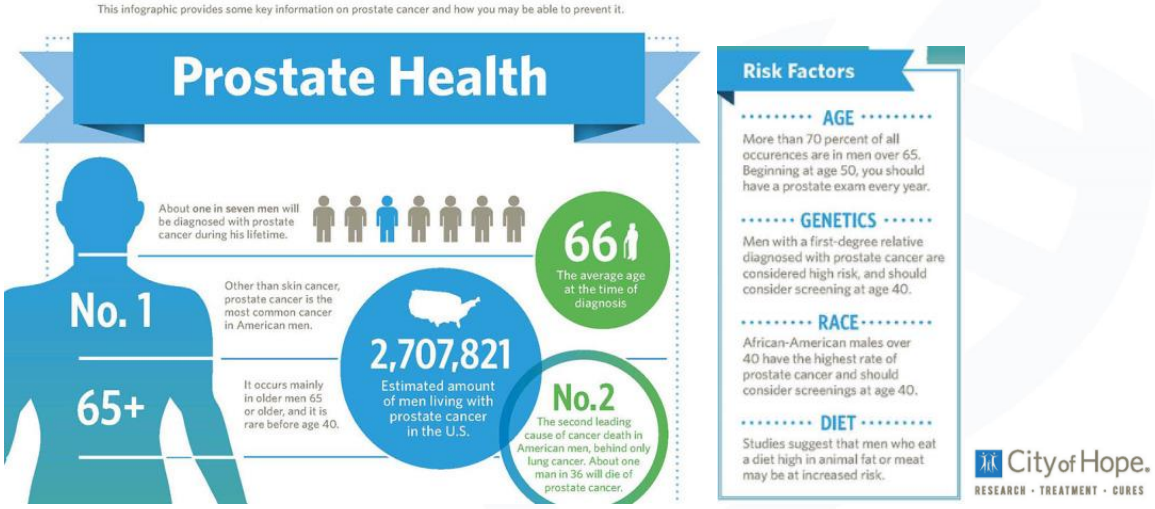
PROSTATE CANCER
Importance of Molecular Characteristics in Support of Therapeutic Decisions

Outline

- Prognostic and diagnostic value of pathologic and molecular alterations in prostate cancer
- Current status of precision medicine/molecular pathology/liquid biopsy in metastatic prostate cancer
- Molecular Profiling of Pca.
- A case study of how precision medicine can guide treatments

Prostate Cancer: some statistics…



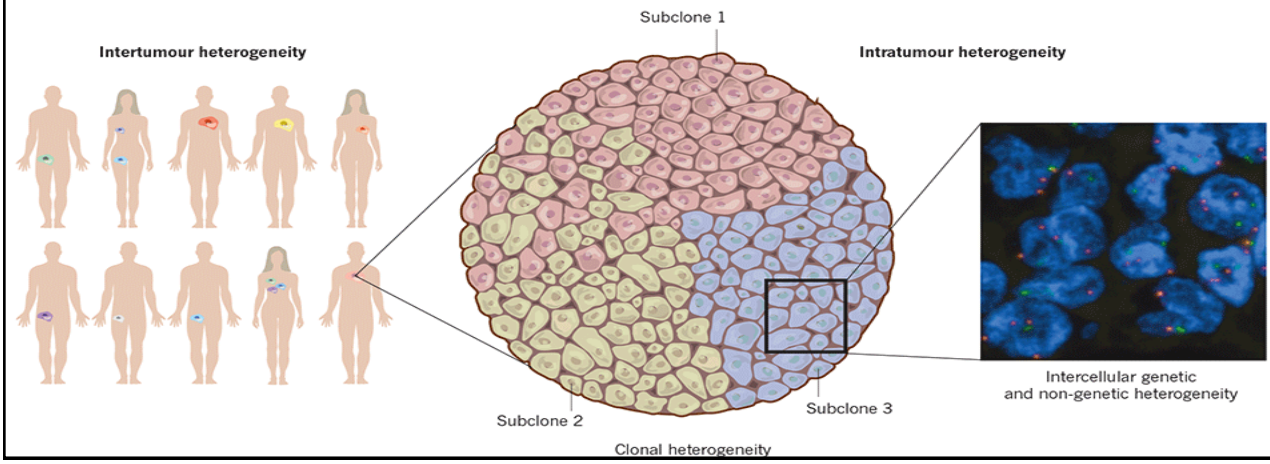
Integrating molecular profiling in the clinical practice of prostate cancer

Prognostic and diagnostic testing in prostate cancer

REVIEW

doi:10.1038/nature12627

Tumour heterogeneity in the clinic



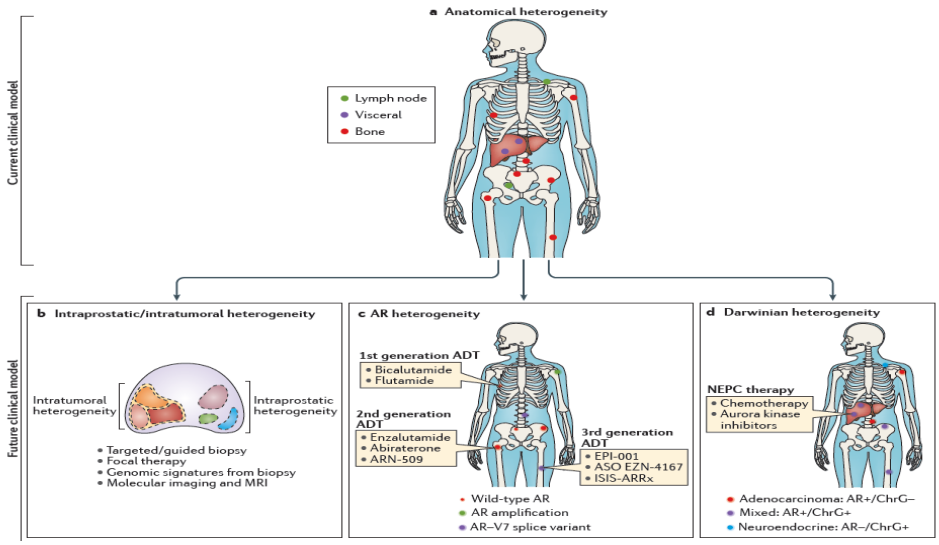
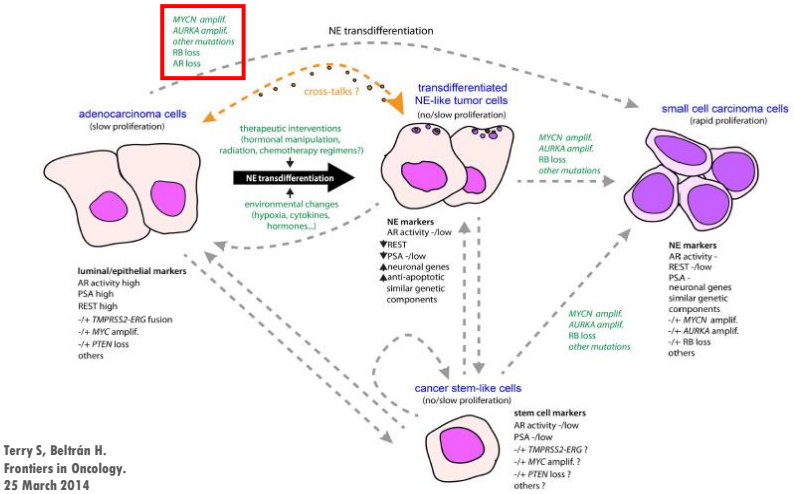


Figure 1 | **Types and implications of prostate cancer heterogeneity. a** | The clinical and anatomical heterogeneity of metastatic prostate cancer fails to capture the immense biological heterogeneity of prostate cancer. **b** | Intraprostatic/intratumoural heterogeneity, **c** | Androgen receptor heterogeneity, and **d** | Darwinian heterogeneity demonstrate clinical strategies and obstacles regarding treatment and diagnosis. AR, androgen receptor; ADT, androgen deprivation therapy; ChrG, chromogranin; NEPC, neuroendocrine prostate cancer.

Schematic model for the emergence of NE phenotype in Pca

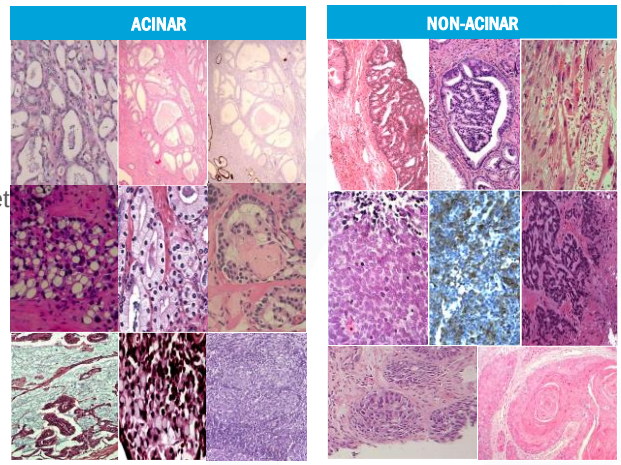


Terry S, Beltrán H.
Frontiers in Oncology.
25 March 2014

Variants of prostate carcinoma

Acinar

- Atrophic
- Pseudohyperplastic
- Foamy gland
- Colloid (mucinous)
- Signet ring (and signet ring-like)
- Mycrocystic
- Pleomorphic Giant Cell
- Sarcomatoid



Non-Acinar

- Ductal adenocarcinoma
- Sarcomatoid Ca
- Squamous cell & adenosquamous carcinoma
- Small cell Ca
- Basal cell Ca
- Urothelial Ca

WHO classification, 2016

EXPERT REVIEW OF ANTICANCER THERAPY, 2018
https://doi.org/10.1080/14737140.2018.1469406

Taylor & Francis
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REVIEW

Check for updates

Prostate cancer with cribriform morphology: diagnosis, aggressiveness, molecular pathology and possible relationships with intraductal carcinoma

Rodolfo Montironi[a], Alessia Cimadamore[a], Silvia Gasparrini[a], Roberta Mazzucchelli[a], Matteo Santoni[b], Francesco Massari[c], Liang Cheng[d], Antonio Lopez-Beltran[e] and Marina Scarpelli[a]

Areas Covered: Cribriform, fused, ill-defined and glomeruloid glands are part of the morphologic spectrum of the current GP 4. Cribriform, derived from the Latin word *cribrum* (i.e. sieve), was introduced by Gleason to describe glands composed of a solid sheet with perforations or lumina. Cribriform morphology has a worse prognosis compared with the other, non-cribriform, GP4 morphologies. A practical implication is that a cribriform growth precludes a patient from selecting an active surveillance (AS) protocol.

Clinically available genomic markers to guide clinical decision making

DIAGNOSTIC BIOMARKERS

PROGNOSTIC BIOMARKERS

Test	Company	Tissue type	No. of genes or proteins	Main results	Utility assessment
Biomarkers of disease risk					
Mi-Prostate Score	University of Michigan, MLabs	Post-DRE urine	2	TMPRSS2:ERG plus PCA3 in combination with PCPT risk calculator improve the prediction of aggressive PCa (AUC = 0.81).	Initial biopsy
SelectMDx	MDxHealth	Post-DRE urine	2	Risk calculator including urinary HOXC6 and DLX1 mRNA levels is a good predictor (AUC = 0.90) for the detection of clinically significant PCa (GS ≥ 7).	Initial biopsy
ExoDx	Exosome Diagnostics	Urine	3	Association of the exosome-gene expression with clinical parameters (PSA, age, race, or family history) can discriminate between insignificant and aggressive disease (AUC = 0.73).	Initial biopsy
PCA3	Hologic	Post-DRE urine	1	PCA3 score predicts biopsy outcome in combination with PSA, DRE, and other clinical parameters (AUC = 0.71–0.75).	Rebiopsy
ConfirmMDx	MDxHealth	Prostate biopsy	3	Methylation status of three genes (*GSTP1*, *APC*, and *RASSF*) is able to identify men at higher need of a repeat biopsy (NPV of 88–90%).	Rebiopsy
Risk stratification biomarkers					
Decipher	GenomeDX Biosciences	Radical prostatectomy	22	Decipher scores, in addition to clinical variables, predict 10-yr distant metastasis after surgery (AUC = 0.81). GC (alone or plus CAPRA score) has a higher ability to predict the occurrence of metastases (AUC = 0.83–85).	Adjuvant treatment after radical prostatectomy
Oncotype DX	Genomic Health Inc.	Prostate biopsy	17	GPS combined with clinical parameters (age, PSA, clinical stage, and biopsy GS) or with the CAPRA score is a predictor of high-grade (primary GS of 4 or any pattern of 5) or high-stage disease (pT3 or higher), and BCR.	Active surveillance or active treatment
Prolaris	Myriad Genetics	Prostate biopsy	31	CCP score is an independent predictor of PCa death, BCR, and metastasis after radical prostatectomy and radiation therapy.	Active surveillance or active treatment
		Radical prostatectomy		The combination of CCP and the CAPRA score achieves a higher prognostic power.	Adjuvant therapy in high-risk patients

AUC = area under the curve; BCR = biochemical recurrence; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression; DRE = examination; GC = genomic classifier; GS = Gleason score; GPS = Genomic Prostate Score; NPV = negative predictive value; PCa = pros PCA3 = Prostate Cancer Antigen 3; PCPT = Prostate Cancer Prevention Trial; PSA = prostate-specific antigen.

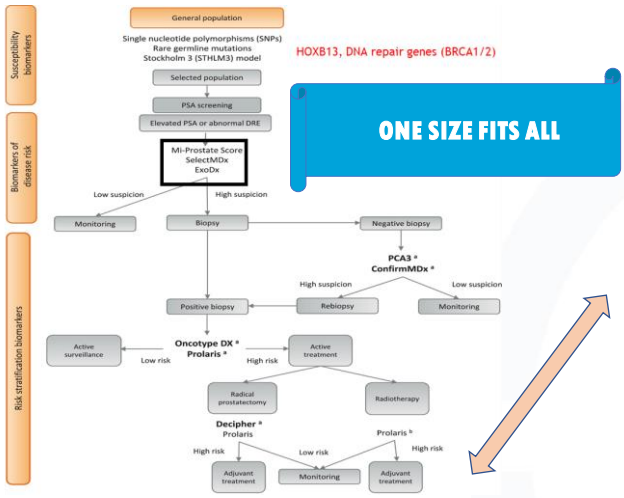
Cucchiara V. *et al*, Eur Urol. 2017

	Decipher	OncoType Dx	Prolaris
Gene panel	22 RNAs from diferente regions of genome	12 cancer-related to different pathways plus 5 reference genes	46 RNAs expression signature
Tissue tested	RP (pT3, margin+ or rising PSA)	Biopsy, very-low-to-intermediate risk	Biopsy or RP
Utility	Predicts probability of metastasis 5 years after RP	Predicts likelihood of favorable pathology	Cell cycle progression score for mortality or biochemical recurrence
Tissue requirements	1 × 1.0-mm diameter punch of highest Gleason grade in FFPE block	6 × 5-µ sections (1.0 mm length) + two H&Es	5 × 5-µ sections (0.5 mm length) + two H&Es

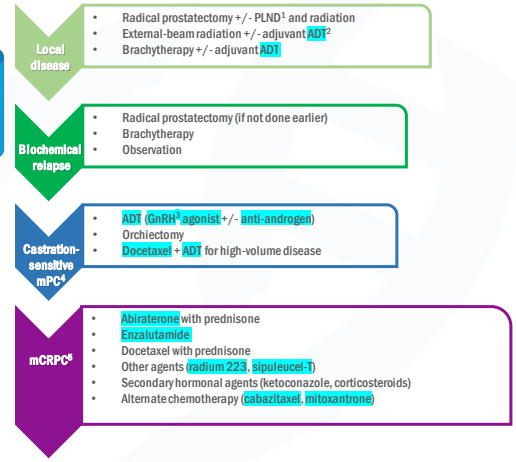
Integrating molecular profiling in the clinical practice of prostate cancer

Current status of precision medicine in metastatic Pca. The role of Molecular Testing

Therapeutic options for the treatment of prostate cancer



Modified from Cucchiara V. *et al*, 2017



Modified from Sundararajan and Vogelzang, 2014

Key Figure

The Snowflake Theory and Changing Drug Development Paradigms

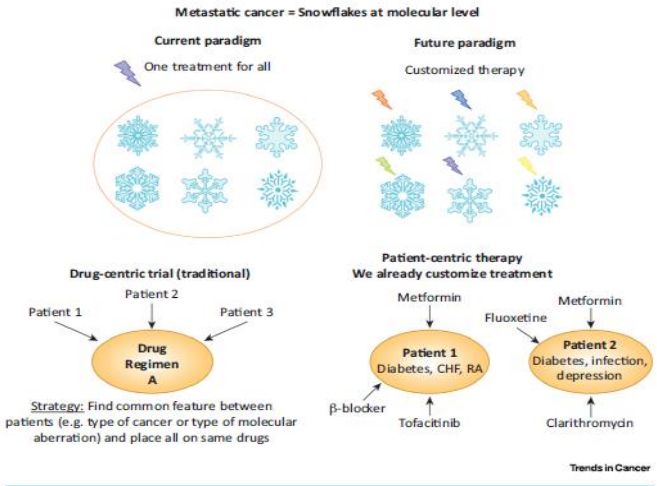
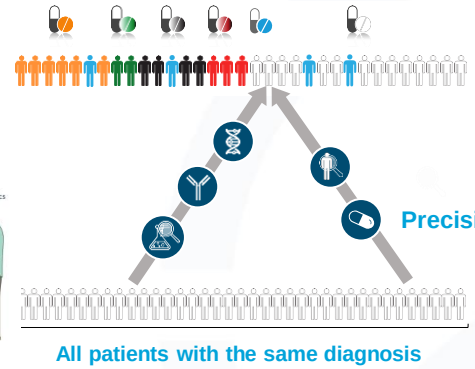


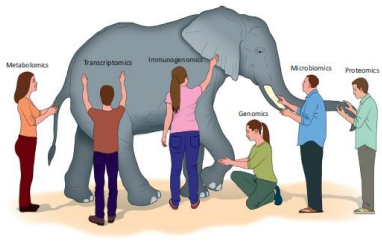
Figure 1. Top panel: cancers are akin to malignant snowflakes. No two snowflakes are identical, and it seems that it is also extremely unusual for two metastatic tumors to have the same genomic fingerprint. As it turns out, if metastatic tumors are akin to malignant snowflakes in their distinctiveness, individual tumors become the ultimate extrapolation of rare and ultra-rare tumors – n-of-one malignancies. Bottom panel: moving from drug-centric to patient-centric trials and care. If each cancer is unique and complex, precisely targeting it requires personalized combination therapy regimens. Bottom panel shows that personalized therapy is already routine in patient care outside the oncology setting. Abbreviations: CHF, congestive heart failure; RA, rheumatoid arthritis.

Subbiah&Kurzrock 2018

Precision Medicine: guiding the best treatment option for each patient

Molecular landscape of each cancer is different → Different people respond differently to therapy





Trends in Cancer

Figure 2. Six Blind Men and Elephants

Beyond genomics – transcriptomics, proteomics, and more. The comprehensive molecular profile of the not-too-distant future may include genomics, transcriptomics, proteomics, metabolomics, microbiomics, epigenomics, mutanomics, lipidomics, and immunogenotyping, and may hence predict response to multiple modalities including immunotherapy and chemotherapy [47–56]. Each of these modalities gives us a piece of the puzzle, akin to the parable of the six blind men who each touch a different part of the elephant, such as the tusk versus the trunk, and therefore have vastly different views of the elephant. Panomics testing is a requisite of comprehensive analysis and may require complex computer algorithms for data integration and computation.

Analysis of tumor molecular landscape can predict treatment sensitivity or resistance

PTEN mutated => Response to inhibitors of PI3K/AKT/mTOR pathway [a]

AZD8186

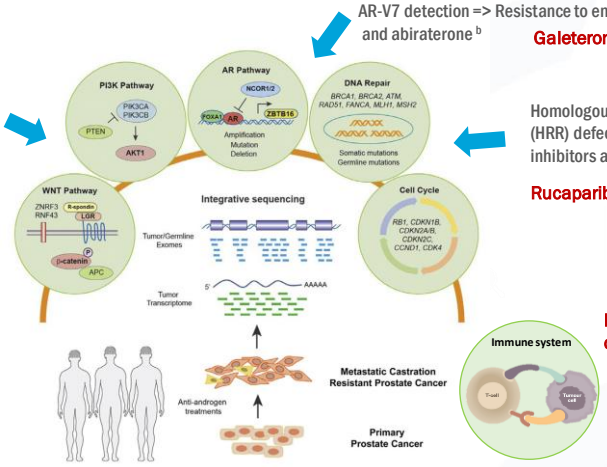
AR-V7 detection => Resistance to enzalutamide and abiraterone [b]

Galeterone

Homologous recombination repair (HRR) defects => Response to PARP inhibitors and platinum salts [c]

Rucaparib

Immune checkpoint inhibitors



Modified from Robinson et al ., 2015

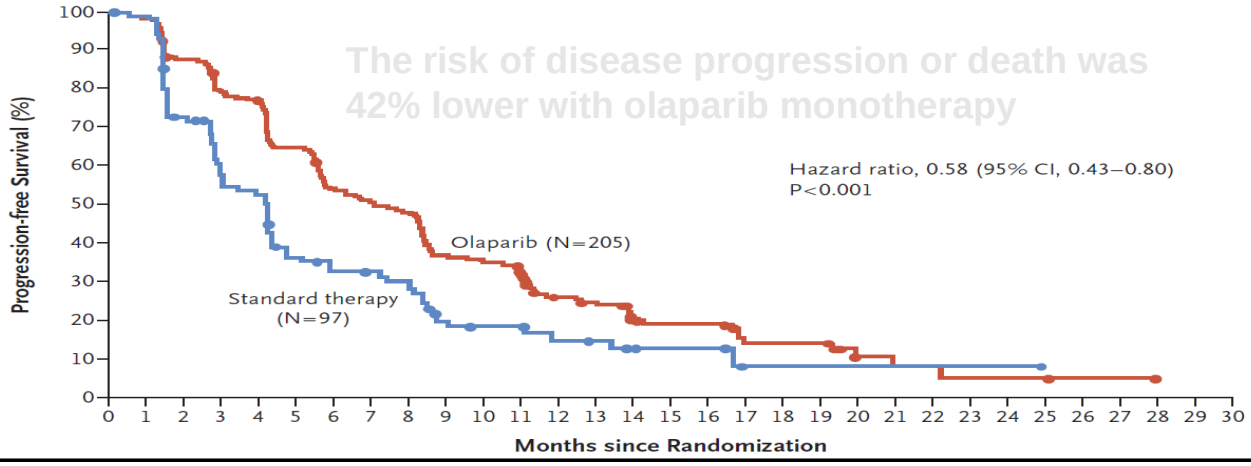
a. doi: 10.3892/ol.2017.5911
b. doi: 10.1056/NEJMoa1315815
c. doi: 10.1158/2159-8290.CD-17-0146

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Poly(adenosine diphosphate–ribose) polymerase inhibitor

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation



Leading Edge

Bench to Bedside

Cell

PARP Inhibitors for Cancer Therapy

8% *BRCA1* germline mutation

3% *BRCA1* somatic mutation

6% *BRCA2* germline mutation

3% *BRCA2* somatic mutation

22,440 Women will receive a new diagnosis of ovarian cancer in the U.S. in 2017

>70 Clinical trials evaluating PARP inhibitors for cancers including

- Ovarian
- Breast
- Prostate
- Head and Neck
- Lung
- Gastric
- Pancreatic
- Endometrial
- Colon
- Rectal
- Germ cell
- Glioblastoma
- Ewing's sarcoma
- Leukemia

1963 Detection of poly(ADP-ribose) in nuclei

1977 Purification of PARP-1

1980 Discovery of benzamide as a competitive PARP inhibitor

Role for nuclear PARPs in DNA damage repair

1987 Cloning of PARP-1 gene

2005 *BRCA1/2*-deficient cells are sensitive to PARP inhibitors

2014 FDA and EMA approval of Olaparib for ovarian cancer

2016 FDA approval of Rucaparib for ovarian cancer and of Olaparib for prostate cancer

1960 1970 1980 1990 2000 2010

Platinum Priority – Prostate Cancer

Editorial by Megan E.V. Caram and David C. Miller on pp. 212–214 of this issue

Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017

Conclusions: The presented expert voting results can be used for support in areas of management of men with APC where there is no high-level evidence, but individualised treatment decisions should as always be based on all of the data available, including disease extent and location, prior therapies regardless of type, host factors including comorbidities, as well as patient preferences, current and emerging evidence, and logistical and economic constraints. Inclusion of men with APC in clinical trials should be strongly encouraged. Importantly, APCCC 2017 again identified important areas in need of trials specifically designed to address them.

8.3. *Somatic mutations*

Recent genomic studies of metastatic prostate cancer have identified new molecular targets in the AR signalling pathway, phosphoinositide 3-kinase pathway, WNT pathway, cell cycle pathways, and perhaps most importantly, in DNA repair pathways [135,141,151].

Fifty-nine percent of the panellists did not vote for DNA sequencing of tumour biopsies in the majority of men with mCRPC in routine daily clinical practice, 37% of the panellists voted for a targeted/panel sequencing approach, and 4% voted for whole genome or exome sequencing.

8.4. *DNA repair testing in daily routine clinical practice*

Recent studies have shown that men with APC commonly have somatic aberrations of genes that make up various elements of the DNA repair machinery with 20–30% of APCs having loss of function of proteins implicated in homologous recombination repair, including *BRCA2*, *BRCA1*, *ATM*, *PALB2*, and others [141]. These aberrations lead to homologous recombination deficiency (HRD) detectable by next-generation sequencing of these genes or of the genomic scars resulting from this repair defect estimated as an HRD score. A clinical trial (TOPARP) of the PARP inhibitor, olaparib, has shown antitumour activity against prostate cancers with HRD [142].

Somatic deleterious aberrations of mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*) have been found in APC, and are possibly associated with ductal pathology, although their precise frequency remains uncertain and is in the range of 5% to 15% [144,155,156].

Table 1 | **Select genomic alterations and their future clinical implications**

Pathway process	Target genes	Drug development	Potential prognostic or predictive biomarkers
AR signalling	*AR*, *NCOR1/2*, *FOXA1*, *ZBTB16*, *SPOP*	N-terminal domain AR inhibitors; dual AR/GR inhibitors	AR-V7 spice variants; *AR* amplification
Cell cycle	*P53*, *MYC*, *CDKN2A*, *RB1*, *AURKA*	DNA-binding domain AR inhibitors; CDK4/6 inhibitors; AURKA inhibitors	*RB1* status; AR low/independence; *AURKA* amplification
DNA repair	*BRCA*, *ATM*, *RAD51*, *MSX2/6*, *SPOP*, *DNAPK*	PARP inhibitors, PD-L1 inhibitors	DNA repair defects
ETS fusion	*ERG*, *ETV1*	HDAC inhibitors, PARP inhibitors	*ETS* fusion status
MAPK pathway	*BRAF*, *RAF1*, *HRAS*	BRAF inhibitors; MEK inhibitors	Mutations or gene fusions
Wnt pathway	*CTNNB1*, *APC*, *ZNRF3*, *RNF43*, *RSPO2*	Porcupine inhibitors	Mutations or gene fusions
PI3K pathway	*PTEN*, *PIK3CA*, *PI3KCB*, *AKT1*	pan-PI3K and dual PI3K–mTOR inhibitors; PI3KCB inhibitors	Mutations or copy number alterations

AKT, v-akt murine thymoma viral oncogene homologue; APC, adenomatous polyposis coli; AR, androgen receptor; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BRCA, breast cancer; CTNNB1, catenin β 1; ERG, v-ets avian erythroblastosis virus E26 oncogene homologue; ETS variant 1; FOXA1, forkhead box A1; GR, glucocorticoid receptor; HDAC, histone deacetylases; HRAS, Harvey rat sarcoma viral oncogene homologue; MSX, msh homeobox; MYC, MYC proto-oncogene protein; NCOR, nuclear receptor co-repressor; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death 1 ligand 1; PIK3C, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit; PTEN, phosphatase and tensin homologue; RAD51, RAD51 recombinase; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; RB1, retinoblastoma 1; RNF43, ring finger protein 43; RSPO2, R-spondin 2; SPOP, speckle type BTB/POZ protein; ZBTB16, zinc finger and BTB domain containing 16; ZNRF3, zinc and ring finger 3.

ONCODNA Platform

- 50 metastatic prostate cancer samples were retrospectively analysed by complete profiling solutions:
  - **OncoDEEP**: Solid biopsy; OR
  - **OncoSTRAT&GO**: solid + liquid biopsy

OncoDNA
THE CANCER THERANOSTIC COMPANY

- The comprehensive analysis includes a combination of:

✓ NGS: Up to 200 genes (mutation, CNV, fusion) → **Targeted therapy**
✓ IHC: Expression/phosphorylation of 7-10 proteins → **Chemo/targeted/Immunotherapy**
✓ Splice-variant (AR-V7) → **Targeted therapy**
✓ MSI, tumor mutation burden (TMB) → **Immunotherapy**

INCLUDES BRCA1/2 and ATM MUTATION ANALYSIS

As a pan-cancer test, FoundationOne® is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature.

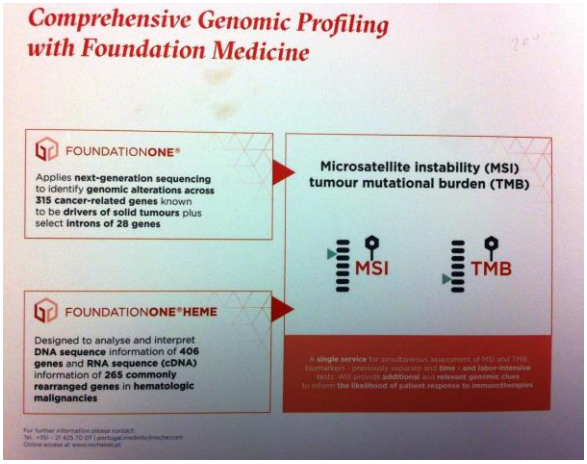
CURRENT GENE LIST

ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCDILG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKC1	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

SELECT REARRANGEMENTS

ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

Foundation Medicine Platform



Liquid biopsies can be used to detect acquired treatment resistance

- Prostate cancer patients treated with hormone therapy or chemotherapy may acquire resistance when on treatment[a]
  - Nearly all men eventually develop progressive disease following ADT[b]

→ Serum PSA measurements lack high sensitivity and specificity for prostate cancer[c]
→ Detection of resistance mechanism-based biomarkers **How?**

- *Serial sampling and non-invasive*
- *Capture tumor heterogeneity*

→ ~~Tissue biopsy~~

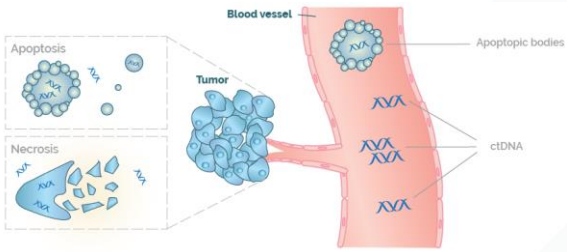
⇒ Through liquid biopsies, physicians can better detect signs of therapy resistance that may be emerging[d]

Earlier therapy switching

a. doi: 10.1016/j.ctrv.2017.04.008
b. https://www.uptodate.com/contents/castration-resistant-prostate-cancer-treatments-targeting-the-androgen-pathway
c. PMID: 11080790
d. https://weillcornellgucancer.org/2017/09/15/liquid-biopsies-in-prostate-cancer-ready-for-prime-time/

Liquid biopsy: focus on ctDNA profiling

- DNA exists as a cell-free form in our blood (cfDNA)
- Healthy person: low concentration of cfDNA
  - Dead cells are cleared afterwards
- Tumor patient: higher levels of cfDNA due to presence of circulating tumor DNA (ctDNA)



It contains DNA mutations of primary and metastatic lesions

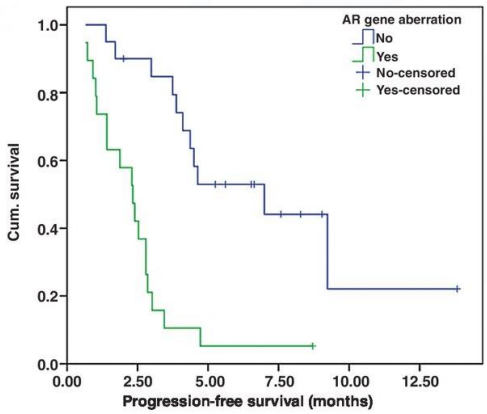
=> Reflects heterogeneity

Liquid biopsy in prostate cancer treatment monitoring

• ctDNA analysis can **guide** Pca treatment with PARP Inhibition, and early detection of reversion mutations associated with **resistance** to treatment[a,b]

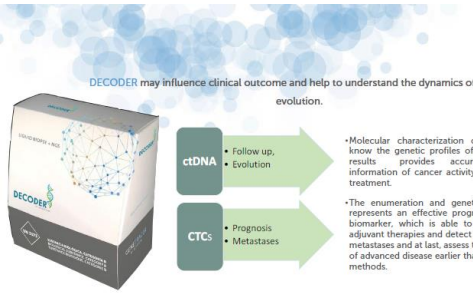
• The decrease of the amount of ctDNA is correlated with prolonged PFS and OS in patients treated with PARP inhibitors[b]

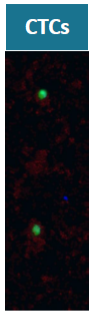
• Presence of AR alteration in ctDNA is associated with reduced PFS in patients treated with enzalutamide[c]



a. doi: 10.1158/2159-8290.CD-17-0146
b. doi: 10.1158/2159-8290.CD-17-0261
c. doi: 10.1158/1078-0432.CCR-14-2666

Liquid Biopsy Decoder Platform





Hotspot genes (SNVs) and short Indels						
ABL1	CDKN2A	FGFR1	HRAS	MLH1	RB1	VHL
AKT1	CHEK2	FGFR2	IDH1	MPL	RET	ARAF
ALK	CSF1R	FGFR3	IDH2	MRE11A	ROS1	ERBB3
APC	CTNNB1	FLT3	JAK2	MTAP	SMAD4	FGFR4
AR	DDR2	FOXA1	JAK3	NOTCH1	SMARCA 4	MAP2K2
ARID1A	DICER1	FOXL2	KDR	NRAS	SMARCB 1	MTOR
ATM	EGFR	GATA3	KIT	PALB2	SMO	NTRK1
BARD1	ERBB2	GNA11	KMT2C	PDGFRA	SPOP	NTRK3
BRAF	ERBB4	GNAQ	KRAS	PIK3CA	SRC	RAF1
BRIP1	ESR1	GNAS	MAP2K1	PTEN	STK11	SF3B1
C11orf65	EZH2	GOPC	MED12	PTPN11	TP53	
CDH1	FBXW7	HNF1A	MET	RAD50	UGT1A1	

Copy number genes (CNVs)						
CCND1	CCND2	CCND3	CDK4	CDK6	EGFR	ERBB2
FGFR1	FGFR2	FGFR3	MET	MYC		

Gene fusions						
ALK	BRAF	ERG	ETV1	FGFR1	FGFR2	FGFR3
MET	NTRK1	NTRK3	RET	ROS1		

Tumor suppressor genes						
APC	FBXW7	PTEN	TP53			

Skipping exon 14 de MET

DECODER BY GENETRACER

82 Genes analizados

Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Jason D. Merker, Geoffrey R. Oxnard, Carolyn Compton, Maximilian Diehn, Patricia Hurley, Alexander J. Lazar, Neal Lindeman, Christina M. Lockwood, Alex J. Rai, Richard L. Schilsky, Apostolia M. Tsimberidou, Patricia Vasalos, Brooke L. Billman, Thomas K. Oliver, Suanna S. Bruinooge, Daniel F. Hayes, and Nicholas C. Turner

A B S T R A C T

Purpose
Clinical use of analytical tests to assess genomic variants in circulating tumor DNA (ctDNA) is increasing. This joint review from ASCO and the College of American Pathologists summarizes current information about clinical ctDNA assays and provides a framework for future research.

Methods
An Expert Panel conducted a literature review on the use of ctDNA assays for solid tumors, including pre-analytical variables, analytical validity, interpretation and reporting, and clinical validity and utility.

Results
The literature search identified 1,338 references. Of those, 390, plus 31 references supplied by the Expert Panel, were selected for full-text review. There were 77 articles selected for inclusion.

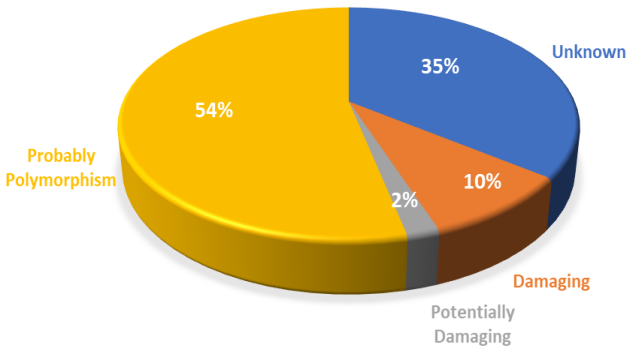
Conclusion
The evidence indicates that testing for ctDNA is optimally performed on plasma collected in cell stabilization or EDTA tubes, with EDTA tubes processed within 6 hours of collection. Some ctDNA assays have demonstrated clinical validity and utility with certain types of advanced cancer; however, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer. Evidence shows discordance between the results of ctDNA assays and genotyping tumor specimens and supports tumor tissue genotyping to confirm undetected results from ctDNA tests. There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial. Given the rapid pace of research, re-evaluation of the literature will shortly be required, along with the development of tools and guidance for clinical practice.

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology and College of American Pathologists

Integrating molecular profiling in the clinical practice of prostate cancer

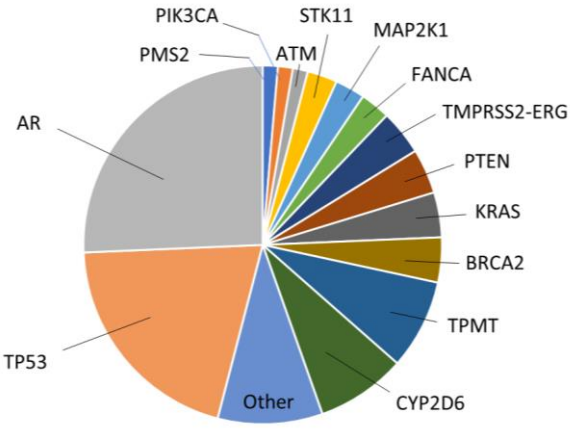
Molecular profiling of metastatic prostate cancer

Distribution of the category of mutations detected by NGS



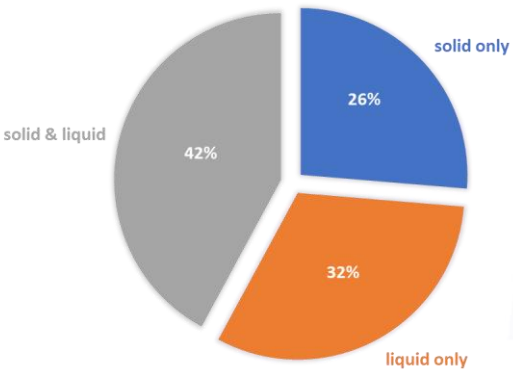
- Average # of mutations per sample:
  - 3.5 (small panel OncoDEEP)
  - 22 (large panel OncoSTRAT&GO)
- In around 72% of the cases, we can detect at least ONE damaging mutation
- ~10% of cases failed or had no detectable mutations
  - ✗ **Low quality of FFPE sample**

Most mutated genes in metastatic prostate cancer



- Pahways most altered:
  - DNA repair
  - Androgen pathway
  - PI3K-mTOR
- AR-V7 was observed in 40% of the samples. This is known to be most frequently altered in advanced or castration-resistant prostate cancer
- TMPRSS2-ERG fusion was observed in 6.4% of patients

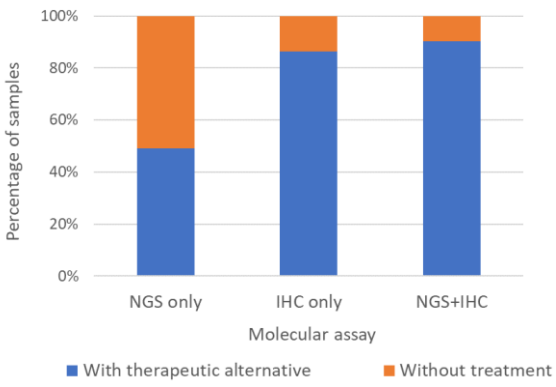
Concordance between solid and liquid biopsies



% Mutations detected in solid only, liquid only or in both biopsies

- **For 23 samples that had both solid and liquid biopsies:**
  - **Concordance between the mutations found in both biopsies was around 42%**
  - **Majority of mutations detected in both solid and liquid were damaging**
  - **70% of the mutations detected ONLY in solid or ONLY in liquid were of unknown significance or probably polymorphism**
  - **Most non-polymorphic mutations observed in the BLOOD were in TP53 (60%).**
  - **Other mutations were found in KRAS, PIK3CA, PTEN, EGFR, ERBB2 and ESR1**

Combining IHC and NGS gives the most useful information regarding potential treatment options



- **NGS analysis alone provided the oncologist with alternative therapy only in 50% of samples**
- **Combining NGS with IHC analysis increases the usefulness of molecular testing**
  - ➢ **In up to 90% of cases, new therapeutic alternative can be recommended**

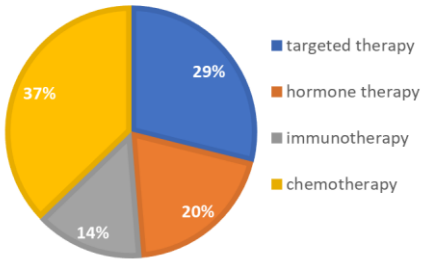
www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 29), pp: 20282-20293

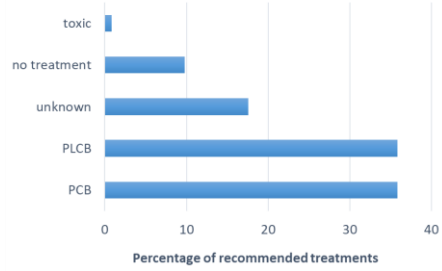
Research Paper

The clinical impact of using complex molecular profiling strategies in routine oncology practice

Jean-François Laes[1], Philippe Aftimos[2], Philippe Barthelemy[3], Joaquim Bellmunt[4,5], Guy Berchem[6], Carlos Camps[7], Ramón de las Peñas[8], Ana Finzel[1], Jesús García-Foncillas[9], Petteri Hervonen[10], Ibrahim Wahid[11], Timo Joensuu[10], Louis Kathan[12], Anthony Kong[13], James Mackay[14], Christos Mikropoulos[15], Kefah Mokbel[16], Jean-Loup Mouysset[17], Sergey Odarchenko[18], Timothy J. Perren[19], Rika Pienaar[12], Carlos Regonesi[20], Shadi Salem Alkhayyat[21], Abdul Rahman El Kinge[22], Omalkhair Abulkhair[22], Khaled Morsi Galal[23], Hady Ghanem[24], Fadi El Karak[25], Angel Garcia[26], Gregori Ghitti[1] and Helen Sadik[1]

Distribution of recommended treatments





* PLCB: potential lack of clinical benefit

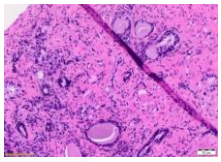
* PCB: Potential clinical benefit

- **Most** recommended treatments based on the complete molecular testing were:
  - ✓ chemotherapies and targeted therapies
  - ✓ Associated with treatment options (potential clinical benefit / resistance)
  - ✓ **Approved**: for prostate cancer (31%), for others (64%)
  - ✓ Mainly based on the combination of IHC+NGS analysis

Integrating genomics in the clinical practice of prostate cancer

A case study in prostate cancer

Utility of complete molecular profiling: a case study in Prostate cancer



Male – 64 years old

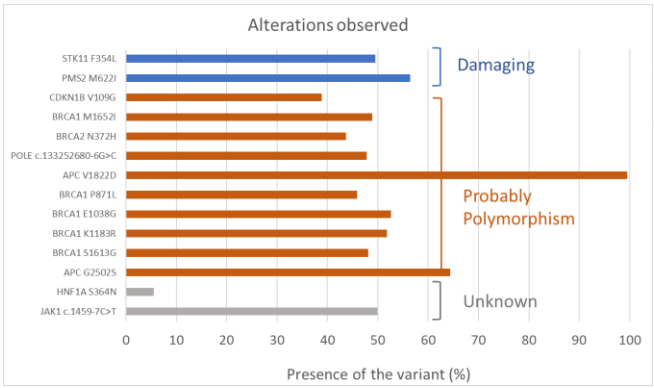
DIAGNOSIS: Metastatic prostate cancer

CURRENT SITE OF METASTASES: Bones, Spleen

PREVIOUS THERAPY: Hormone therapy

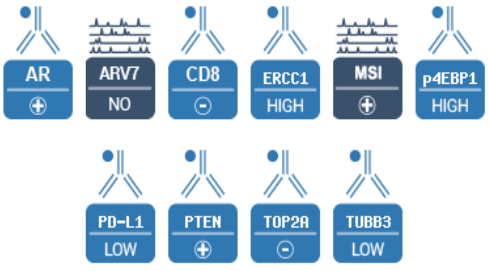
CURRENT THERPAY: Taxane therapy

Results of the NGS analysis



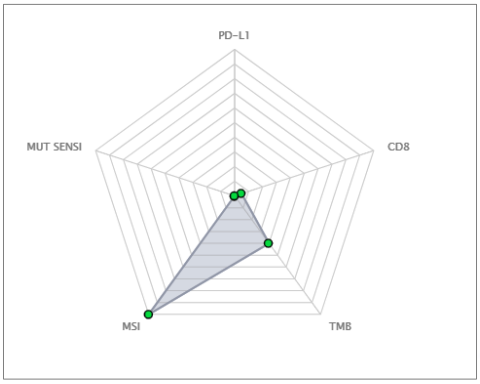
- Many mutations observed (especially in BRCA1/2); most are considered polymorphisms
- A damaging STK11 mutation
  - ✓ mTOR inhibitors could be of benefit
- A damaging PMS2 mutation
  - ✓ PMS2 is a component of the DNA mismatch repair system (MMR)
  - ✓ Inactivating of PMS2 can lead to microsatellite instability
  - ✓ Potential response to immune checkpoint inhibitors

Results of the IHC analysis and other tests



- High AR expression + NO AR-V7 mutation
  - ✓ Potential benefit to **AR inhibitors** (enzalutamide/ abiraterone)
- Low TUBB3 expression
  - ✓ Potential benefit to **taxane therapy**
- Low TOP2A expression
  - × Potential lack of benefit to **topo II inhibitors**
- High ERCC1 expression
  - × Potential lack of benefit to **platinum therapy**

Analysis of immunotherapy response



5 tests that could predict response to immunotherapy were performed:

1. **PD-L1 expression**: negative (0%)
2. **CD8 expression**: low (1%)
3. **TMB**: Medium
4. **MSI**: High
5. **Mutation of sensitivity:** Not present

➡ Based on these data, PD-1/PD-L1 inhibitors- **approved for MSI-high solid tumors**- are associated with potential clinical benefit for this patient

Many potential treatment alternatives based on this complete molecular profiling

- **An inactivating mutation of STK11 was observed, suggesting that the mTOR pathway could be activated**
  - **High p4EBP1 expression (by IHC) confirms pathway activation**
  - **mTOR inhibitors could be of potential benefit**
- **An inactivating mutation of PMS2 was observed which can result in microsatellite instability**
  - **Analsysis of MSI confirms genomic instability (MSI-H)**
  - **Pembroluzimab is approved for MSI-H solid tumors**
- **The additional IHC analysis can shed light on the best option for the next chemotherapy regimen:**
  - **Taxane-based chemotherapy could be of benefit**
  - **Topoisomerase II inhibitors and platinum chemotherapy could be of potential lack of benefit**

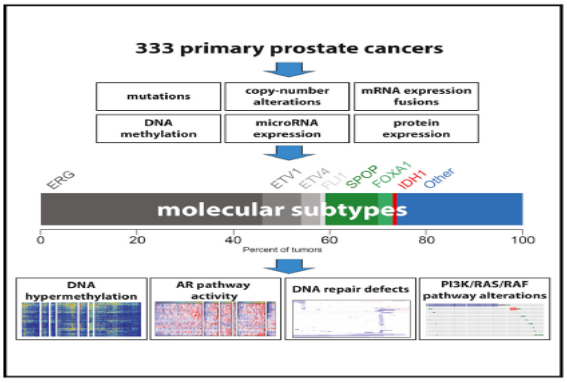
The long tail of oncogenic drivers in prostate cancer. Armenia et al, Nature Genetics 2018

- Prostate cancer represents a substantial clinical challenge because it is difficult to predict outcome.
- We sequenced the whole genomes of 112 primary and metastatic prostate cancer samples. From joint analysis of these cancers with those from previous studies (930 cancers in total)
- Found evidence for 22 previously unidentified putative driver genes harboring coding mutations, as well as evidence for *NEAT1* and *FOXA1* acting as drivers through noncoding mutations.
- Through the temporal dissection of aberrations, we identified driver mutations specifically associated with steps in the progression of prostate cancer, establishing, for example, loss of *CHD1* and *BRCA2* as early events in cancer development of *ETS* fusion-negative cancers.

Cell

The Molecular Taxonomy of Primary Prostate Cancer

Graphical Abstract



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In Brief

Molecular analysis of 333 primary prostate carcinomas reveals substantial heterogeneity and major subtypes among patients, as well as potentially actionable lesions valuable for clinical management of the disease.

Highlights

- Comprehensive molecular analysis of 333 primary prostate carcinomas
- Seven subtypes defined by ETS fusions or mutations in *SPOP*, *FOXA1*, and *IDH1*
- Substantial epigenetic heterogeneity, including a hypermethylated *IDH1* mutant subset
- Presumed actionable lesions in the PI3K, MAPK, and DNA repair pathways

Prostate Cancer Prognosis, Treatment Response Informed by Breast Cancer Expression Signature

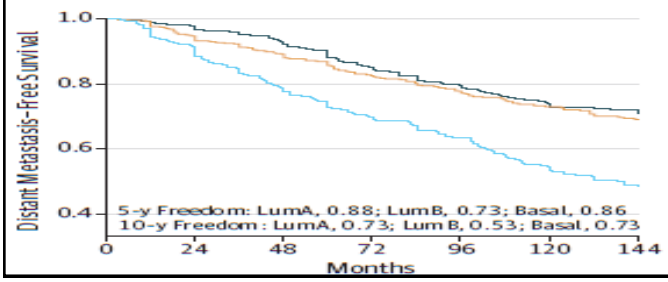
May 12, 2017 | staff reporter

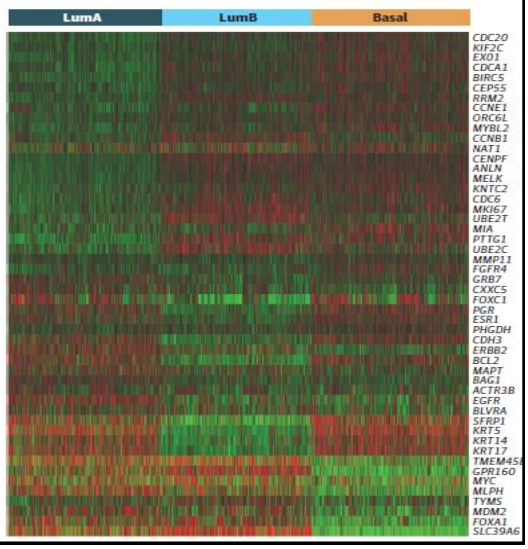
JAMA Oncol May 2017

JAMA Oncology | Original Investigation

Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy

3782 patients





Take home message…

- Prostate cancer progression is associated with genetic heterogeneity
- New molecular studies/tests are being developed for recognizing PCa risk and aggressive disease, and provide a personalized approach to treat these patients
- Precision Medicine seems to be:
  - More accurate, more beneficial
  - More cost effective (personalizing care and monitoring it)
  - Globalization of medicine
- Personalized medicine, liquid biopsy and immunotherapies have the potential to improve survival of metastatic prostate cancer patients; but there are still many hurdles to overcome

Champalimaud Foundation

Thank you!

Questions?