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Therapeutic Use of Genetic Testing in Advanced Prostate Cancer

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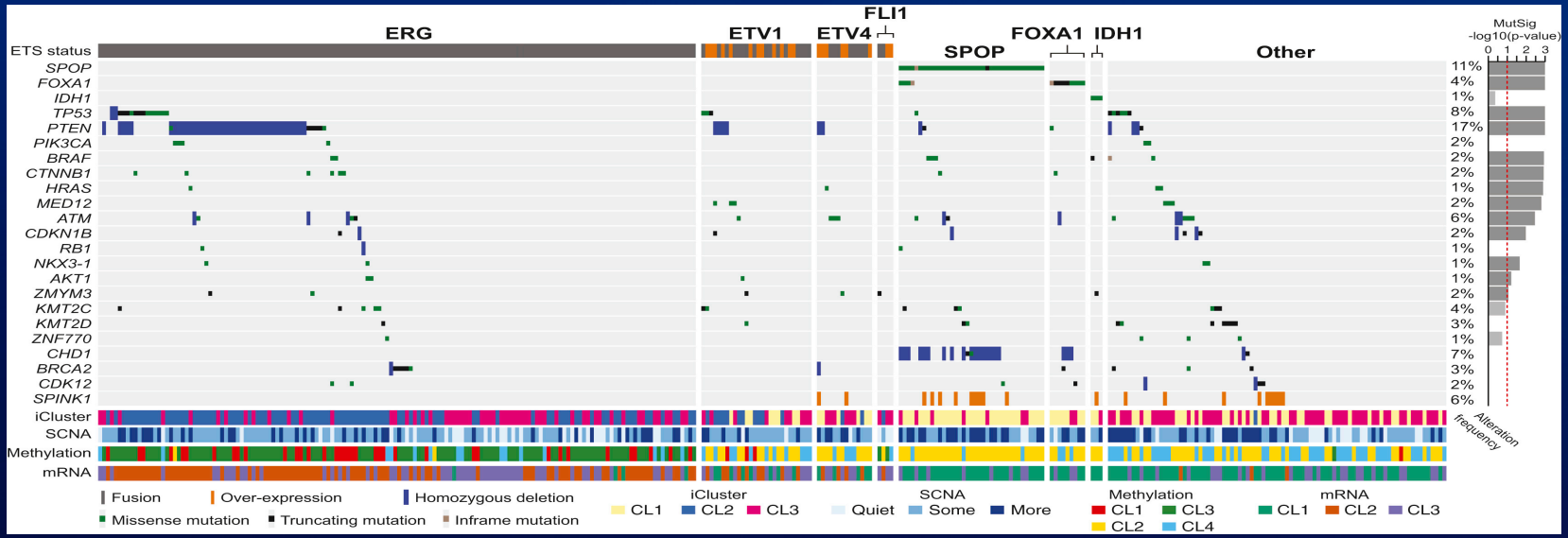
Roles for Genetic Testing in Advanced Disease

- Identification of germline variants
- Prognosis
- Predicting response to therapy
- Characterizing disease evolution/disease states

Genetic Diversity in Primary Prostate Cancer

The Cancer Genome Atlas



TCGA Research Network. Cell 2015; 163(4): 1011-1025.

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

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	—	—	—	—

* The denominators for genes for which data were censored were 561 (*BAP1*, *BARD1*, *BRIP1*, and *FAM175A*), 437 (*GEN1*), and 534 (*CHEK2*).
† Data are for the persons in the Exome Aggregation Consortium, minus the patients included in the TCGA studies. The percent with a mutation was calculated on the basis of the total number of persons for whom sequence coverage was adequate for the given allele, which differed slightly from the total of 53,105 persons, depending on the specific mutation.
‡ Data for metastatic cases with inadequate sequencing for this gene were censored.

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

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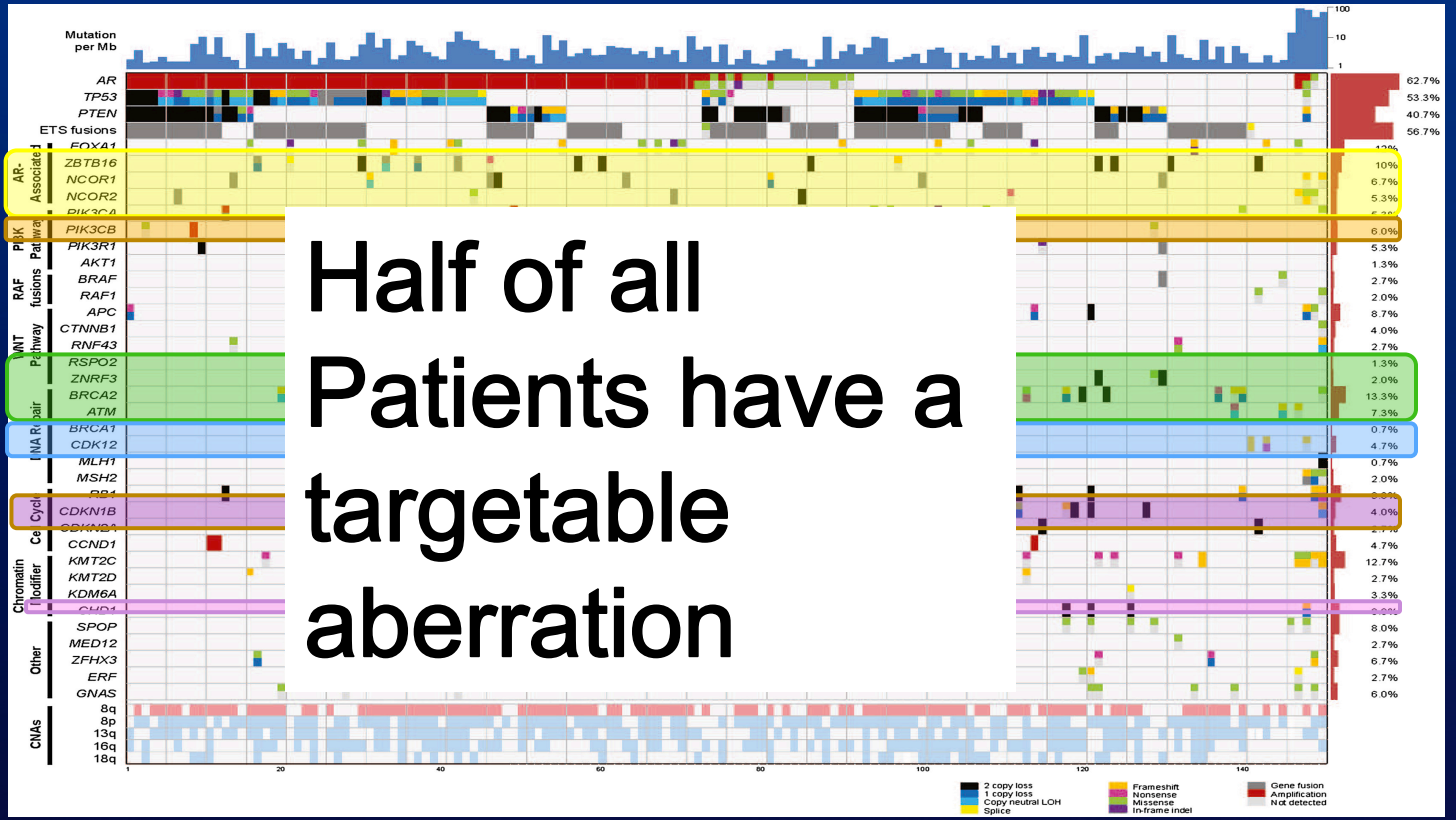
Genetic Diversity in Metastatic Prostate Cancer



Half of all Patients have a targetable aberration

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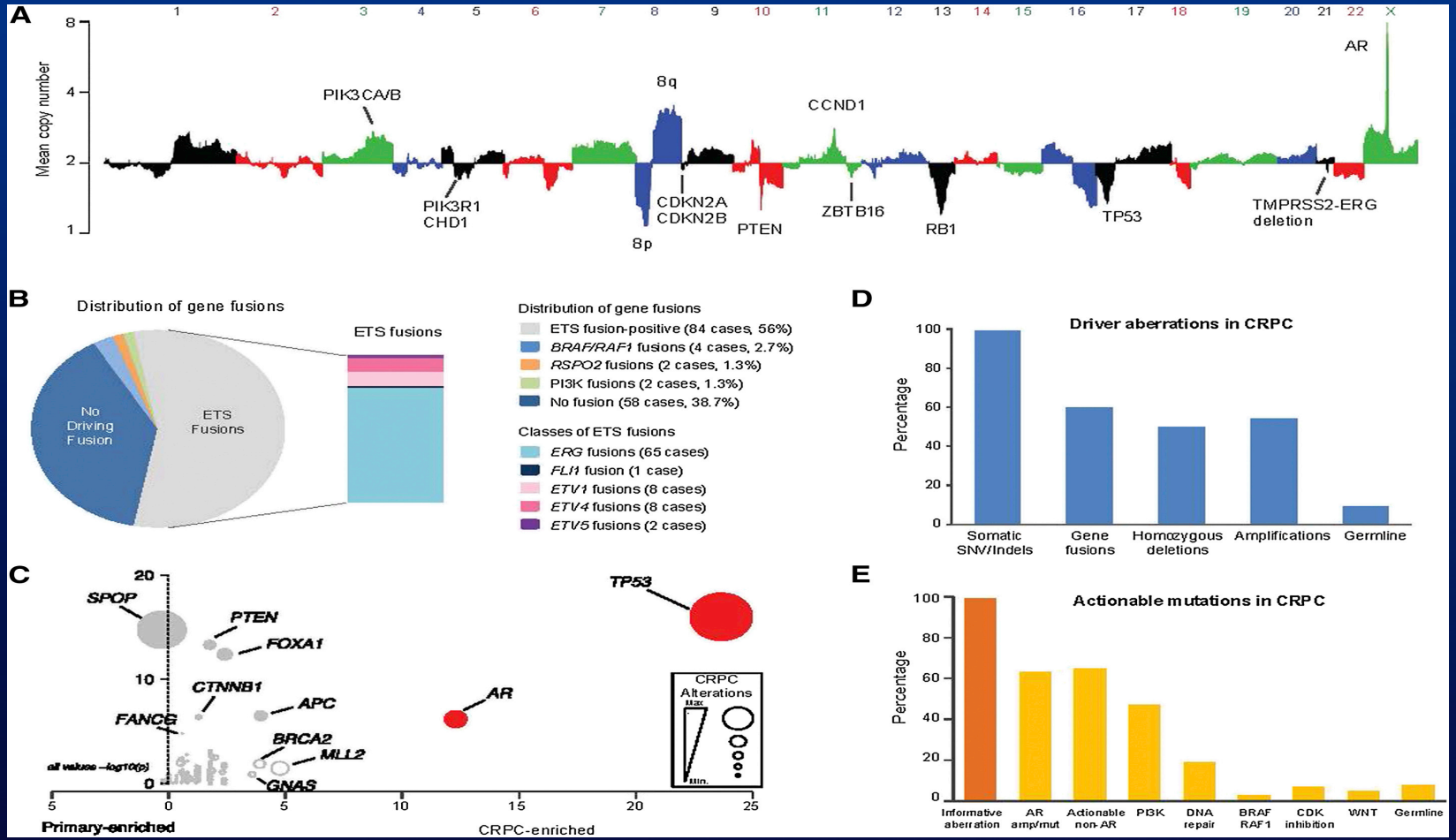
Robinson D. et al. Cell 2015; 161(5):1215-1228



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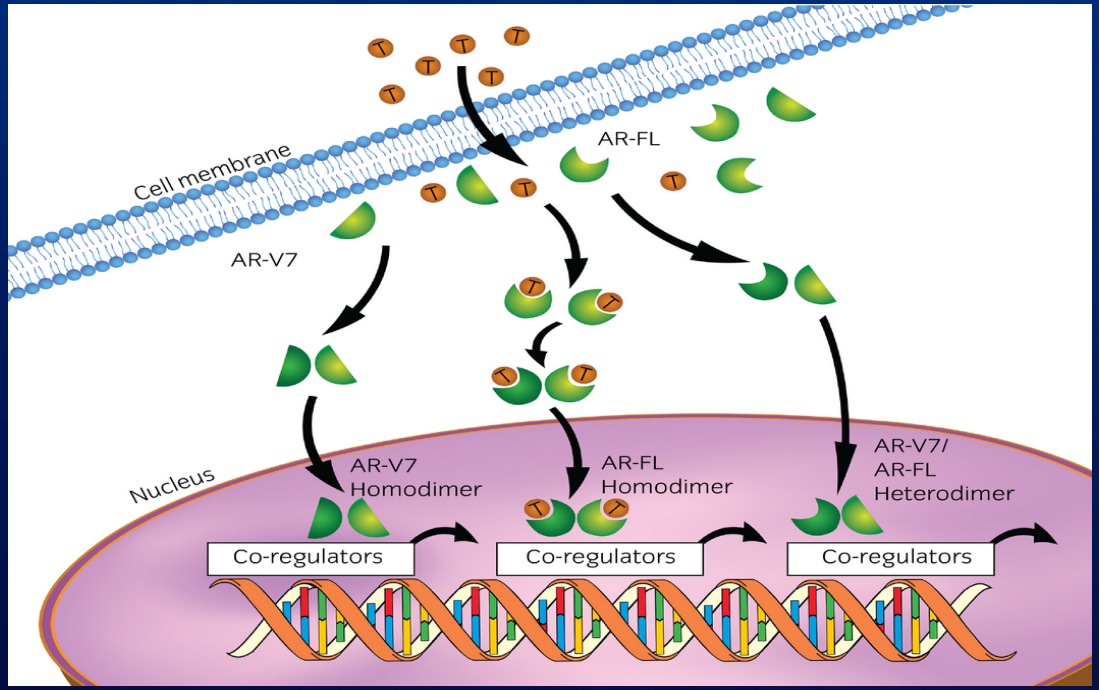
Robinson D. et al. Cell 2015; 161(5):1215-1228

The Past as Prelude

- Biomarker driven treatment is common in most cancers
  - Breast Cancer- ER/PR, Her2
  - Colon Cancer- KRAS, BRAF, NRAS
  - Lung Cancer- EGFR, ALK, ROS-1
  - Melanoma- BRAF, NRAS, KIT, NF1, GNAQ
- Argument: Progress in Prostate Cancer has been held back by nihilism and conservatism

Emerging Data
AR-V7 in mCRPC



Bryce, AH at al. International Journal of Urology Volume 23, Issue 8, pages 646-653, 3 JUN 2016 DOI: 10.1111/iju.13134

AR-V7 in mCRPC

Response to Treatment in AR-V7–Expressing Prostate Cancer

Study	Therapeutic	Prevalence of AR-V7 (%)	PSA Response AR-V7+ vs AR-V7– patients (%)	AR-V7 Assay
Antonarakis et al. (25)	Abiraterone, Enzalutamide	19% 39%	0% vs 68% (P<0.01) 0% vs 53% (P<0.01)	CTC-derived mRNA (AdnaTest, Qiagen)
Steinestel et al. (27)	Abiraterone or Enzalutamide	64%	7% vs 63% (P=0.01)	CTC-derived mRNA (AdnaTest, Qiagen)
Todenhofer et al. (28)	Abiraterone	11%	0% vs 42% (P=0.04)	Whole-blood mRNA (PAXgene, PreAnalytiX)
Antonarakis et al. (29)	Docetaxel or Cabazitaxel	46%	41% vs 65% (P=0.19)	CTC-derived mRNA (AdnaTest, Qiagen)
Onstenck et al. (30)	Cabazitaxel	55%	8% vs 22% (P=0.70)	CTC-derived mRNA (CellSearch, Janssen)

Bryce, AH at al. International Journal of Urology Volume 23, Issue 8, pages 646-653, 3 JUN 2016 DOI: 10.1111/iju.13134

Emerging Data
BRCA as a Target in mCRPC

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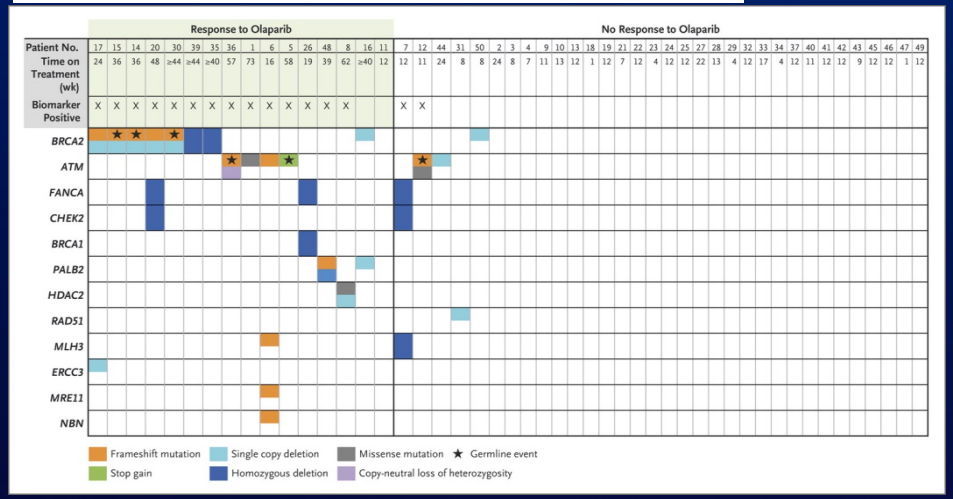
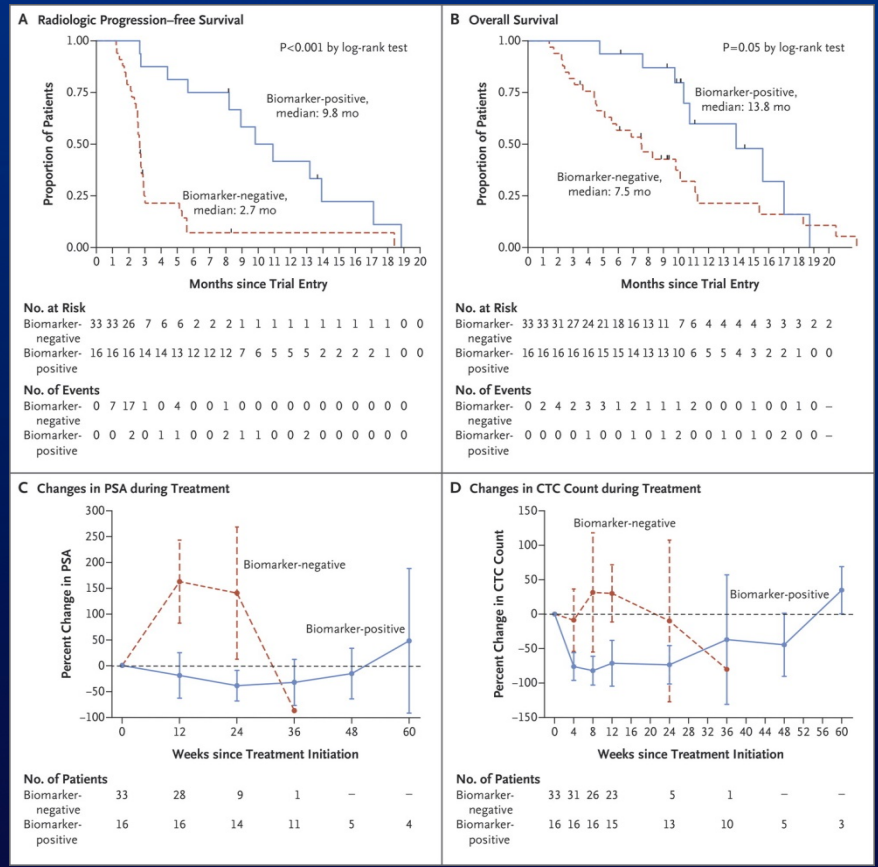
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

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





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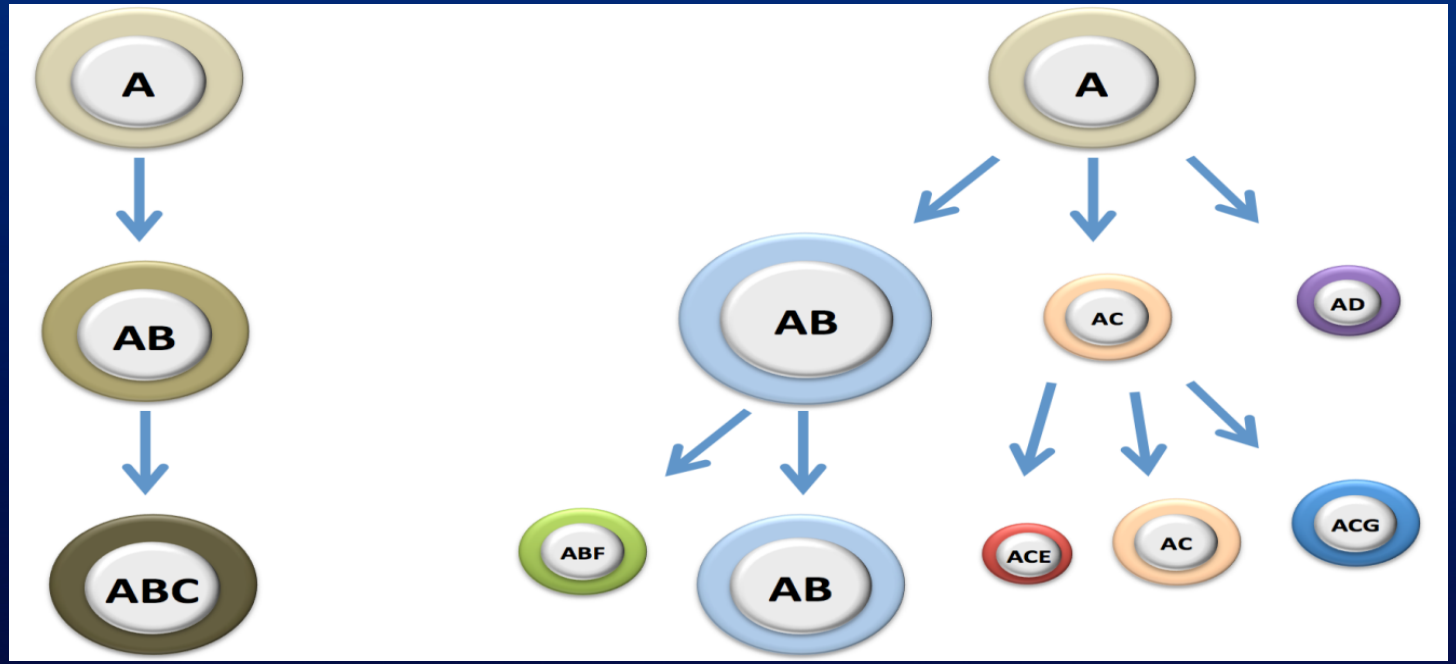
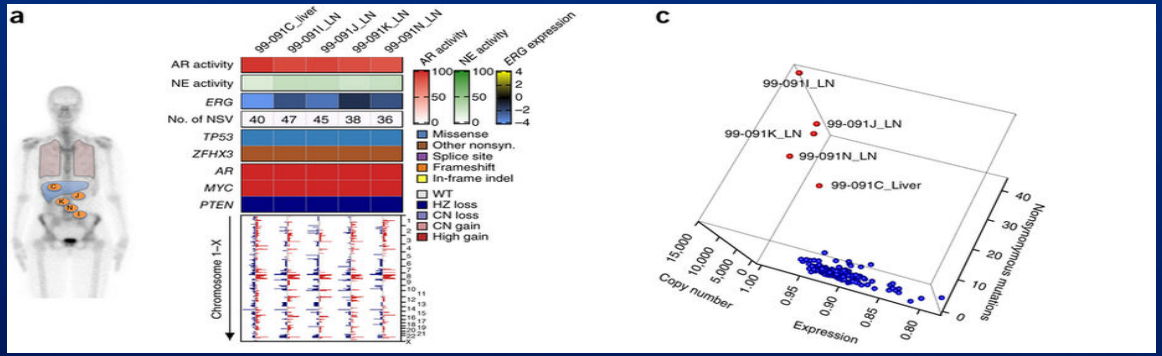
Mateo J et al. N Engl J Med 2015;373:1697-1708.

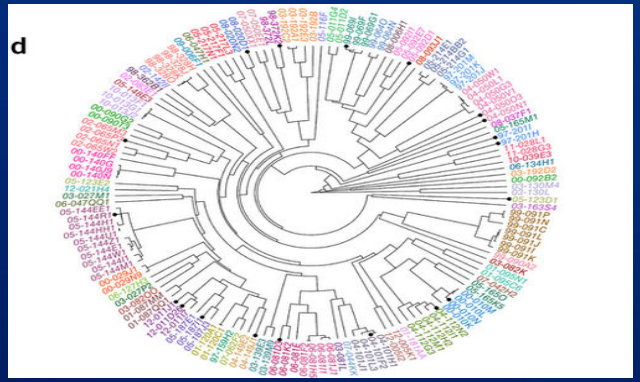
Clonality and Heterogeneity

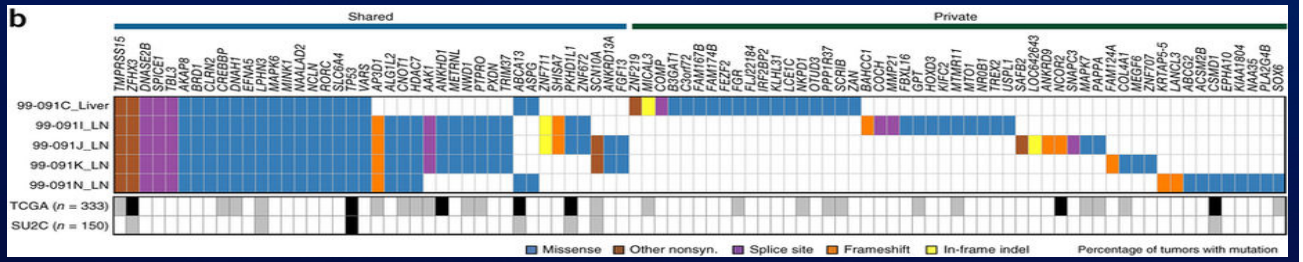


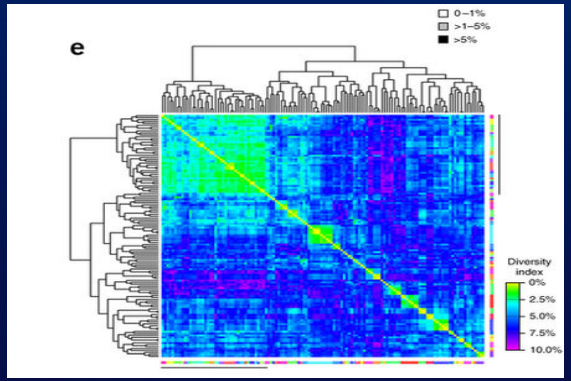
Braggio et al. Leukemia 2012;26(7):1698-1701

Tumor Heterogeneity





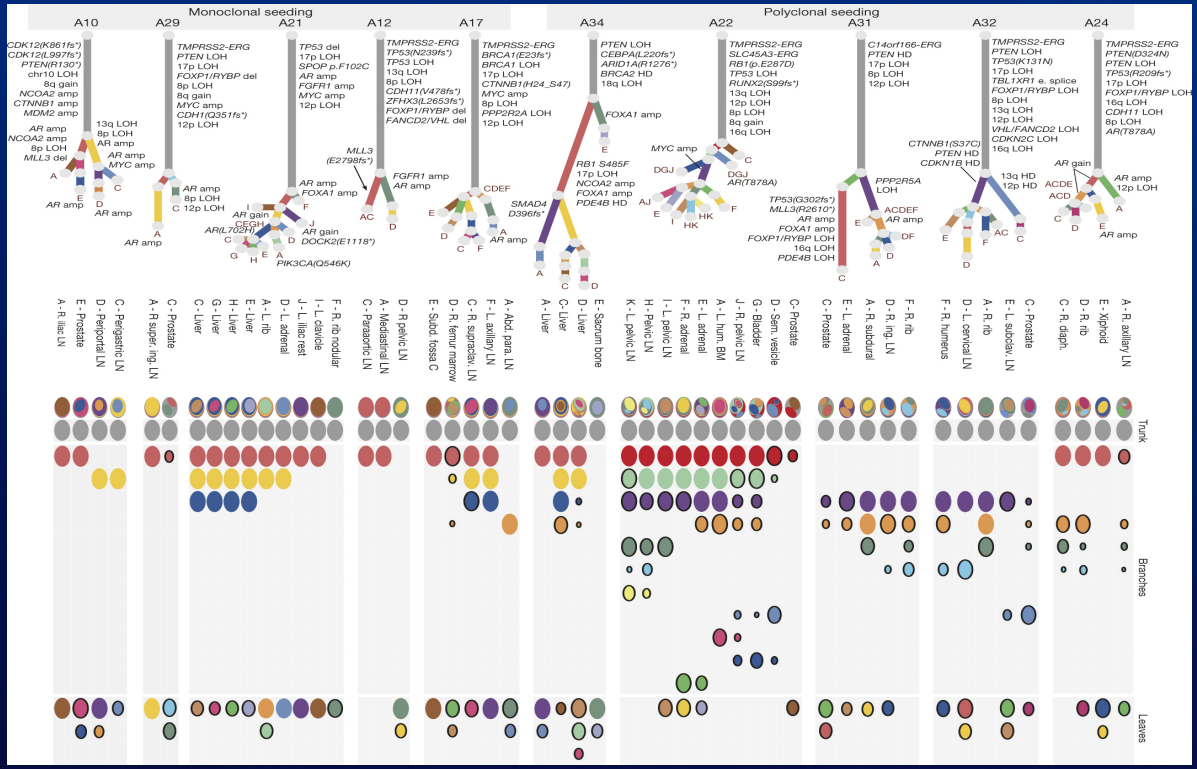




Kumar A, et al. Nature Med 2016; 22: 369-378

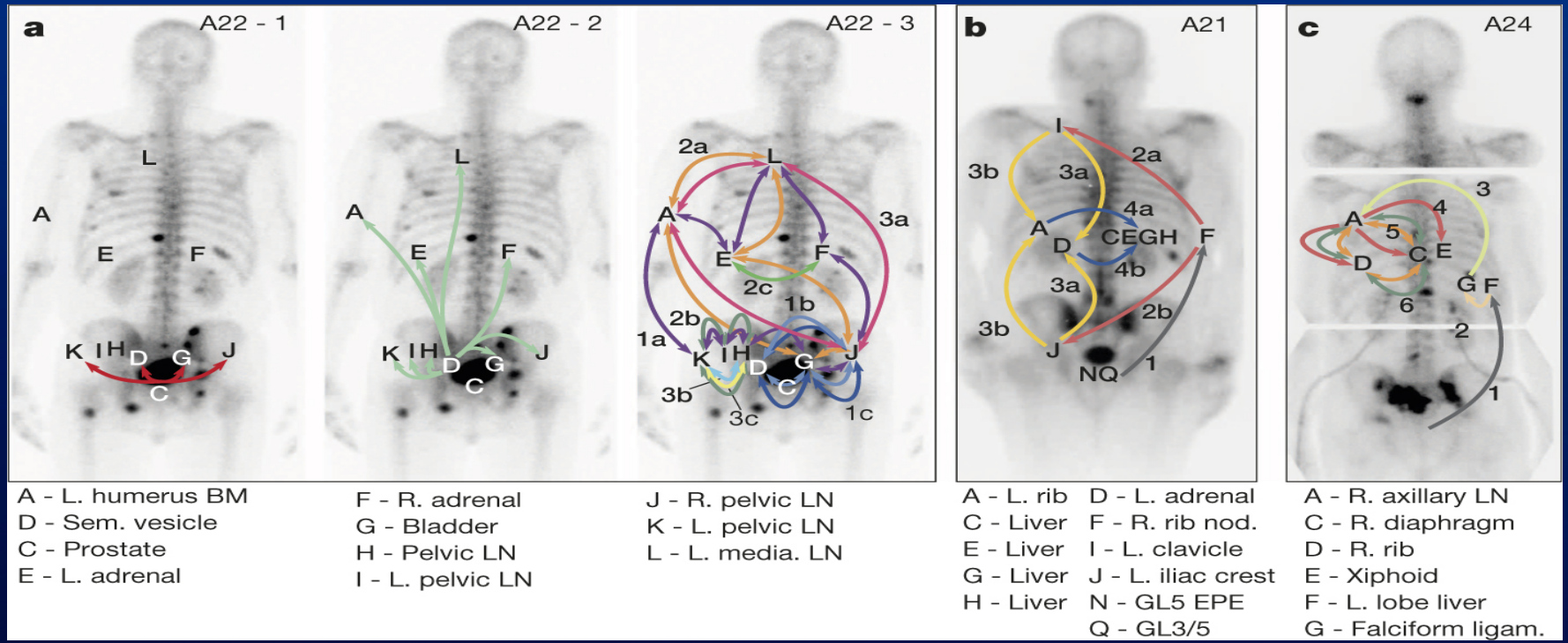
Tumoral Evolution

Subclonal structure within 10 metastatic lethal prostate cancers.



G Gundem *et al. Nature* **000**, E1-E5 (2015) doi:10.1038/nature14347

Metastasis-to-metastasis seeding occurs either by a linear or by a branching pattern of spread.



G Gundem *et al. Nature* **000**, E1-E5 (2015) doi:10.1038/nature14347

nature

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Back to the Clinic

- NCI currently lists over 100 approved targeted cancer therapies
  - Non AR targeted therapies in PCa: 0
- You can’t find what you’re not looking for
- Clonality and Evolution are long recognized clinical realities
  - Aberrations accumulate over time
    - So sequence like you are voting in Chicago… Early and Often

“When you change the way you look at things, the things you look at change.”

“Experiment is the only means of knowledge at our disposal. Everything else is poetry, imagination.”

“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”

Max Planck 1858-1947
Nobel Prize for Physics
1918

