

GENE ANALYSIS IS IMPERATIVE IN ADVANCED PROSTATE CANCER AND BIPOLAR HIGH TESTOSTERONE TREATMENT

RVA US TOO SEPT 19, 2019
PETER MOON

Knowing your Gene Mutations can help
you to:

Choose the more effective treatments
and avoid lost treatment time and side
effects of trial and error failures!!!

My History of Gene Analysis- Germline only so far no Somatic!
Germline id what cause family inherited cancer -2brothers&GF

Germ line is DNA inherited from parents but somatic gene mutations occur from defects formed as cancer grows!

Somatic mutations in body cells not passed on in the germline but changes the characteristics of the cancer usually to make it more aggressive.

I have been taking Polyphenol (green tea, curcumin & quercetin) anti-oxidants and anti-inflammatories for 20 years to Prevent Somatic Mutations!!! and age well.

My Germline Mutation Analysis: 23 & Me(\$100)&Prometheus.com (\$5)

- ▶ The variant **T** allele of the TMPRSS2 SNP GENE, rs12329760 (C,T), was positively associated with TMPRSS2-ERG fusion with multiple copies of the gene fusion (p=0.03).
- ▶ Conclusion: If replicated it contributes to determining the subset of men who will go on to develop metastatic prostate cancer. Prostate cancer T allele appears to have lower survival, and higher recurrence.
- ▶ Dutasteride can inhibit ERG fusion-positive Cells & with anti-androgen, significantly reduce the tumor burden. Anti-androgens used with dutasteride could augment the treatment of ETS-positive prostate cancer. **History of Me and my Brothers!!**
- ▶ **Role of Dutasteride in Pre-Clinical ETS Fusion-Positive Prostate Cancer Models: The Prostate 72:1542^1549 (2012)**

PCa Mutation Tests using cancer tissue (F-1) or Circulating Ca cells&DNA(360 & F1)

Foundation 1 Versus Guardian 360

F-1 = CHUNG JH, JCO PRECIS ONCOL. 2019;DOI:10.1200/PO.18.00283. 07/01/2019

4.5 MUTATIONS-PER-TUMOR-WITH 57% TARGETABLE TREATMENTS

TP53 (43.5%), PTEN (32.2%), TMPRSS2ERG (31.2%), AR (22.5%), MYC (12.3%), BRCA2 (9.8%), RB1 (9.7%), APC (9.3%), MLL3/KMT2C (7.8%), SPOP (7.7%), PIK3CA (6%) AND CDK12 (5.6%).

GUARDIAN 360 - LIQUID BIOPSY IS WHEN NO BIOPSY CAN BE PERFORMED

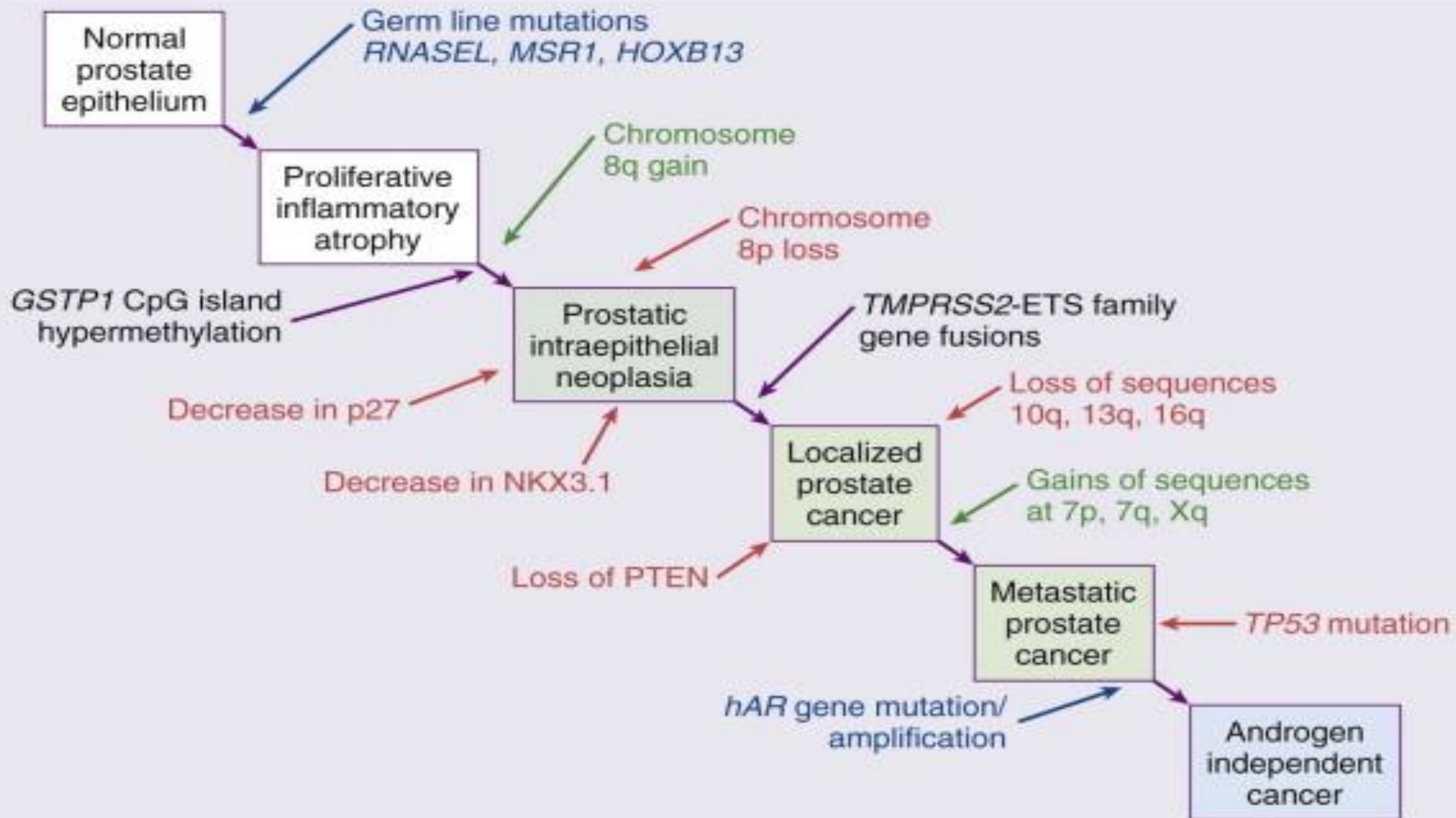
1. WHEN NO TUMOR TISSUE IS AVAILABLE FOR AN EVAL

2. WHEN ARCHIVED BIOPSIES OR RESULTS ARE OUTDATED

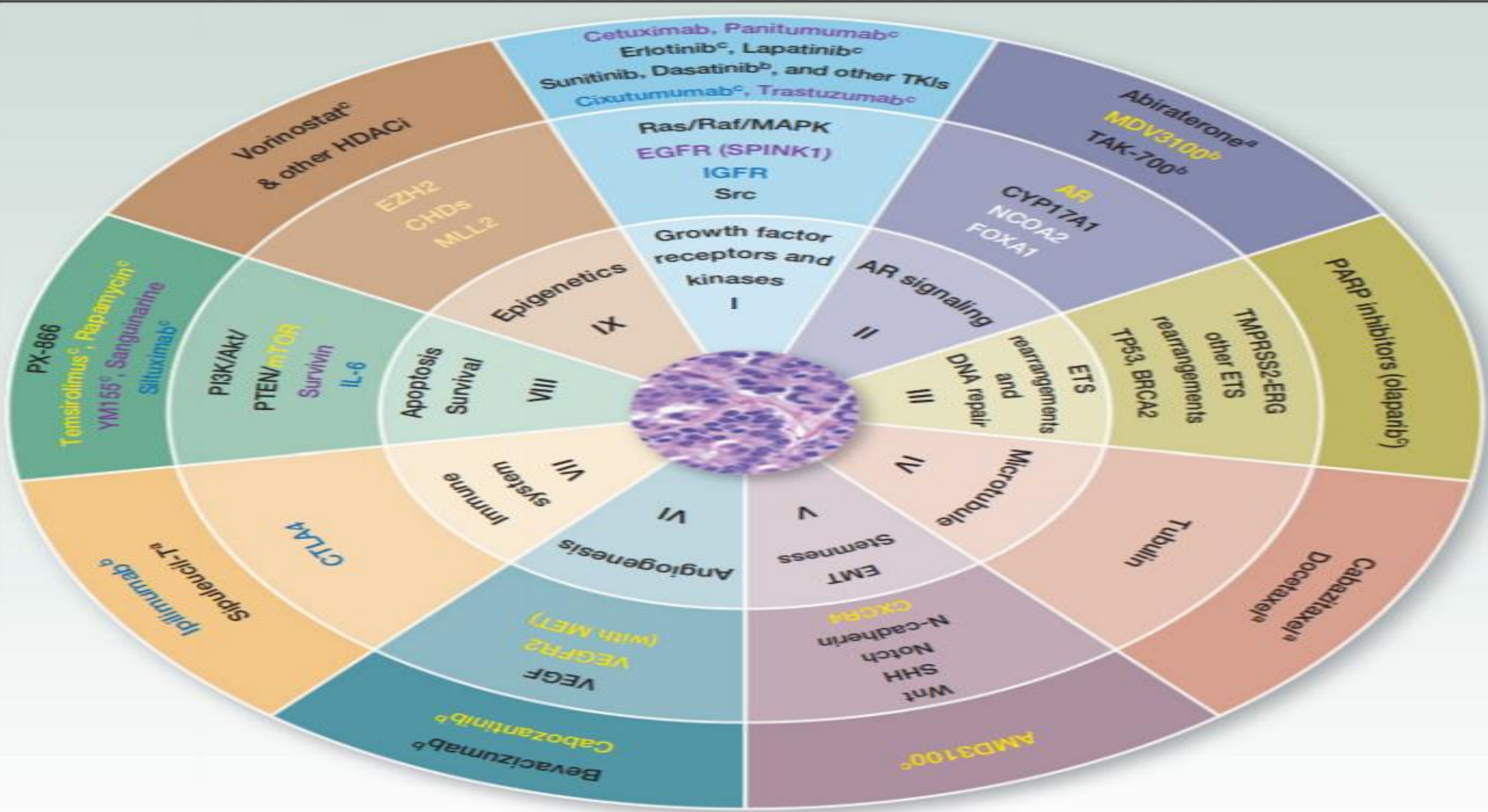
3. ONE OR MORE INTERVENTIONS HAVE OCCURRED SINCE THE

LAST BIOPSY- 73 MUTATIONS CHECKED BUT **NO TP53**

[HTTPS://ASCOPUBS.ORG/DOI/10.1200/PO.19.00014](https://ascopubs.org/doi/10.1200/PO.19.00014)



- Figure 2. Considerations for targeted therapy based on key pathways perturbed in prostate cancer. Current standard of care involves active surveillance for low risk localized prostate cancers; hormonal therapy, radical prostatectomy, or radiation therapy for higher-risk localized disease; and androgen pathway suppression for metastatic disease with chemotherapy and immunotherapy at the time of disease progression. This figure shows the potential for targeted therapy in molecularly defined subtypes of prostate cancer. Genomic alterations are classified on the basis of the class of molecular pathways affected (inner circle). Therapeutic agents (outer circle) targeting respective pathways are grouped with the genes (middle circle) commonly altered in these pathways, coordinated by color wherever possible. Selected agents in various phases of clinical trials are superscripted: a FDA-approved, b phase III clinical trials, c phase I/II clinical trials; preclinical development not marked. Although the antiandrogen therapy abiraterone, the microtubule inhibitor cabazitaxel, and the immunotherapy sipuleucel-T are already in clinical use, aberrations of NCOA2 and FOXA1 genes (white) are recent findings, the functional significance and therapeutic implications of which await further investigation. HDACi, histone deacetylase inhibitor. Prostate Cancer Genomics www.aacrjournals.org Clin Cancer Res; 19(15) August 1, 2013

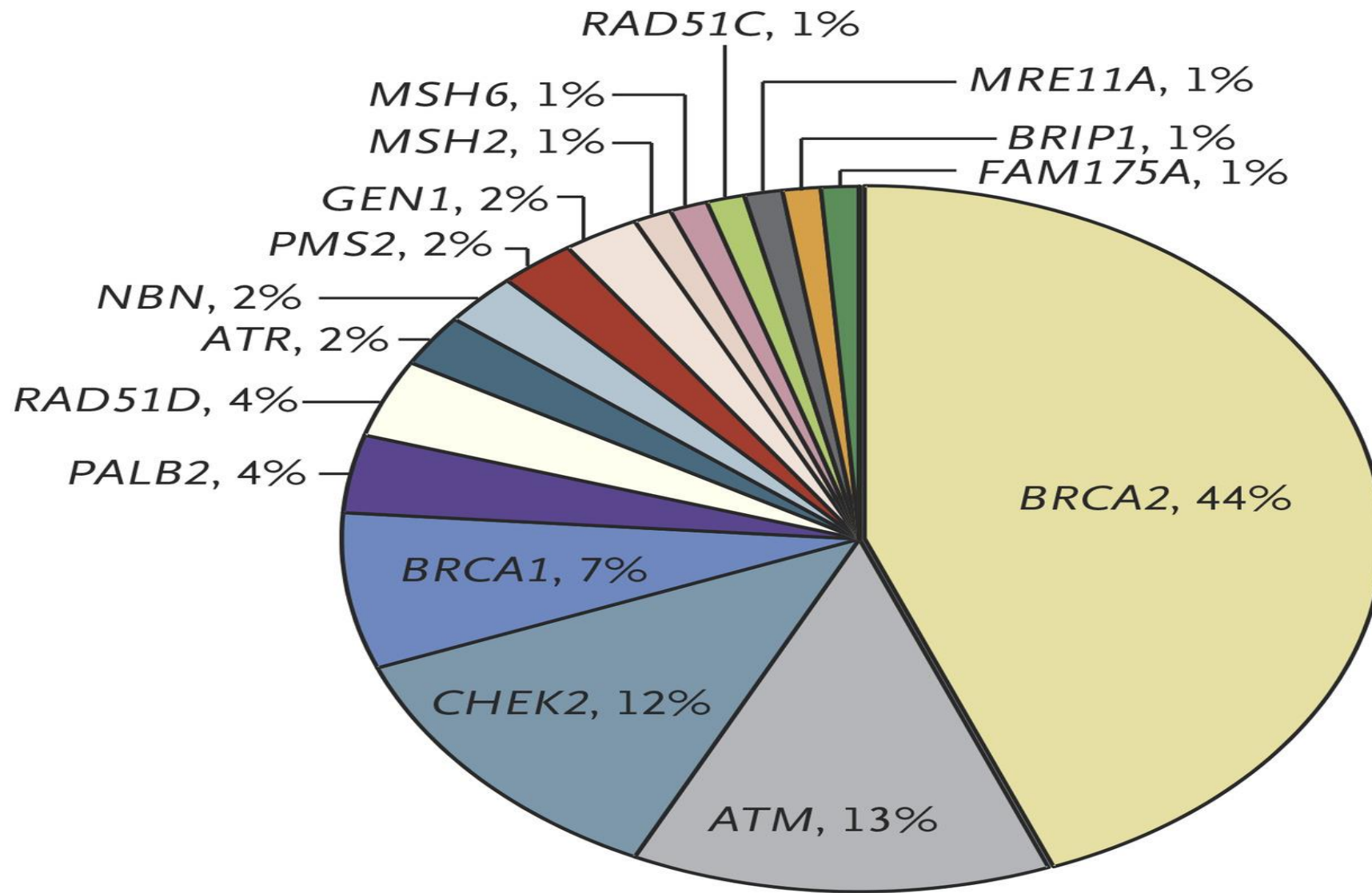


▶ Possible Treatments for PCa Mutations(300 genes)

- ▶ TMPRSS2-ERG → Casodex, Avodart and Metformin (PARPs Do not work)
- ▶ P10 deletion → PARP Inhibitor (Olaparib) median PFS 12months
- ▶ BRACA1/2 – PARP Inhibitors Olaparib works well on DNA repair mutations
- ▶ P53 – PARP inhibitors Olaparib
- ▶ ATM- “ “ “
- ▶ Chek2- “ “ “
- ▶ PARP Inhibitors do not act long enough! Median PFS ~6 to 12 months!
- ▶ BRCA1/2 of 80% (24/30; m PFS 8.1mo); PALB2 57% (4/7; mPFS 5.3mo); ATM 37% (7/19; mPFS 6.1mo)-**TOPARP Clinic study-Fatigue 3&4 level side effect.**
- ▶ **AR V-7+ =1% Germline; Somatic V7+~ 30% after CRPC ADT progression**

Taxane doubles median survival over AR agonists (Xtandi) not AR V-7minus

- ▶ <https://www.targetedonc.com/publications/targeted-therapy-news/2017/may-2017/role-of-parp-inhibitors-clarified-in-prostate-cancer>



- ▶ Bipolar Androgen Therapy = **Hi dose T** repeated (30d/3 Mo cycle) with **ADT**
- ▶ Works for PCa Mutations that respond to PARP Inhibitors
- ▶ **Hi Dose Testosterone** in BRCA2- & ATM Mut. PCa, P53 & P10 deficient
- ▶ Eur Urol. 2017 March ; 71 (3): 499. Teply- john Hopkins

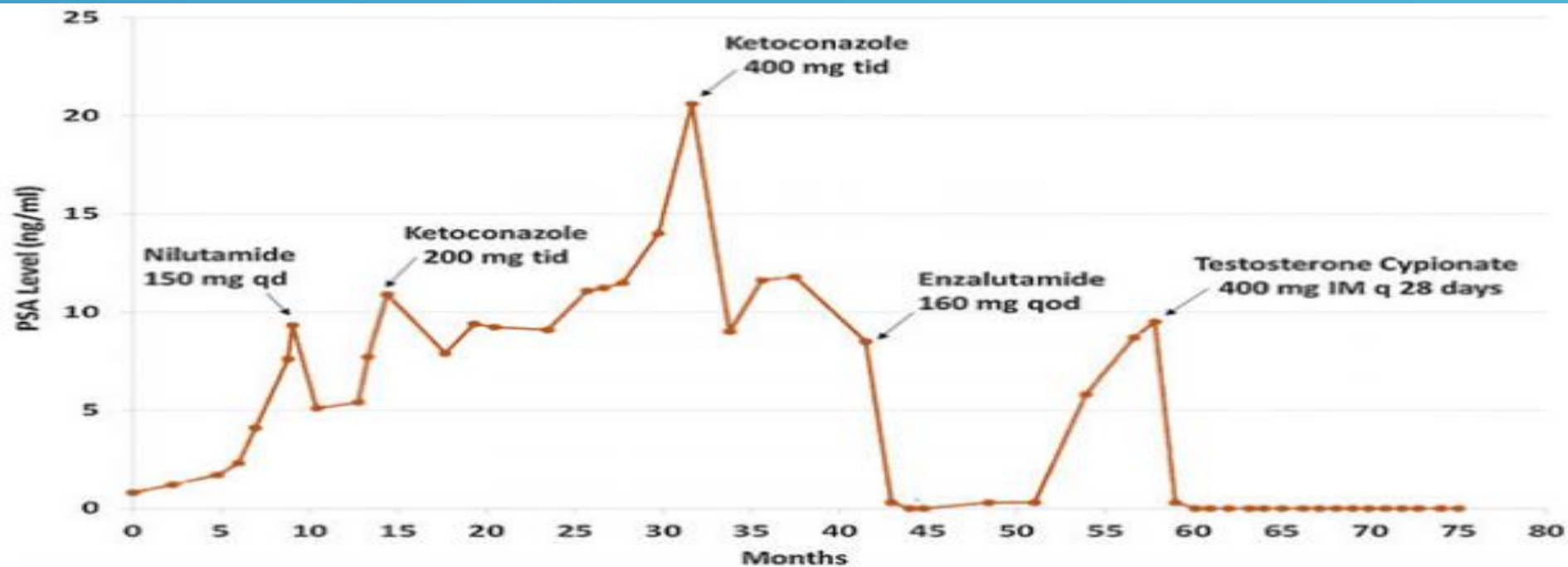


Fig. 1. Prostate-specific antigen (PSA) levels over time in response to the hormonal therapies indicated.

BIPOLAR ANDROGEN THERAPY IN MEN WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER AFTER PROGRESSION ON ENZALUTAMIDE: AN OPEN-LABEL, PHASE 2, MULTICOHORT,

(B A TEPLY MD, H WANG PHD, B LUBER MS, R SULLIVAN RN, I RIFKIND RN, A BRUNS RN, A SPITZ RN, M DECARLI BS, V SINIBALDI CRNP, C F PRATZ CRNP, M T SCHWEIZER MD, PROF C G DRAKE MD, PROF M A CARDUCCI MD, C J PALLER MD, E S ANTONARAKIS MD, PROF M A EISENBERGER MD, PROF S R DENMEADE MD) AND DEPARTMENT OF UROLOGY (C LU PHD, J L SILBERSTEIN MHS, J LUO PHD), JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD, USA; DIVISION OF ONCOLOGY AND HEMATOLOGY, UNIVERSITY OF NEBRASKA MEDICAL CENTER, OMAHA, NE, USA (B A TEPLY); DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY, UNIVERSITY OF WASHINGTON, SEATTLE, WA, USA (M T SCHWEIZER); AND DIVISION OF HEMATOLOGY/ONCOLOGY, COLUMBIA UNIVERSITY MEDICAL CENTER, NEW YORK, NY, USA (C G DRAKE)

Bipolar Androgen Therapy in the Treatment of Prostate Cancer

S.R.Denmeade, JHU, Clinical Advances in Hema.&Onco.V16(6) 2018

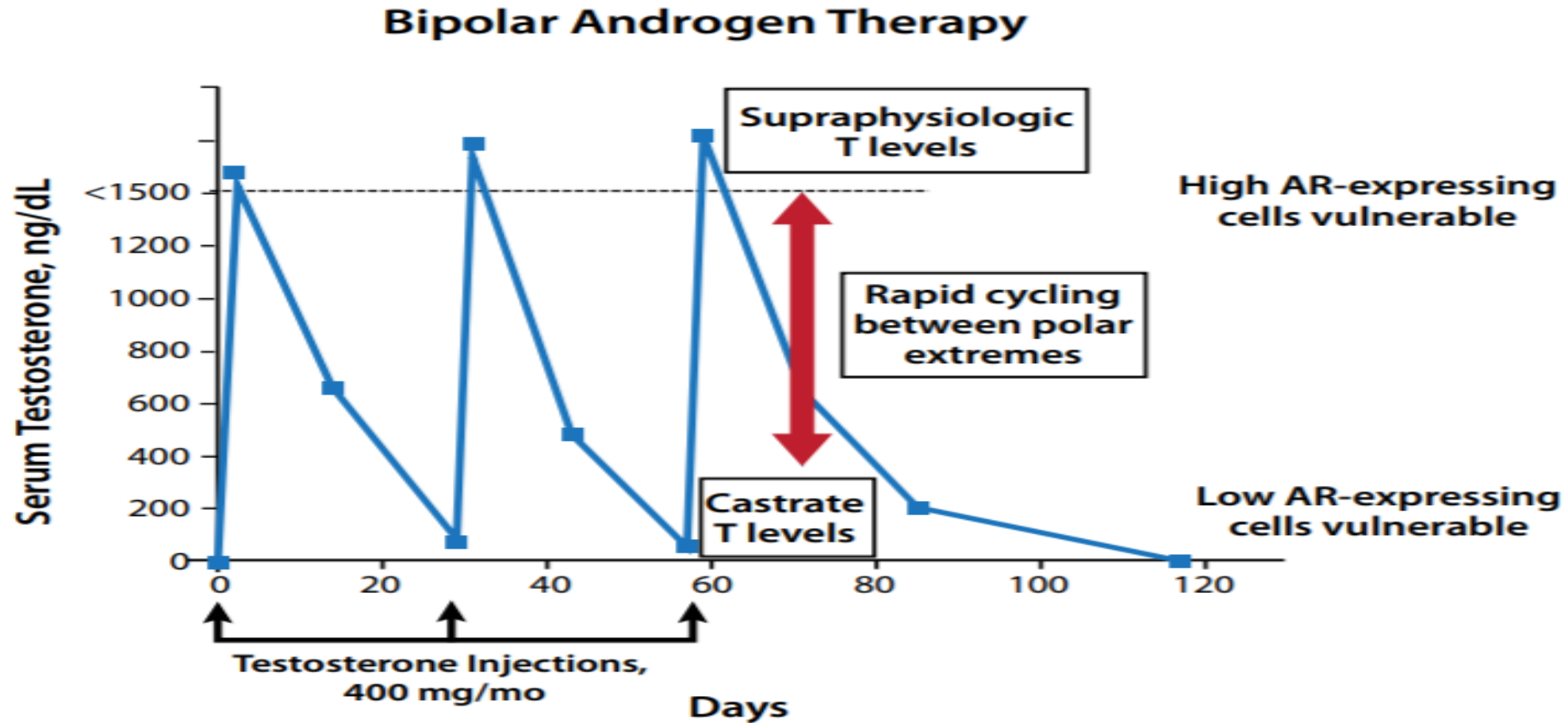


Figure. Alterations in serum testosterone in bipolar androgen therapy.

AR, androgen receptor; mo, month; T, testosterone.

SUPRAPHYSIOLOGICAL TESTOSTERONE THERAPY AS TREATMENT FOR CASTRATION-RESISTANT PROSTATE CANCER

HUNG-MING LAM & EVA COREY - UROLOGY DEPT, U. WASHINGTON, SEATTLE, WA, FRONT. ONCOL., 22 MAY 2018 | [HTTPS://DOI.ORG/10.3389/FONC.2018.00167](https://doi.org/10.3389/fonc.2018.00167)

“BIPOLAR ANDROGEN THERAPY SHOWS GREAT CLINICAL PROMISE IN A SUBSET OF PATIENTS. HOWEVER, UNIVERSAL TO ALL CANCER TREATMENT MODALITIES, NOT ALL PATIENTS RESPOND TO THIS TREATMENT AND RESISTANCE TO BAT DEVELOPS. THEREFORE, THERE IS AN OPPORTUNITY TO IMPROVE THIS THERAPY. IT IS NOTABLE THAT A CRITICAL STEP IN DRUG DEVELOPMENT, DETERMINING THE OPTIMAL DOSING SCHEDULE, WAS BYPASSED IN THE CLINICAL DEVELOPMENT OF BAT.”

“CYCLING OR NOT CYCLING—THAT IS THE QUESTION. WHILE WE CURRENTLY DO NOT HAVE SUFFICIENT EVIDENCE WHETHER BAT RESULTS IN BETTER CLINICAL OUTCOME THAN CONTINUOUS SPT, IT IS POSSIBLE THAT LONG-TERM CONTINUOUS SPT AND BAT COULD ALTER AR SIGNALING DIFFERENTLY.”