Precision Oncology for Veterans with Prostate Cancer: Who, What, How, and Why

Bruce Montgomery, MD
Professor, Medicine
VA Puget Sound HCS
Univ Washington

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
VA Puget Sound Health Care System

UW Medicine | FRED HUTCH CURES START HERE™

Conflicts and Off Label Uses

Research support in the last 2 years from;

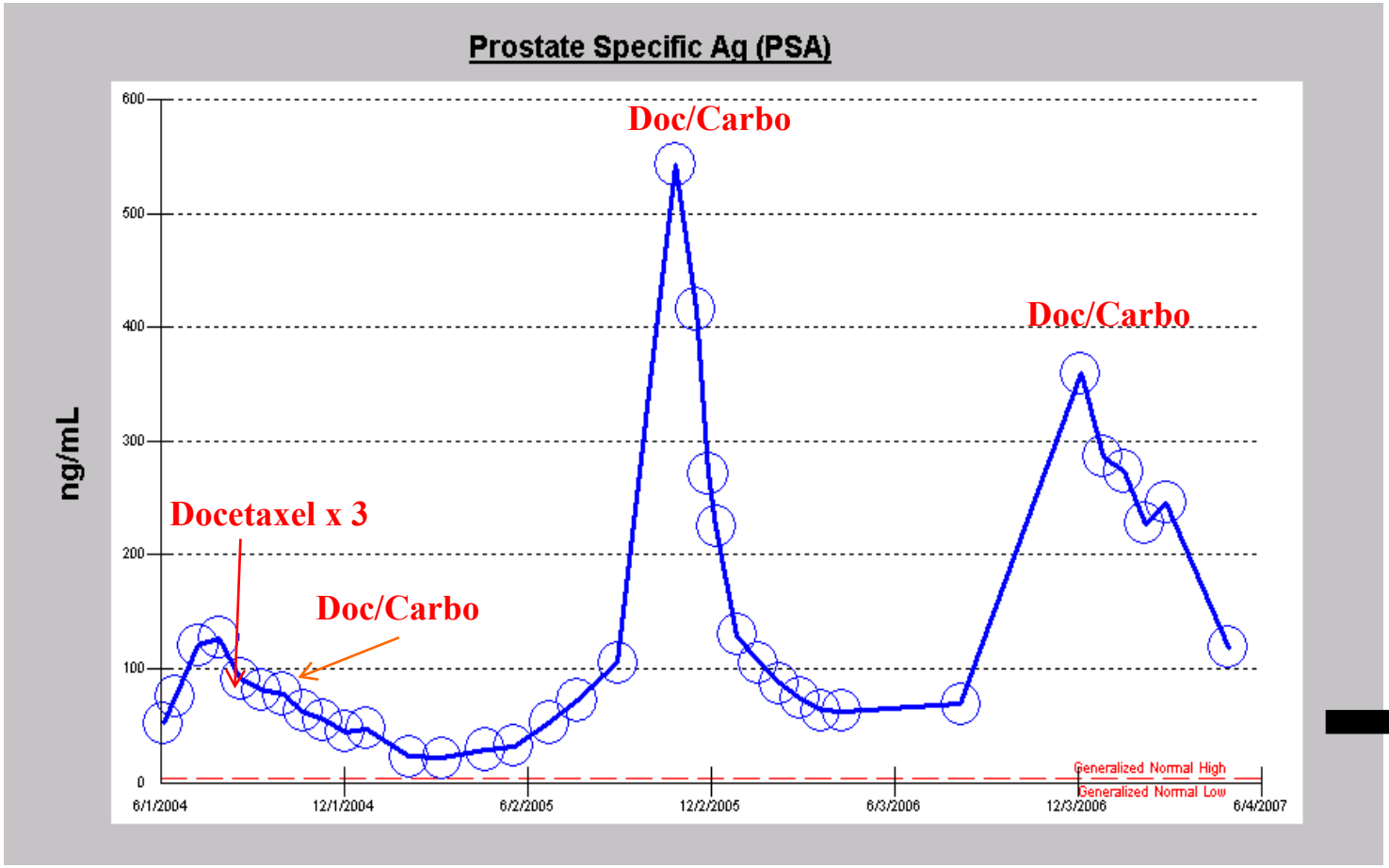
Janssen Oncology, AstraZeneca, Clovis, Beigene, Essa, Astellas

Off label uses: Off label use of PARP inhibitors and platinum agents to treat prostate cancer will be discussed

Precision Oncology for Veterans with Prostate Cancer

"Who"	The scope of prostate cancer in the VA
"What"	Precision Oncology. What is it and how is it relevant to prostate cancer? What are the targets in prostate cancer?
"How"	How do you approach instituting a system that could be implemented across the VA?
"Why"	Benefits for veterans and their families

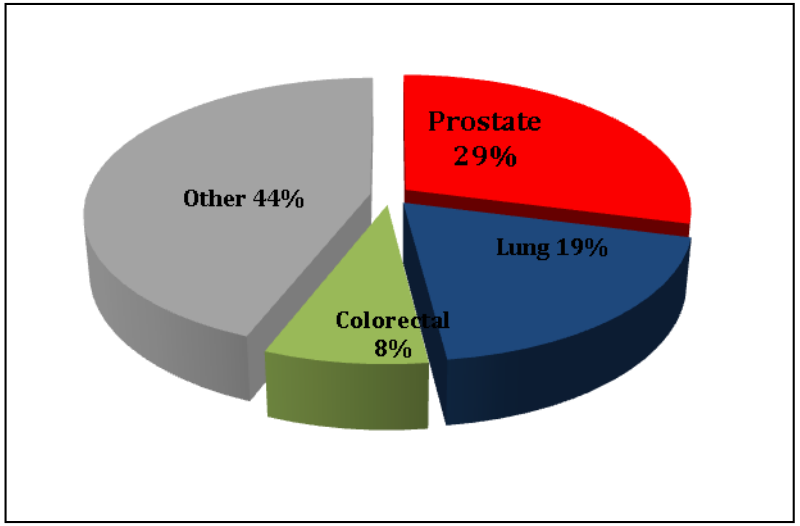
“Who” – A Veteran With Prostate Cancer



Mito x 5
DC x 6

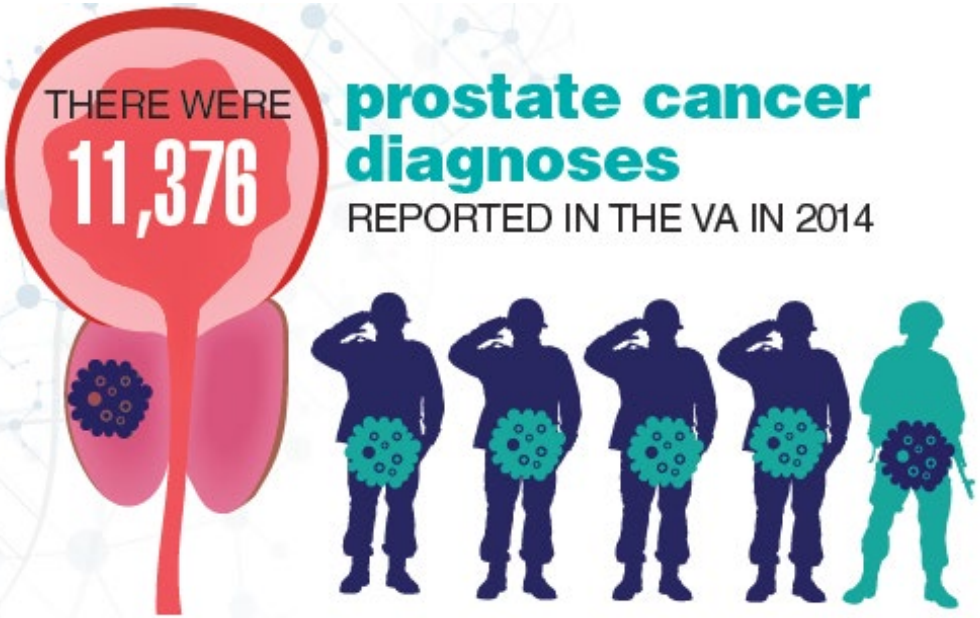
“Who” – Cancer In Veterans

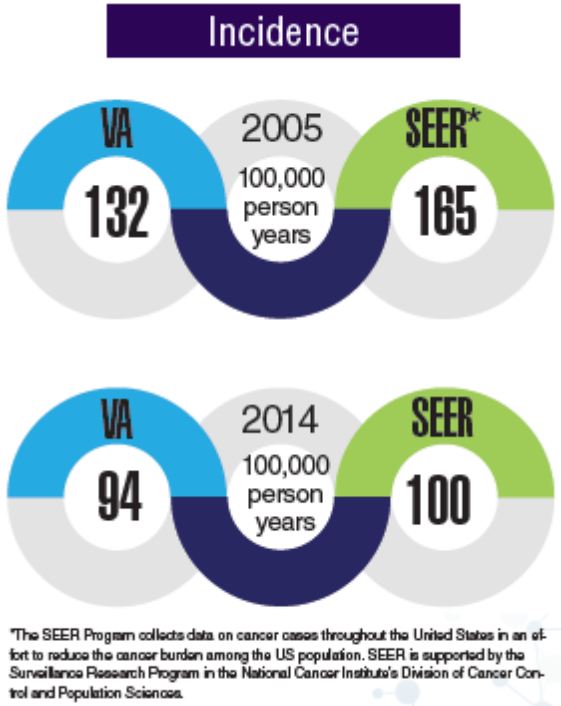
- 50,000 Veterans diagnosed with and treated for cancer annually
- Veterans account for 3.5% of all cancer cases in the U.S
- Prostate cancer is the most common cancer in veterans



Zullig and Kelley, Military Medicine, 2017.

“Who” – Prostate Cancer In Veterans

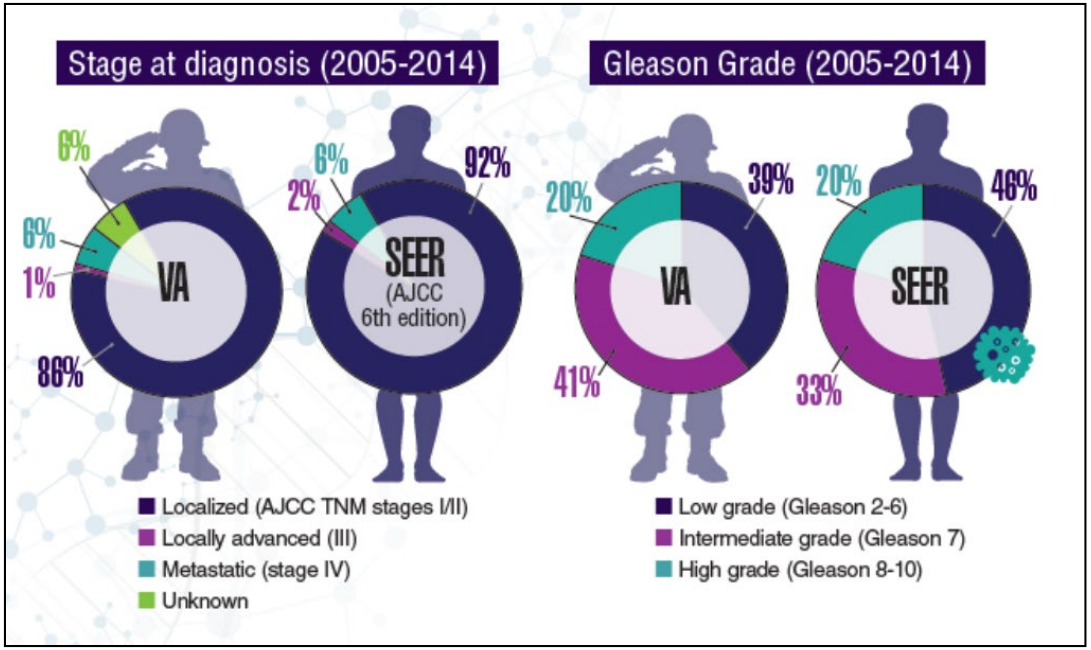


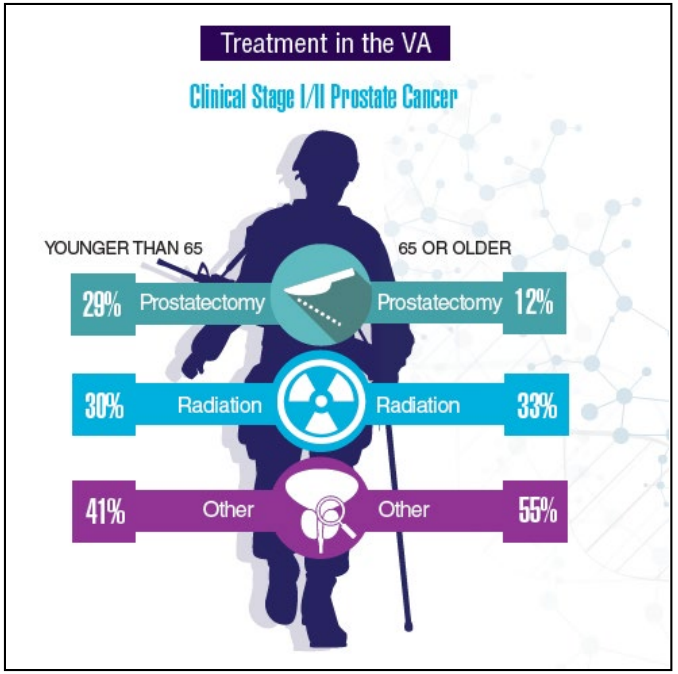


*The SEER Program collects data on cancer cases throughout the United States in an effort to reduce the cancer burden among the US population. SEER is supported by the Surveillance Research Program in the National Cancer Institute's Division of Cancer Control and Population Sciences.

Montgomery & Williams Federal Practitioner, 2019.

“Who” – Prostate Cancer In Veterans





Montgomery & Williams Federal Practitioner, 2019.

“What” Is Precision Oncology?

“Identifying treatment based on a biomarker which reflects biology and targeting that biology to optimize efficacy and minimize toxicity”

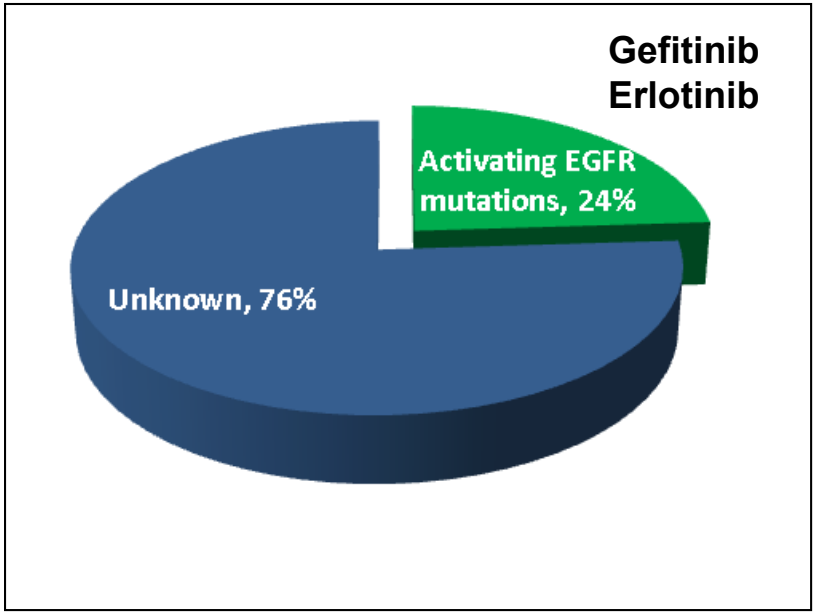
The most effective therapy with the fewest side effects

Success;

- CD20 (Rituxan), HER2 (Herceptin), BCR-ABL (imatinib), mismatch repair deficiency (pembrolizumab)…
- 150 indications for targeted therapy in 28 different tumors

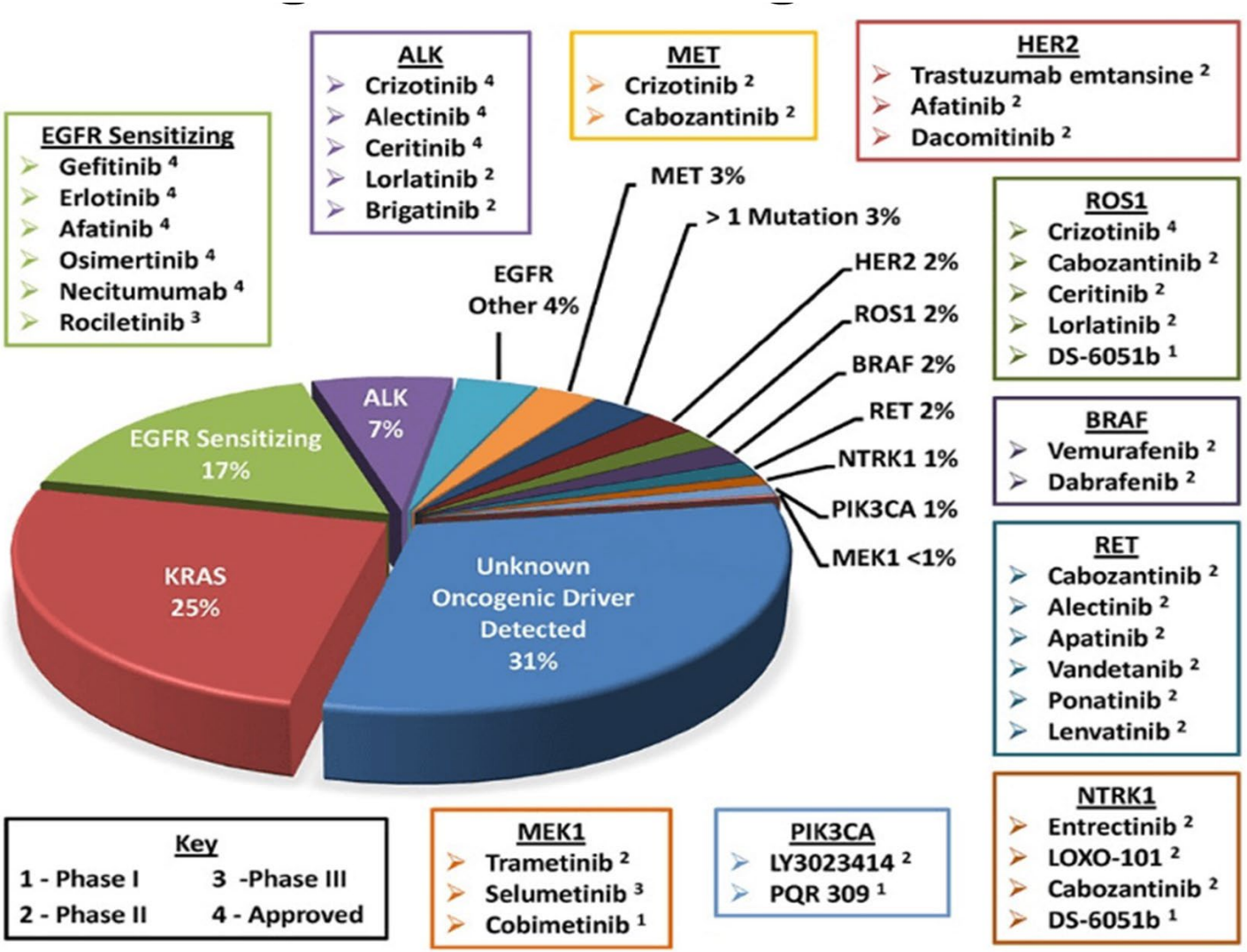
NIH: www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.

Success In Precision Oncology
Carcinoma of Lung



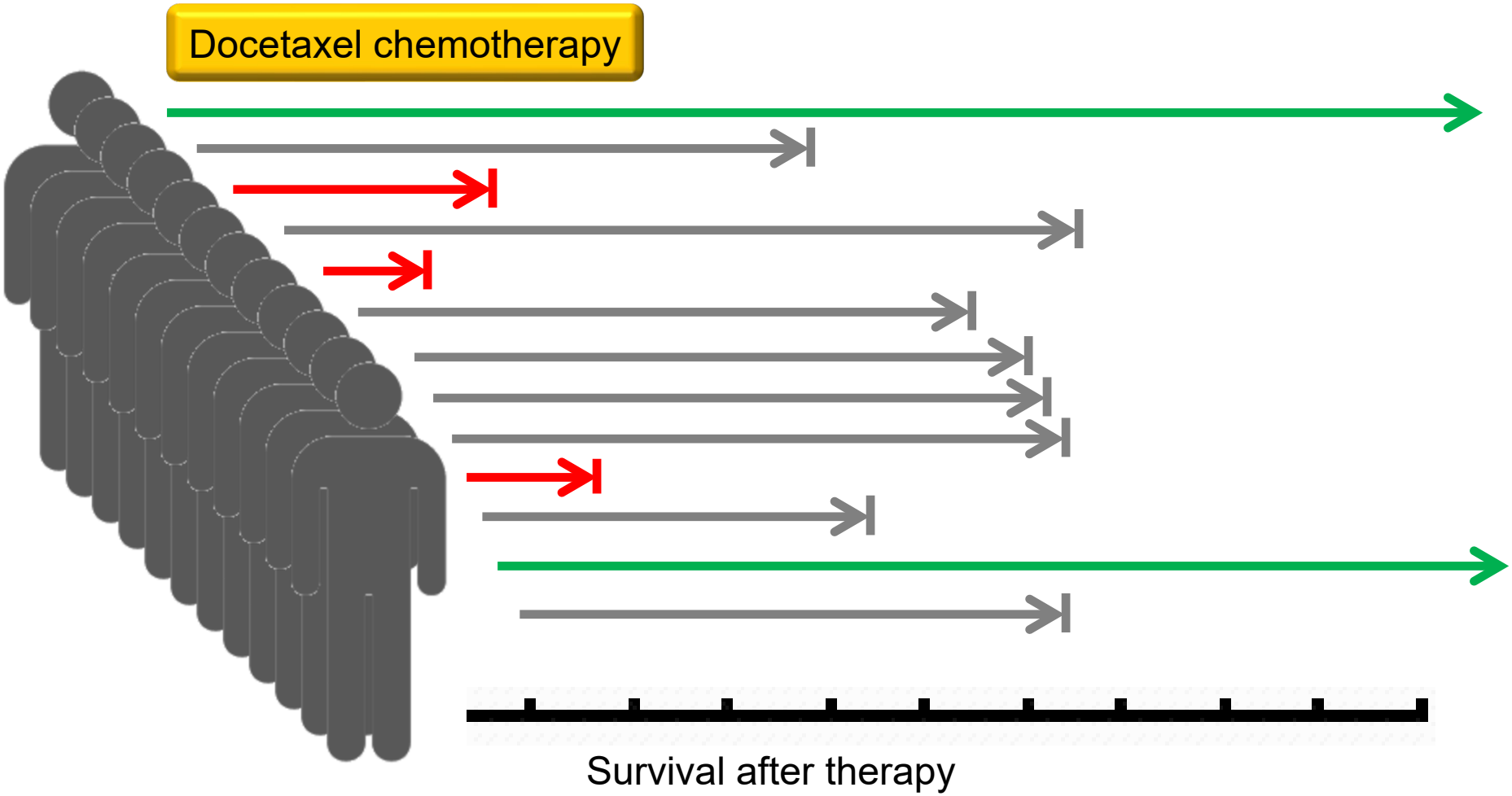
The therapeutic landscape of targeted therapy for adenocarcinoma of the lung, circa 2006

Success In Precision Oncology
Carcinoma of Lung



Frances Shepherd - 2019 ASCO Annual Meeting

Why Do Patients Have Such Diverse Outcomes?



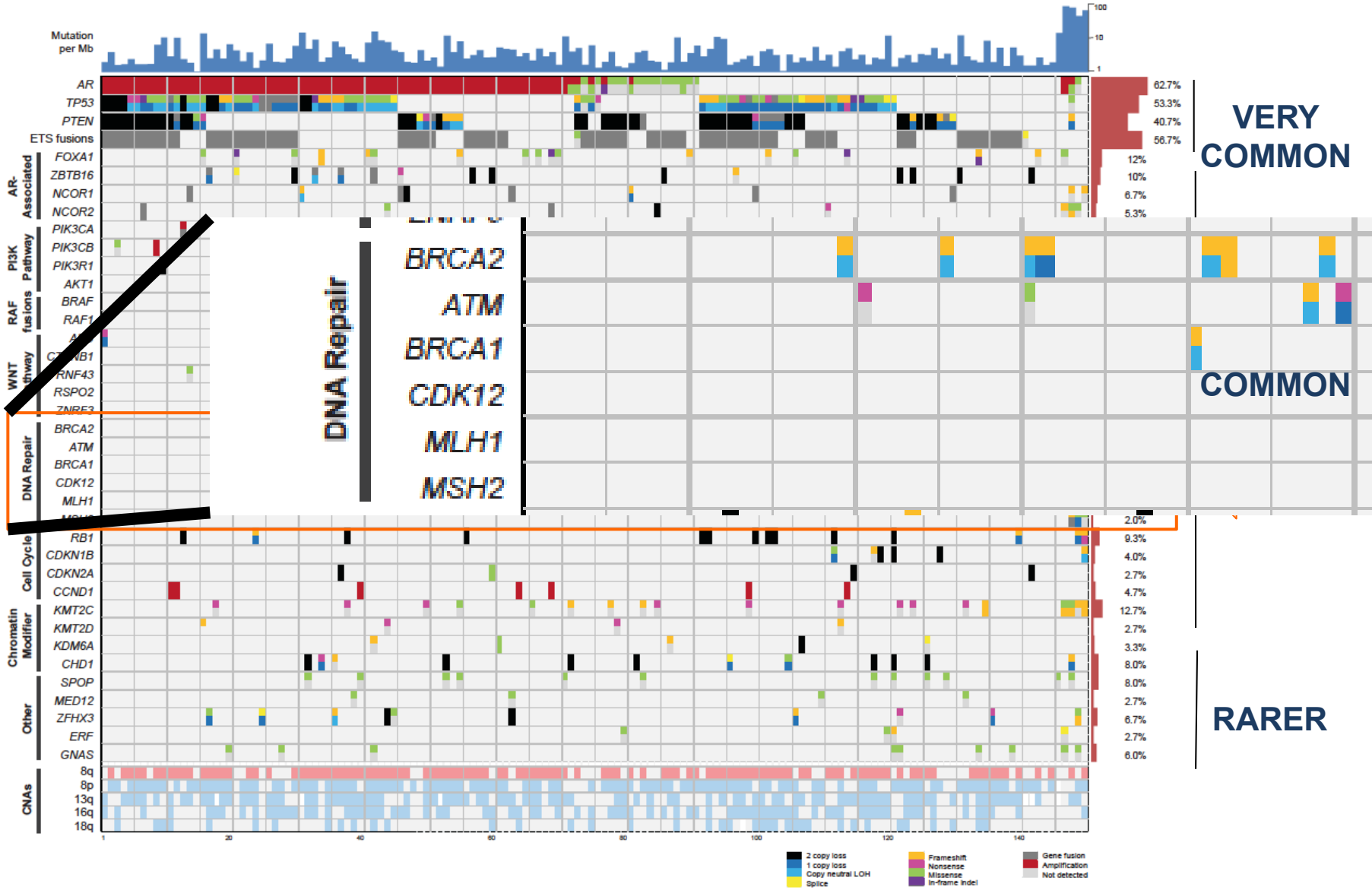
Resource

Cell

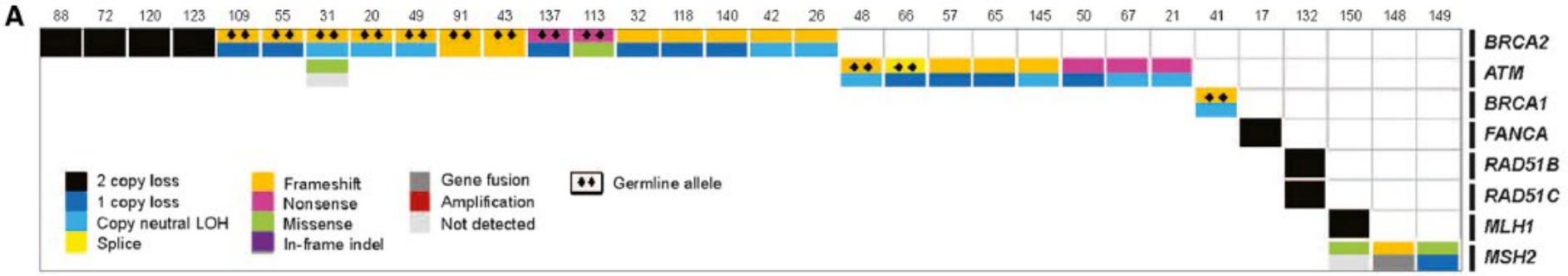
Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson,[1,2,43] Eliezer M. Van Allen,[3,4,43] Yi-Mi Wu,[1,2] Nikolaus Schultz,[5,40] Robert J. Lonigro,[1] Juan-Miguel Mosquera,[6,7,8,38] Bruce Montgomery,[9,10] Mary-Ellen Taplin,[3] Colin C. Pritchard,[26] Gerhardt Attard,[11,12] Himisha Beltran,[7,8,13,38] Wassim Abida,[14,20] Robert K. Bradley,[9] Jake Vinson,[15] Xuhong Cao,[1,42] Pankaj Vats,[1] Lakshmi P. Kunju,[1,2,17] Maha Hussain,[16,17,18] Felix Y. Feng,[1,17,19] Scott A. Tomlins,[1,2,17,18] Kathleen A. Cooney,[16,17,18] David C. Smith,[16,17,18] Christine Brennan,[1] Javed Siddiqui,[1] Rohit Mehra,[1,2] Yu Chen,[13,14,20] Dana E. Rathkopf,[13,20] Michael J. Morris,[13,20] Stephen B. Solomon,[21] Jeremy C. Durack,[21] Victor E. Reuter,[22] Anuradha Gopalan,[22] Jianjiong Gao,[40] Massimo Loda,[3,4,23,39] Rosina T. Lis,[3,23] Michaela Bowden,[3,23,39] Stephen P. Balk,[24] Glenn Gaviola,[25] Carrie Sougnez,[4] Manaswi Gupta,[4] Evan Y. Yu,[10] Elahe A. Mostaghel,[9,10] Heather H. Cheng,[9,10] Hyojeong Mulcahy,[27] Lawrence D. True,[28] Stephen R. Plymate,[10] Heidi Dvinge,[9] Roberta Ferraldeschi,[11,12] Penny Flohr,[11,12] Susana Miranda,[11,12] Zafeiris Zafeiriou,[11,12] Nina Tunariu,[11,12] Joaquin Mateo,[11,12] Raquel Perez-Lopez,[11,12] Francesca Demichelis,[7,29] Brian D. Robinson,[6,7,8,38] Marc Schiffman,[7,31,38] David M. Nanus,[7,8,13,38] Scott T. Tagawa,[7,8,13,38] Alexandros Sigaras,[7,30,32] Kenneth W. Eng,[7,30,32] Olivier Elemento,[30] Andrea Sboner,[6,7,30,38] Elisabeth I. Heath,[33,34] Howard I. Scher,[13,20] Kenneth J. Pienta,[35] Philip Kantoff,[3,44] Johann S. de Bono,[11,12,44] Mark A. Rubin,[6,7,8,38,44] Peter S. Nelson,[10,36,37,38,44] Levi A. Garraway,[3,4,44] Charles L. Sawyers,[14,41,44,*] and Arul M. Chinnaiyan[1,2,17,18,42,44,*]

Precision Oncology: Prostate Cancer



Types of Targetable Alterations In Prostate Cancer



- DNA repair deficiency is present in > 20% of metastatic, resistant prostate cancer
- In the first cohort, half of the patients had inherited the DNA repair deficiency
- DNA repair deficiency is immediately targetable

Cell. 2015 161:1215-28

Frequency of an Inherited Reason for Metastatic Prostate Cancer

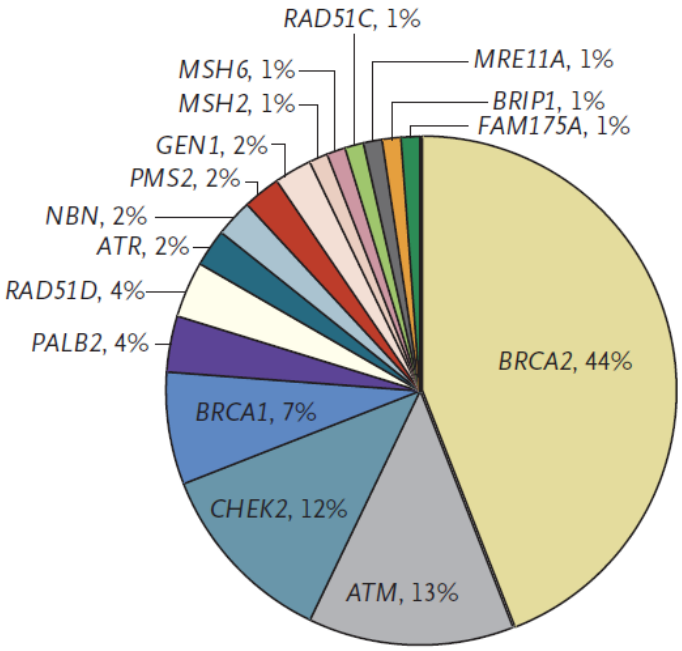


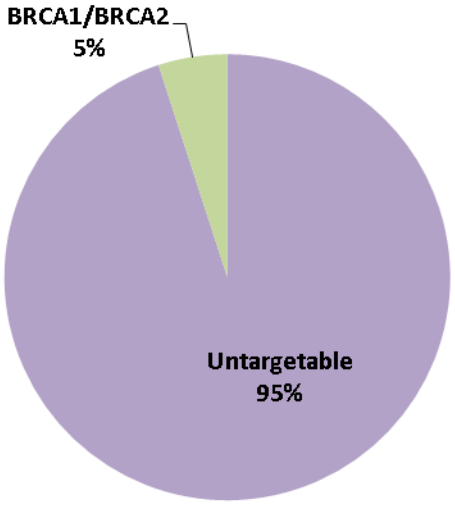
Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

Pritchard, NEJM July 2016

Precision Oncology In Prostate Cancer

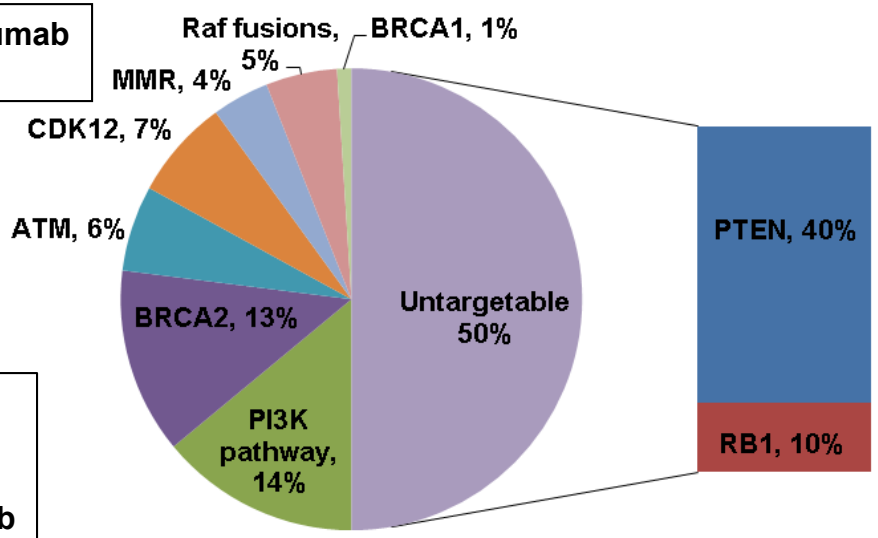
Prostate cancer
2014



Prostate cancer
2020

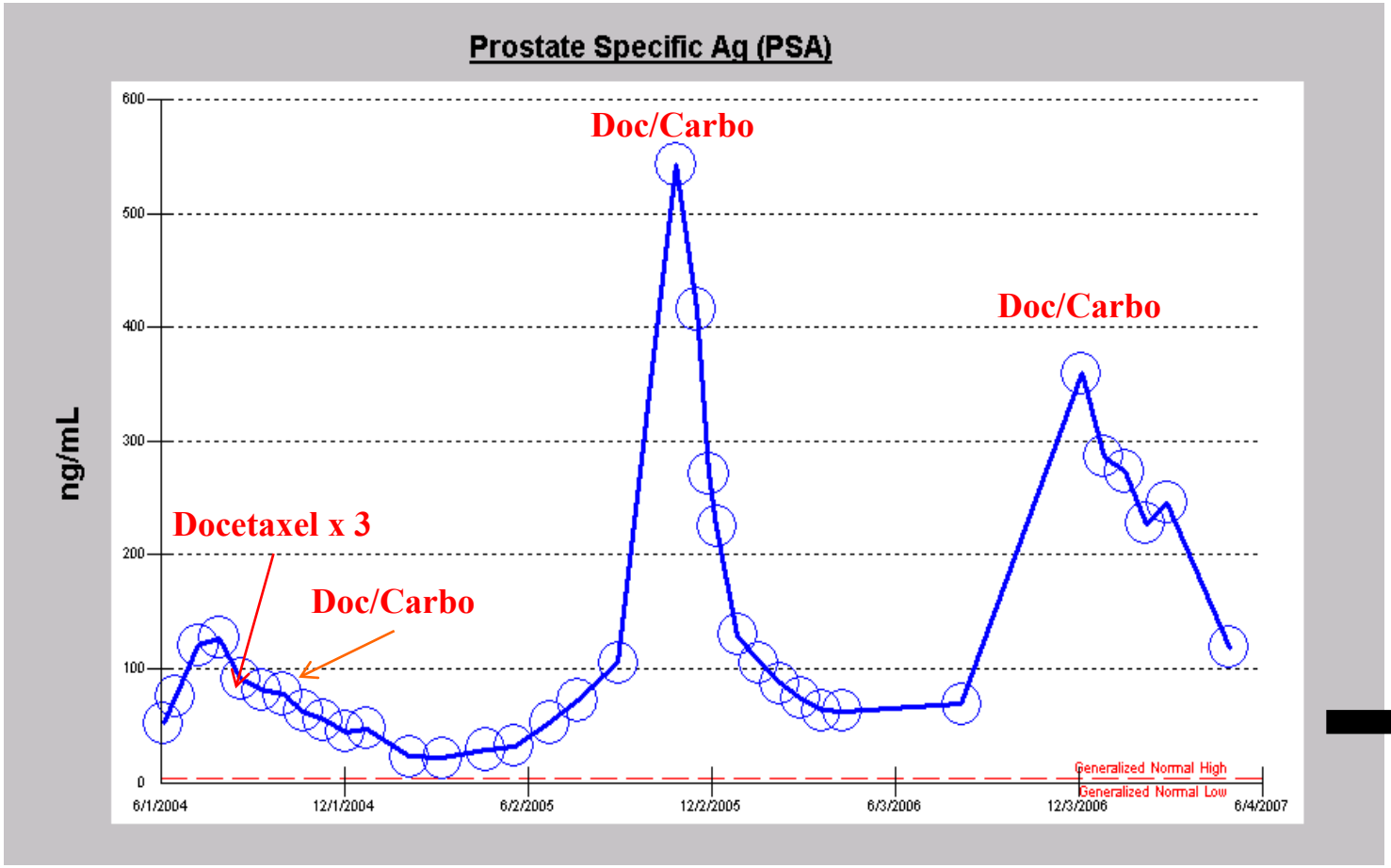
- Trametinib
- Dabrafenib

- Pembrolizumab
- Nivolumab



- Platinum
- Olaparib
- Niraparib
- Rucaparib

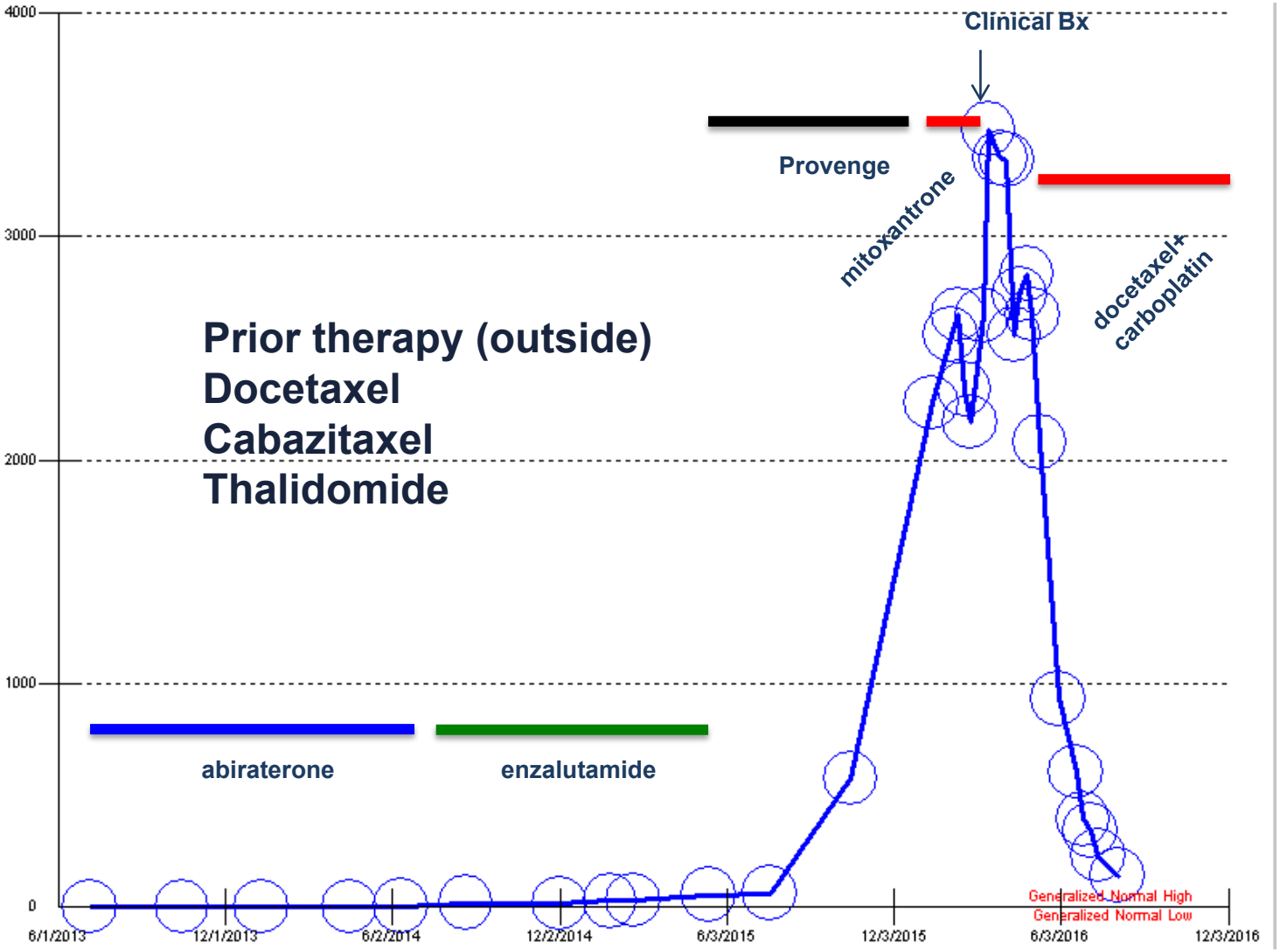
“Who” – A Veteran with Prostate Cancer



Mito x 5
DC x 6

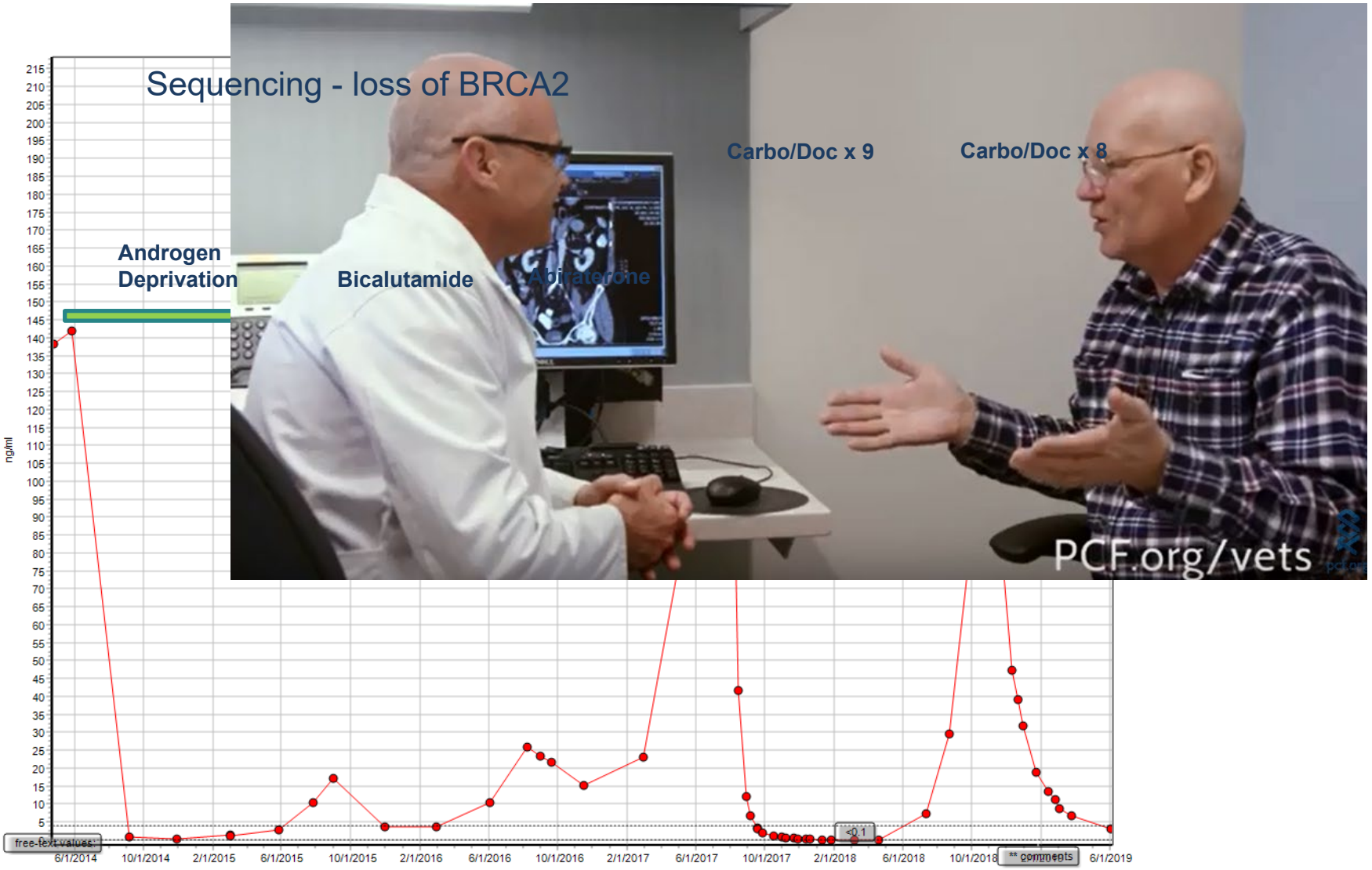
Primary biopsy = BRCA2 biallelic copy loss

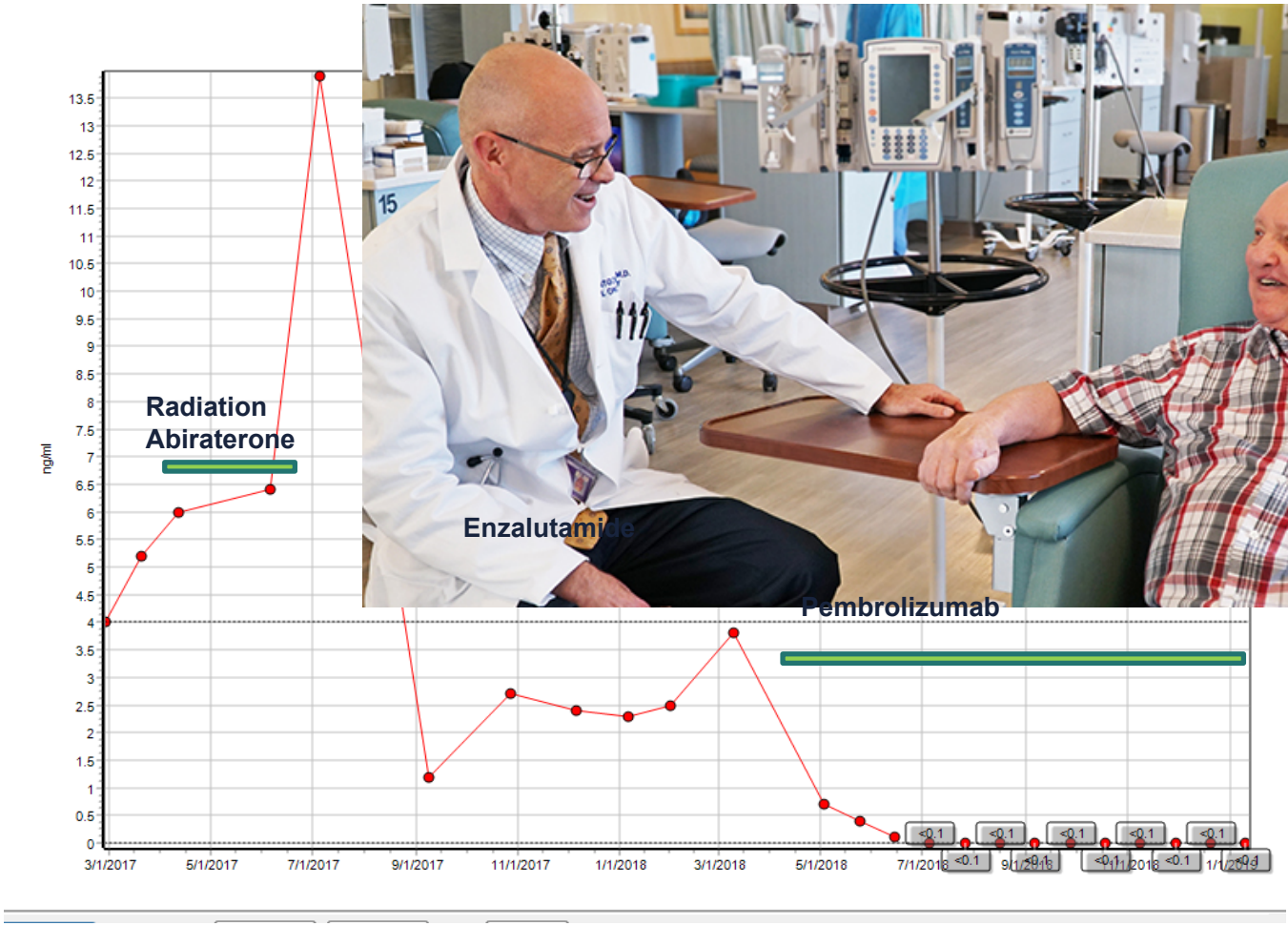
Precision oncology – BRCA+ Prostate Cancer



Gene	Mutation(s)	
PALB2	c.1032 1033 dup FS	Germline
PALB2	COPY LOSS	

The Impact of DNA Sequencing



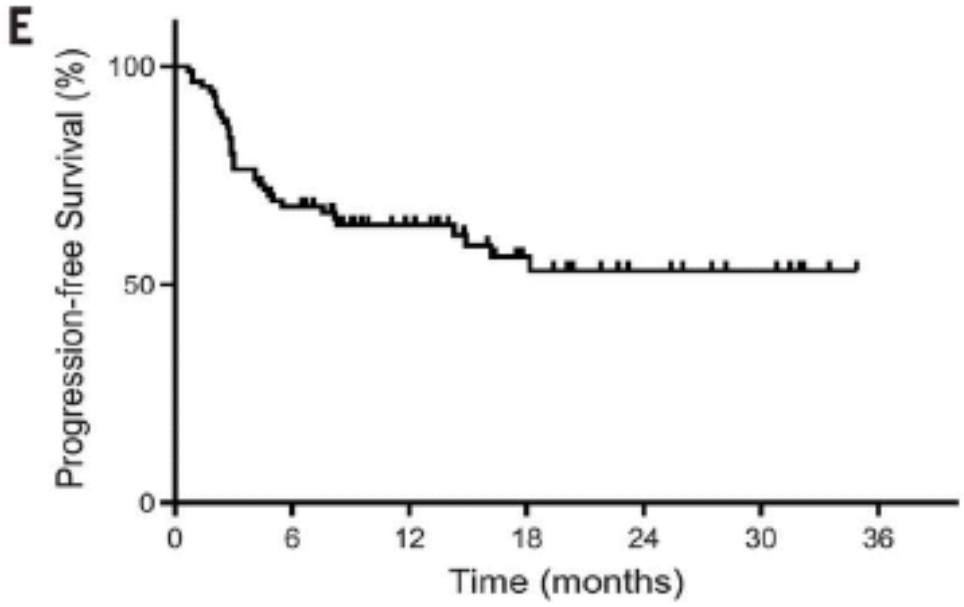


Sequencing – mismatch repair deficiency

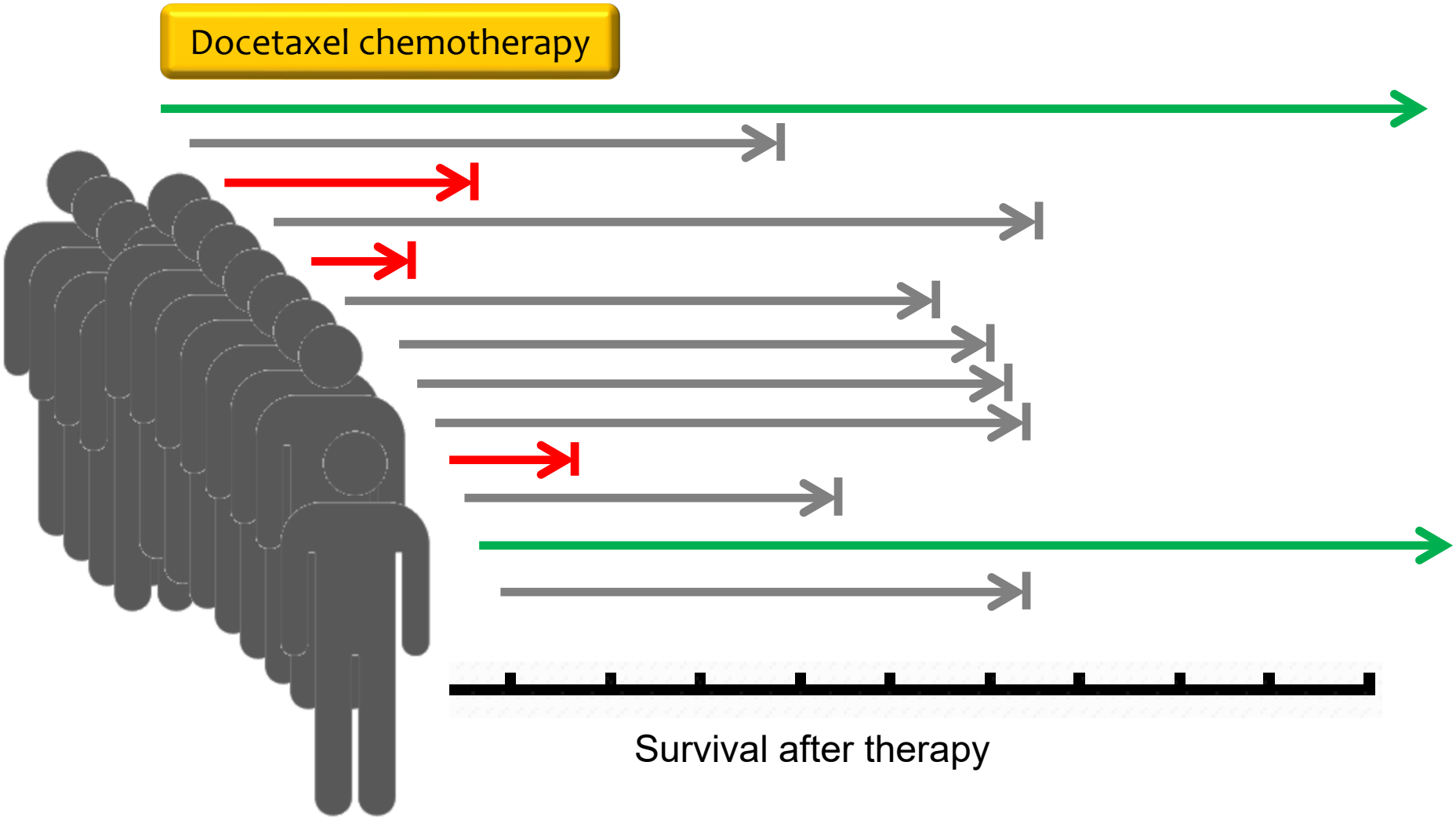
The benefits of immunotherapy in the right veteran

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

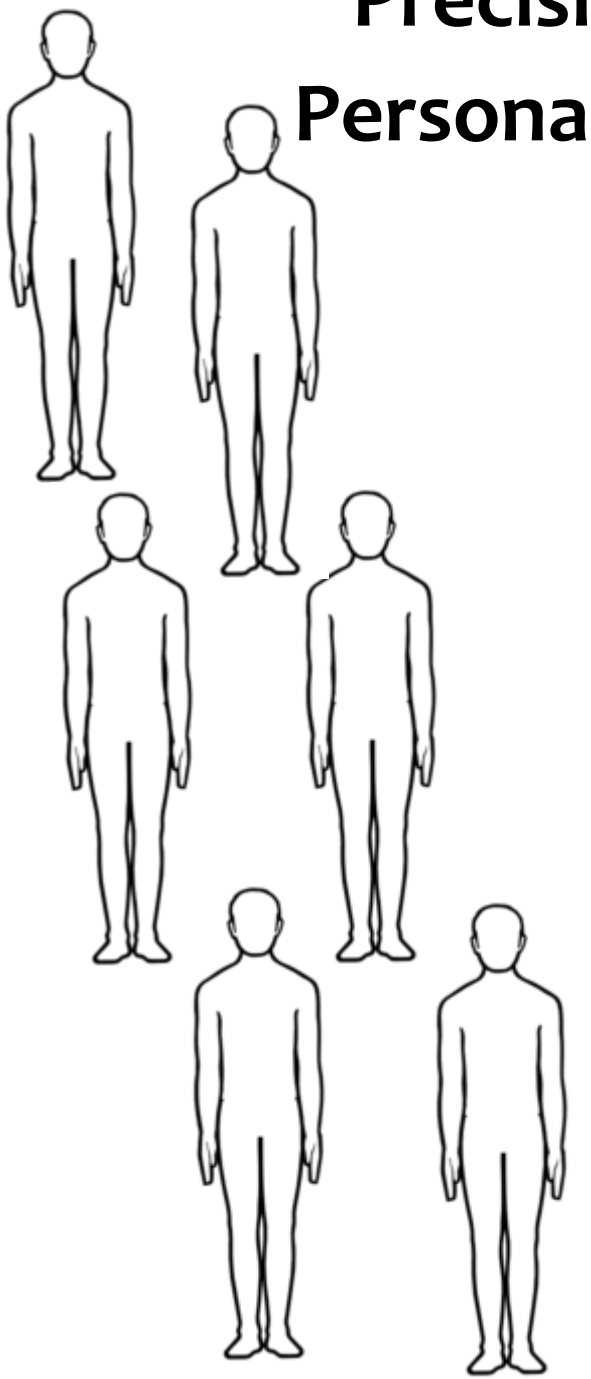
Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡



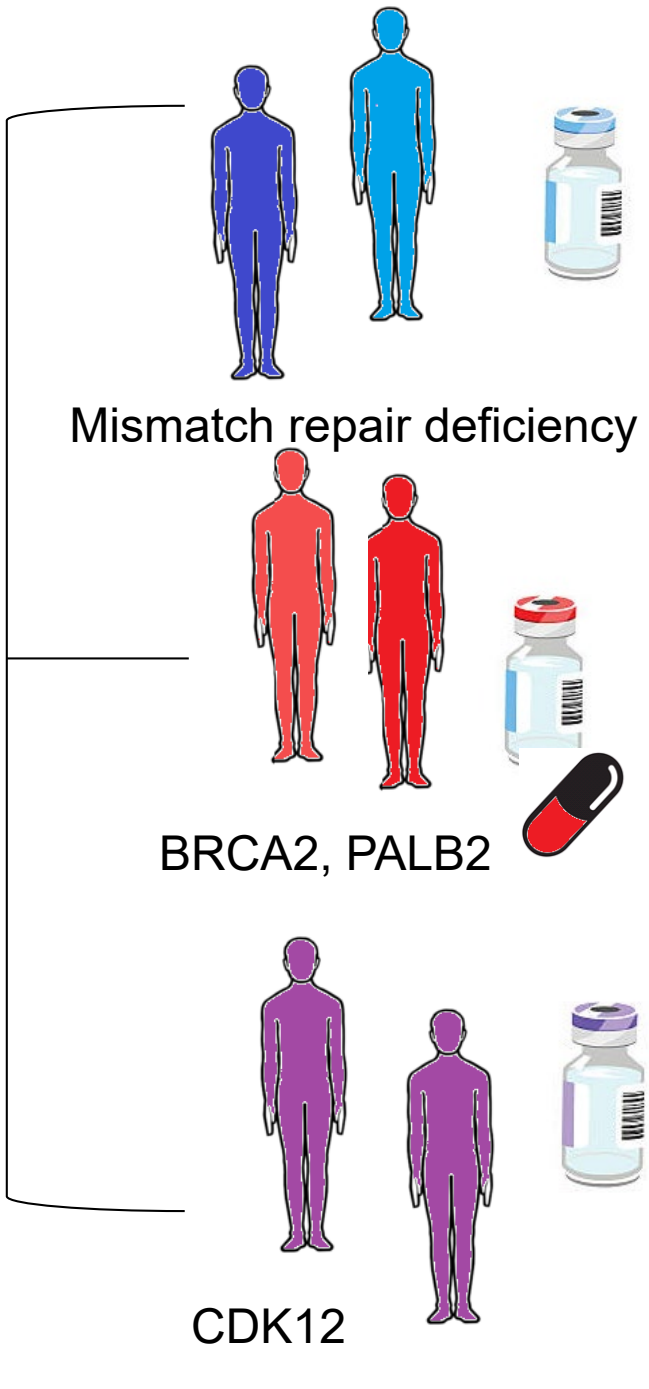
Old School Oncology



Precision Oncology
Personalized Medicine



DNA sequencing



Mismatch repair deficiency

BRCA2, PALB2

CDK12

How Do We Implement Precision – Culture

- “If you don’t look, you won’t find”
- How you look matters
- System wide access, standardized approaches
- Education
- Access to drugs
- Access to studies
- Leveraging VA data

"How" – A Nationwide Precision Oncology Program

original report

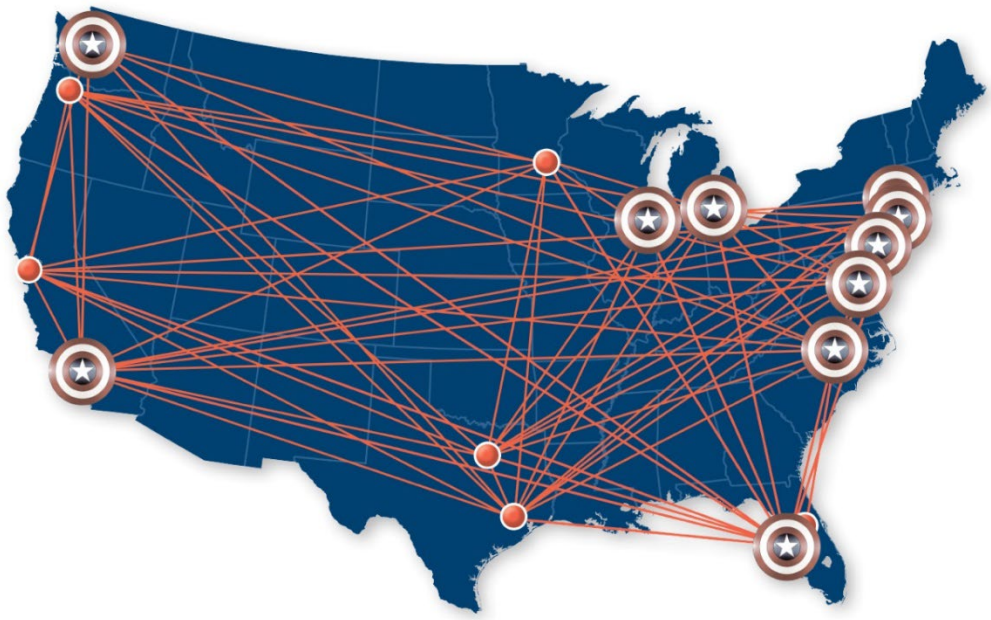
Genomic Analysis of Metastatic Solid Tumors in Veterans: Findings From the VHA National Precision Oncology Program

Pradeep J. Poonnen, MD, MPH[1,2]; Jill E. Duffy, MHS, PA-C[1]; Bradley Hintze, PhD[1,4]; Maulik Shukla, MS[3]; Thomas S. Brettin, MS[3]; Neal R. Conrad, MS[3]; Hyunseung Yoo, MS[3]; Christopher Guertin, PharmD[1]; Jane A. Looney, MHA[1]; Vishal Vashistha, MD[1,2]; Michael J. Kelley, MD[1,2,4]; and Neil L. Spector, MD[1,2,4]

- DNA sequencing of tumor tissue for any veteran with incurable malignancy
- Available to any VA clinical site which is interested in subscribing
- The largest system-wide sequencing effort in any health care system in the U.S.

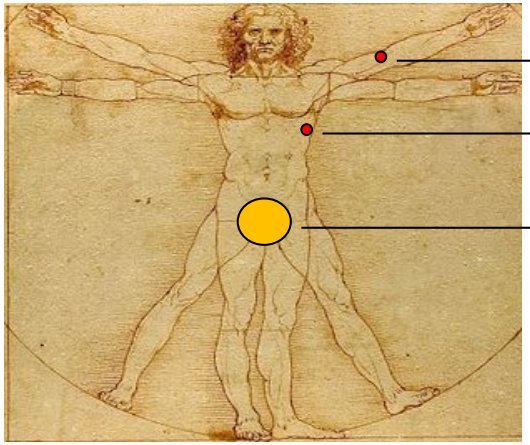
"How" –VA/PCF NETWORK OF PRECISION ONCOLOGY CENTERS

- **Manhattan, NY** – The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Manhattan
- **Bronx, NY** – The Blavatnik Family Foundation Precision Oncology Center of Excellence at the VA Bronx
- **Durham, NC** – PCF Durham VA Center of Excellence
- **Ann Arbor, MI** – The Stewart J. Rahr Foundation Precision Oncology Center of Excellence at the VA Ann Arbor
- **Chicago, IL** – The Robert Frederick Smith Precision Oncology Center of Excellence at the VA Chicago
- **Minneapolis, MN** – Minneapolis VA Health Care System
- **Seattle, WA** – The Stephen J. Cloobeck Precision Oncology Center of Excellence at the VA Puget Sound
- **Portland, OR** – VA Portland Health Care System
- **San Francisco, CA** – San Francisco VA Health Care System
- **Los Angeles, CA** – The Michael and Lori Milken Family Foundation Precision Oncology Center of Excellence at the West Los Angeles VA
- **Dallas, TX** – Dallas VA Medical Center
- **Houston, TX** – The Michael E. DeBakey Houston VA Medical Center
- **Philadelphia, PA** – PCF Philadelphia VA Center of Excellence
- **Washington, DC** – The Evans Foundation Precision Oncology Center of Excellence at the VA Washington, DC
- **Tampa, FL** – The John and Daria Barry Foundation Precisio Oncology Center of Excellence at the VA Tampa
- **Orlando, FL** – Orlando VA Medical Center

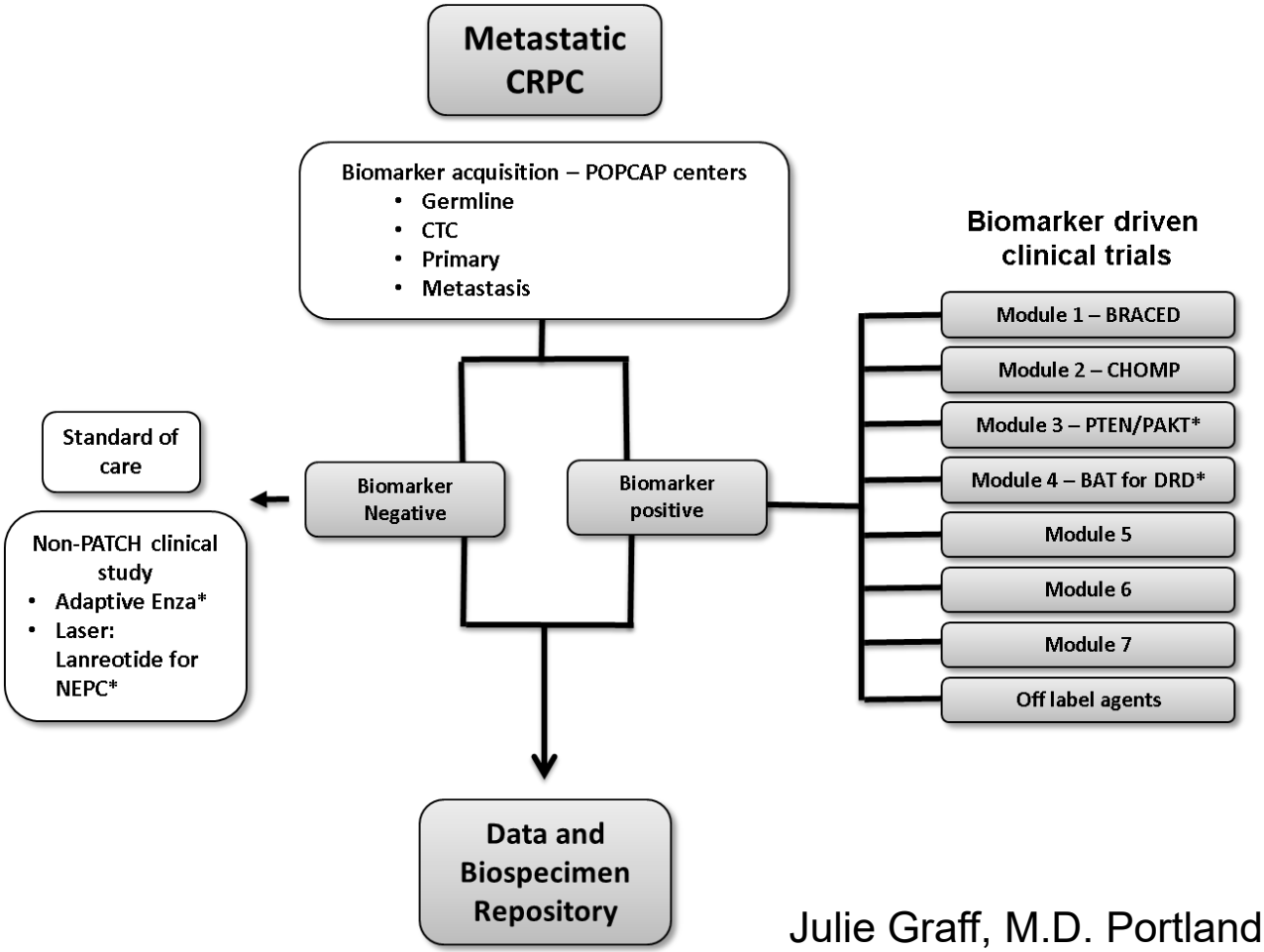


“How” Do We Look

- Germline testing – DNA sequencing of normal DNA to look for inherited defective genes predispose to cancer (e.g. BRCA, Lynch)
- Genetic/genomic/somatic testing – DNA sequencing of tumor DNA to look for tumor specific alterations. Tumor biopsies or circulating tumor DNA (e.g. BRCA, tumor only mismatch repair deficiency)
- Others – analysis of RNA or protein expression is not as consistent or as targetable as DNA alterations at the moment

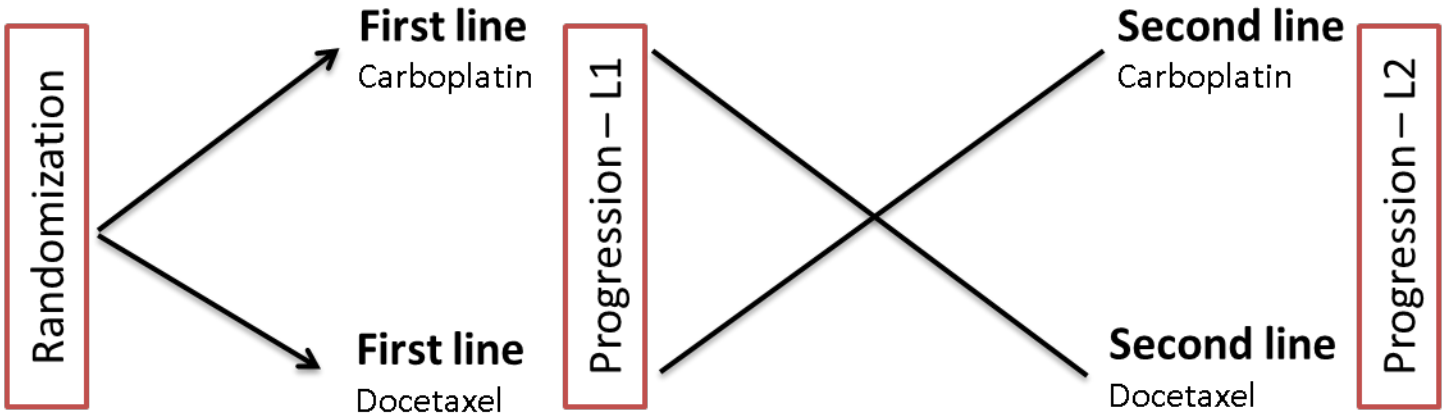


How Do We Give Access to Research Prostate cancer Analysis for Therapy Choice "PATCH"



Julie Graff, M.D. Portland VAMC
& POPCAP investigators

Phase II study to compare the efficacy of carboplatin followed by docetaxel versus docetaxel followed carboplatin: BRACeD: **BR**c**A** deficient prostate cancer treated with **C**arboplatin or **D**ocetaxel



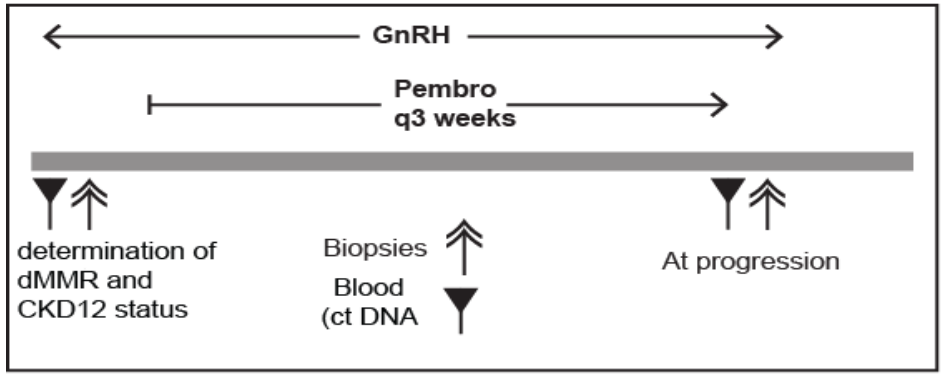
- University of Washington/FHCRC
- VA Puget Sound
- VA Greater LA
- VA Ann Arbor
- VA Bronx
- VA Manhattan
- Jesse Brown VA Chicago

A single-arm, open-label, phase II study of CHeckpoint inhibitors in men with prOgressive Metastatic castrate resistant Prostate cancer characterized by a mismatch repair deficiency or biallelic CDK12 inactivation. (CHOMP)

Inclusion Criteria

Progressive mCRPC with at least prior abi and/or enz
Metastatic lesion suitable for biopsy
dMMR or CDK12-/- status via OncoPlex seq of biopsy or ct DNA
ECOG 0-2
Adequate organ function

Protocol Outline



Treatments During Study Period

anti PD-1 Pembrolizumab 200 mg IV every 3 weeks until disease progression or unacceptable toxicity

GnRH analog to maintain T < 50 ng/dL

Endpoints

Primary: Composite of objective resopnse rate (iRECIST), or radiographic progression free survival at 6 months, or PSA50 ≥ 12 weeks after treatment initiation

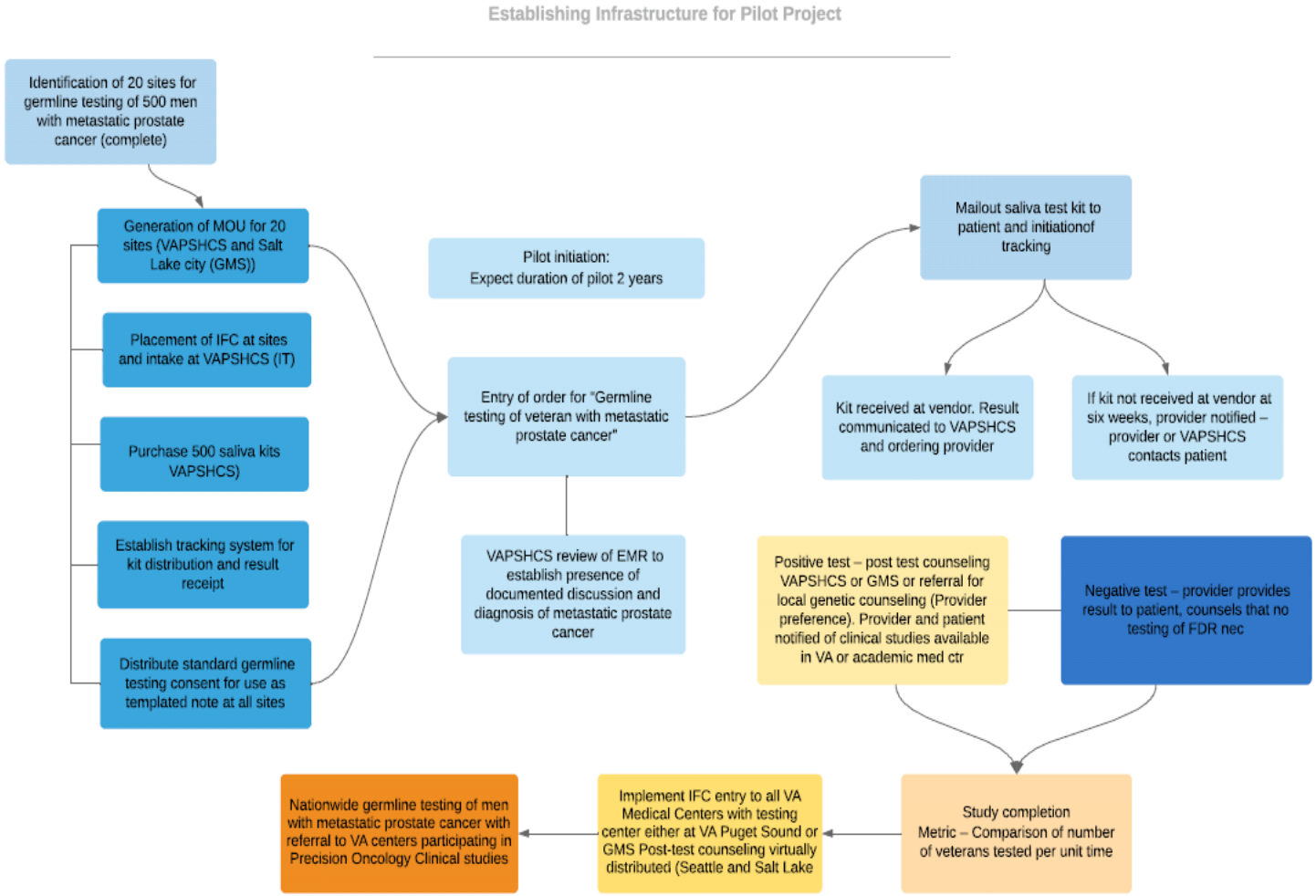
Secondary: time to PSA progression, maximal PSA response,time to initiation of alternative anti-neoplastic therapy,time to radiographic progression, overall survival, safety/tolerability

Statistics

N = 26 evaluable patients for 0.90 power and alpha of 0.05 to detect a 50% response rate. Total study N = 30.

Matt Rettig, VA CSR&D

How Do We Test for Inherited Prostate Cancer



Montgomery, Ball, Lynch

How Do We Leverage VA Data

MILLION VETERAN PROGRAM

A Partnership with Veterans

Returning clinically actionable results to MVP participants with metastatic prostate cancer: a pilot study

Montgomery, Lynch, Pritchard, Cheng, Meeks

VA | U.S. Department of Veterans Affairs

DISCOVERY ★ INNOVATION ★ ADVANCEMENT

Why Do We Test

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Prostate Cancer

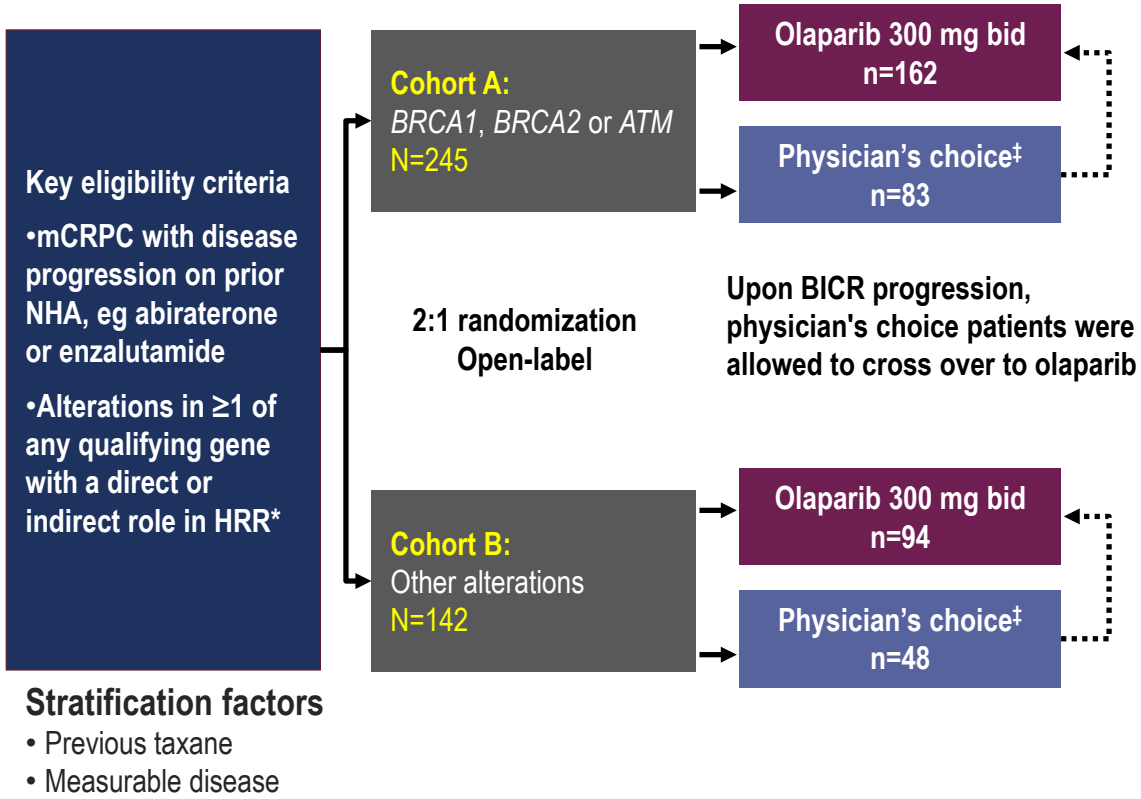
NCCN Guidelines Index
Table of Contents
Discussion

GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER

Risk group	Clinical/pathologic features	Germline testing	Molecular and biomarker analysis of tumor[l]	Initial therapy
Regional	Any T, N1, M0	Recommended[c,k]	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)[dd,ee]	See PROS-10
Metastatic[ff]	Any T, Any N, M1	Recommended[c,k]	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR [dd,ee]	See PROS-14

Why We Test

PROfound STUDY DESIGN



Stratification factors
- Previous taxane
- Measurable disease

Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

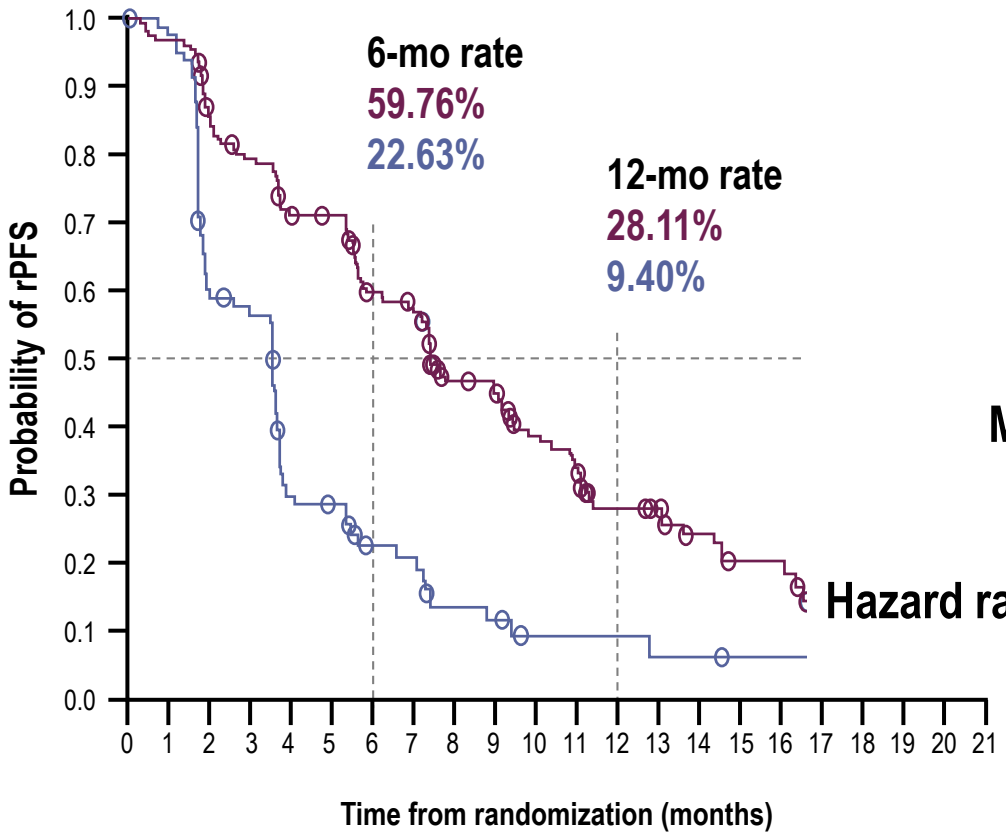
BARCELONA 2019 ESMO congress

Hussain et al 2019

Why We Test

Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)

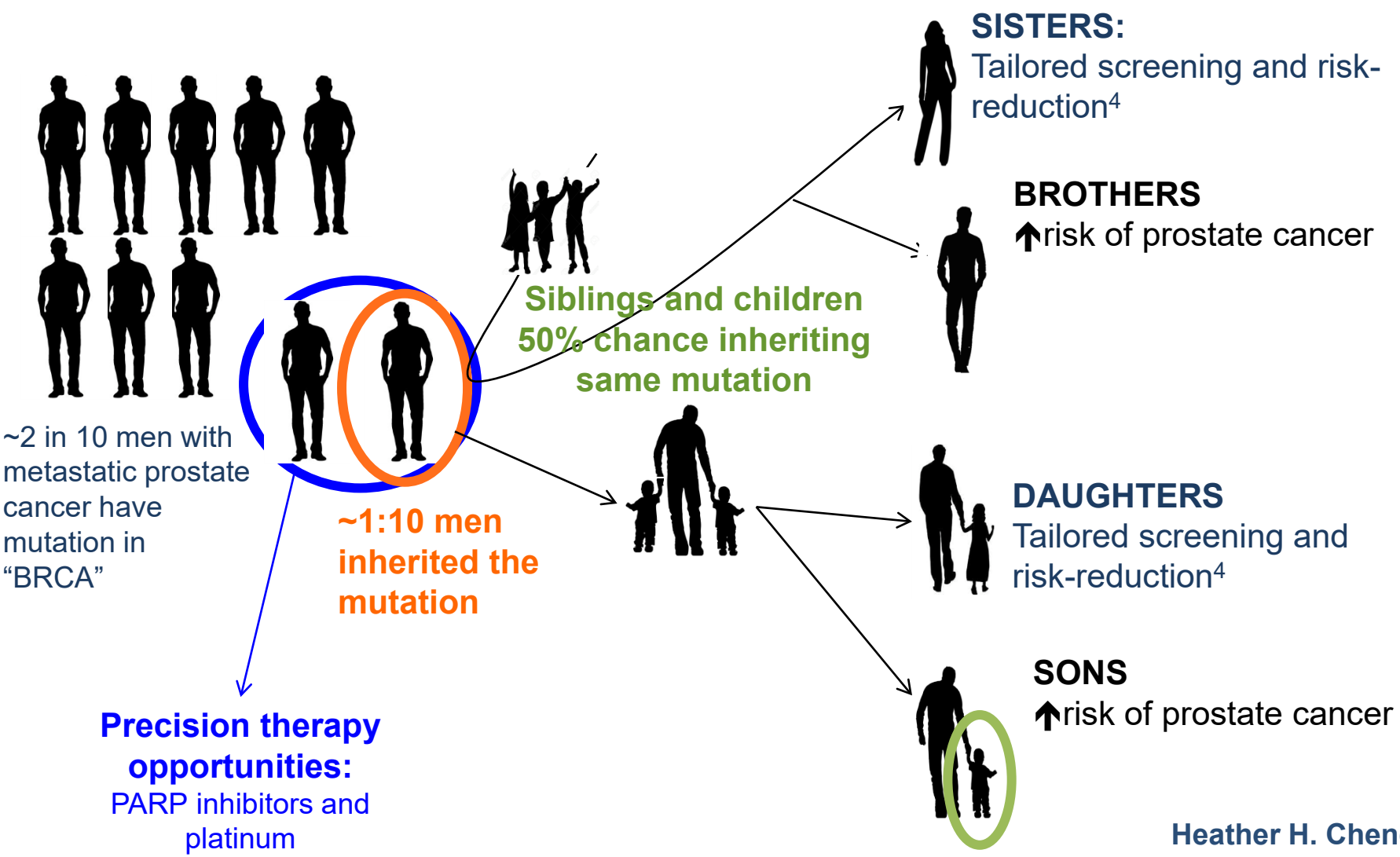


	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

BARCELONA 2019 ESMO congress

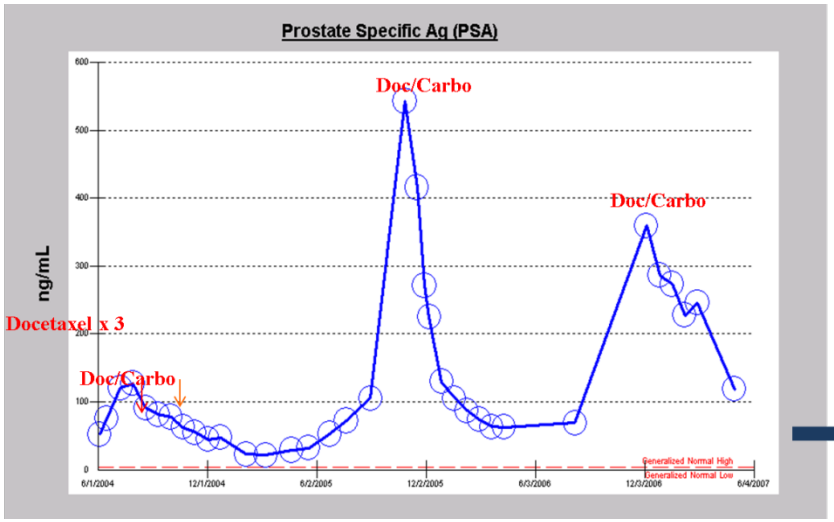
Hussain et al 2019

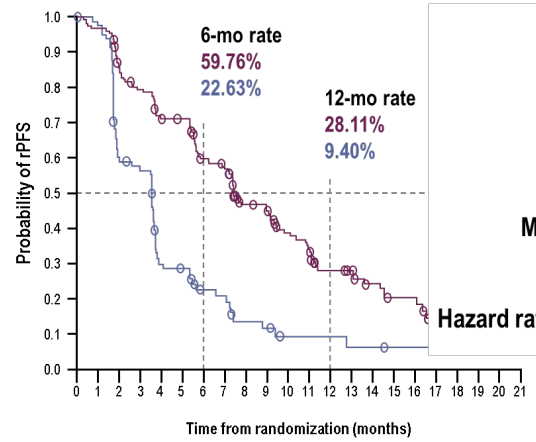
Why We Test – Cascading Impact



Heather H. Cheng

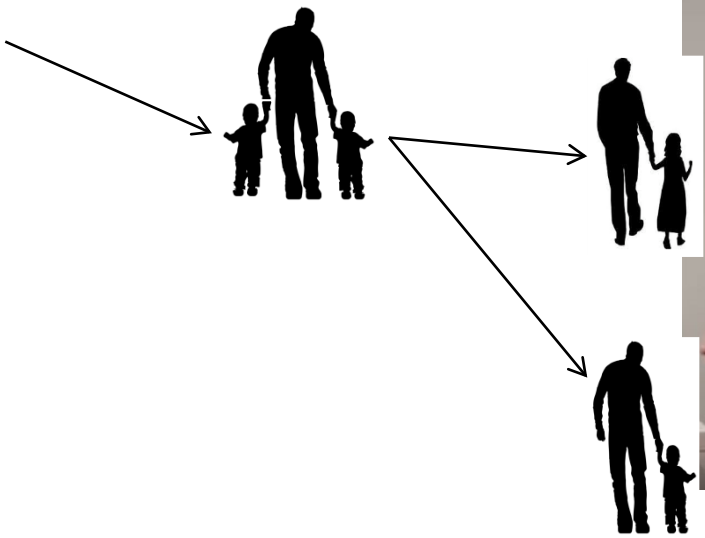
Why Do We Test

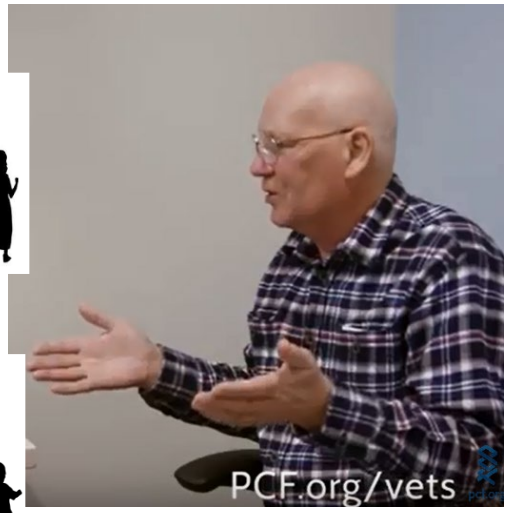


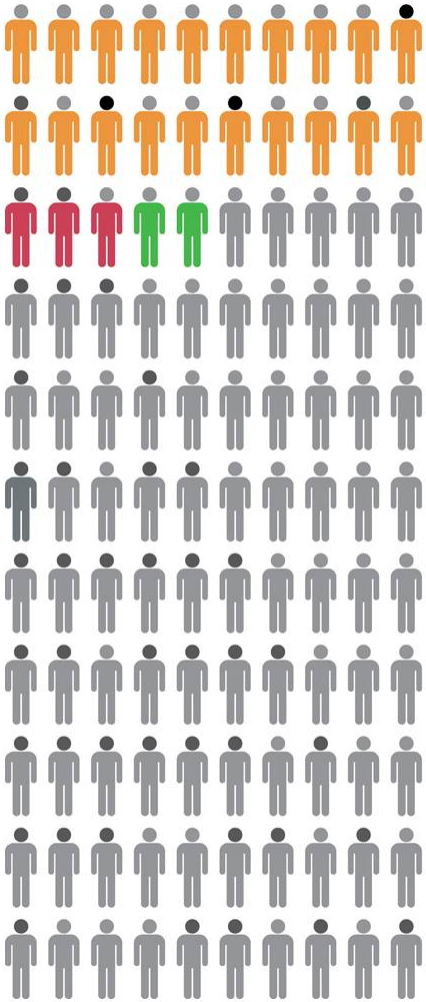


	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

Mito x 5
DC x 6







DNA Repair (BRCA1/2, ATM, etc.) 20%

MMR /MSI 5%

CDK12 7%

The challenge 70%

Conclusions

- Improving precision oncology in lung and prostate cancer is the vision for the future in VA
- VA is the right health care system for precision oncology (EMR, largest care system in the US, standardized practice)
- VA data can inform care for veterans and their families
- VA can lead the way in research for men with prostate cancer
- All veterans with metastatic prostate cancer should undergo germline and somatic testing (mismatch repair, BRCA, PALB2)

Conclusions (for veterans)

- If you haven't been screened for prostate cancer, discuss with your provider
- If you have prostate cancer, discuss this information with your doctor and if appropriate reach out to a VA/PCF network site
- If you know a veteran with prostate cancer, tell them about this initiative in VA

Conclusions (for all of us)

- Together we can make this effort successful and lead the nation in oncology care


Thank you
VA
U.S. Department of Veterans Affairs
Veterans Health Administration
VA Puget Sound Health Care System
UW Medicine
FRED HUTCH
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