Prostate Cancer, DNA Repair Pathways and Clinical Implications for Inherited Cancer Risk

Heather H. Cheng, MD, PhD
Associate Professor, University of Washington
Associate Professor, Fred Hutch Cancer Research Center

Genetics in Clinical Cancer Care
April 18, 2020

FRED HUTCH
CURES START HERE™

Disclosures

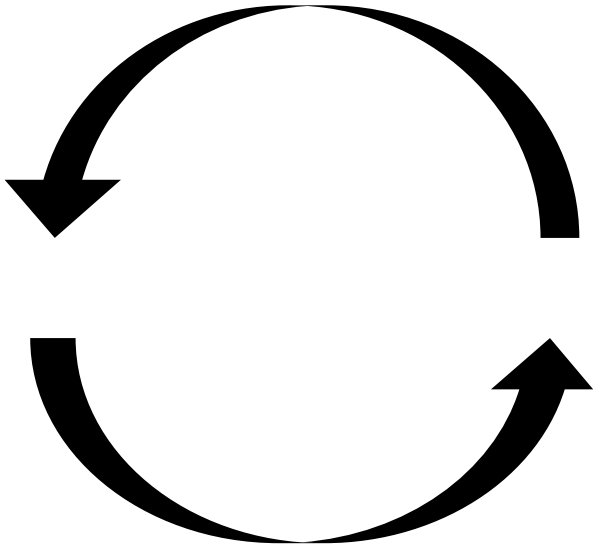
- Research funds to institution: Clovis, Color Genomics, Janssen, Medivation, Sanofi
- Consultant: Astra Zeneca
- Royalties: UpToDate

Multiple Goals for Genetic Testing in Prostate Cancer

"From Family Reunions to the Frontline of Developmental Therapeutics"

TREATMENT DRIVEN

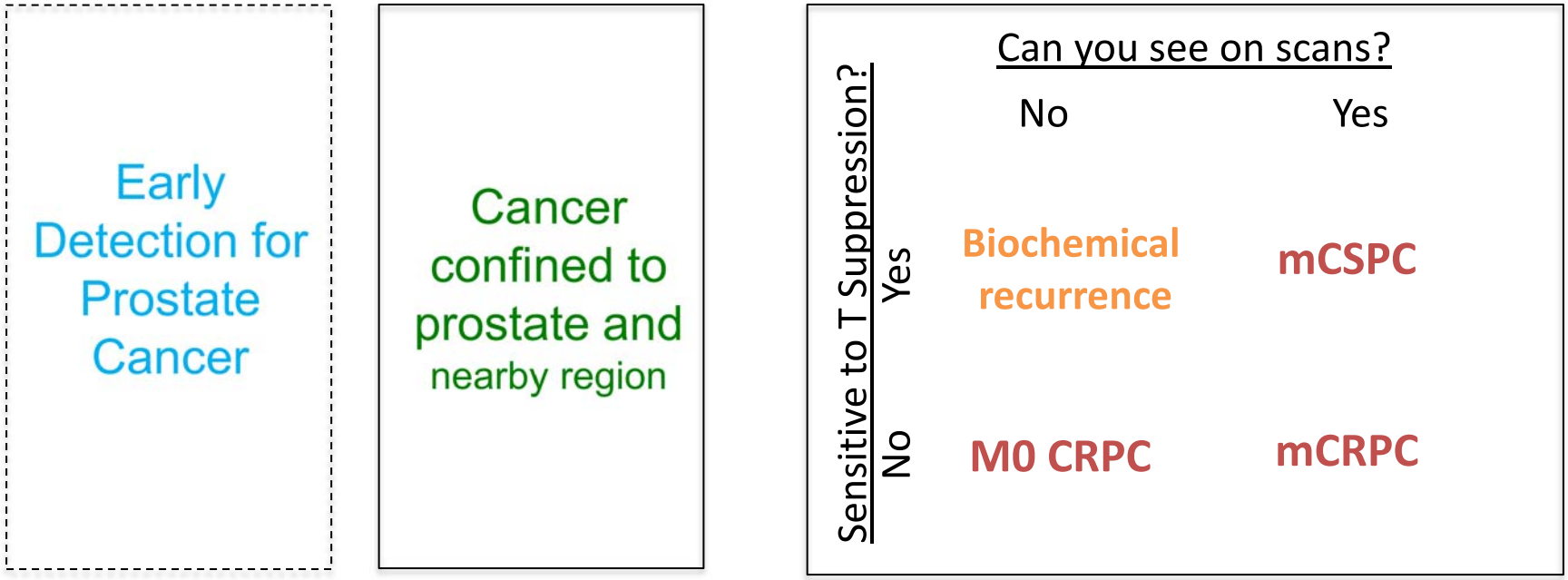
Somatic ±
Germline



RISK DRIVEN

Germline

Prostate Cancer Disease States



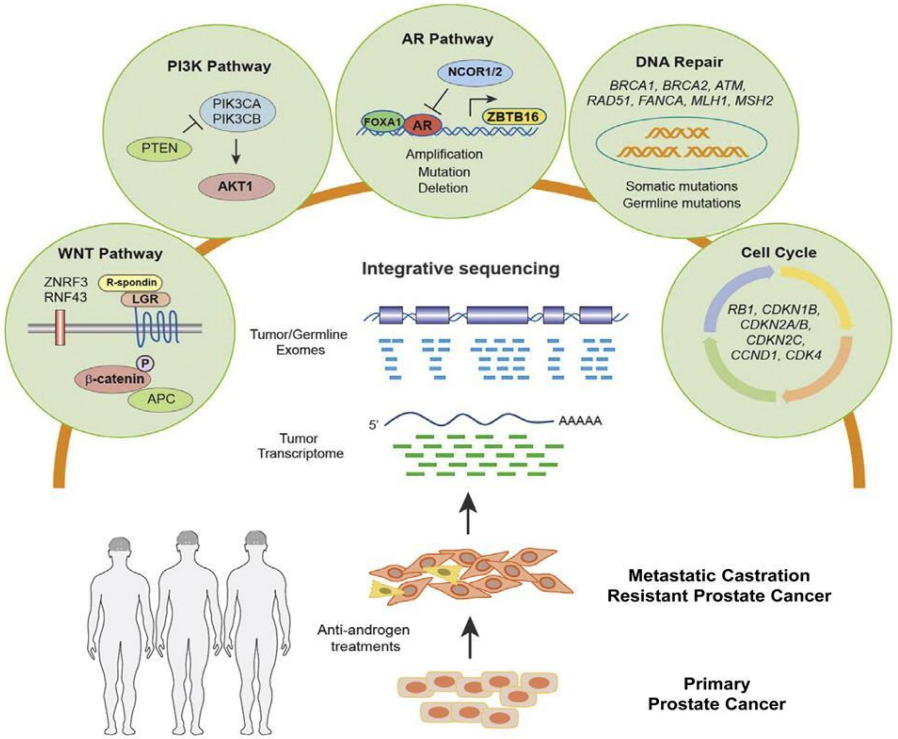
At Risk:

Localized:
Curable

Advanced (rising PSA):
Treatable

Molecular Landscape of Advanced Prostate Cancer

- 150 mCPRC biopsies
- ~25% mCRPC have defects in DNA repair genes (eg, *BRCA2, ATM, BRCA1, MSH2, MSH6*)[1]
- 8% of DNA repair defects were found in germline



FRED HUTCH
CURES START HERE™

Robinson, et al. *Cell.* 2015

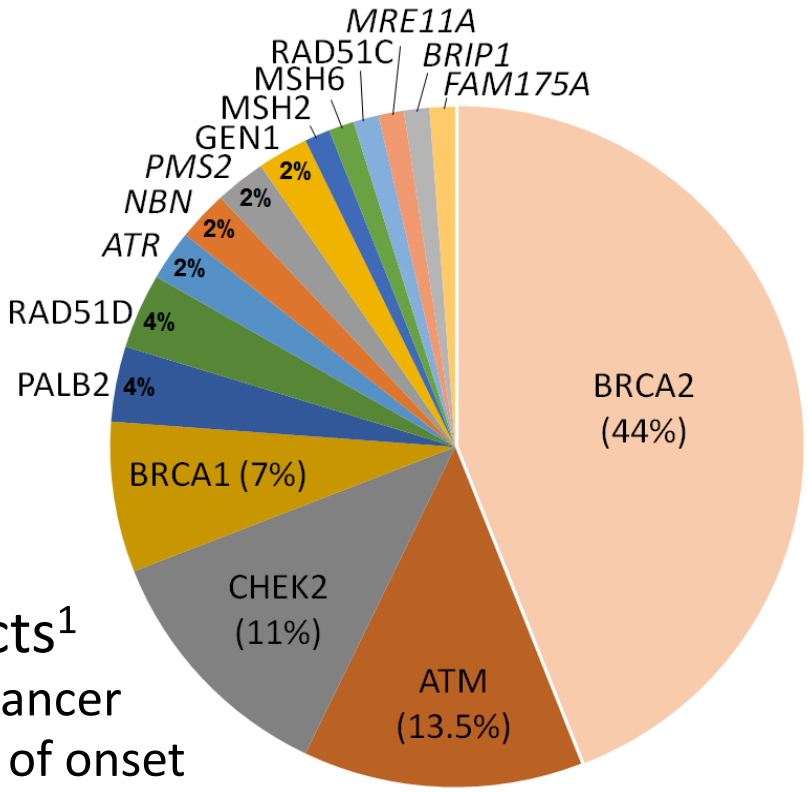
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

August 2016

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran,



>10% with germline DNA repair defects[1]

- n=692 men with metastatic prostate cancer
- Irrespective of family history AND age of onset
- Majority had evidence of defect's relevance in tumor

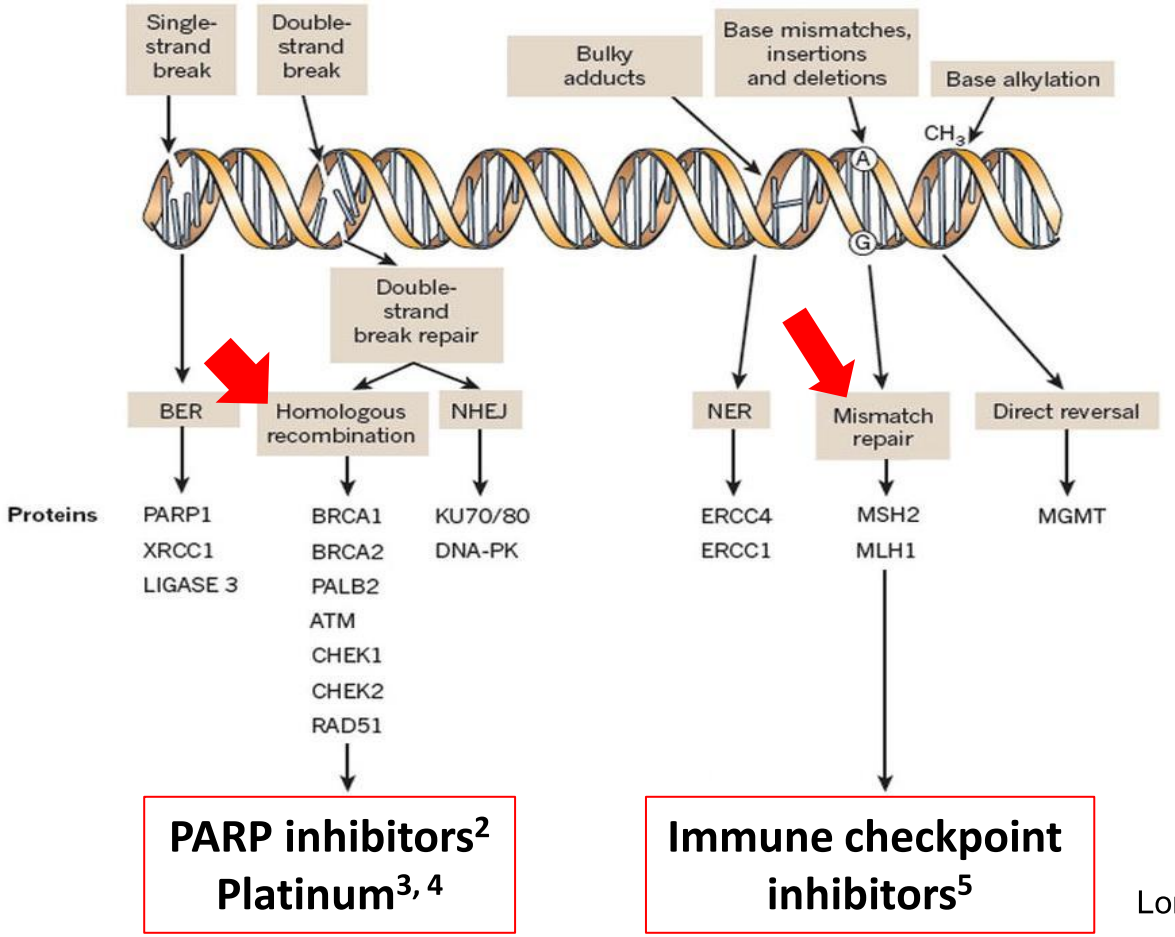
1. 40% of men germline DNA repair defects did NOT meet (NCCN 2016) guideline criteria [2]

FRED HUTCH
CURES START HERE™

1. Pritchard, Mateo, Walsh, et al. *N Engl J Med.* 2016
2. Nicolosi et al *JAMA Onc* 2019

DNA repair defects in Prostate Cancer:

homologous recombination and mismatch repair deficiency



PARP inhibitors[2]
Platinum[3, 4]

Immune checkpoint inhibitors[5]

Figure adapted from
Lord and Ashworth. *Nature.* 2012

2 Hussain, et al ESMO 2019
3. Cheng, et al Eur Urol 2016
4 Pomerantz, et al Cancer 2017
5. Le, et al NEJM 2015

FRED HUTCH
CURES START HERE™

MSI-H and dMMR in prostate is uncommon but actionable: anti-PD1/PD-L1

- 5-7% with MSI-H in metastatic PrCa

- 3% with MSI-H/dMMR in all stages PrCa
  - ~20% have Lynch Syndrome (mutation is germline)
  - ~50% pts receiving anti-PD-1/PD-L1 achieve durable benefit

Pritchard, et al. (2014) Nat Communic
Robinson and Van Allen, et al. (2015) Cell
Abida, et al. (2019) JAMA Oncol.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER[c]

Risk Group	Clinical/Pathologic Features	Germline Testing[c]	Molecular and Biomarker Analysis of Tumor[c]	Initial Therapy
Regional	Any			
Metastatic[ee]	Any			

Risk Group	Clinical/Pat
Very low[d]	Has all of the • T1c • Grade Grou • PSA <10 ng • Fewer than ≤50% canc • PSA density
Low[d]	Has all of the • T1–T2a • Grade Grou • PSA <10 ng
Intermediate[d]	Has all of the • No high-risk features • No very-high group featu • Has one or intermediat factors (IRF ▸ T2b–T2c ▸ Grade Gro ▸ PSA 10–2
High	Has no very-h feature: • T3a OR • Grade Grou • PSA >20 ng
Very high	Has at least o • T3b–T4 • Primary Gle • 2 or 3 high- • >4 cores wi

Risk/Stage	Molecular Testing of TUMOR	GERMLINE Testing
Very low	Not indicated	**Recommended for strong FH, personal history of intraductal/cribriform**
Low	Consider if life expectancy ≥10 y	**Recommended for strong FH, intraductal/cribriform**
Favorable Intermediate	Consider if life expectancy ≥10 y	**Recommended for strong FH, intraductal/cribriform**
Unfavorable Intermediate	Not routinely recommended	**Recommended for strong FH, intraductal/cribriform**
High	Not routinely recommended	**Recommended**
Very High	Not routinely recommended	**Recommended**
Regional	Consider tumor testing for HR gene mutations, MSI, or dMMR	**Recommended**
Metastatic	**Recommend tumor testing for HR gene mut., MSI, or dMMR**	**Recommended**

A New Model to Remove Barriers

GENetic Testing for MEN
with metastatic prostate cancer

www.gentlemenstudy.org

OBJECTIVE: **Remove barriers and determine if acceptable delivery of** genetic testing that may provide critical information for men with metastatic prostate cancer and their families

Intended to complement, not replace, existing frameworks

GENTleMEN:

GENetic Testing for MEN with metastatic prostate cancer.

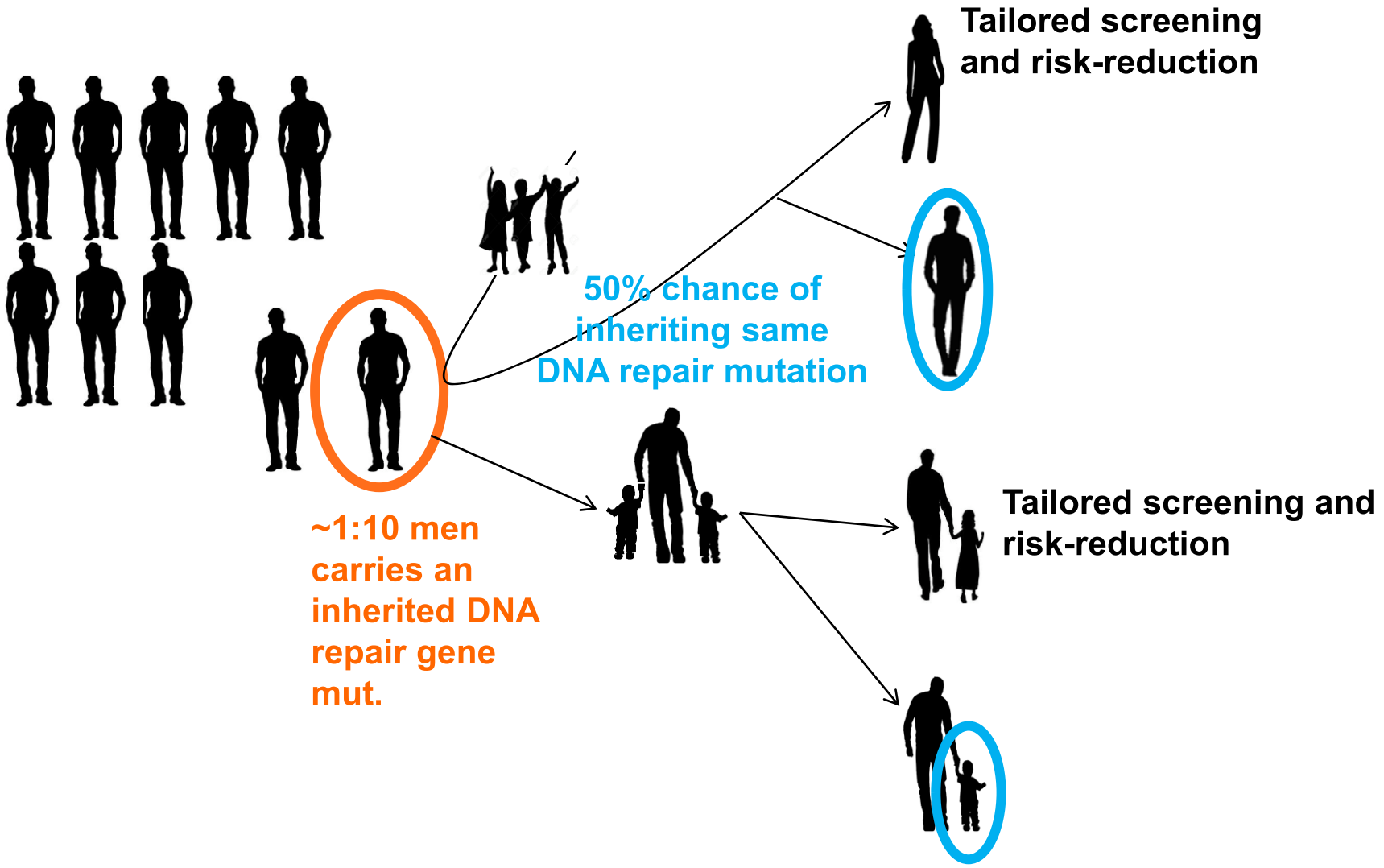
(Germline screening for all men with metastatic prostate cancer)

1. Men learn about the study through variety of means
2. Web-consent, patient or study team uploads supporting medical data
3. Brief patient survey: demographics, fam history, knowledge, distress
4. Participants mailed a Color Genomics Saliva Kit
5. Participants receive results with genetic counseling support and encouraged to share with their families and doctors.

6. Participants invited to follow up as relevant to: genetic counseling, cascade testing, opportunities for research/registry participation, etc.

>500 patients with results returned,
Availaable NATIONWIDE

Cascade Testing



Heather Cheng

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

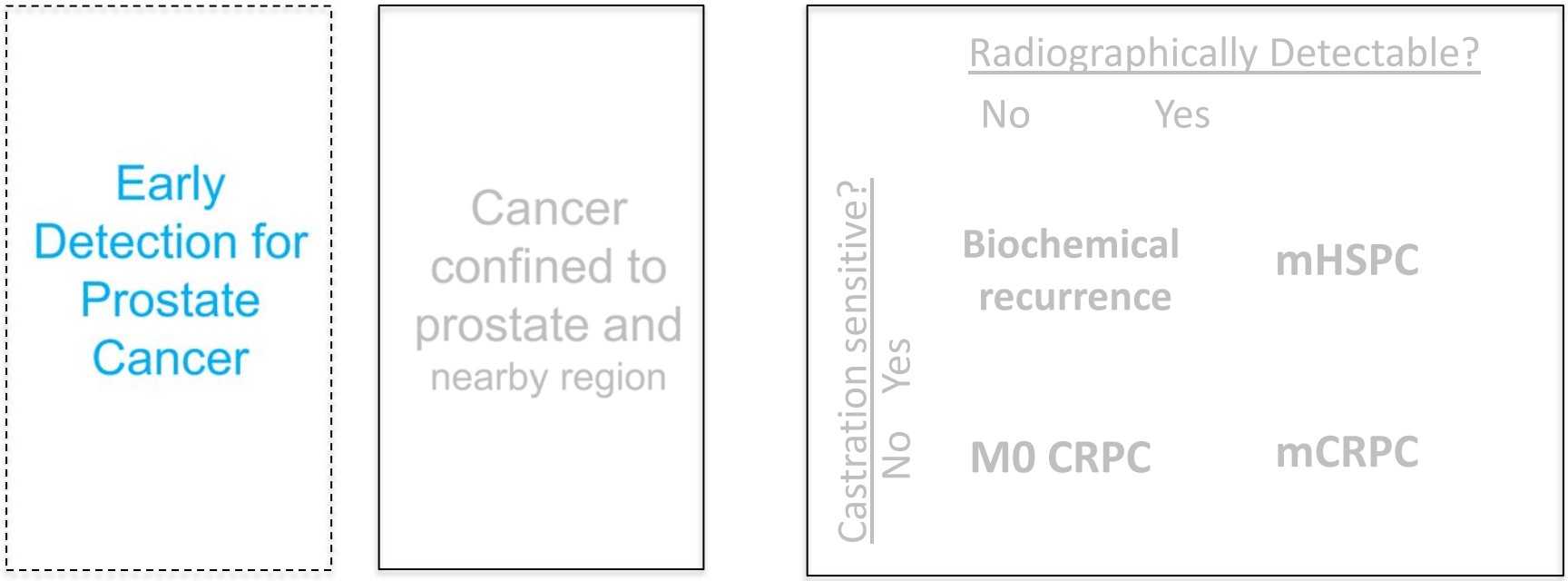
Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic …and Prostate, and…

Version 1.2020 — December 4, 2019

HNPCC → Lynch Syndrome
HBO(P+P)C → King Syndrome

to raise awareness among men…

Prostate Cancer Disease States



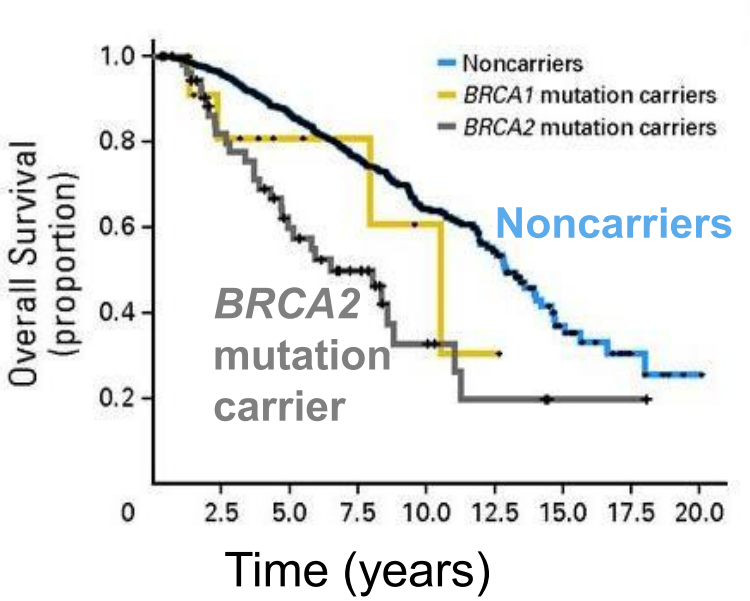
At Risk:

Localized:
Curable

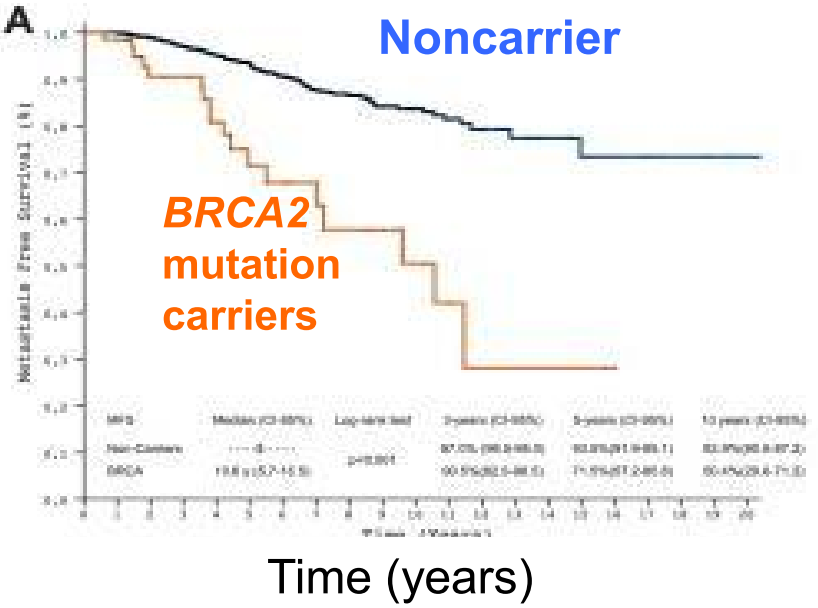
Advanced:
Treatable

Evidence for causality and contribution to lethal progression, I

Poorer overall survival



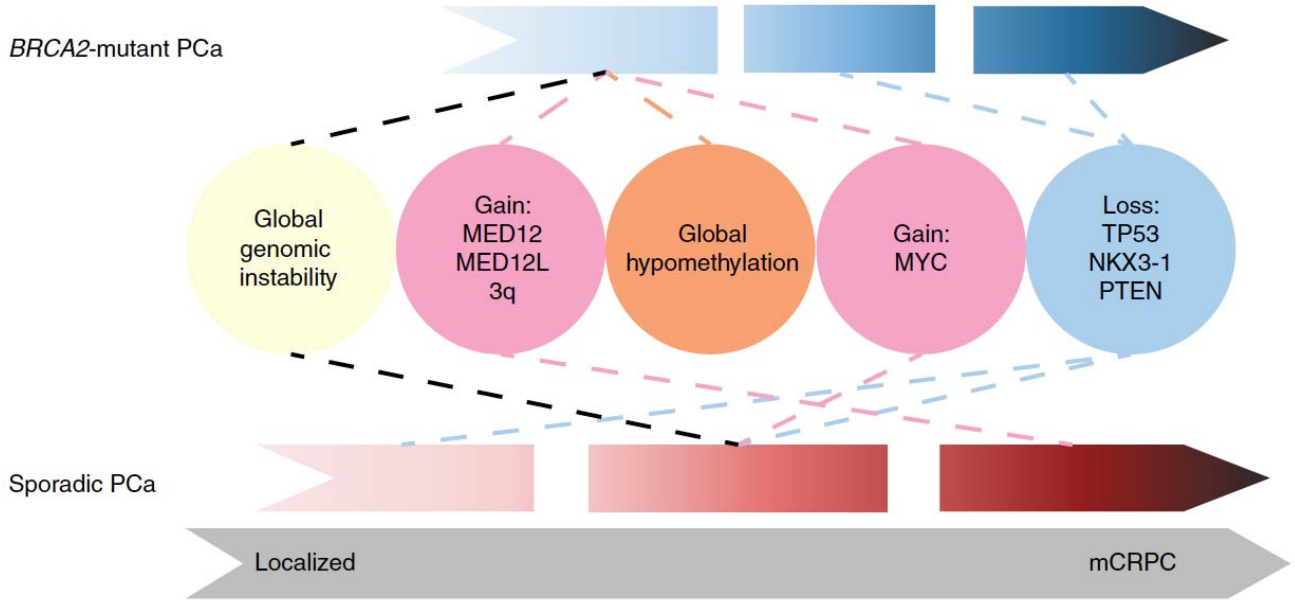
Poorer metastases-free survival



FRED HUTCH
CURES START HERE™
Heather H. Cheng, MD, PhD

Castro, et al (2013) JCO
Castro, et al (2014) Eur Urol

Evidence for causality and contribution to lethal progression, II



BRCA2-mutant prostate cancers

- Harbour increased global genomic instability
- Mutational profile more closely resembles metastatic than localized disease (e.g. dysregulation of MED12L/MED12)
- **Justifies aggressive initial treatment**

Taylor, et al 2016 Nat Communications

Evidence for causality and contribution to lethal progression, III

	mPC vs EXAC (pop)		mPC vs TCGA (localized)	
	Relative Risk	P Value	Relative Risk	P Value
BRCA2	**18.6**	**<0.001**	**26.7**	**<0.001**
BRCA1	**3.9**	**0.005**	1.4	0.32
ATM	**6.3**	**<0.001**	1.6	0.12
PALB2	**3.5**	**0.05**	1.1	0.76

mPC = metastatic prostate cancer

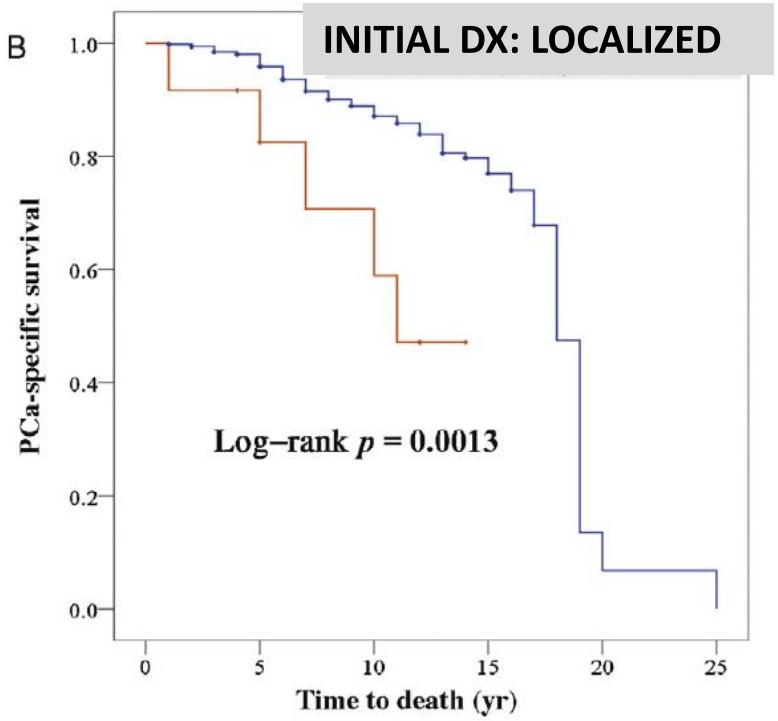
- 59% (36/61) with available tumor had 2nd allele inactivation by loss-of-function mutation or copy loss

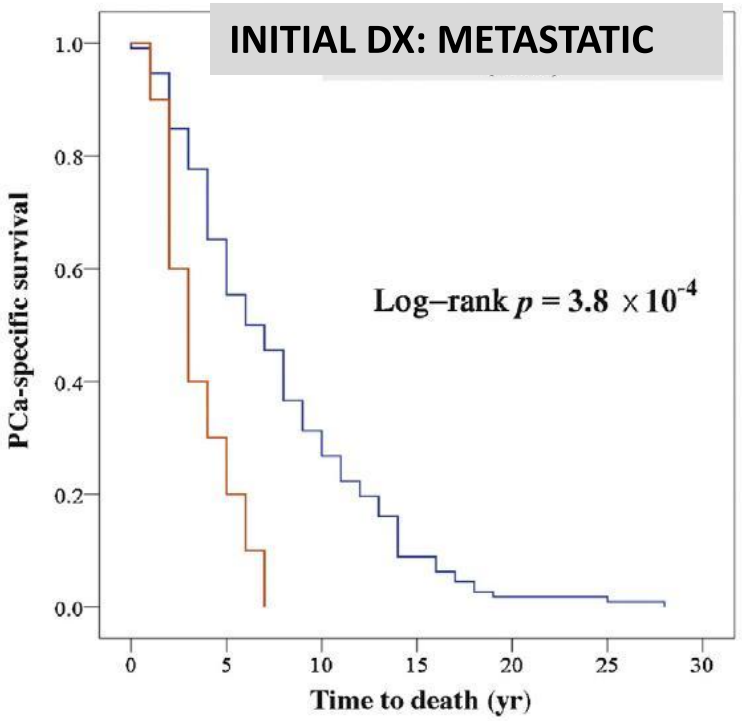
Pritchard, et al 2016 NEJM

Evidence for causality and contribution to lethal progression, IV

Mutation Carriers: *BRCA1* (4), *BRCA2* (15), *ATM* (8)

Non-Mutation Carriers





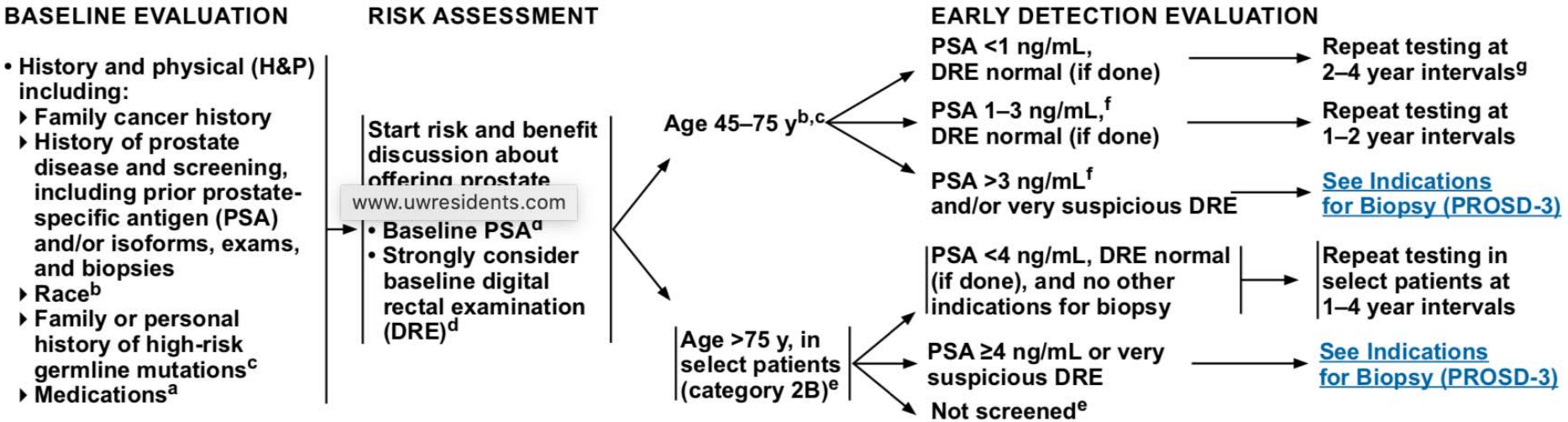
FRED HUTCH
CURES START HERE™
Heather H. Cheng, MD, PhD

Na, et al 2017 Eur Urol

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Prostate Cancer Early Detection

NCCN Guidelines Index
Table of Contents
Discussion



[c] If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, it is reasonable for men with germline *BRCA1/2* mutations to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual intervals rather than every other year.

for the early detection of
nd-alone test, but should be
RE may be considered as
n-grade cancers associated
for biopsy if DRE is very
Prognostic significance of digital
the prostate, lung, colorectal
2017;197:363-368.
n very healthy men with
er undergone PSA testing)
that pose a significant risk
Widespread screening in
f overdetection and is not

[f] The median PSA values for men aged 40–49 years range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.

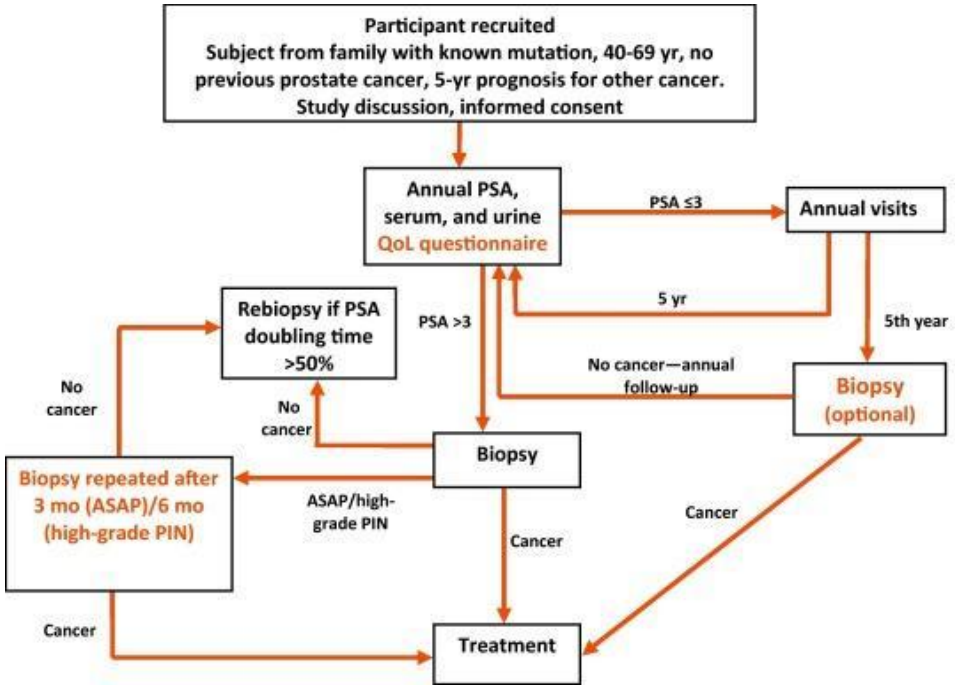
IMPACT: PCa Screening in *BRCA1/2* mut carriers
Biopsy at PSA >3.0

***BRCA2* Carrier Summary:**
- 8.1% required further investigations
- 3.3% cancer incidence
- 48.0% PPV of biopsy
- 68.0% intermediate-/high-risk disease

BRCA2mut CARRIERS N=731

***BRCA2* Control Summary:**
- 6.5% required further investigations
- 1.6% cancer incidence
- 33.3% PPV of biopsy
- 42.9% intermediate-/high-risk disease

BRCA2 w.t. CONTROLS N=428



Bancroft et al. 2014 Eur Urol
(updated results to be reported)

Men at High Genetic Risk for Prostate Cancer

NCI Study - Bethesda
(NCT03805919)

Who Can Participate? Men, 30 to 70 years old without prostate cancer, who have tested positive for BRCA1, BRCA2, HOXB13, ATM, NBN, TP53, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, PALB2, RAD51D, FANCA. Genetic testing is not offered.

What is Involved?

- Screening MRI of the prostate every 2 years
- Biopsy of the prostate if any MRIs are abnormal
- No cost for study-related tests or procedures
- No cost for travel
- Clinical information will be shared with you and your doctor, if you choose

1-800-411-1222, study #19-C-0040
couvilla@mail.nih.gov

PATROL STUDY:

Prostate Screening For Men with Inherited Risk of Developing Aggressive Prostate Cancer

Men ≥40y with germline PV/LPV in

- ***BRCA2***
- ***BRCA1***
- ***HOXB13***
- ***MLH1***
- ***MSH2***
- ***MSH6***
- ***PMS2***
- ***TP53***
- ***ATM***
- ***CHEK2***
- ***PALB2***

BASELINE and EVERY 6-12 MONTHS:

- History and Physical, QOL
- Family history of cancer (and interval updates)
- PSA
- Urine MDx test
- Research urine and blood collected

Prostate Biopsy if ANY of:

- if ≤49Y, PSA≥0.75
- if >50-59y, PSA≥1.0
- if >60Y, PSA≥1.5
- *optional* baseline biopsy
- Clinical indication for biopsy +/-MRI
- Urine MDx, research urine and blood

IF NO cancer:

urine MDx ≤27.5

- Continue 6-12 month follow up

urine MDx >27.5

- F/U q6 mos
- Repeat PSA and bx as clinically indicated +/-MRI

IF GG1-2:

- Collect path report, staging data
- Collect biopsy material
- Options, as clinically indicated:
  - Repeat bx +/-MRI in 6 mos
  - Definitive therapy
  - Discuss clinical trial options

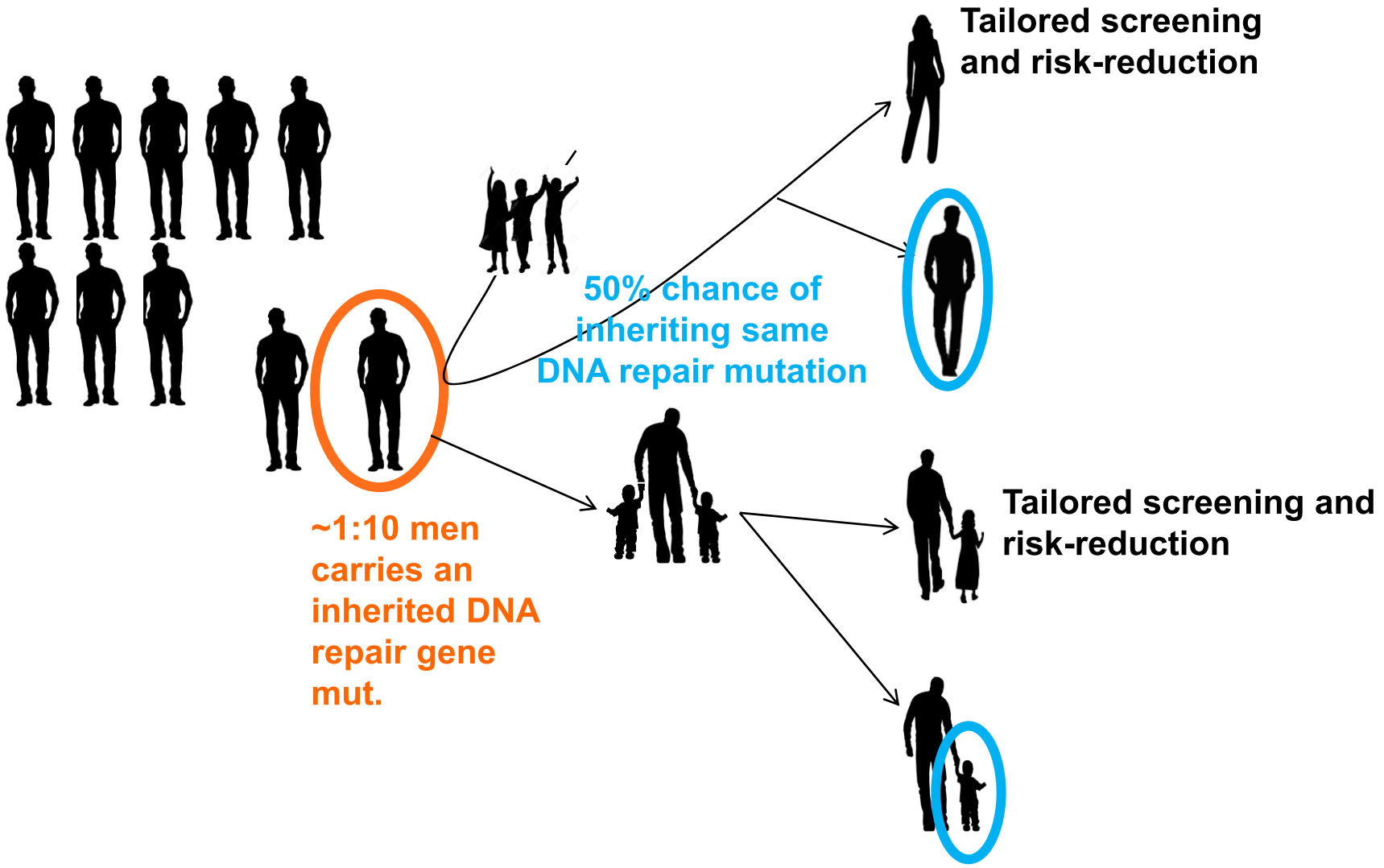
IF ≥GG3:

- Collect path report, staging data
- Collect bx material
- Options, as clinically indicated:
  - Definitive therapy
  - Discuss clinical trial options

With Dan Lin, Colin Pritchard, Janet Stanford

Looking for collaborating sites

Cascade Testing



Heather Cheng

Conclusions

1. For ***BRCA2*** *(>BRCA1>ATM)*, evidence for causality and progression to lethal disease
2. Proposed list of genes for testing should account for: **treatment/trials** (mCRPC > BCR > localized) **AND family**
3. Knowledge evolving; decision framework can be practical.
4. More to learn about less common genes/variants
5. Early-stage disease management needs evid, clinical trials
6. PC screening should factor potential for progression to metastatic dz **(Consider ALL geno/phenotype info, NCI Study, PATROL Study)**

FRED HUTCH
CURES START HERE™
Heather H. Cheng, MD, PhD

Question 1

A 64 yo man with metastatic castration-resistant prostate cancer has been doing well after starting androgen-deprivation therapy and abiraterone acetate with prednisone. Tumor sequencing reveals two inactivating *BRCA2* mutations (biallelic).

Which of the following is TRUE?

A. PARP inhibitors would not be among the future treatment options.

B. It is necessary to refer to genetic counseling for dedicated germline testing if he is wondering about his relatives' risk of cancer.

C. Pembrolizumab is a standard of care treatment option now.

D. It is not necessary to refer to genetic counseling for dedicated germline testing because tumor sequencing is sufficient.

ANSWER: B. It is necessary to refer to genetic counseling for dedicated germline testing if he is wondering about his relatives' risk of cancer, the other choices are wrong

Question 2

A 72 yo man with metastatic castration-resistant prostate cancer had tumor sequencing done and was found to have MSI-H in his tumor and MSH2 inactivation. He has very limited family history information (adopted), but has 4 kids. Based on current available evidence, what is the estimated likelihood that he has Lynch Syndrome**?**

A. 20%

B. 50%

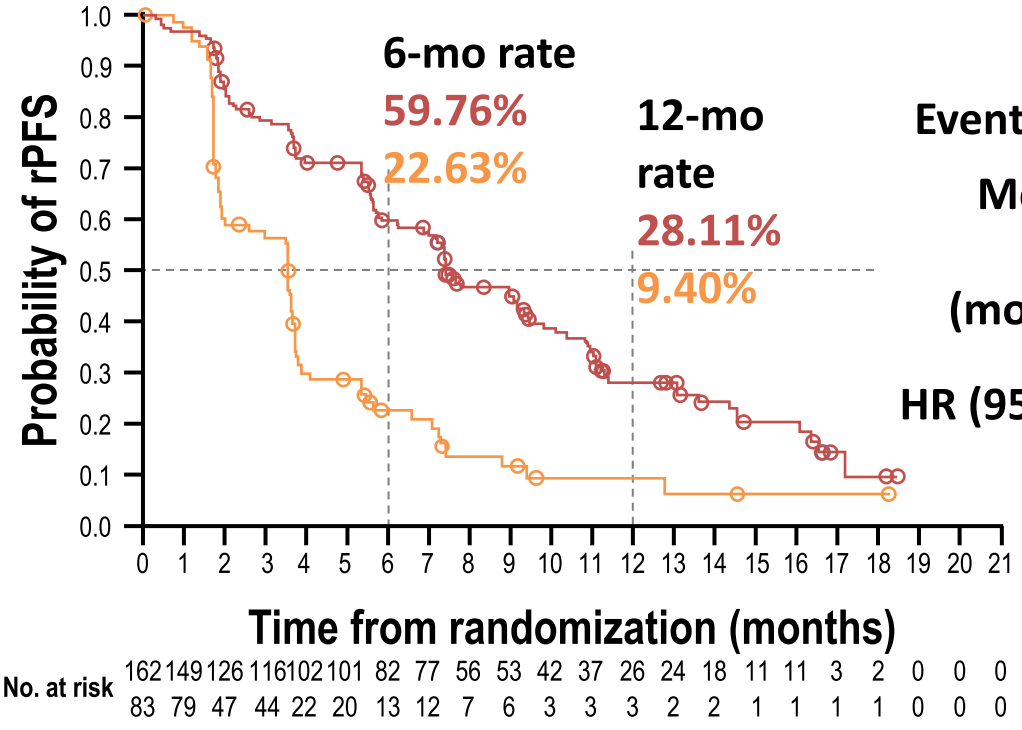
C. 80%

ANSWER: A. 5-7% of men with metastatic prostate cancer have MSI-H/dMMR. Of those, 20% have germline mutations consistent with Lynch Syndrome (Abida, et al. (2019) JAMA Oncol). Thus, patients with MSI-H/dMMR should be offered germline testing, if not already done.

Thank You

PHASE 3 PROFOUND STUDY

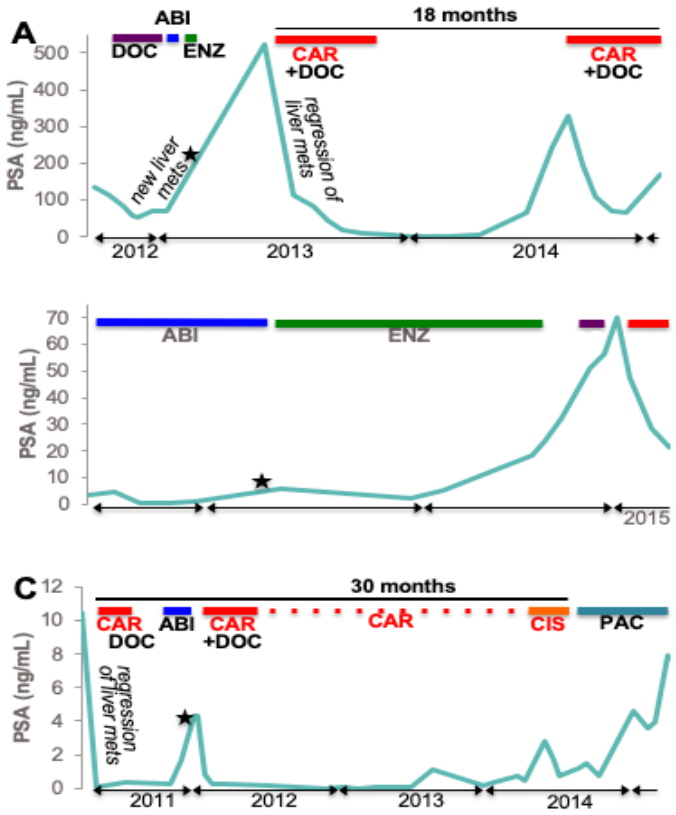
Primary Endpoint: rPFS IN PATIENTS WITH TUMOR ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)

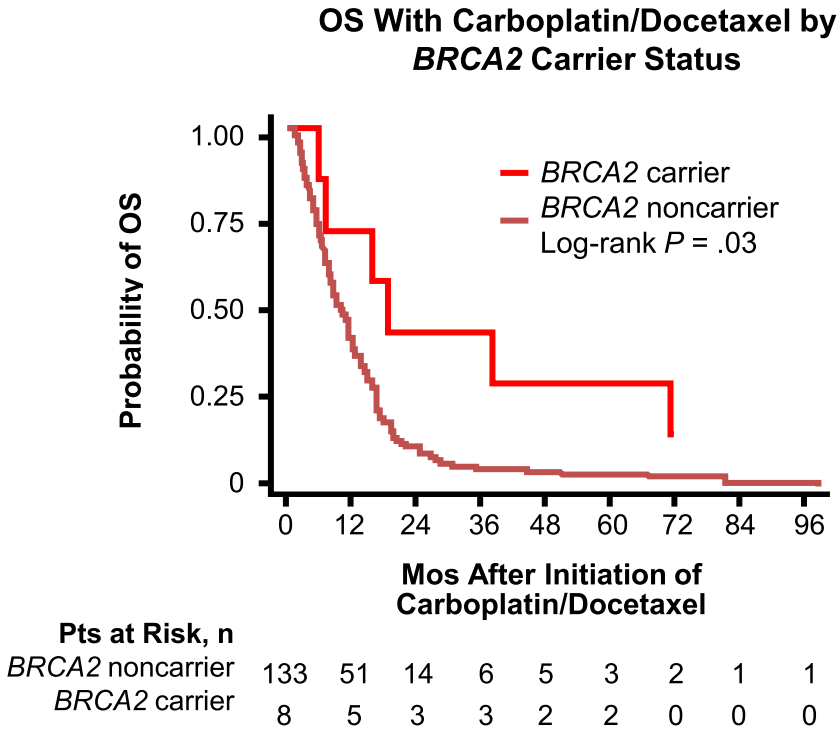


	Olaparib (N=162)	Physician's Choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
HR (95% CI)	0.34 (0.25, 0.47) *P* <0.0001	

Hussain, et al ESMO 2019

Platinum* chemotherapy in mCRPC germline *BRCA2mut*





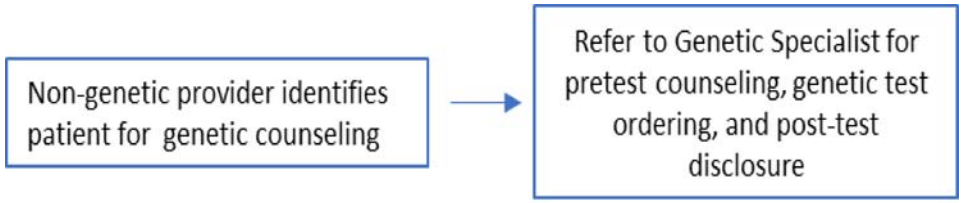
**Platinum not standard agent for prostate cancer*

FRED HUTCH
CURES START HERE™

1 Cheng, et al (2016) Eur Urol
2 Pomerantz, et al (2017) Cancer

Figure 3: Models of collaboration between genetics and healthcare practices for prostate cancer genetic evaluation

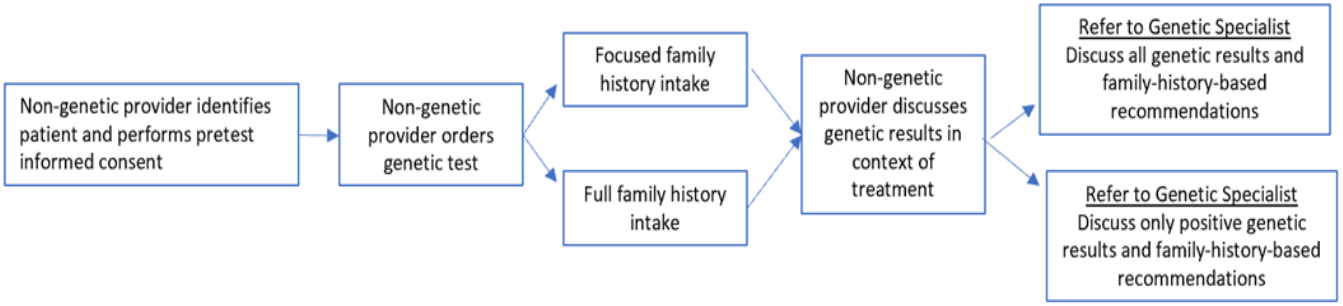
(a) Traditional model: upfront referral to genetic counseling



Note:

- Benefits: Full FH intake by GC, FH-based recommendations by GC, all genetic results disclosure by GC
- Considerations: Difficulty with access, potentially long appointment wait times, potential delay in genetic testing

(b) Collaborative/Point-of-Care/Hybrid Model: Pretest engagement by healthcare provider; Post-test engagement with genetics and/or healthcare provider



Note:

- Benefits: Rapid genetic testing by non-genetics provider
- Considerations: Non-genetic providers need to address FH intake, FH-based recommendations, pretest informed consent, and referral to GC based on results

2019 Philly Consensus Conference; Giri, et al JCO, In press