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Prostate cancer:

Your Guide to Prostate Health and What to Know About the Leading Cancer in Men

David M. Nanus, MD

Chief, Division of Hematology and Medical Oncology

Director of New York Presbyterian Hospital - Weill Cornell Medicine Healthcare Services Cancer Program

Scott T. Tagawa, MD, MS

Medical Director, Genitourinary Oncology Research Program

Associate Professor of Clinical Medicine & Urology

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weillcornellgucancer.org

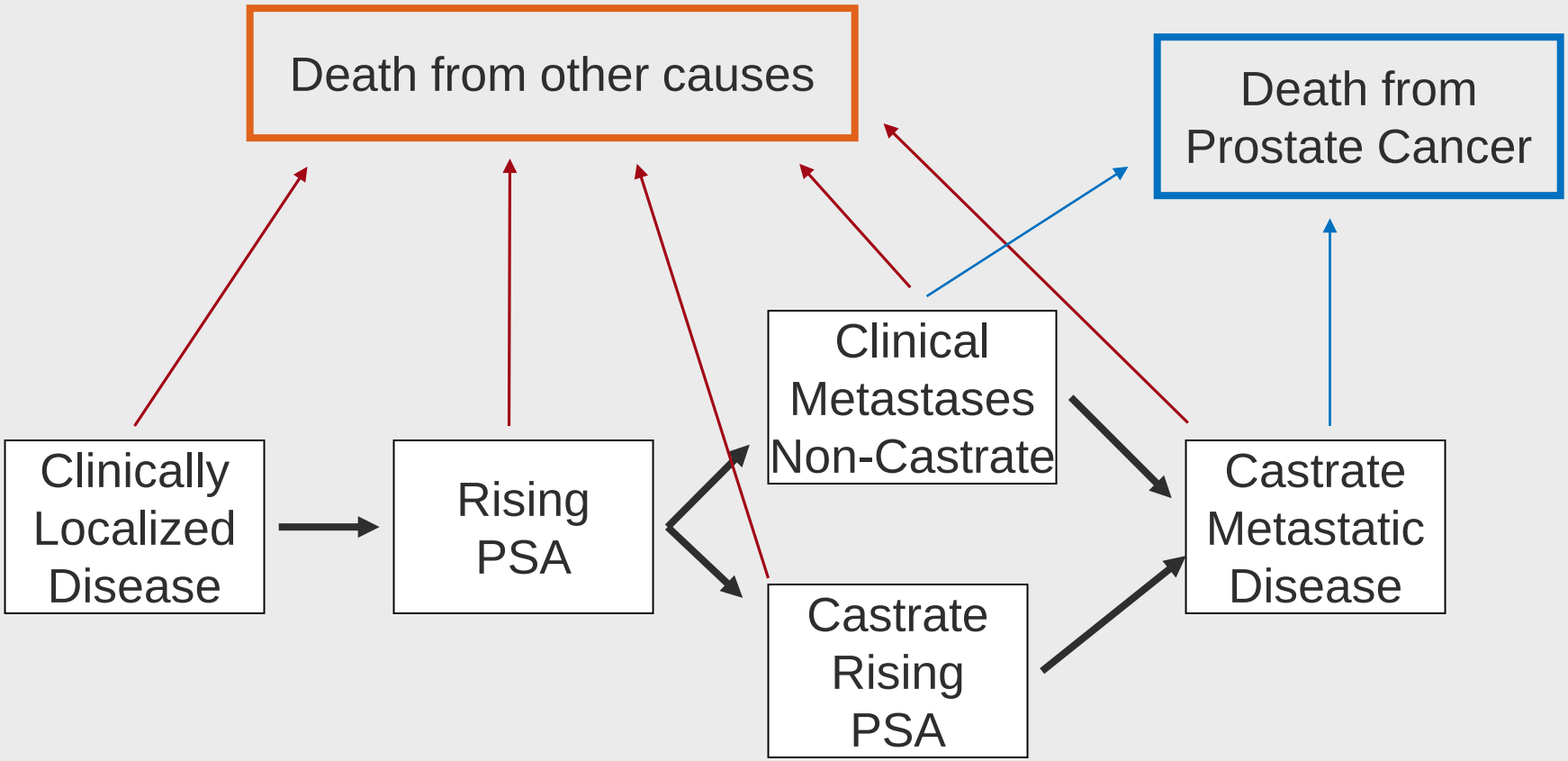
Prostate Cancer Screening

Demographics

- 180,890 estimated new cases in 2016
  - 21.5% of all cancers in males
  - most common cancer in men
  - Lifetime risk: 1 in 7

- 26,120 estimated deaths
  - 8.3% of cancer deaths in males
  - second to lung cancer in men
  - decreased by 3.5% per year 2003 to 2012

"Clinical states"



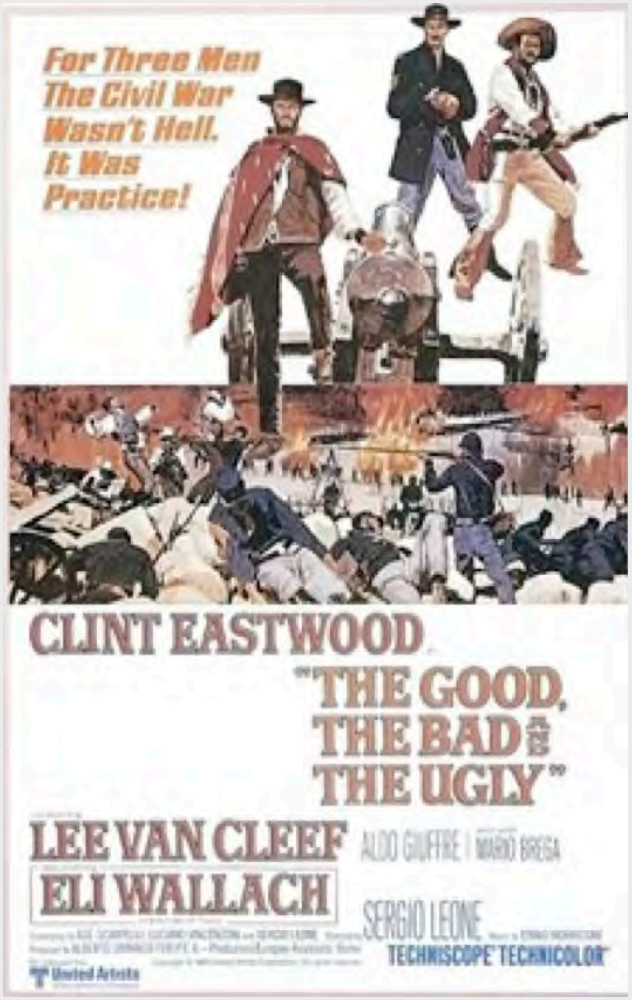
Prostate Cancer Screening:

PSA

+

DRE

PSA – Like a Clint Eastwood Movie



- **The Good**

  PSA-based early detection decreases mortality

- **The Bad**

  Not perfectly sensitive or specific

  → Over-detection ***compounded by Over-treatment***

- **The Ugly**

  Treatment arbitrary, variable, often unnecessary and costly

Who is at Risk for Prostate Cancer?

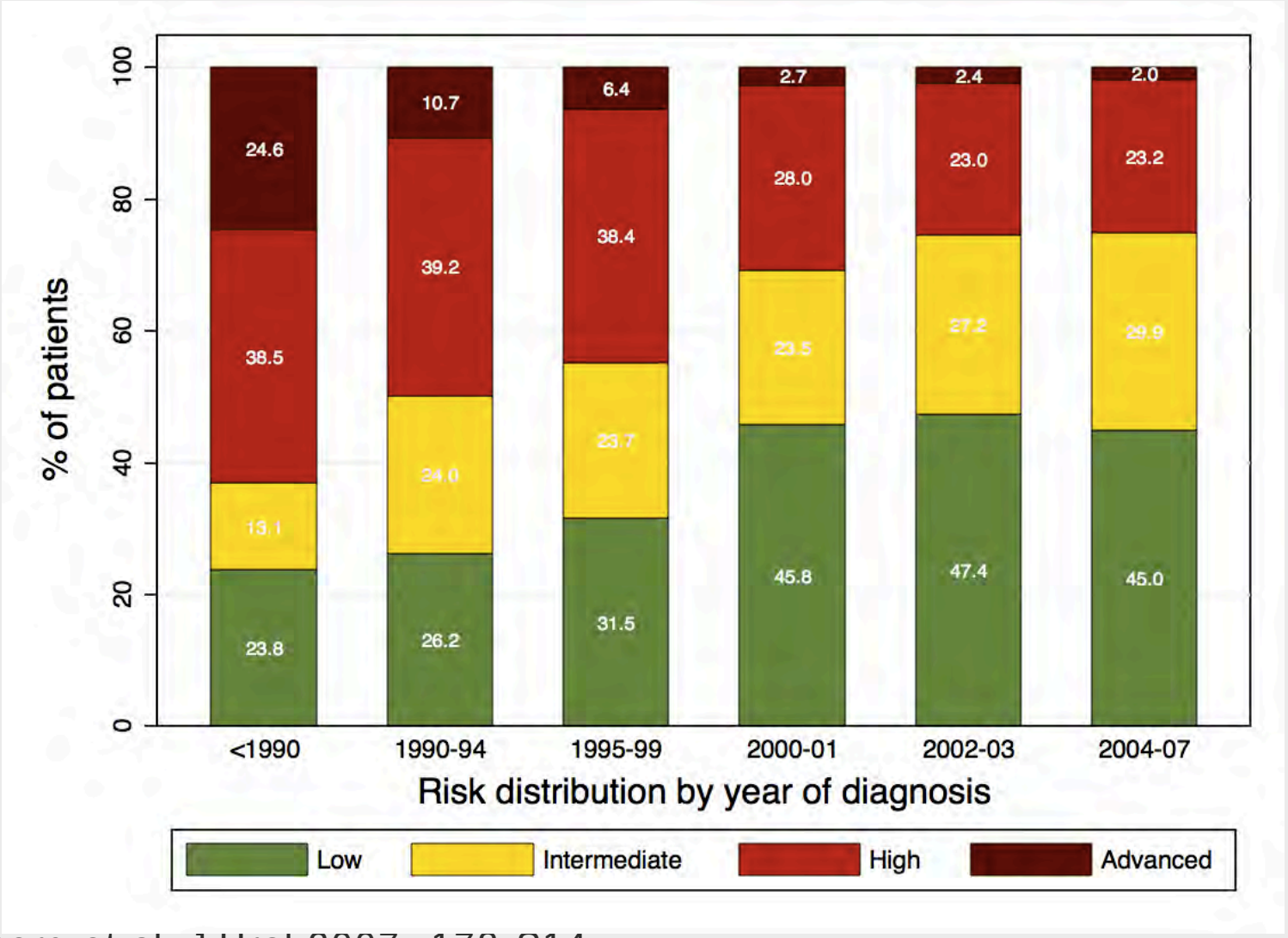
- Men
- Increasing age
- African ancestry (U.S. and Caribbean)
- Family history (5-10%)
- Inherited genetic conditions
  - Lynch syndrome
  - BRCA1 and BRCA2 mutations
  - Other DNA repair mutations

Incidence (per 100,000) and Death Rates for Prostate Cancer by Race and Ethnicity 2008-2012

Incidence	Non-Hispanic white	Non-Hispanic black	Asian and Pacific Islander	American Indian and Alaska Native	Hispanic/Latino
Incidence	123.0	**208.7**	67.8	90.5	112.1
Deaths	19.9	**47.2**	9.4	20.2	17.8

Siegel et al, CA Cancer J Clin 2016;66:7-30

The Changing Face of Prostate Cancer in the United States



Cooperberg et al. J Urol 2007; 178:S14

NCCN Guidelines (September 2017) Prostate Cancer Early Detection

Shared decision making

“The guidelines are specifically for men opting to participate in an early detection program (after receiving the appropriate counseling on the pros and cons)”

“The guidelines are continuously in a state of evolution based on new evidence”

Baseline Evaluation

- History and physical including:
  - Family history
  - Medications
  - History of prostate disease and screening, including prior PSA and/or isoforms, exams, and biopsies
  - Race (African American)
  - Family or personal history of BRCA 1 or 2 mutations

Risk Assessment

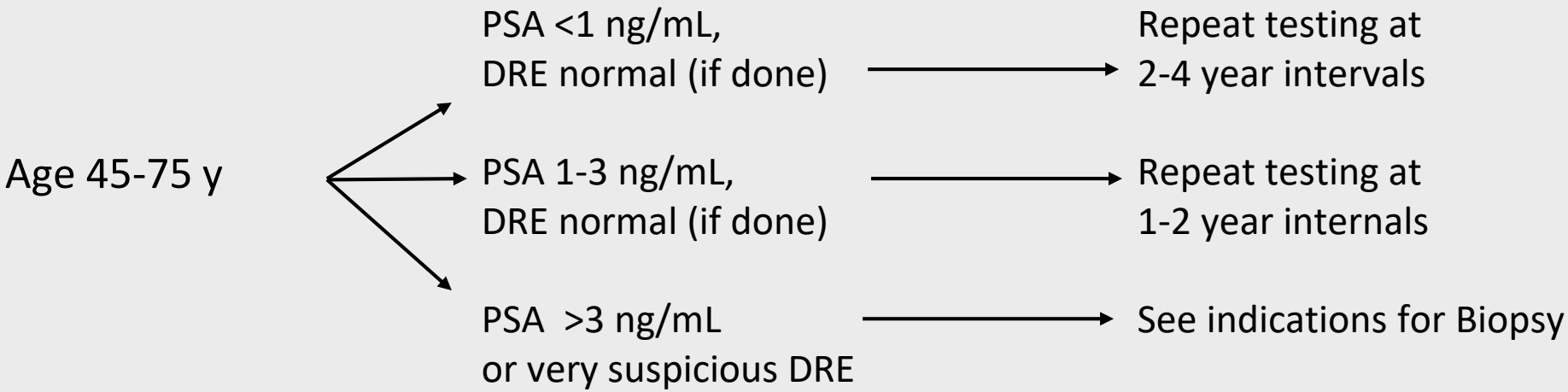
Start risk and benefit discussion about offering prostate screening:

- Baseline PSA
- Strongly consider baseline digital rectal examination (DRE)

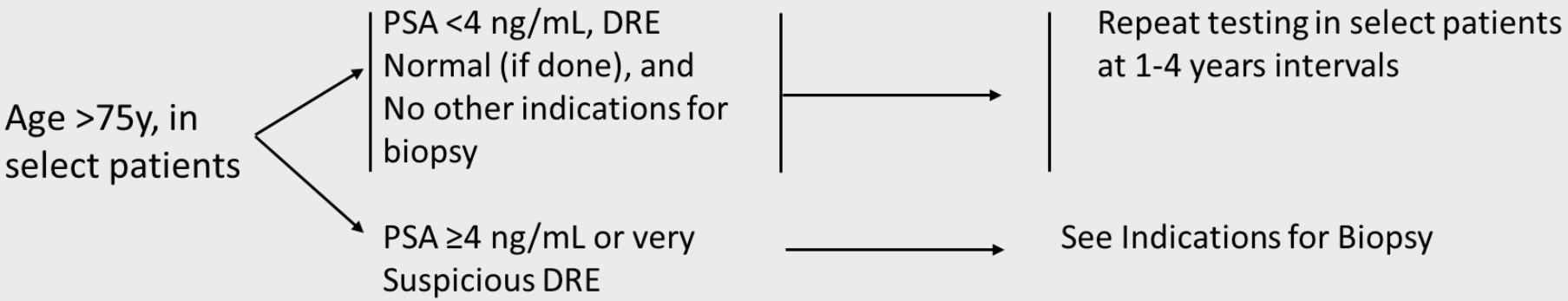
Age 45-75 y

Age >75y, in select patients (healthy men with no co-morbidities)

Early Detection Evaluation



Early Detection Evaluation



Significance of cancer: Determining need for treatment

- Patient (age, comorbidities)
- Gleason score
  - sum of two predominant areas
- Tumor characteristics
  - Number of positive cores
  - Percent positive within each core
- Molecular profiling

Active Surveillance

Rationale

- Screening results in the detection of very early stage/grade lesions - many indolent
- Current staging/grading techniques accurate
- Natural history prolonged and can be measured

Hypotheses

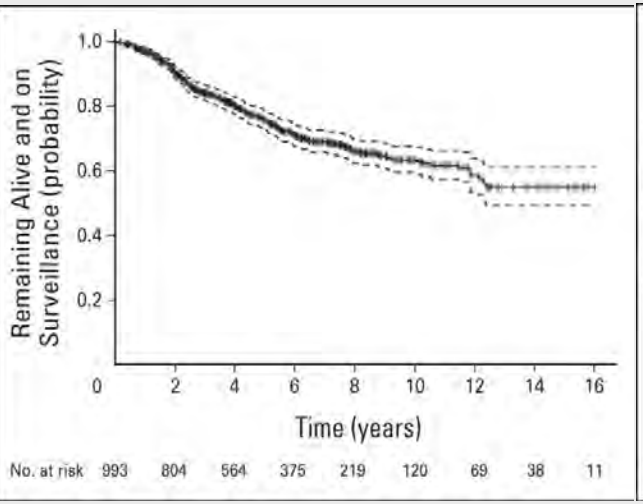
- Surveillance in low risk patients is feasible and associated with a limited risk of progression
- Progression can be quantitated
- Predictors of progression and treatment can be identified

Active Surveillance

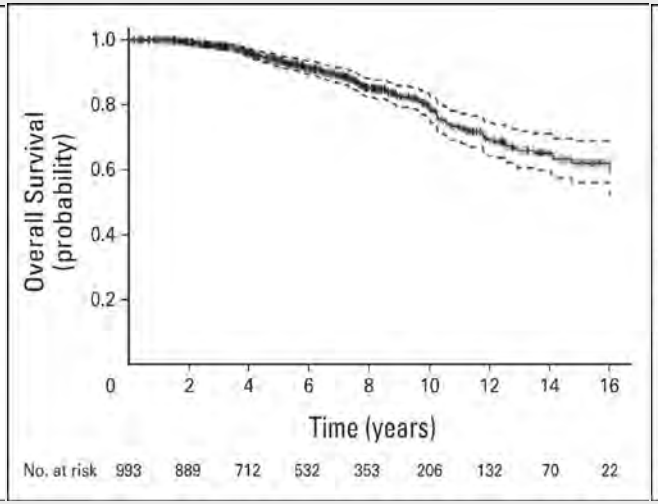
- Patients with low-risk (Gleason score ≤ 6) localized PC
- Select patients with low-volume Gleason 3+4=7 localized PC
- Surveillance Protocol
  - PSA test every 3 to 6 months
  - DRE every year
  - 12- to 14-core confirmatory TRUS biopsy within 6 - 12 months, then serial biopsy a minimum of every 3 to 5 years.
  - MRI scan and MRI guided prostate biopsy

Active Surveillance

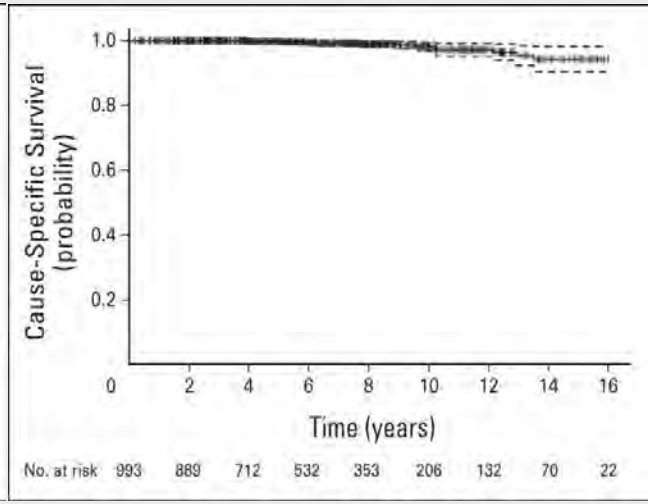
Intervention



Overall Survival



Ca-Specific Survival



76% free of intervention at 5yr

63% free of intervention at 10 yr

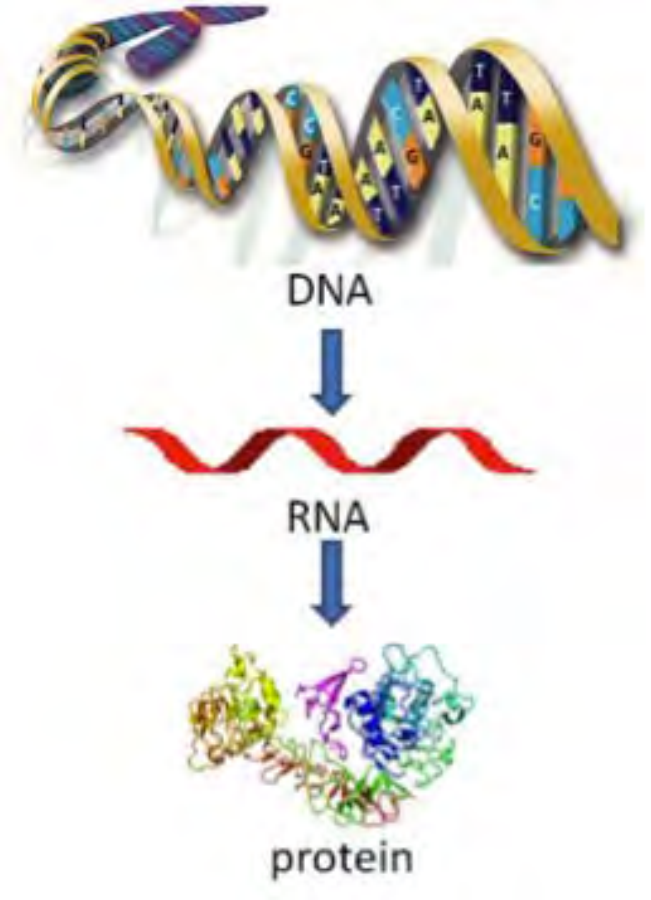
55% free of intervention at 15 yr

Klotz L, et al. J Clin Oncol 2015;33:272

Defining the Triggers for Intervention

- Change in PSA kinetics (doubling time)
- Progression on MRI scan or other imaging
- Progression on follow-up prostate biopsy
  - Increase in Gleason grade
  - Increase in tumor volume
- Patient preference
- Inherited cancer syndrome

Genomics: Analysis of molecular information that provide information about biology



Management Decisions

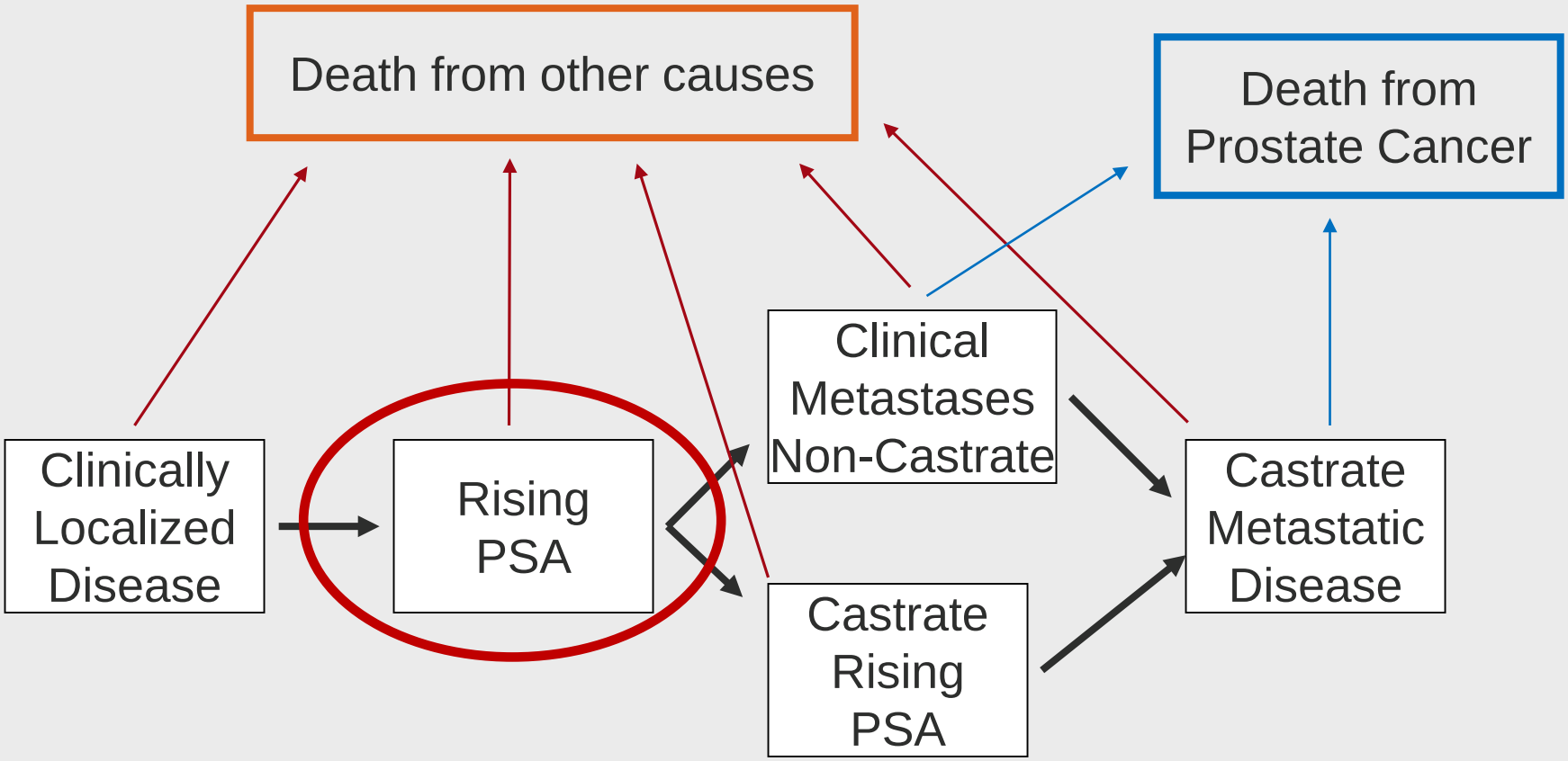
- Biopsy or repeat biopsy
- Treat or active surveillance
  - indolent vs aggressive
- Prognosis after surgery
- Guide therapy choices
- Inform families about cancer risks

Genomic Tests: Early Stage PC

Test	Indication	Outcome Predicted
Opko 4K	To biopsy or not	Risk of having PC
ConfirmMDx	Reduce repeat biopsies	Presence/absence PC
Oncotype DX	Active Surveillance decision	Adverse pathology (Primary GS 4, GS 5, pT3)
Prolaris	Bx Active Surveillance decision Post RP risk assessment	Adverse pathology PC progression
Decipher	Post RP risk assessment	Risk of clinical metastases Adjuvant radiation

A journey through possible “clinical states” of prostate cancer

"Clinical states"



50,000 new men per year fall into this category in the U.S. alone
Estimated to be about 700,000 men currently

Why doesn’t surgery and/or radiation cure everyone?

What is PSA?

- Prostate Specific Antigen (PSA) is a protein produced in prostate and prostate cancer cells
- It is secreted from these cells and can be detected in blood

Did my doctor miss something?

There are 2 possibilities for biochemical "recurrence"

- Cancer was left behind with surgery or missed with radiation
  - Possible, but uncommon
  - These cases may be cured ("salvage" therapy)
- At least 1 cancer cell had already spread prior to treatment
  - "Micrometastatic" disease

Does a rising PSA mean that I have cancer?

- Probably yes (if levels are significant)
- Residual prostate tissue after surgery may produce very low, generally not rising PSA after surgery
- Residual normal prostate tissue following radiation typically produces some level of PSA which may fluctuate
- However, a steadily rising PSA after surgery or radiation essentially signifies the presence of cancer

Will a rising PSA shorten my life?

- **Not necessarily** (usually not)
- The average length of life for the 2/3 of men without biochemical recurrence after local therapy (i.e. those that are cured) is the same as the average length of life for the 1/3 of men with PSA recurrence
  - **Though some choose to receive or require treatment**
    - And some unfortunately develop metastatic disease and may die earlier

Where is my PSA coming from?

Imaging

- Current imaging tools:
  - **Xray**
  - **Ultrasound**
  - **CT scans**
  - **MRI**
  - **Bone scan**
    - ^{99m}Tc-MDP bone scintigraphy
  - **Other available/approved nuclear medicine techniques**
    - ^{18}F-FDG-PET/CT
    - ^{18}F-NaF bone PET/CT
    - ^{111}In-capromab penditide (Prostascint®)
    - ^{11}C choline PET/CT
    - ^{18}F-fluciclovine (FACBC, Auxumin®)
    - ^{111}In-capromab penditide (Prostascint®)

Problems with current imaging

- Not sensitive enough
- Not specific
- May not change treatment options

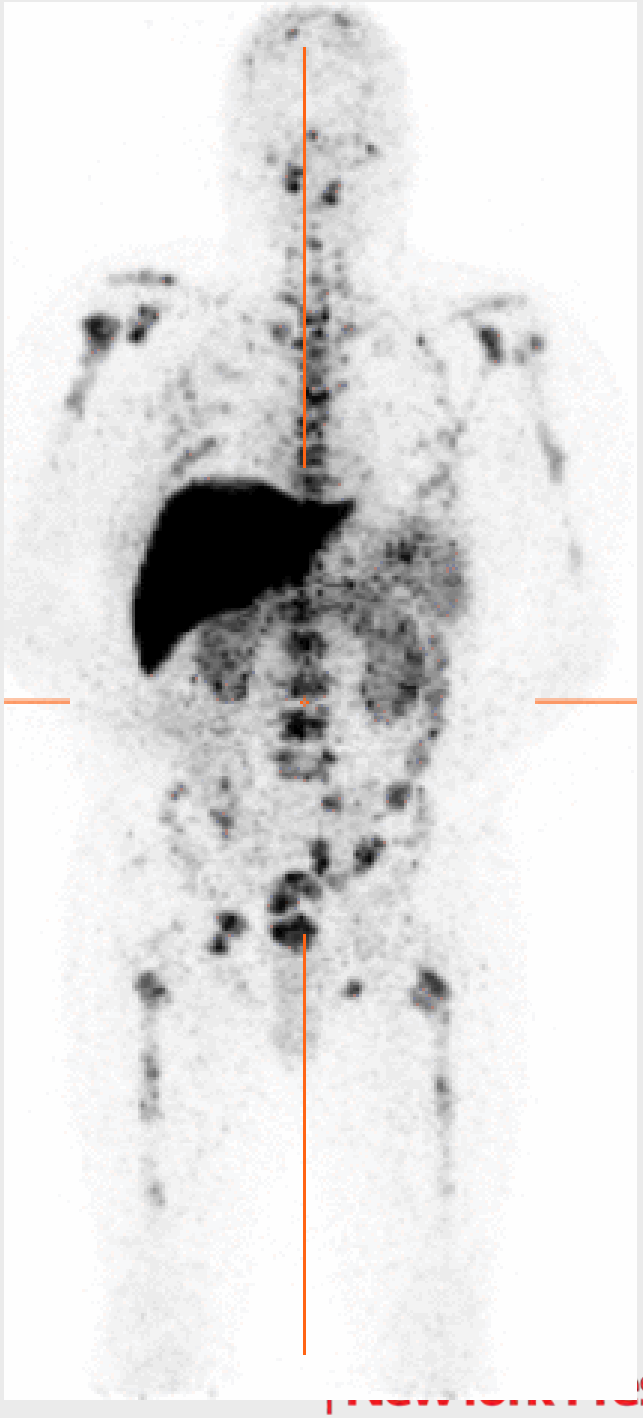
APPLICATIONS

PSMA-Targeted PET Scan

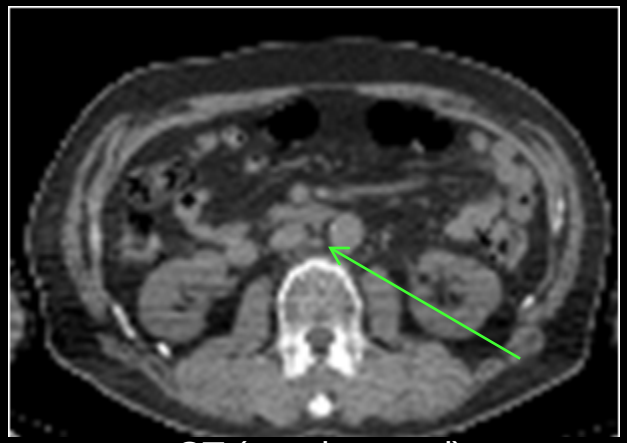
Substantial improvement over conventional imaging (bone, CT, MR, FDG-PET)

Confirms ability of J591 to target PC wherever it is in body

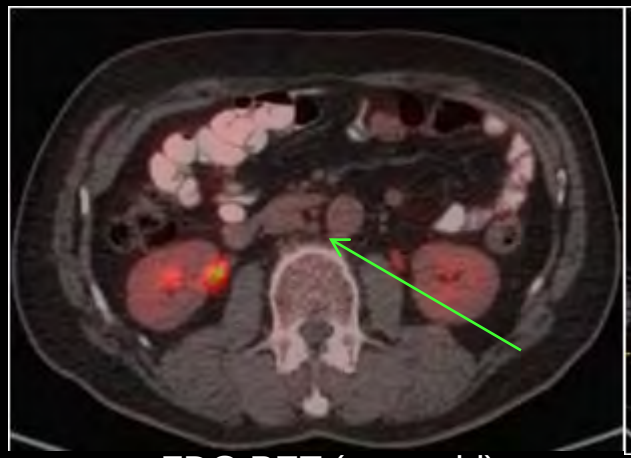
Allows quantitative imaging



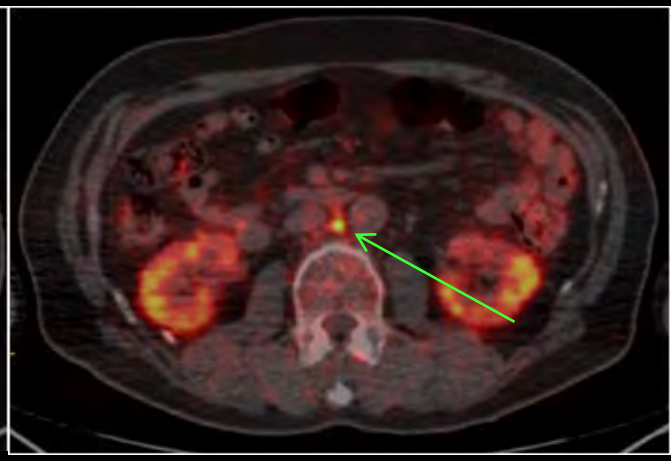
Pt with no known soft tissue disease until ^{89}Zr-J591 detected this LN met



CT (not detected)



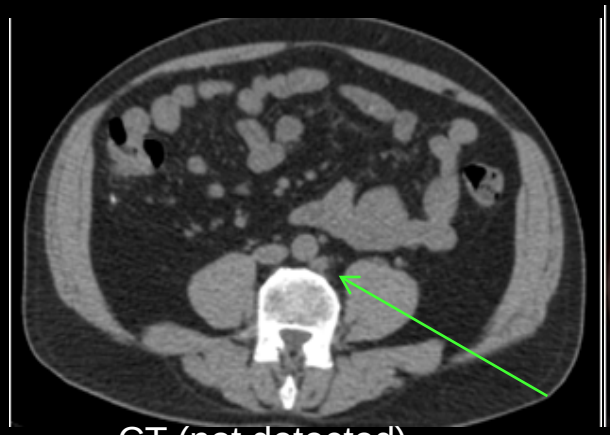
FDG PET (non avid)



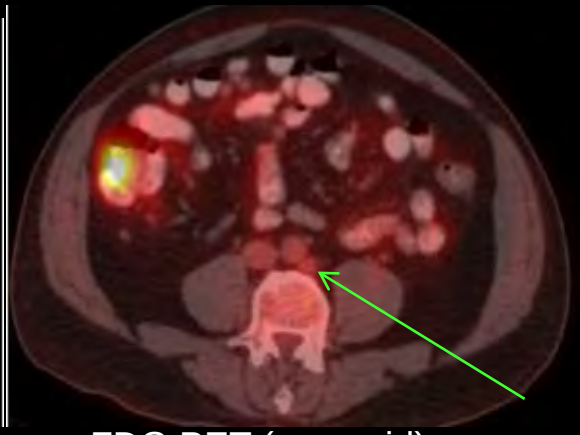
Zr89-J591 PET (avid)

Aortocaval node biopsy: Prostatic adenocarcinoma. Positive for PSA and PSAP by IHC.

Patient with rising PSA, suspicious LN on MRI, but CT and FDG negative. ^{89}Zr-J591 avid; biopsy-proven as the first metastatic site in the patient.



CT (not detected)



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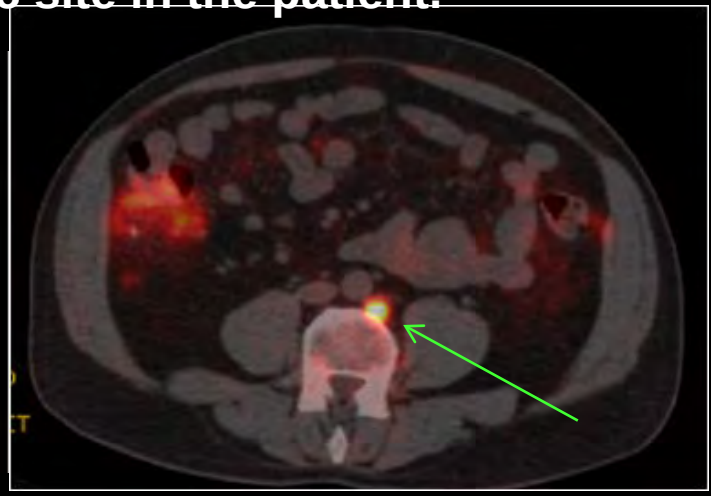
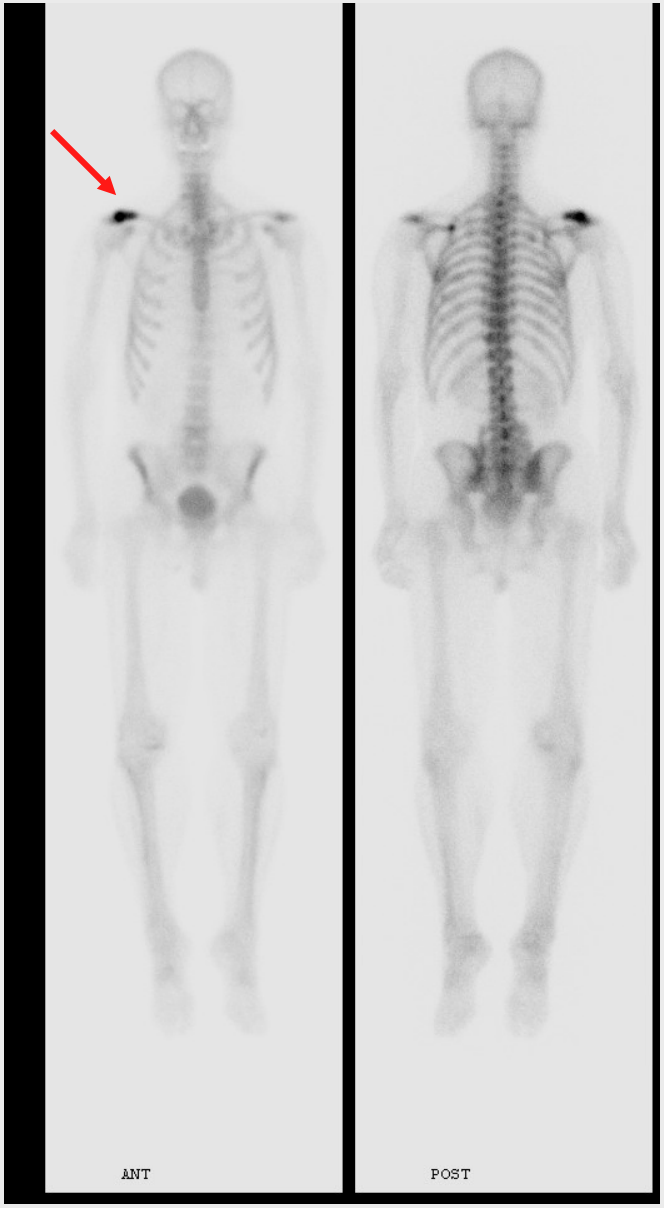


Zr89-J591 PET (avid)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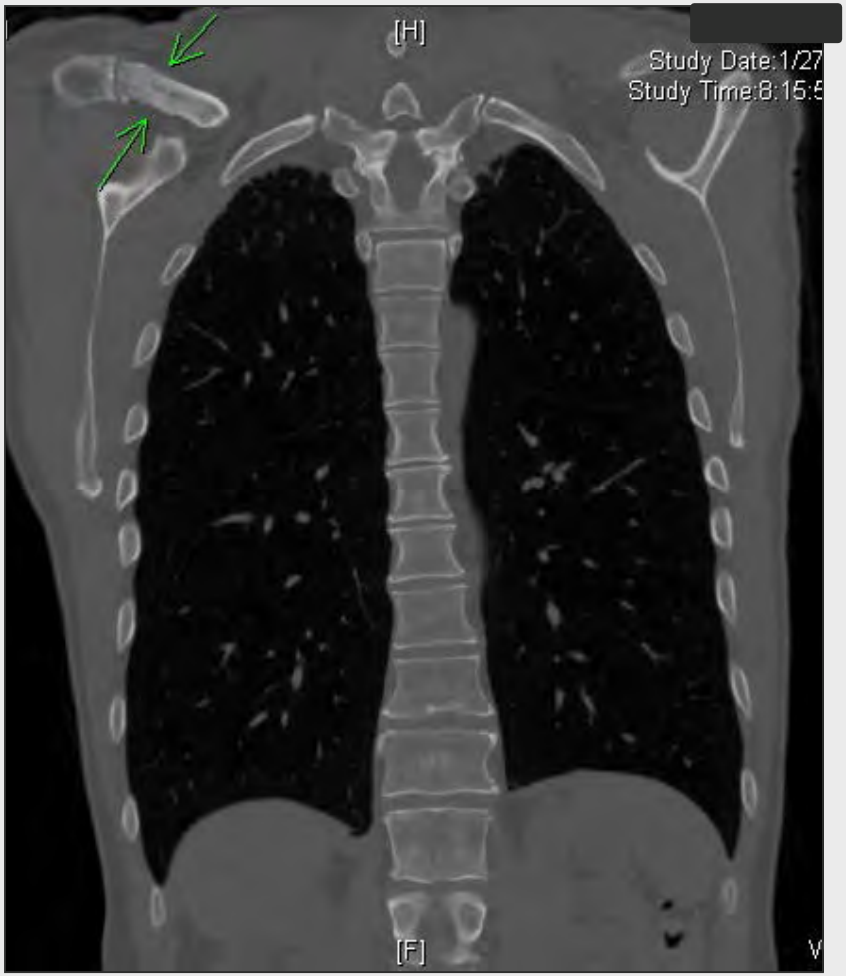
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Study Time:8:15:
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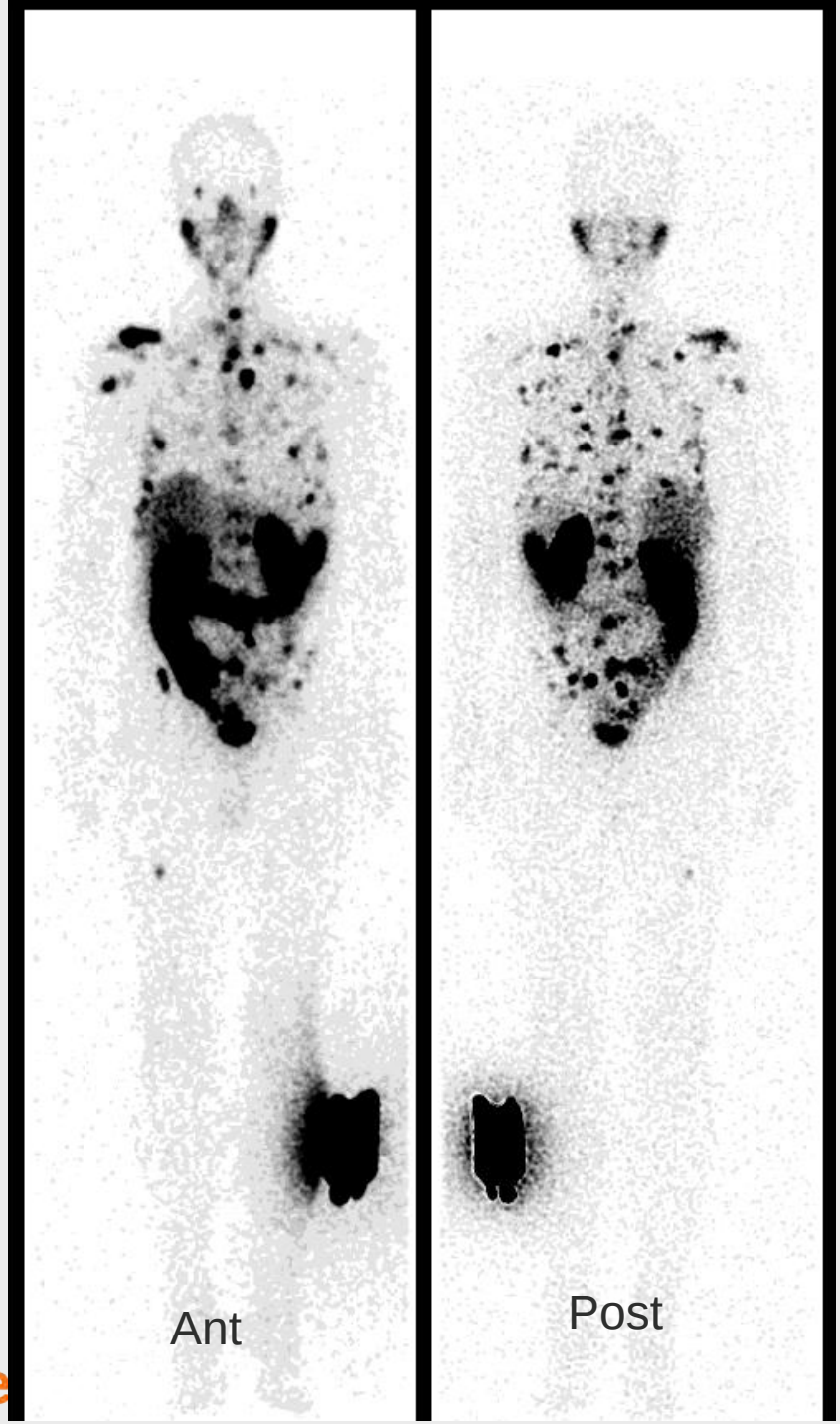


MIP ^{99m}Tc 1405

Now what?

“Advanced prostate cancer”

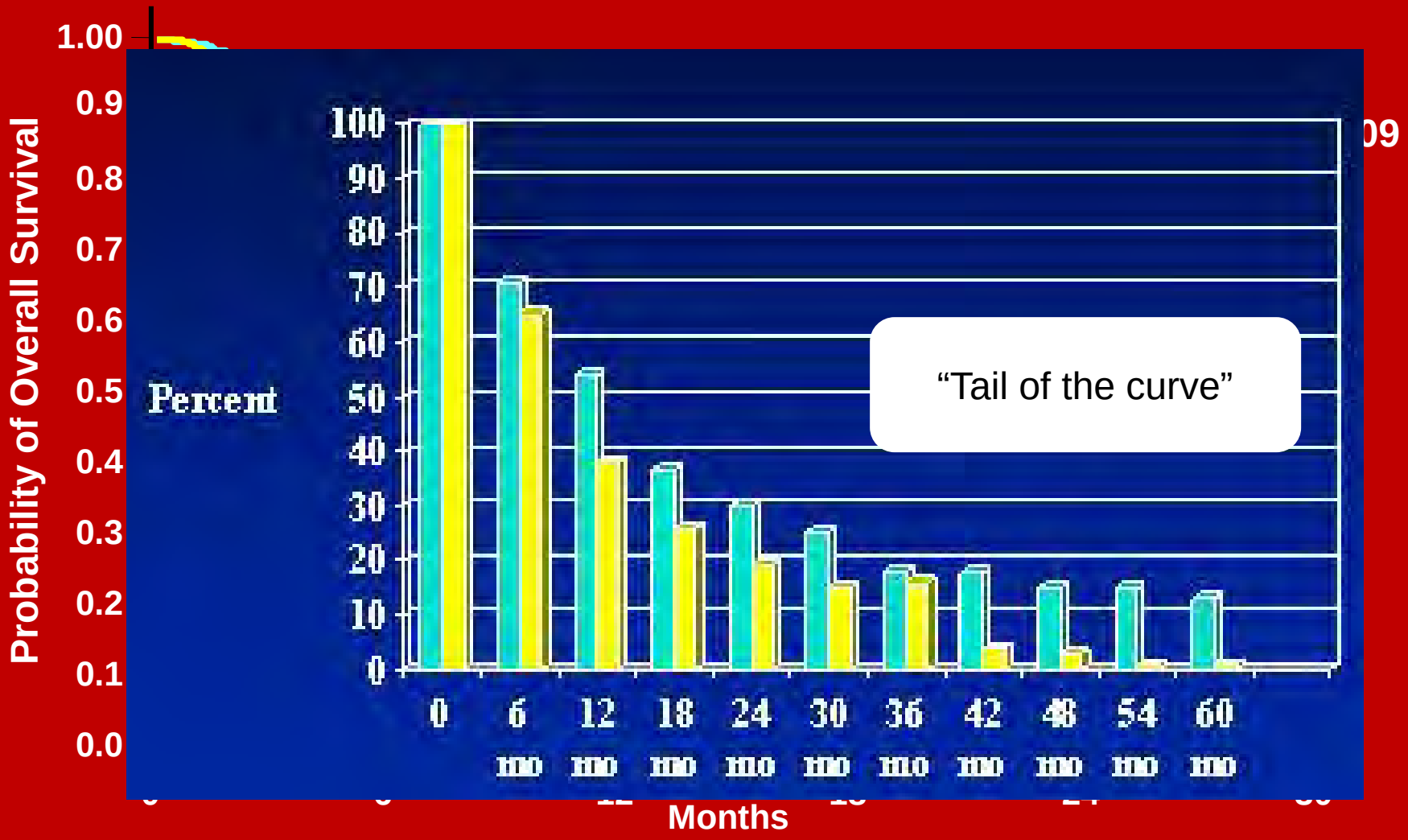
Hormones and prostate cancer

- In animal experiments, Huggins and Hodges (1938) demonstrated that castration and estrogen therapy resulted in clinical quiescence of prostate cancer
- This was successfully emulated in humans (1941)
- Translational therapeutics was born
- Charles Huggins - **NOBEL PRIZE 1966**

Where We Are Now (2014): Positive Phase 3 Trials in mCRPC

Trial	Design	HR	Endpoint	Comment
Canadian N = 161	**Mitoxantrone**/prednisone vs prednisone	NR	Palliation in 29% vs 12% (duration 42 vs 18 wks)	Approval of mitoxantrone (also CALGB 9182)
TAX 327 N = 1006	**Docetaxel**/prednisone vs mitoxantrone/prednisone	0.76	OS 18.9 vs 16.5 mo	Doce/pred approved as new SOC
SWOG 9916 N = 770	**Docetaxel**/estramustine vs mitoxantrone/prednisone	0.80	OS 17.5 vs 15.6 mo	Support doce as new standard
ZAPCSG N = 643	**Zoledronic acid** vs placebo	NR	SRE 33.2% vs 44.2%	Zoledronic acid reduces SRE's
IMPACT N = 512	**Sipuleucel-T** vs Control	0.78	OS 25.8 vs 21.7 mo	Sip-T approved min sympt metCRPC
Dmab 103 N = 1904	**Denosumab** vs zoledronic acid	0.82	SRE-free 20.7 vs 17.1 mo	Denosumab approved
TROPIC N = 755	**Cabazitaxel**/prednisone vs mitoxantrone/prednisone	0.70	OS 15.1 vs 12.7 mo	Cabazitaxel approved post-doce
COU-AA-301 N = 1195	**Abiraterone**/prednisone vs Placebo/prednisone	0.65	OS 14.8 vs 10.9 mo	Abi/pred approved post-doce
ALSYMPCA N = 922	**Radium-223**/BSC vs placebo/BSC	0.70	OS 14.0 vs 11.2 mo	Rad223 approved
AFFIRM N=1199	**Enzalutamide** vs Placebo	0.63	OS 18.4 vs 13.6 mo	Enzalutamide approved post-doce
COU-AA-302 N = 1088	**Abiraterone**/prednisone vs Placebo/prednisone	0.81	OS 34.7 vs 30.3 mo	rPFS HR 0.43 Led to broad approval
PREVAIL N=1715	**Enzalutamide** vs Placebo	0.7	OS 32.4 vs 30.2 mo	rPFS HR 0.18 Led to broad approval
ELM-PC 4 N=1560	**Orteronel**/prednisone vs Placebo/prednisone	0.71	rPFS 13.8 vs 8.7 mo	Negative for OS;

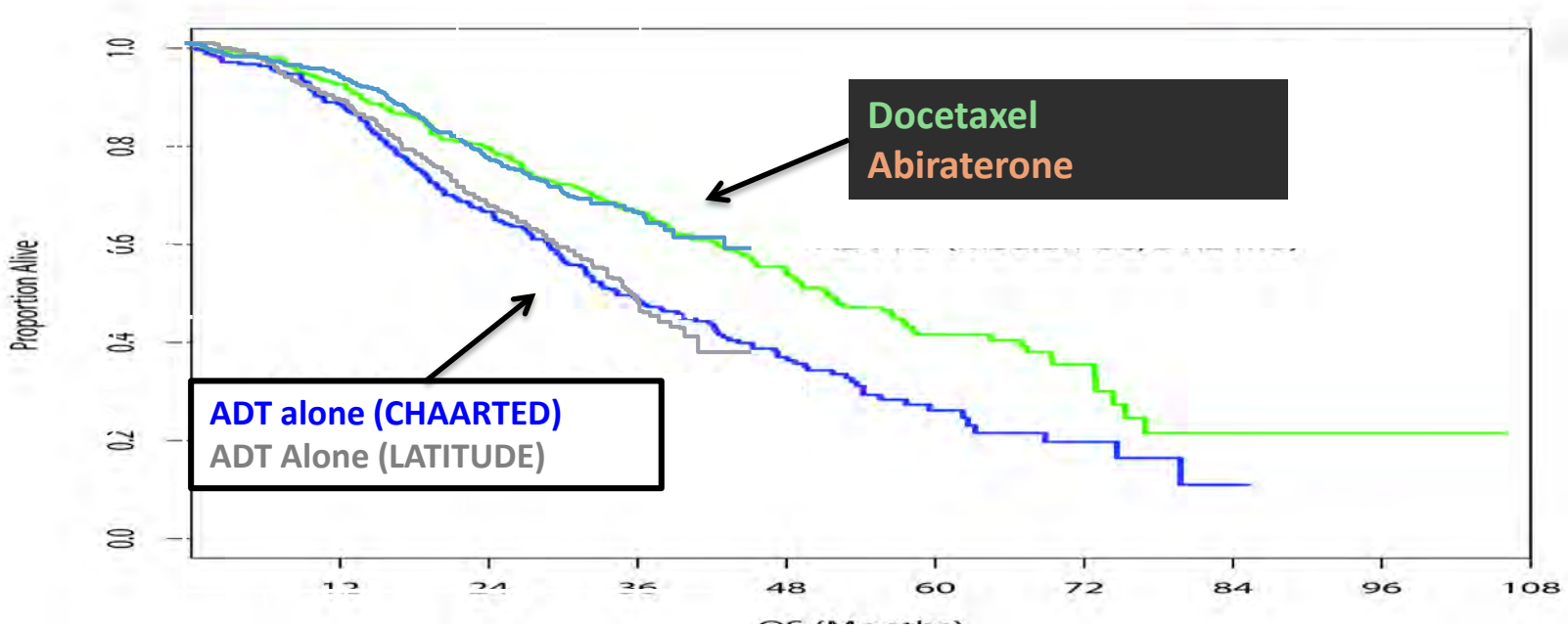
A word on medical clinical trial terminology and implications



Where are we going from here?

- Additional uses for approved drugs
  - Additional (generally earlier) settings
  - Combinations
- New versions of similar drugs
- Treatment optimization
  - Mechanisms of resistance, Sequencing
  - Predictive biomarkers
- New targets / drugs
- New disease classifications
  - Precision medicine

CHAARTED (Docetaxel..2014) and LATITUDE (Abiraterone…2017) resulted in virtually identical survival curves in similar patients.

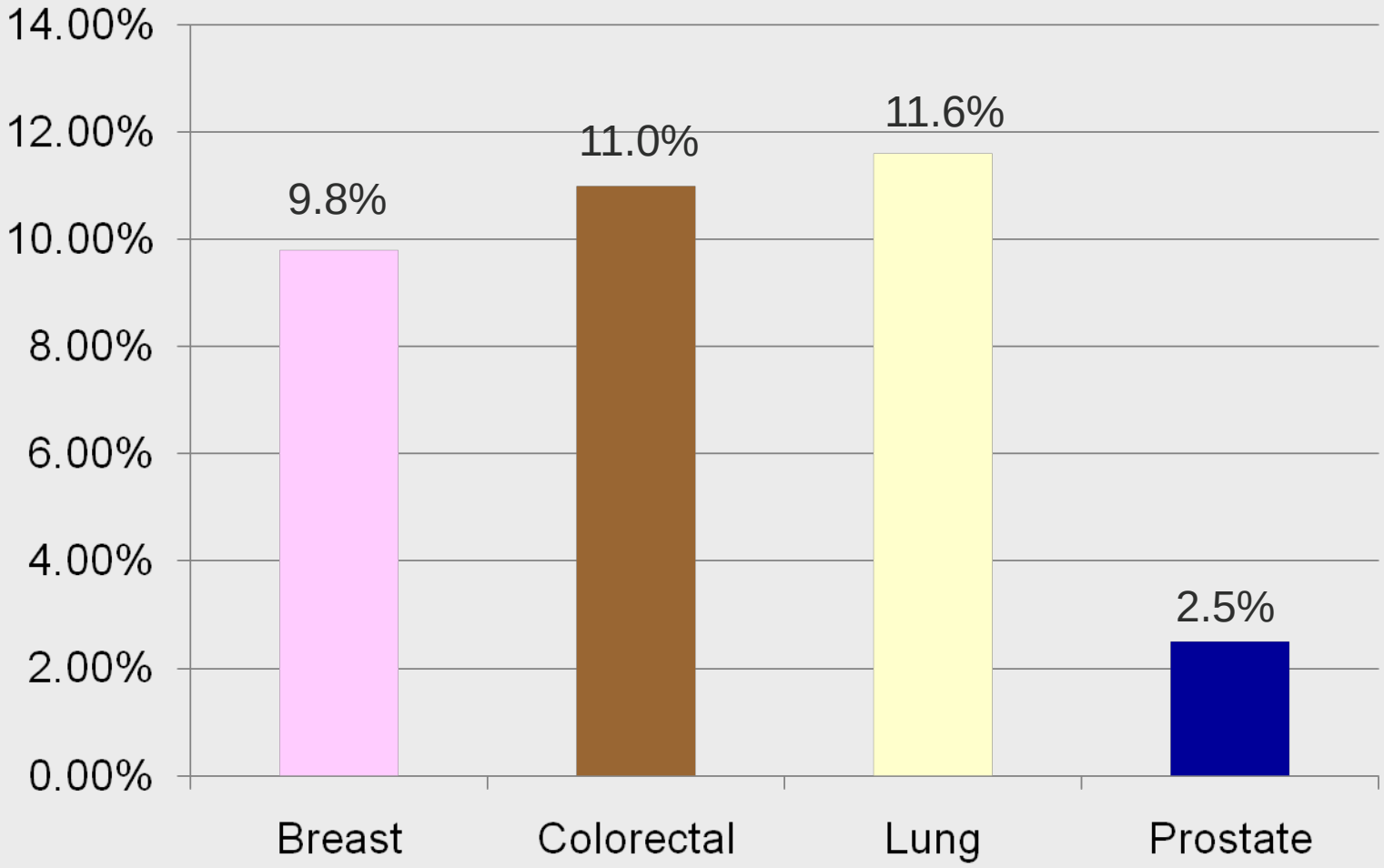


Nearly 40% relative improvement in survival translates to median 17 months longer to live

(using the same drugs that previously improved median of 3-4 months)

How do we make improvements in medicine?

Percent of patients participating in clinical trials



Wassenaar et al, ASCO 2008

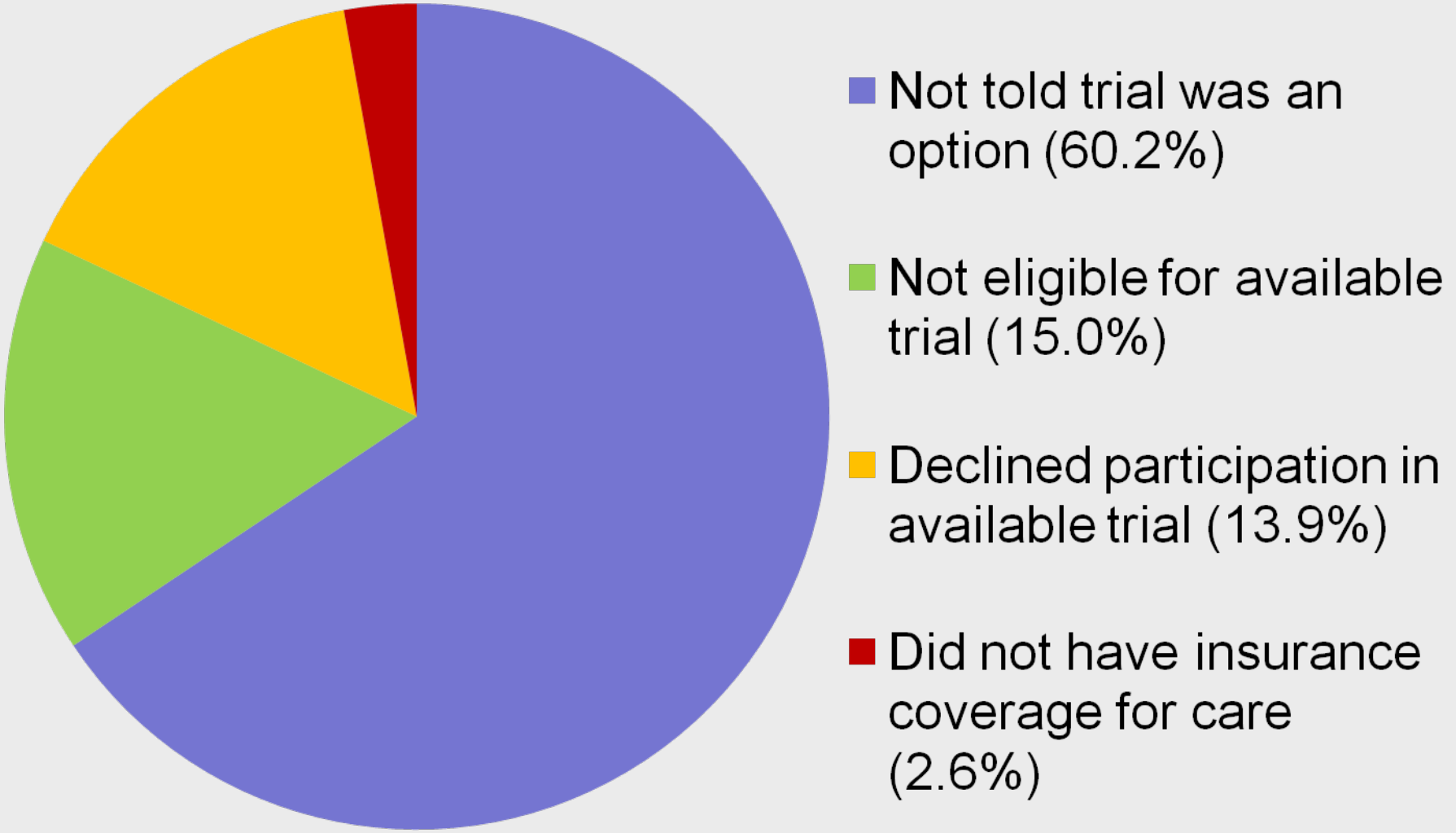
Patient satisfaction with care

Cancer Type	Treated with standard care	Treated on clinical trial	Statistical significance
Prostate Cancer	60.1%	69.4%	P=0.03
Colorectal Cancer	45.5%	58.9%	P=0.009
Lung Cancer	37.7%	63.6%	P=0.001

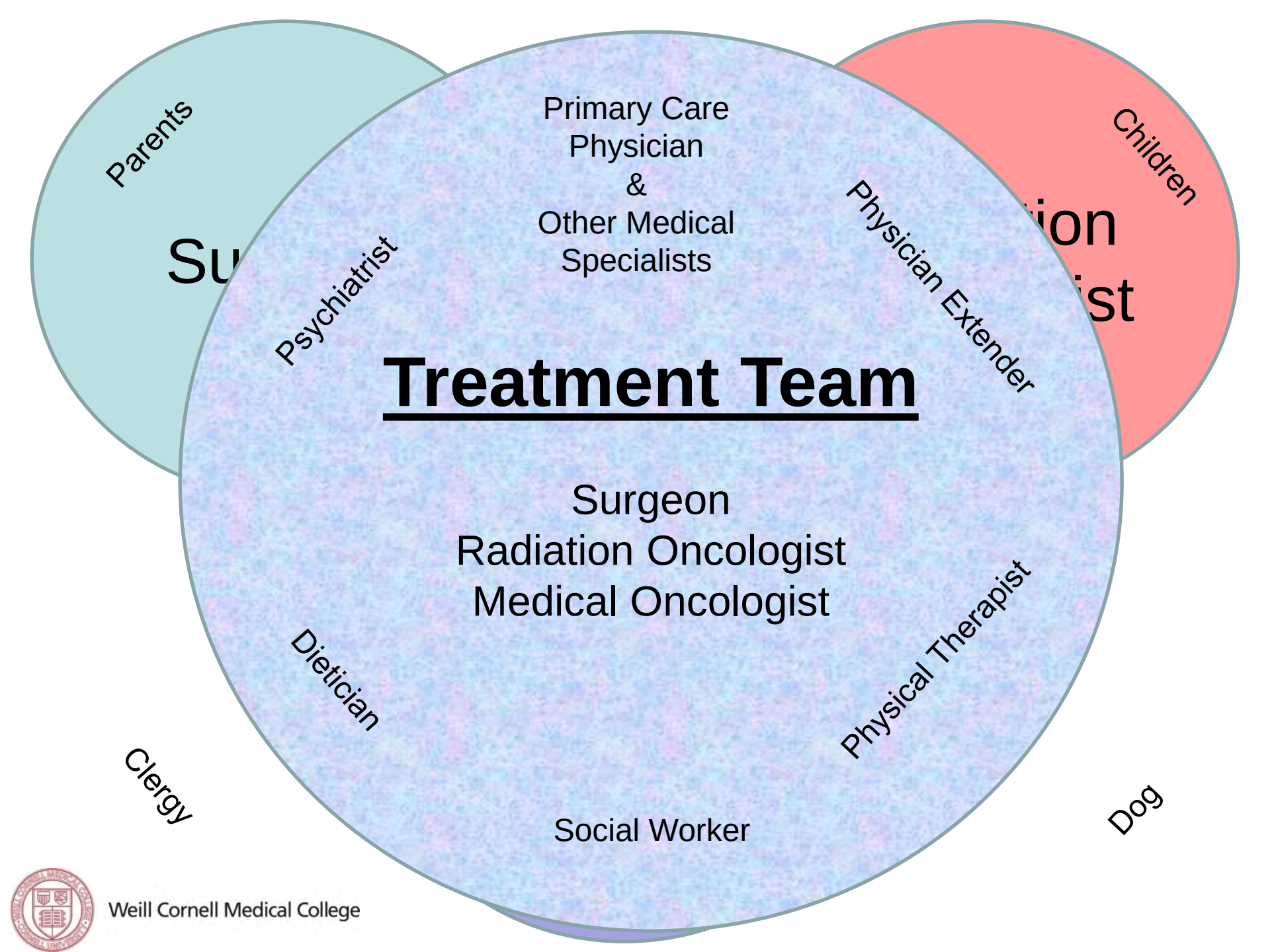
Wassenaar et al, ASCO 2008

Why don’t more patients participate in clinical trials?

Primary reason for not participating in clinical trial



Wassenaar et al, ASCO 2008


Parents
Children
Primary Care
Physician
&
Other Medical
Specialists
Psychiatrist
Physician Extender
Treatment Team
Surgeon
Radiation Oncologist
Medical Oncologist
Dietician
Physical Therapist
Clergy
Social Worker
Dog

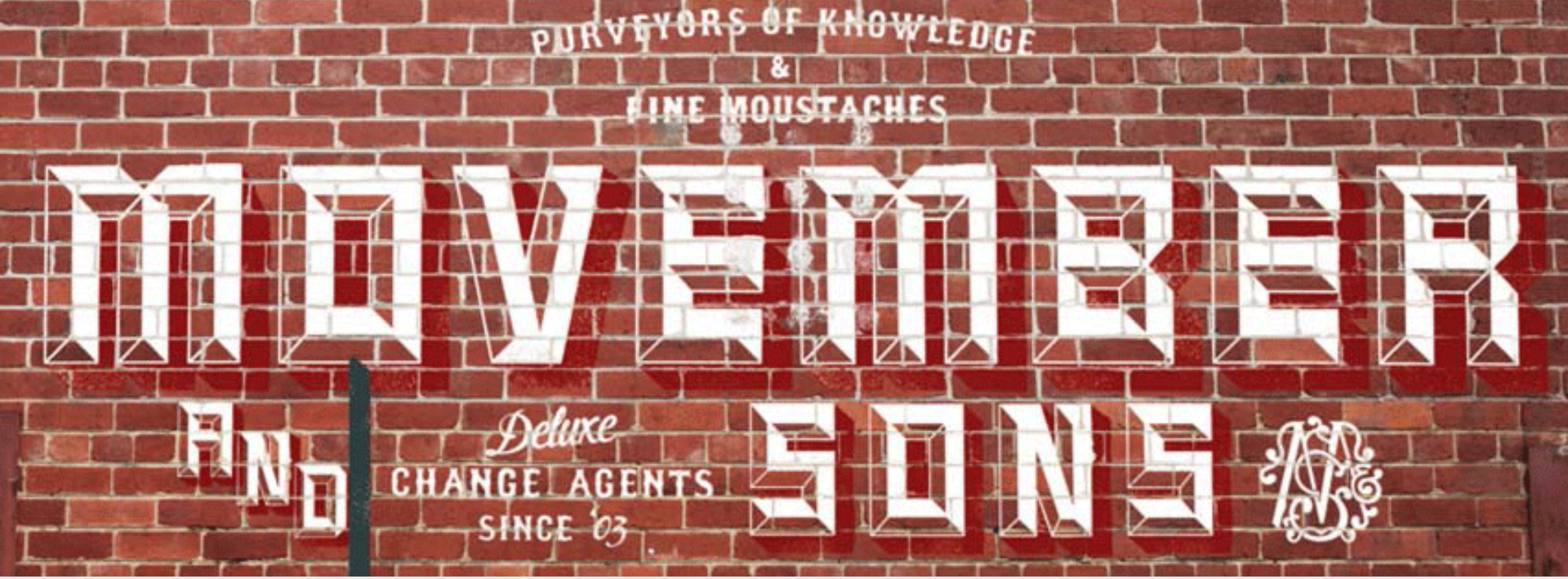
How can I (we) help?

Two very important elements to make progress:

Awareness /Advocacy

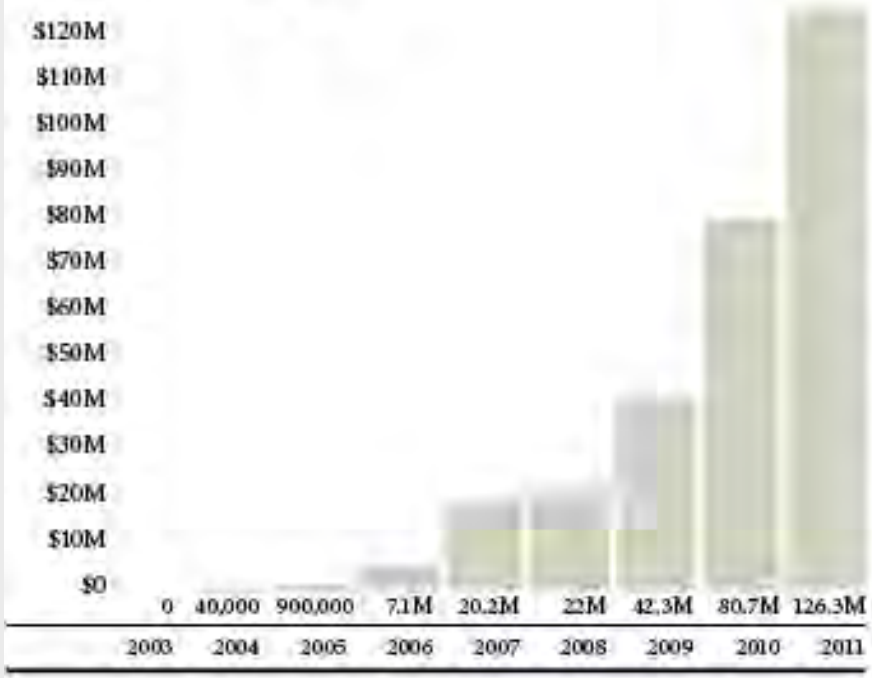
and

Funding

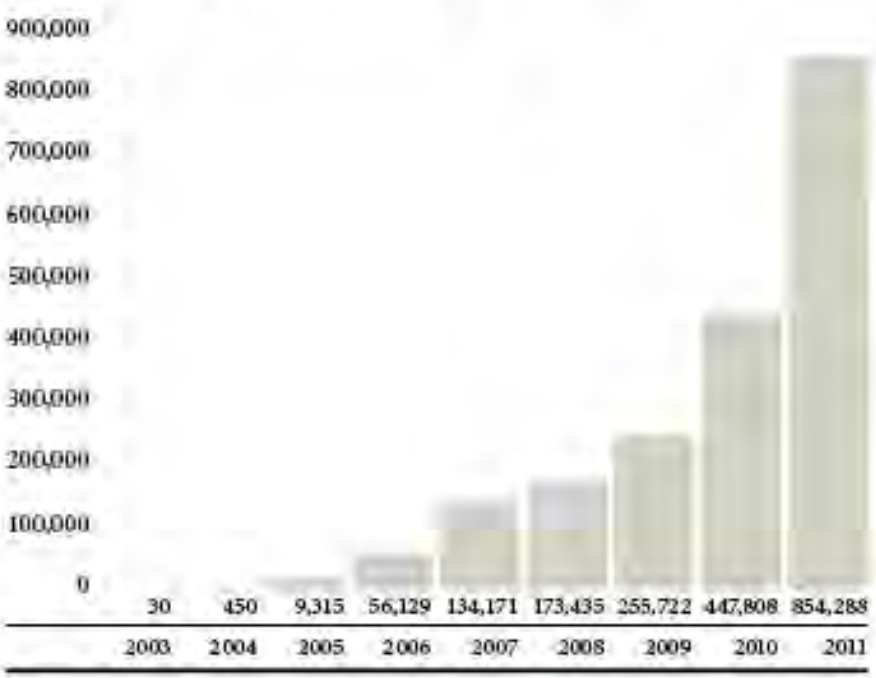


- “Mo” slang for moustache in Australia
- A conversation starter, raises awareness
- Funds raised in the U.S. go towards prostate and testicular cancer and mental and physical health initiatives

GLOBAL FUNDS RAISED
$299 MILLION USD... SO FAR



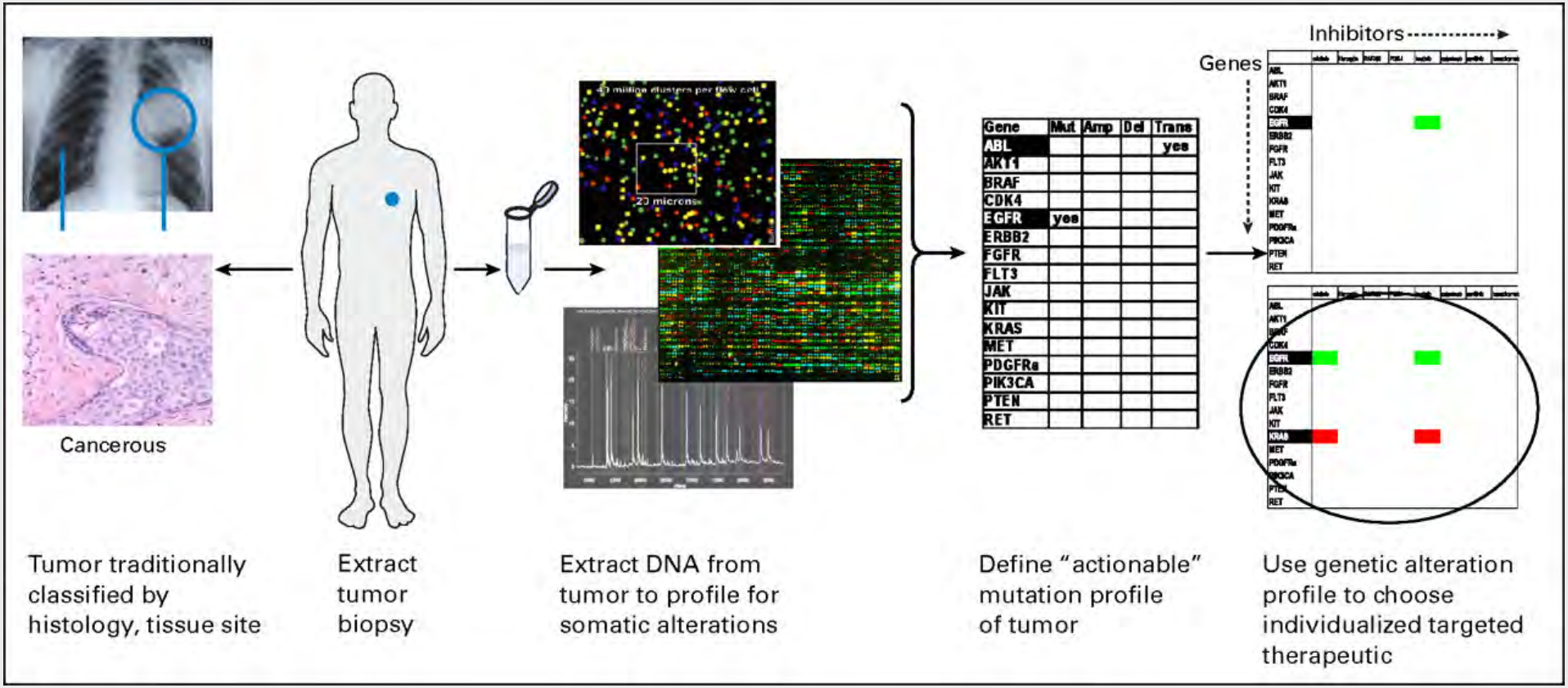
GLOBAL REGISTRANTS
1.9 MILLION MO BROS & MO SISTAS... SO FAR



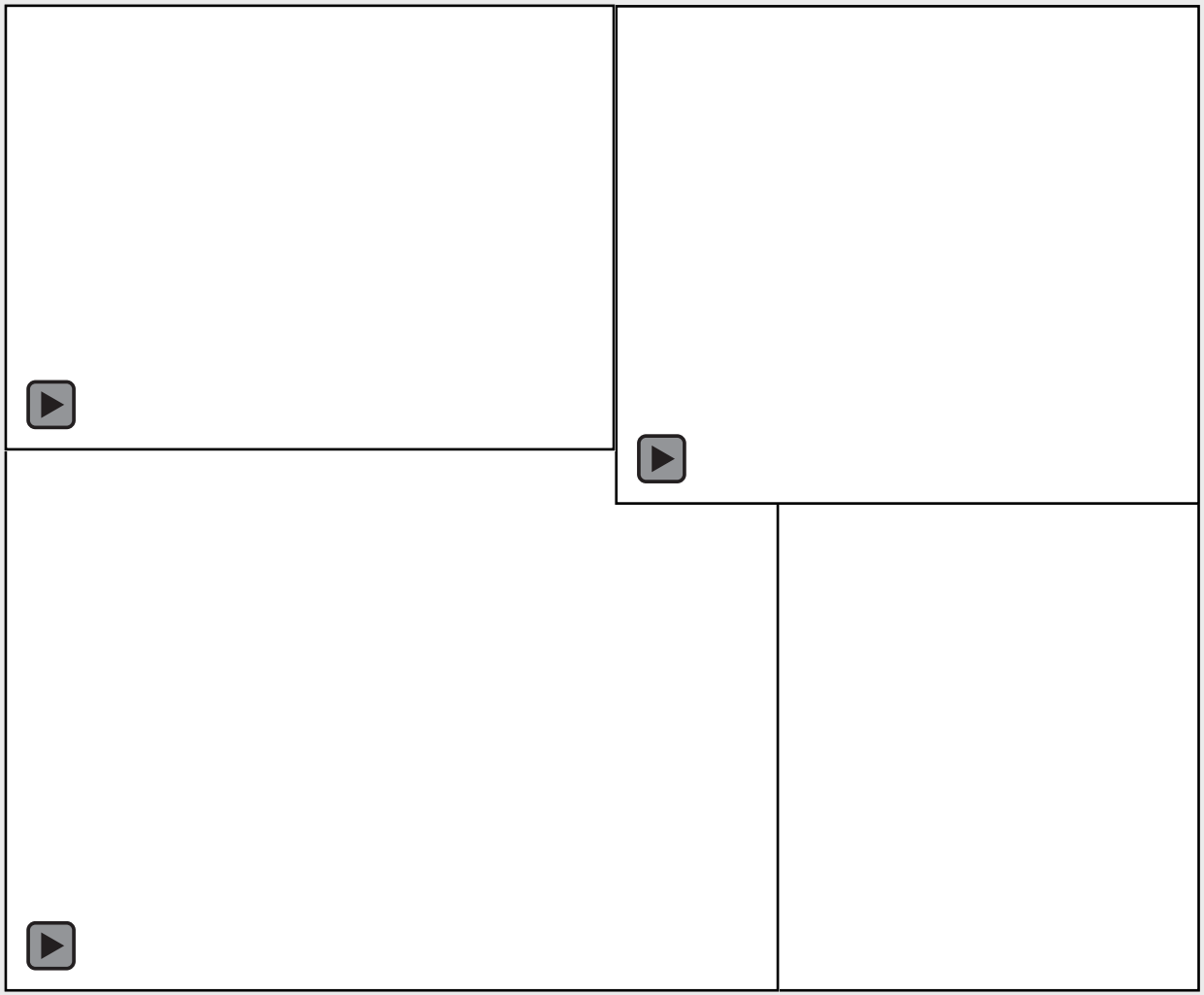
Precision Medicine…

*The **right treatment** for the **right patient** at the **right time***

Molecular Classification of Prostate Cancer → **Precision Medicine**



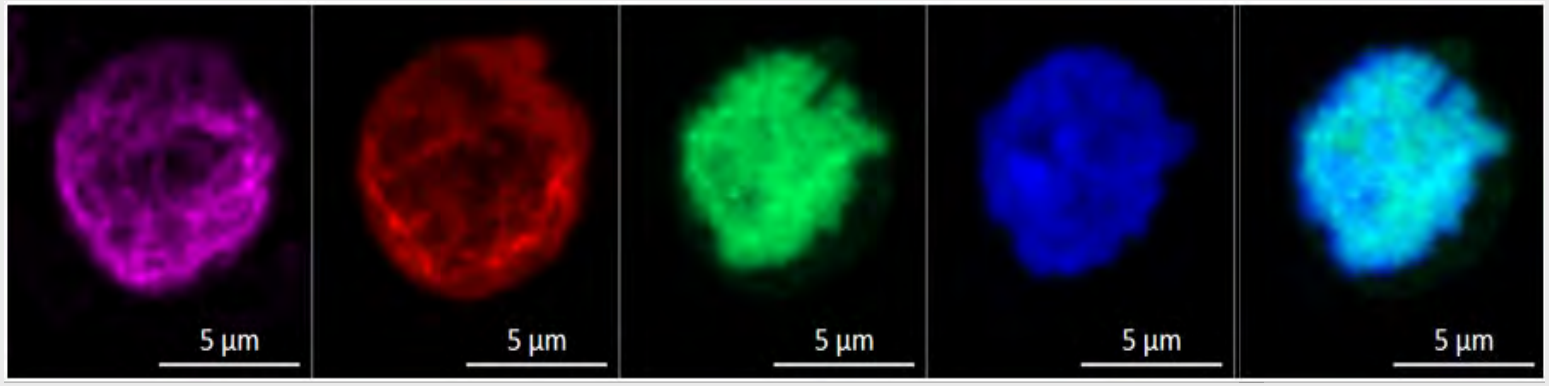
Understanding the mechanism of action



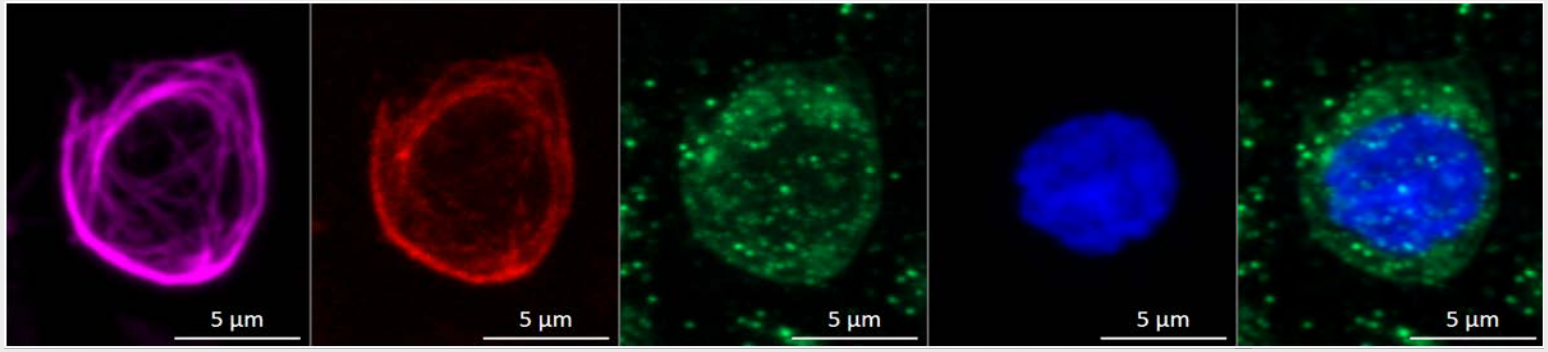
Bundling tracks (microtubules) and keeping green out of the center (nucleus) is good

Case: man with rapidly progressive, symptomatic, metastatic prostate cancer

Tumor just before treatment



Tumor shortly after 1st treatment



Felt better, stopped narcotics, went back to work

(PSA dropped and scans improved as well)

Do I need a biopsy? Maybe just a blood test = liquid biopsy….

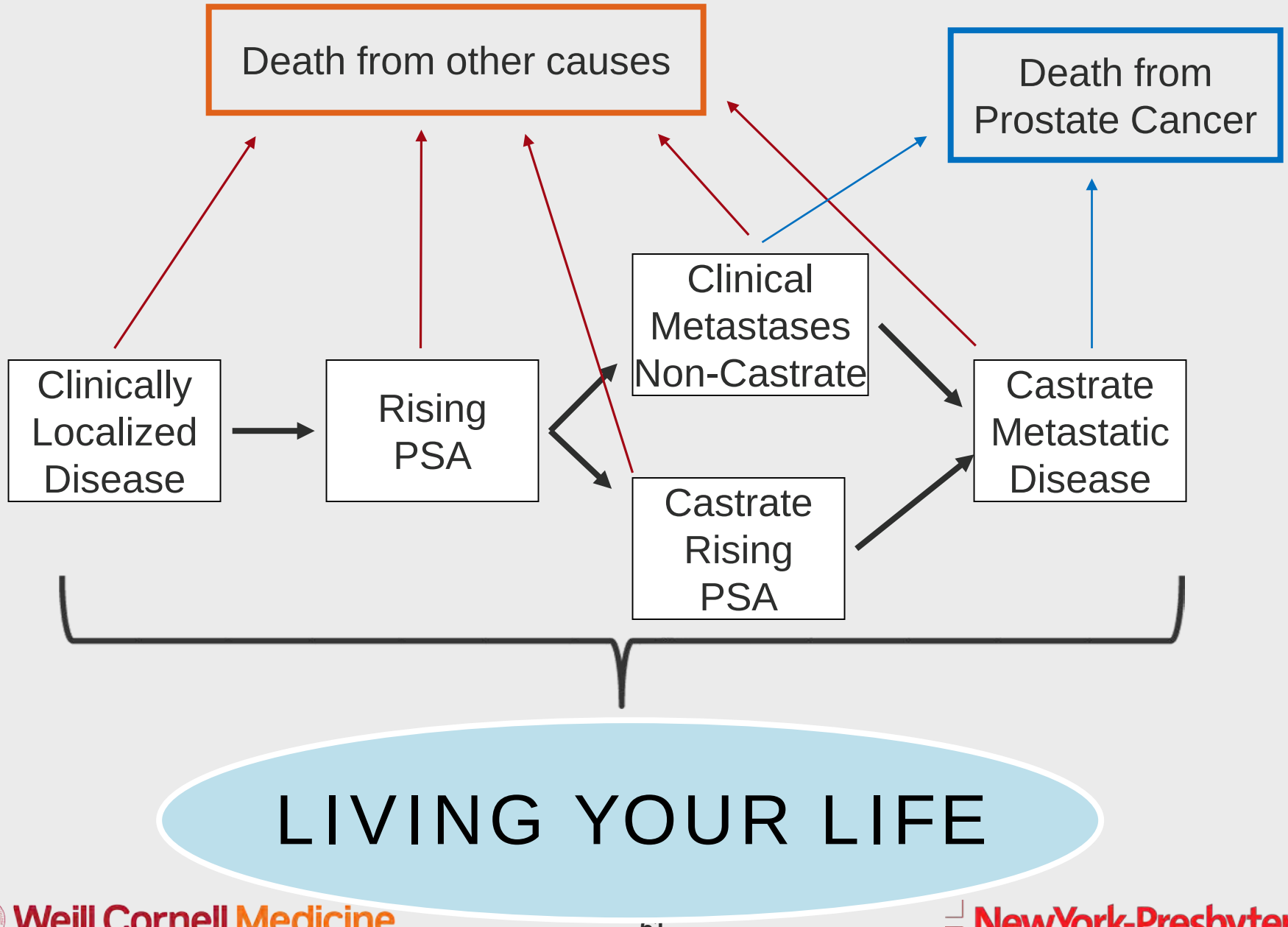
Is recurrent prostate cancer curable?

- How can we combat heterogeneity and resistance?
- With combination therapy, what if we could:
  - Ablate AR ligand(s)
  - Inhibit AR (ligand-binding domain and N-term)
  - Inhibit microtubules
  - Inhibit neuroendocrine pathways
  - Deliver targeted lethal DS DNA breaks
  - Then eliminate the rest with immunotherapy following broader antigen exposure

Androgen Annihilation

- LHRH + CYP17 + AR signaling inhibitor
- Alternating non-cross-resistant therapy
  - Taxane
  - Aurora kinase inhibitor?
  - Platinum?
- Targeted alpha particle
- Other “targeted” (PI3K, MET, PARP, etc)
- Following antigen release, checkpoint inhibitor

"Clinical states"



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