

Prostate Cancer and Genetics

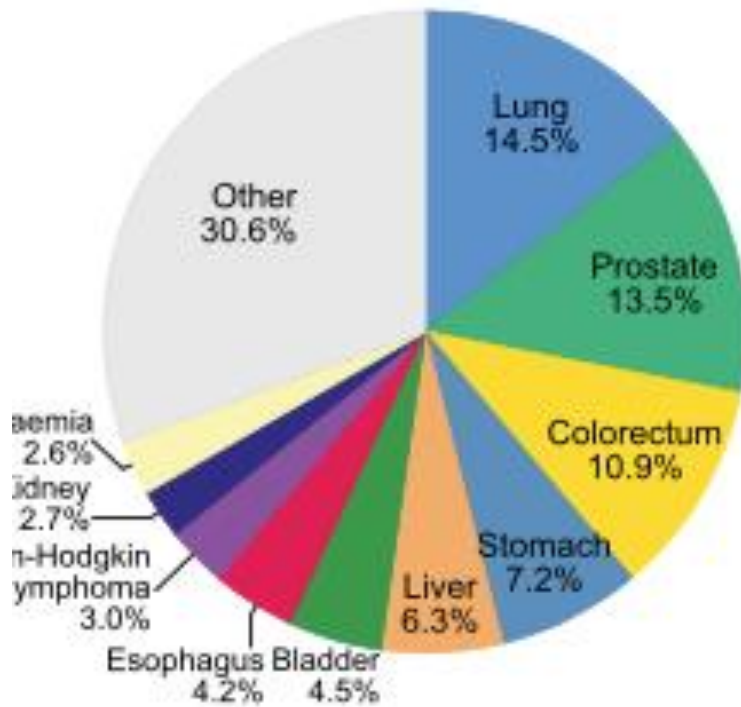
Achille Manirakiza, MD
Rwanda Military Hospital

Outline

- Prostate Cancer Epidemiology
- Historical Milestones in Prostate Cancer discovery
- Current knowledge + practices in screening & treatment
- Application of genetics in screening & treatment

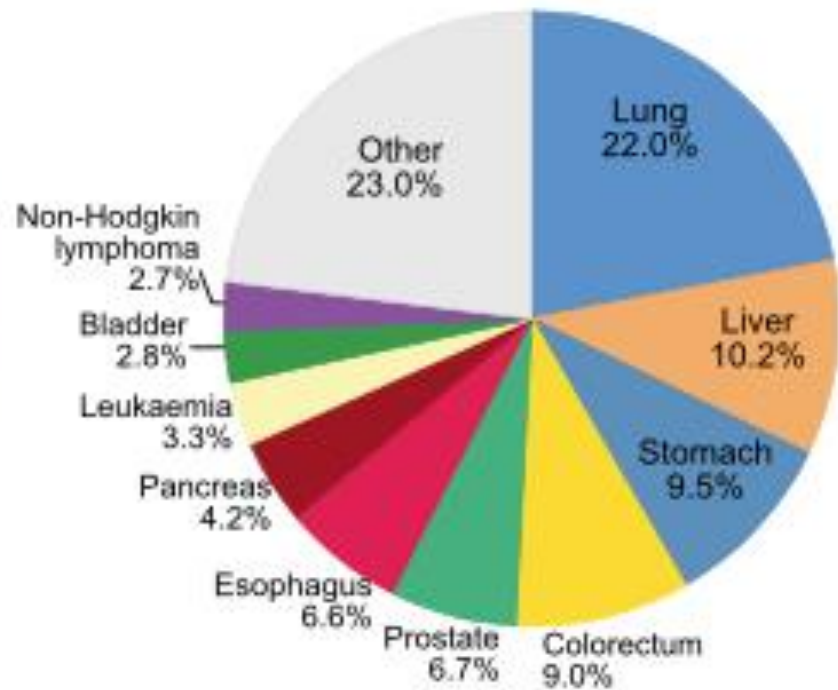
Prostate Cancer at a Glance

Incidence



9.5 million

Mortality

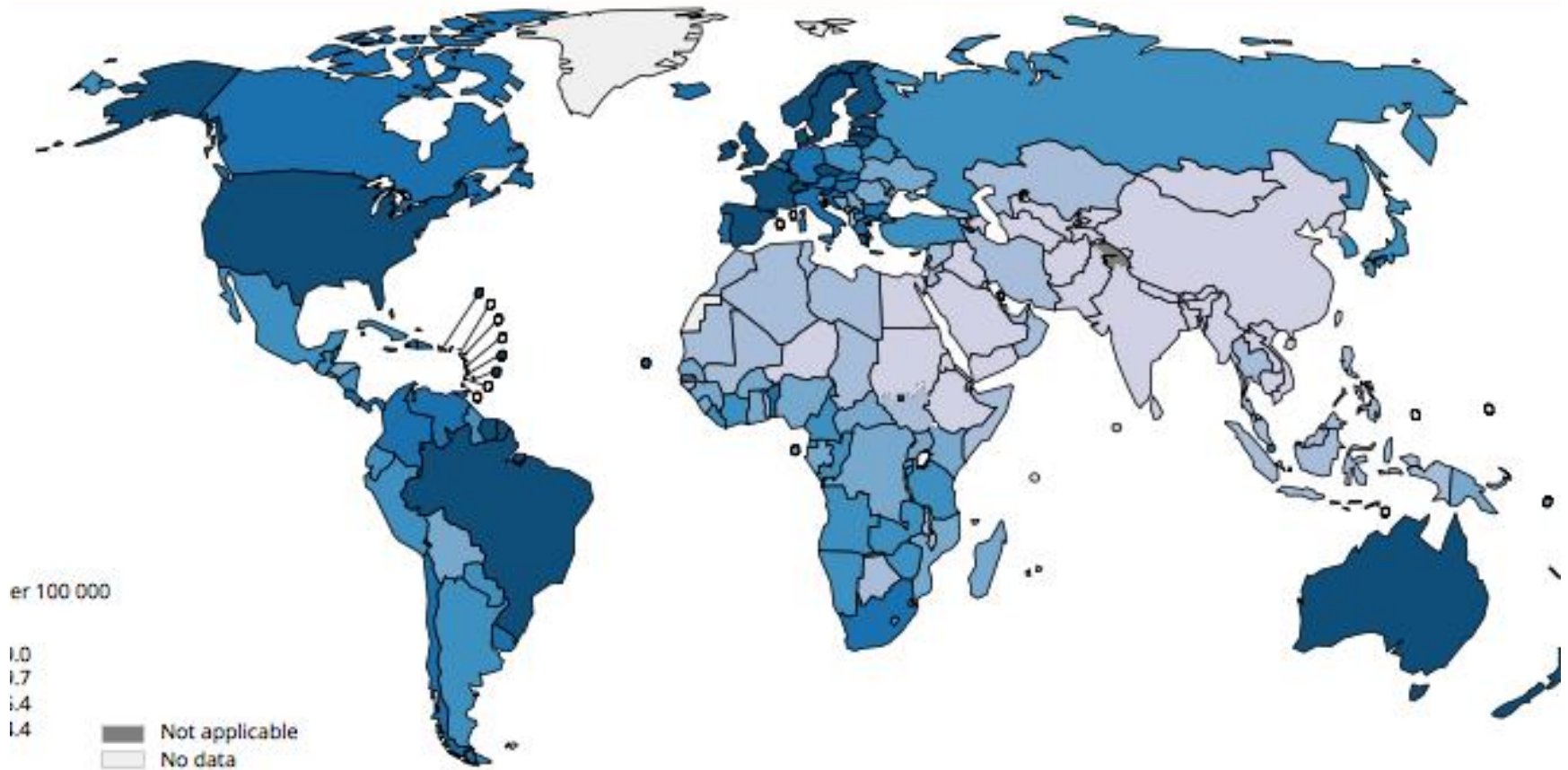


5.4 million

Cancer Incidence & Mortality in Males - 2018

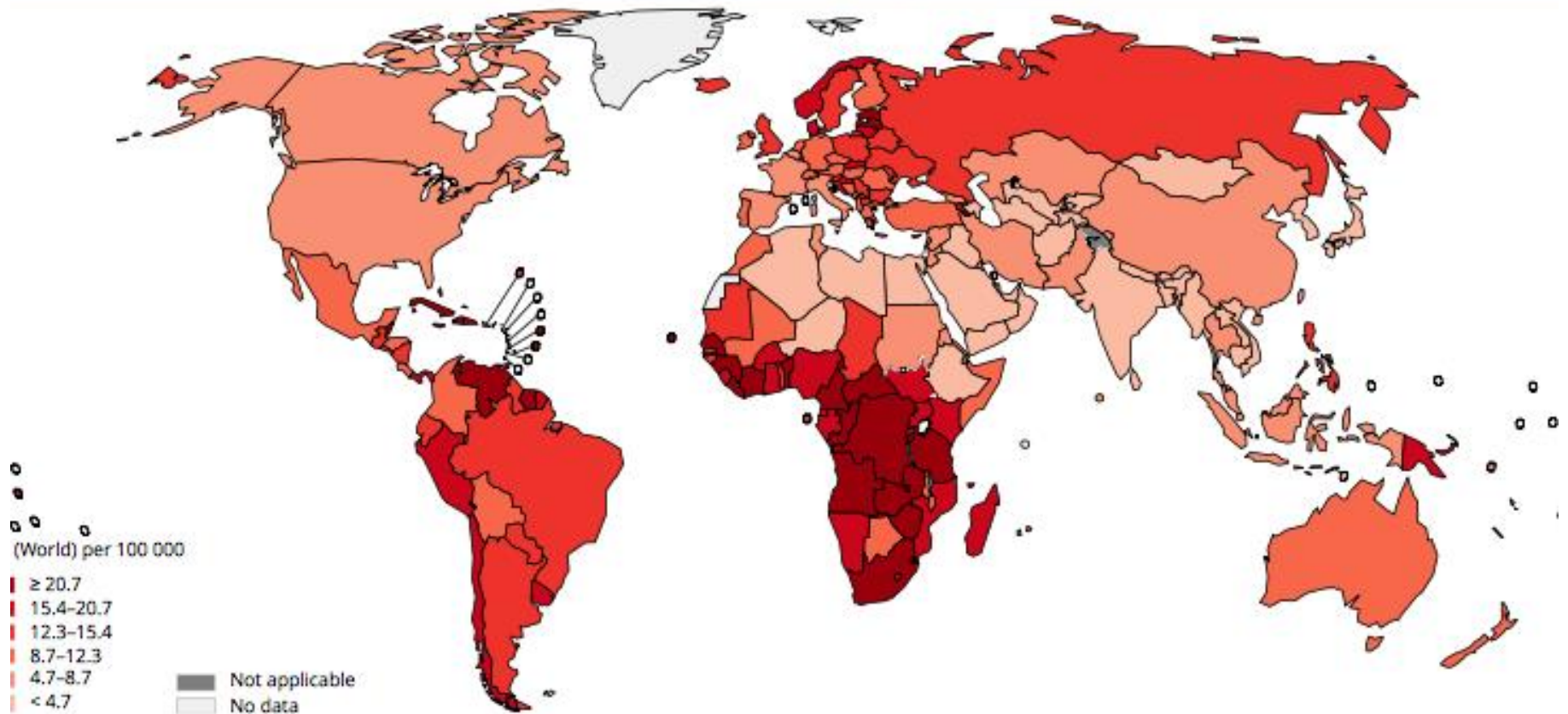
World Incidence

Age standardized (World) incidence rates, prostate, all ages



World Mortality

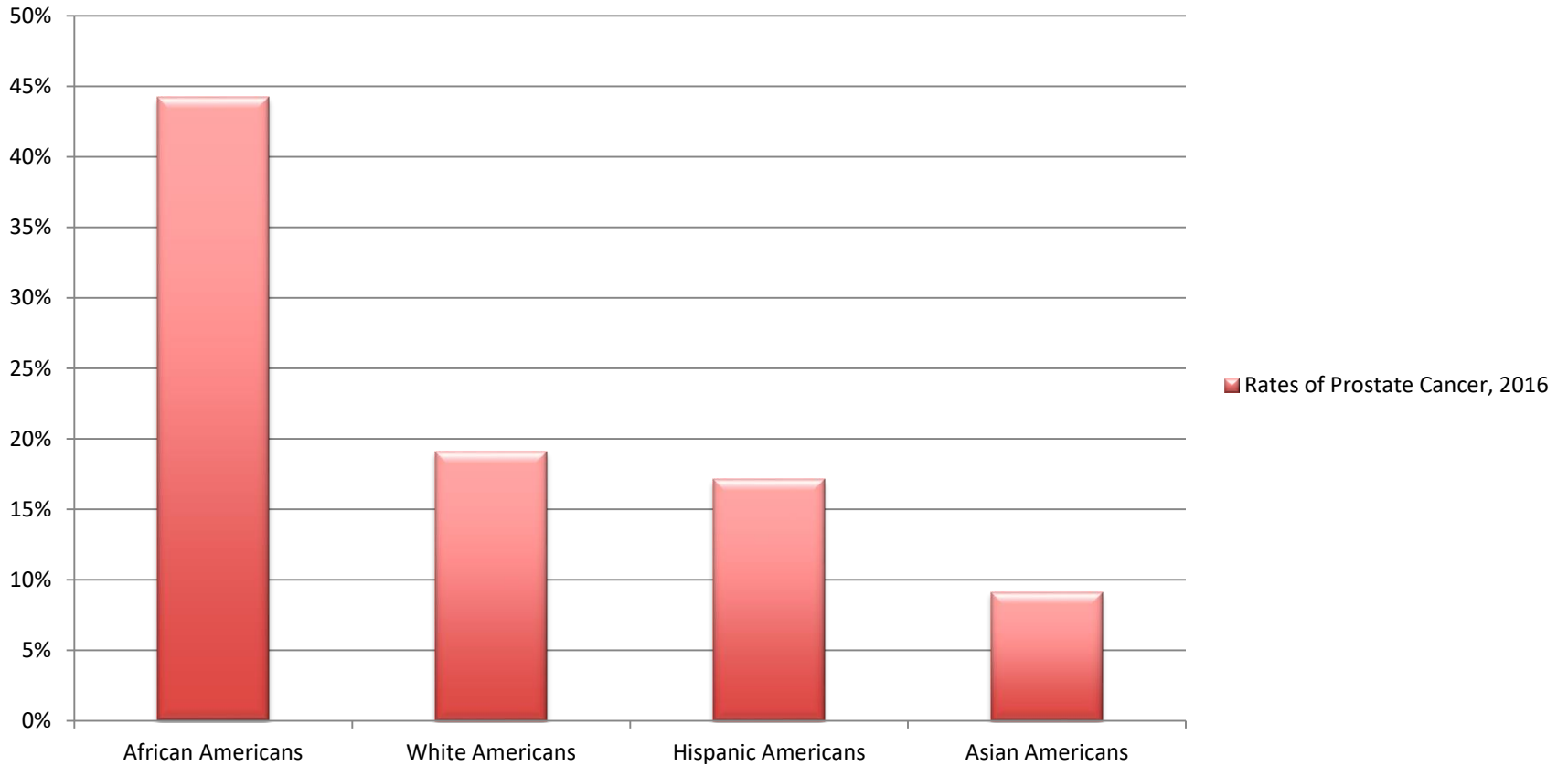
Age standardized (World) mortality rates, prostate, all ages



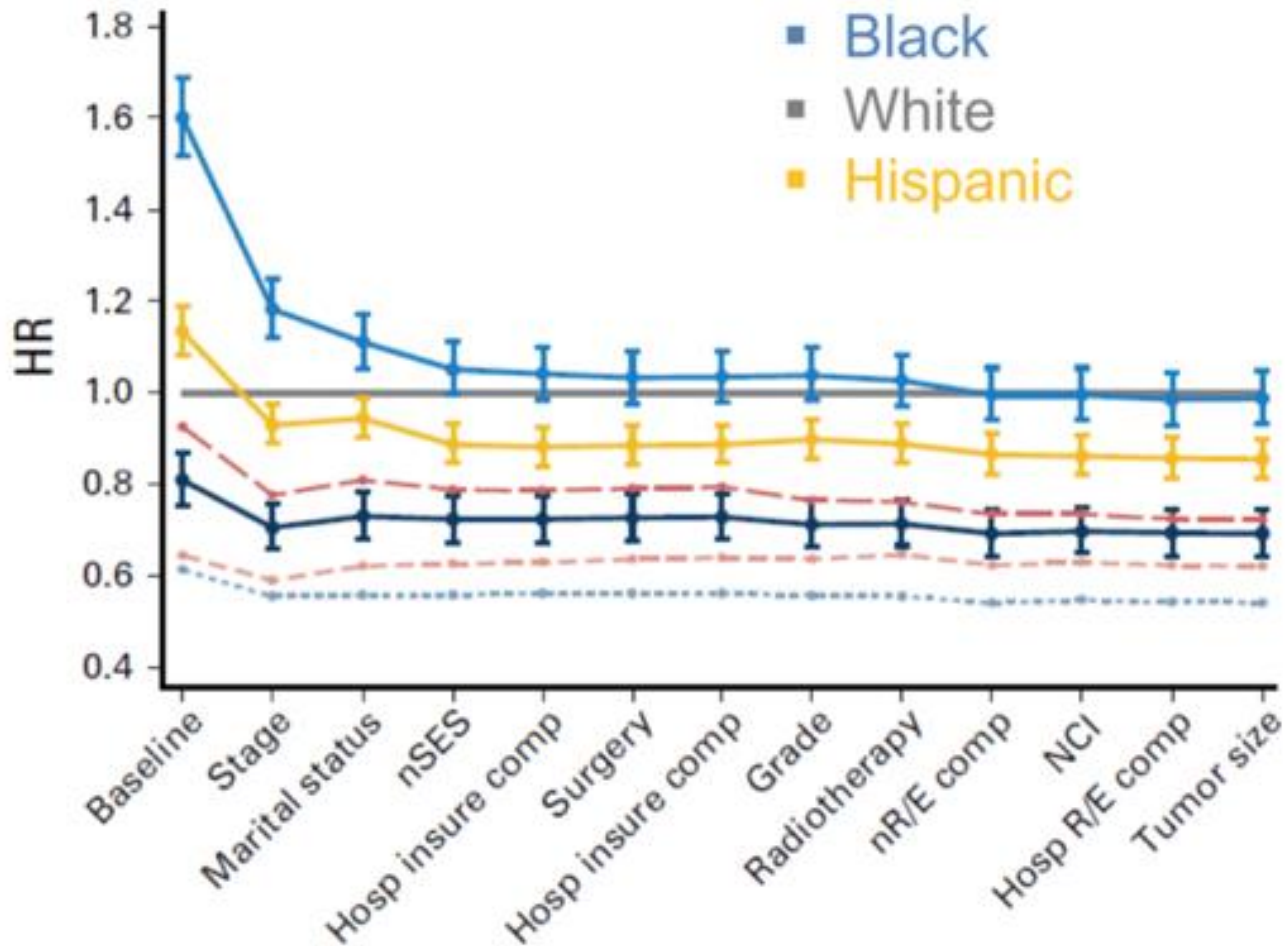
source: GLOBOCAN 2018
production: IARC (<http://gco.iarc.fr/today>)
World Health Organization

Racial Disparities

Rates of Prostate Cancer, 2016

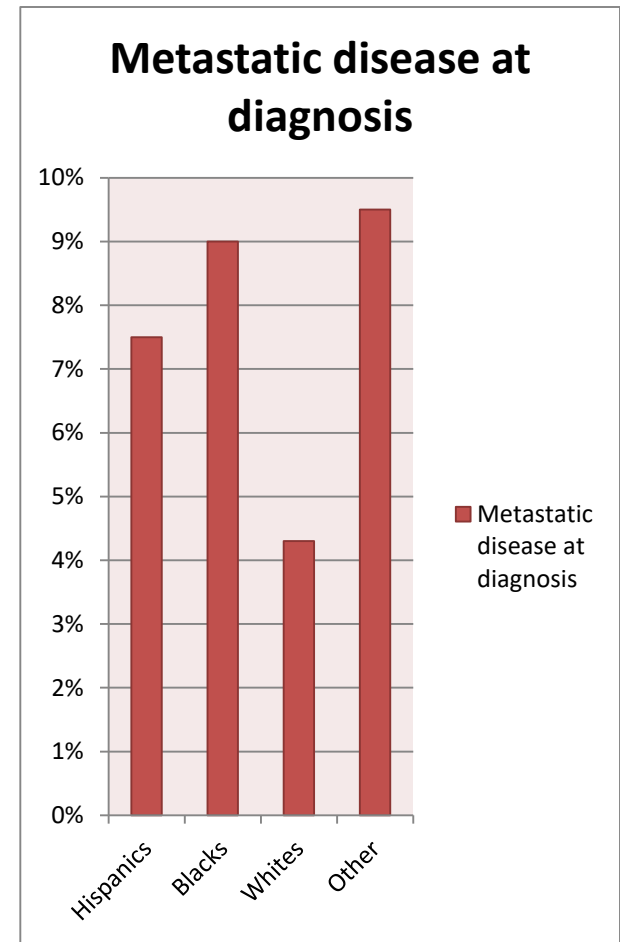
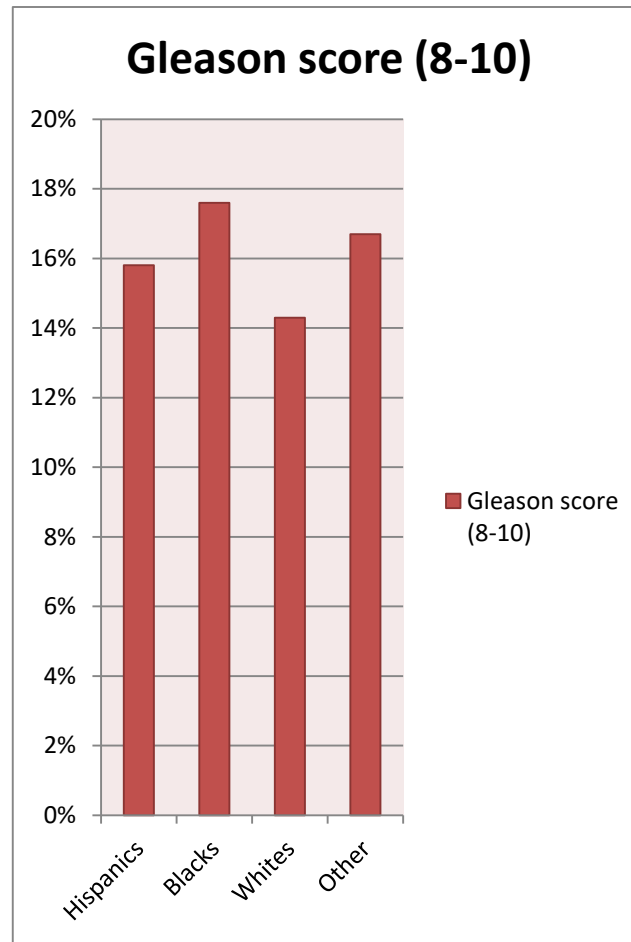
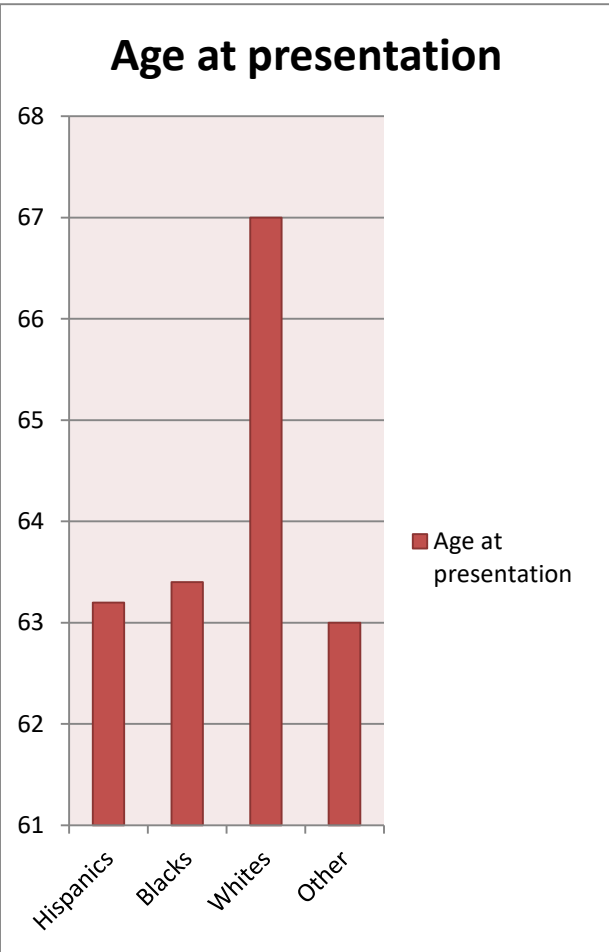


Racial Disparity – Prostate Cancer



Ellis L. JCO, 2018

Racial Disparities, cont'd



Historical Perspective – Prostate Cancer

*H. Young –
First Radical
Prostatectomy*

*C.Huggins –
Prostate Cancer
responds to
androgen
ablation*

*V Schally–
ADT use*

*A.Ragde – U/S
guided Biopsies*

*Genetic research;
Vaccine; targeted
therapy*

1853 1904 1935 1940 1965 1971 1979 1988 2004 *The future*

3

*J.Adams –
CaP
description*

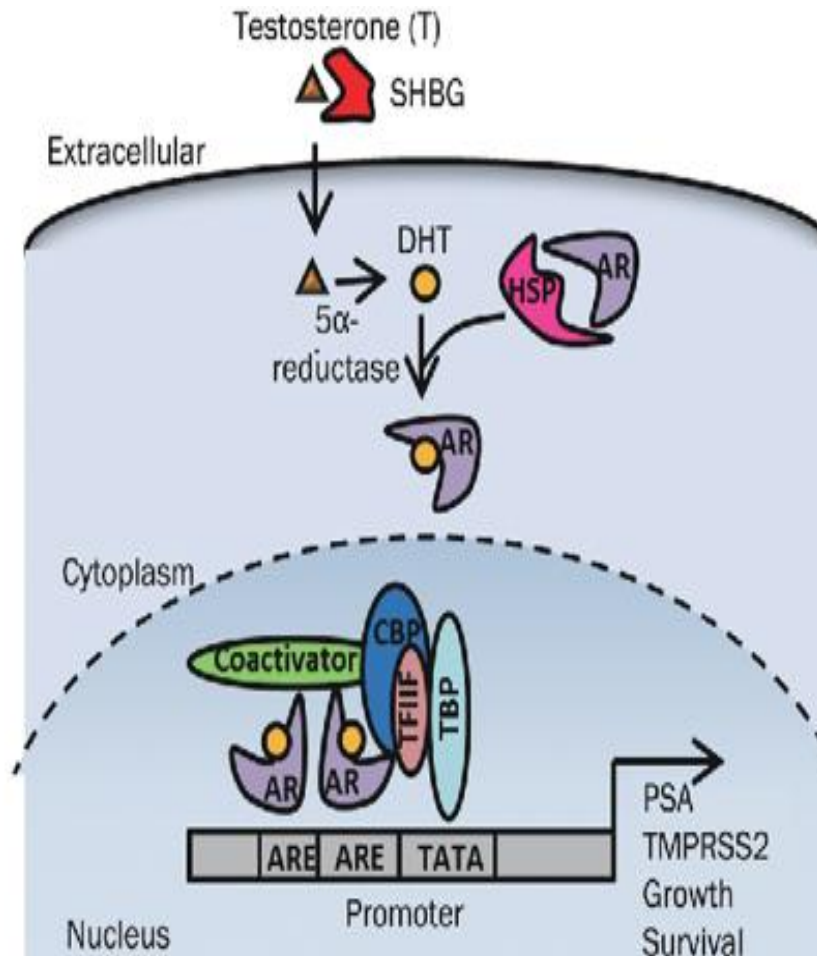
*Kutscher – Acid
Phosphatase in
prostate tissue*

*Bragshaw –
Established
radiation role*

*Wang – PSA
discovery*

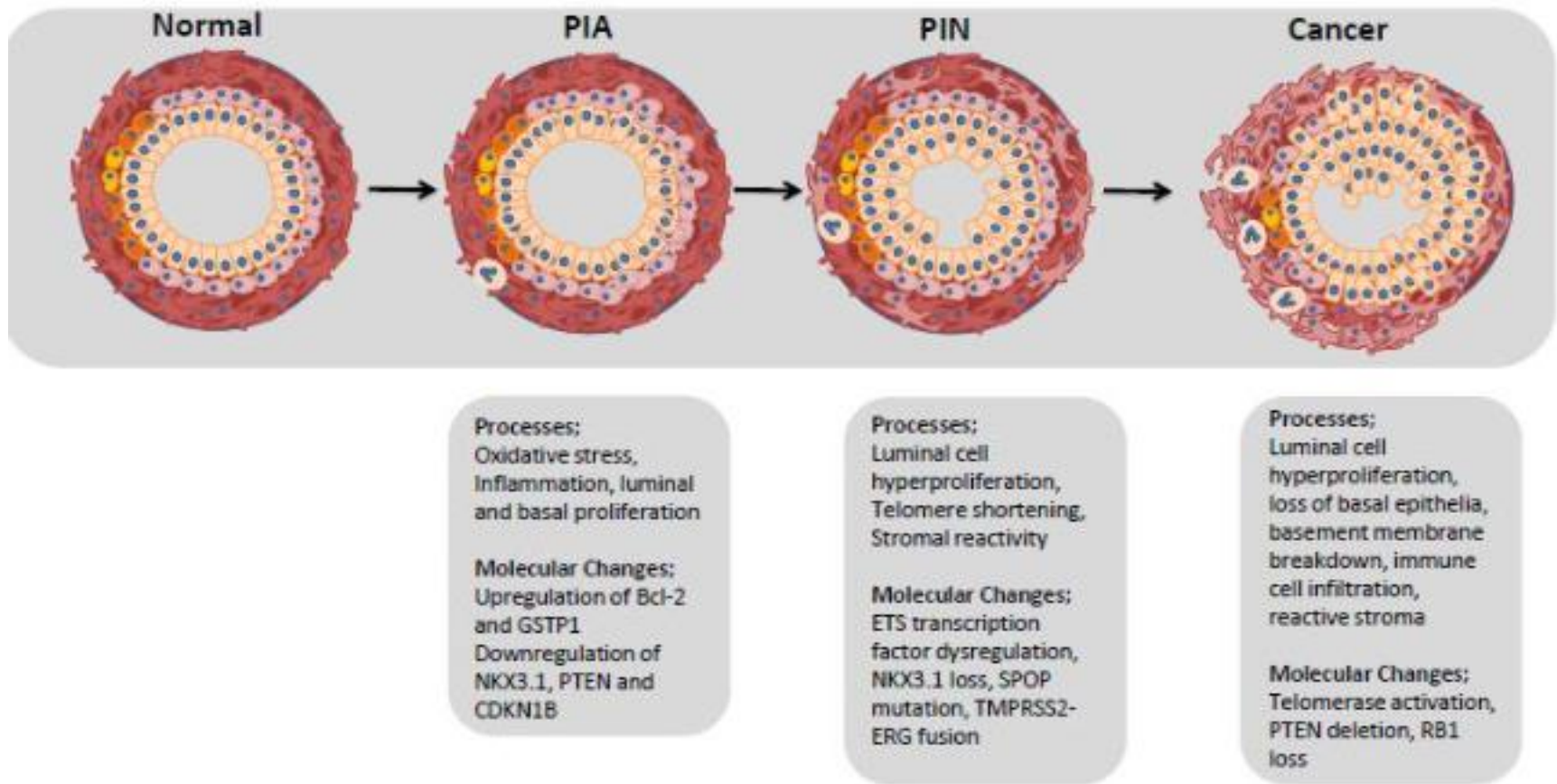
*Docetaxel- use in
castrate resistant
prostate cancer*

Androgen Receptors - Summary



***Normal Prostate –
balance between
proliferation &
apoptosis***

Natural Evolution – Prostate Cancer



Guidelines - Screening

BASELINE EVALUATION

- History and physical (H&P) including:
 - ▶ Family cancer history
 - ▶ History of prostate disease and screening, including prior prostate-specific antigen (PSA) and/or isoforms, exams, and biopsies
 - ▶ Race^b
 - ▶ Family or personal history of high-risk germline mutations^c
 - ▶ Medications^a

RISK ASSESSMENT

Start risk and benefit discussion about offering prostate screening:

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

Age 45–75 y^{b,c}

EARLY DETECTION EVALUATION

PSA <1 ng/mL,
DRE normal (if done)

Repeat testing at
2–4 year intervals^g

PSA 1–3 ng/mL,^f
DRE normal (if done)

Repeat testing at
1–2 year intervals

PSA >3 ng/mL^f
and/or very suspicious DRE

[See Indications
for Biopsy \(PROSD-3\)](#)

PSA <4 ng/mL, DRE normal
(if done), and no other
indications for biopsy

Repeat testing in
select patients at
1–4 year intervals

Age >75 y, in
select patients
(category 2B)^e

PSA ≥4 ng/mL or very
suspicious DRE

[See Indications
for Biopsy \(PROSD-3\)](#)

Not screened^e

Risk Groups

Risk Group	Clinical/Pathologic features
Very Low Risk	<ul style="list-style-type: none">-T1c AND-Gleason score ≤ 6/grade group 1 AND-PSA < 10 ng/mL AND Fewer than 3 prostate biopsy fragments/cores positive, $\leq 50\%$ cancer in each fragment/core AND-PSA density < 0.15 ng/mL/g
Low Risk	<ul style="list-style-type: none">-T1 to T2a AND-Gleason score ≤ 6/grade group 1 AND-PSA < 10 ng/mL
Favorable Intermediate	<ul style="list-style-type: none">-T2b to T2c OR-Gleason score 3+4 = 7/grade group 2 OR-PSA 10 to 20 ng/mLAND-Percentage of positive biopsy cores $< 50\%$

Risk Groups, cont'd

Definitive RT - Risk group	Clinical/Pathological features
Unfavorable Intermediate	-T2b to T2c OR -Gleason score 3+4 = 7/grade group 2 or Gleason score 4+3 = 7/grade group 3 OR -PSA 10 to 20 ng/mL
High	-T3a OR -Gleason score 8/grade group 4 or Gleason score 4+5 = 9/grade group 5 OR -PSA >20 ng/mL
Very High	-T3b to T4 OR -Primary Gleason pattern 5 OR >4 cores with Gleason score 8 to 10/grade group 4 or 5

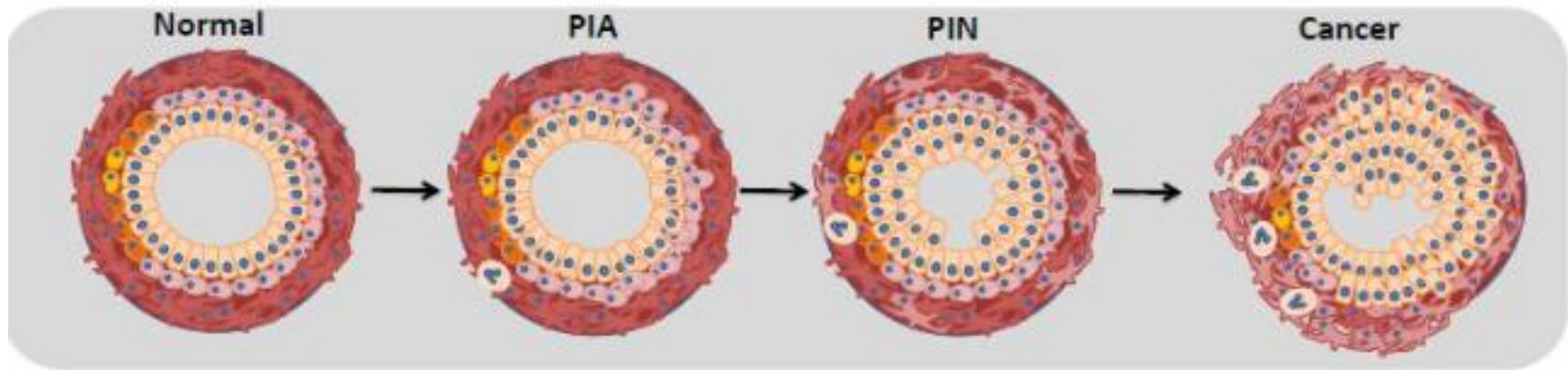
Established Treatment per risk groups

Risk Group	Treatment
Very Low risk	Life expectancy > 10 years – active surveillance OR surgery/RT; < 10 years – watchful waiting
Low Risk	Active surveillance OR radical Prostatectomy OR Radiation (External Beam Radiation or Brachytherapy)
Intermediate Risk	Favorable AND Unfavorable: Radiation therapy (external beam and/or brachytherapy) + short term ADT OR Radical Prostatectomy Active Surveillance
High Risk	Similar to Intermediate Risk; RT + long term ADT
Very High Risk	Same as High

Genetic changes in prostate cancer

Genetic change	Description	Mechanism	Example
Somatic copy number alterations	Gain or loss in genetic material	Role in oncogenic activation and tumor suppressor inactivation	PTEN, BRCA-2 and RB1
Structural re-arrangements	Due to improper DNA repair	Unrelated Genes placed in juxtaposition	TMPRSS2:ERG
Point Mutations	Specific nucleotides or AA resulting in altered genes	Impaired gene stability + function	Regulation of AR target genes
Single Nucleotide Polymorphisms (SNP)	Variation in a single nucleotide between individuals OR chromosomes	Markers in gene mapping	NCOA4 an AR co-activator

Summary – genetic changes in CaP



Processes;
Oxidative stress,
Inflammation, luminal
and basal proliferation

Molecular Changes;
Upregulation of Bcl-2
and G5TP1
Downregulation of
NKX3.1, PTEN and
CDKN1B

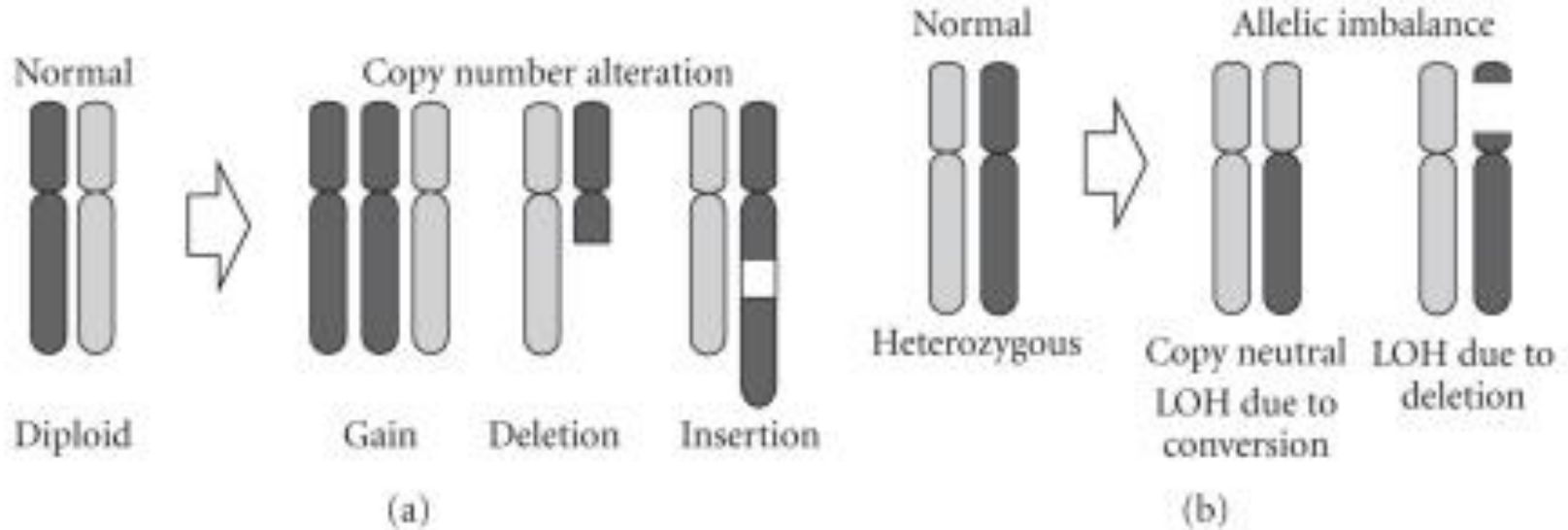
Processes;
Luminal cell
hyperproliferation,
Telomere shortening,
Stromal reactivity

Molecular Changes;
ETS transcription
factor dysregulation,
NKX3.1 loss, SPOP
mutation, TMPRSS2-
ERG fusion

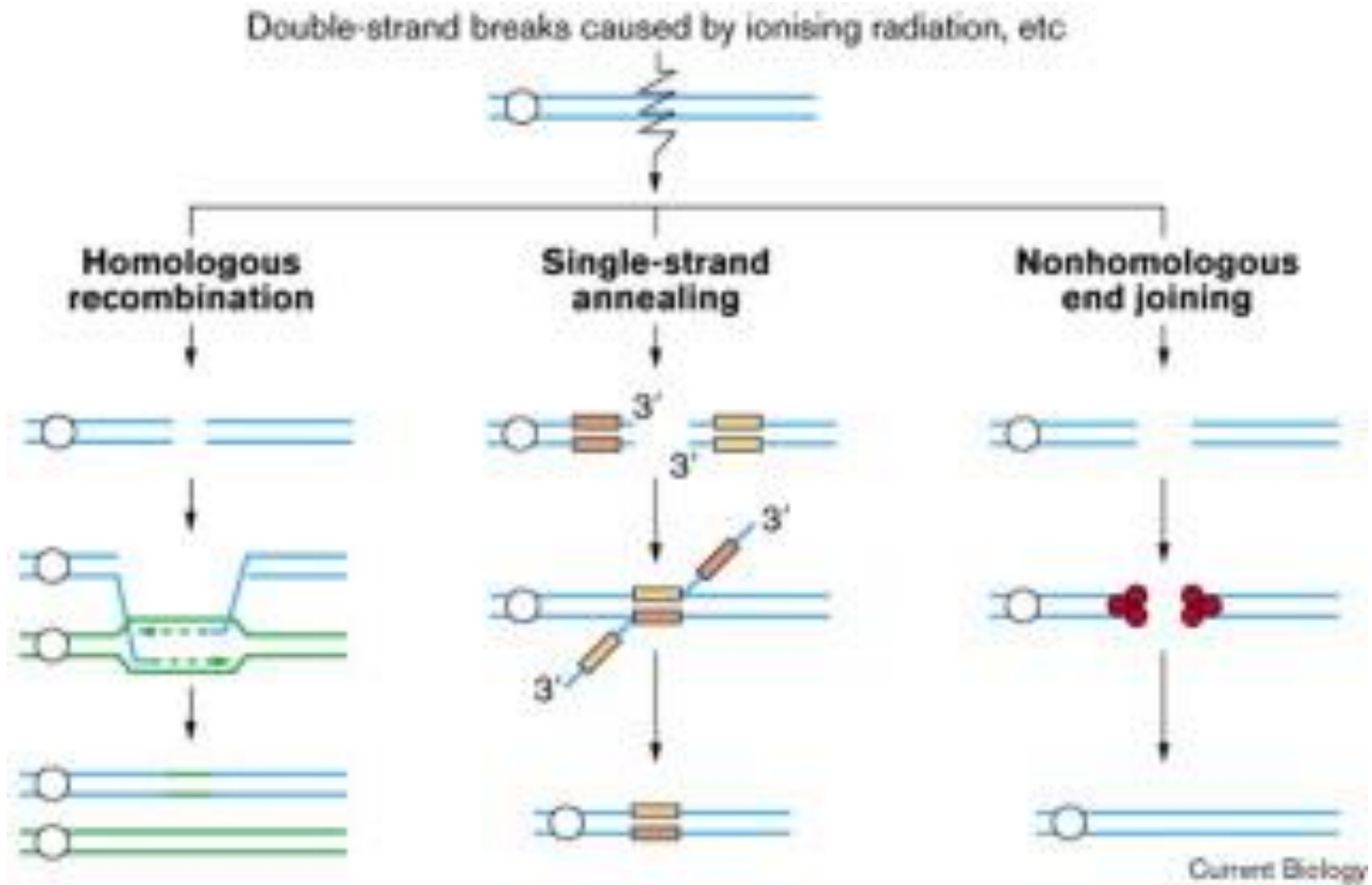
Processes;
Luminal cell
hyperproliferation,
loss of basal epithelia,
basement membrane
breakdown, immune
cell infiltration,
reactive stroma

Molecular Changes;
Telomerase activation,
PTEN deletion, RB1
loss

Somatic Copy number alterations

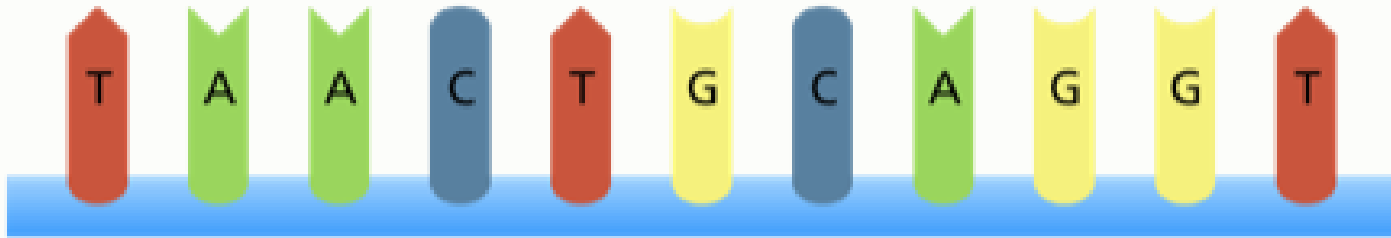


Structural Rearrangements

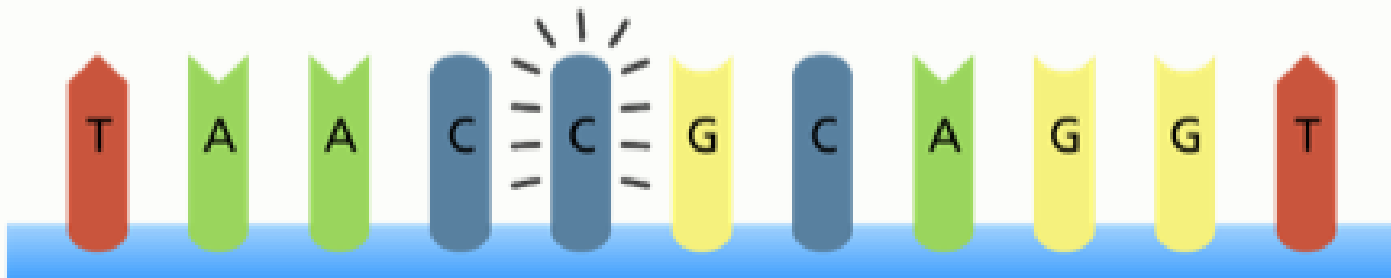


Point Mutation

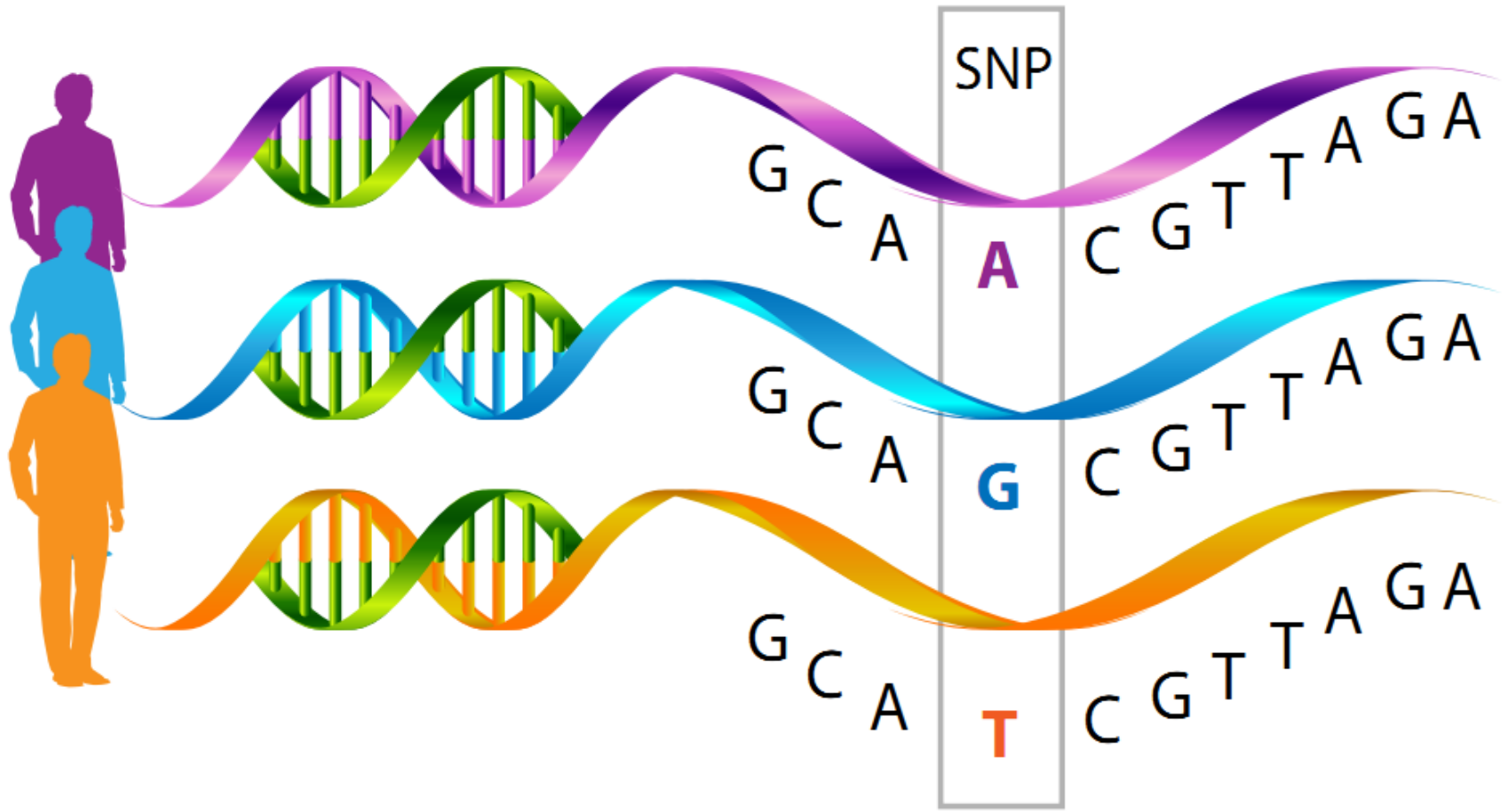
Original sequence



Point mutation



Single Nucleotide Polymorphisms



Changing trends – CaP screening with genetics assessment

Indications – Genetic testing	NCCN Genetic/Familial High – Risk Assessment
Family history Criteria	>3 cancers on same side of family, diagnosed < 50 y (breast, colorectal, melanoma, ovarian, prostate); Lynch Syndrome; Black Race
Disease Characteristics	History of metastatic prostate cancer (radiographic evidence/biopsy proven); High or Very High risk disease
BRCA-1 carriers	Consider prostate cancer screening starting at age 45
BRCA-2 carriers	Similar to BRCA-1

Gene Therapy

Strategy	Description
Immunomodulation	Optimizing the body's immunity capacity to destroy cancer cells
Corrective Therapy	Replacing defective gene – current efforts – replacing a defective p53
Cytoreductive therapy	Suicide therapy – enzyme encoding gene metabolizing an inactive prodrug into an active metabolite (viruses for medications + bystander effect to non-transduced neighboring cell)

END