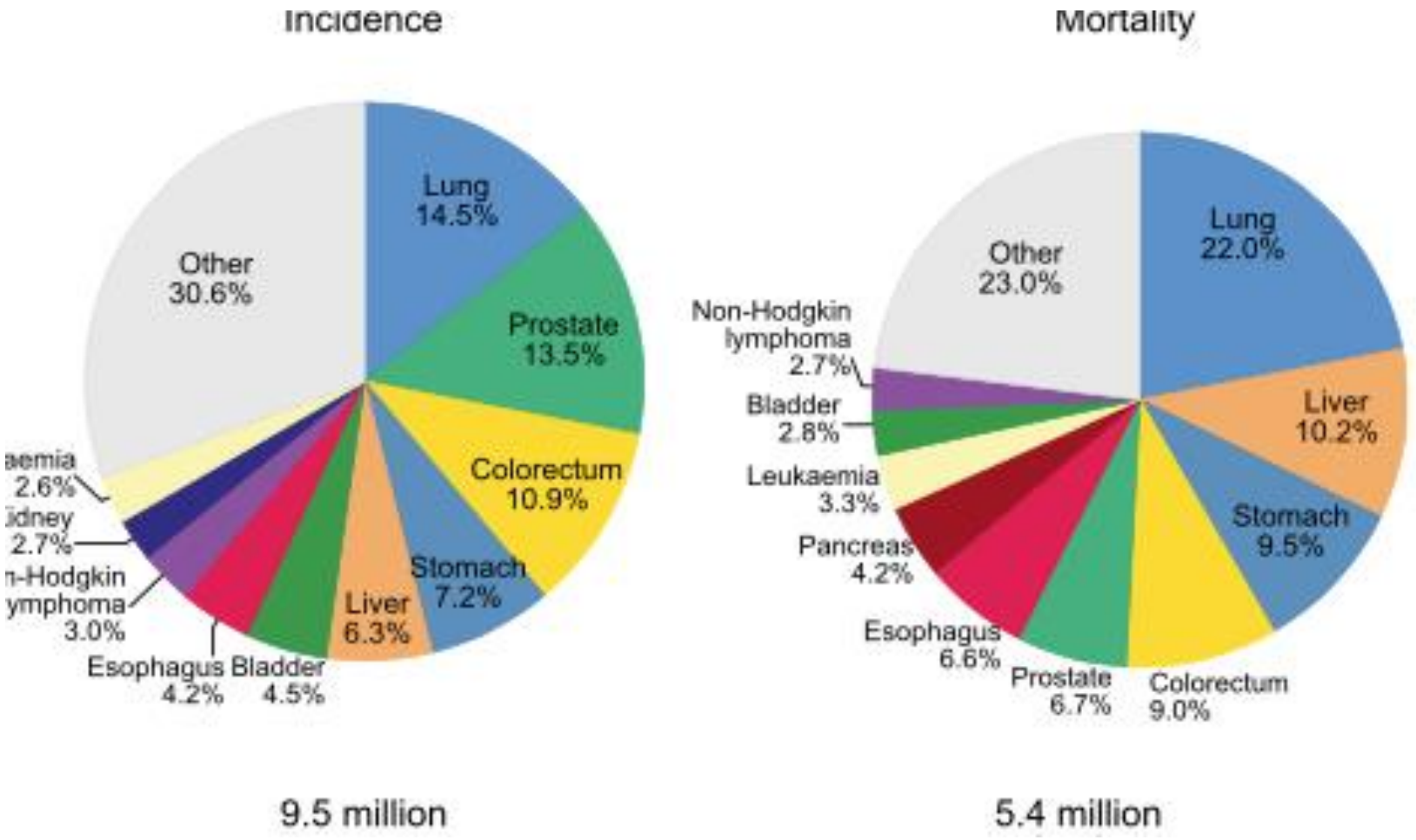
Prostate Cancer and Genetics

Achille Manirakiza, MD
Rwanda Military Hospital

Outline

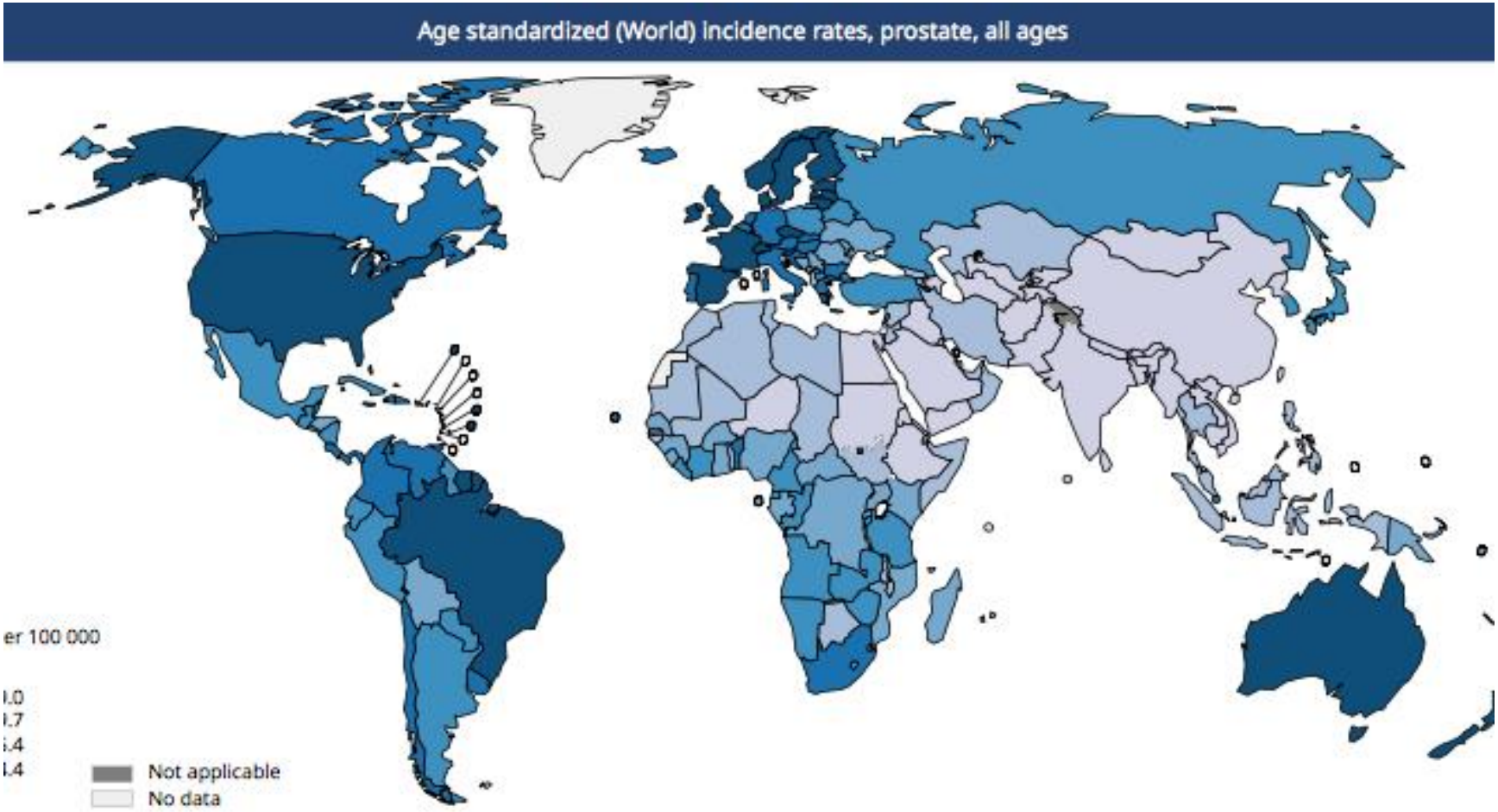
- Prostate Cancer Epidemiology
- Historical Milestones in Prostate Cancer discovery
- Current knowledge + practices in screening & treatment
- Application of genetics in screening & treatment

Prostate Cancer at a Glance

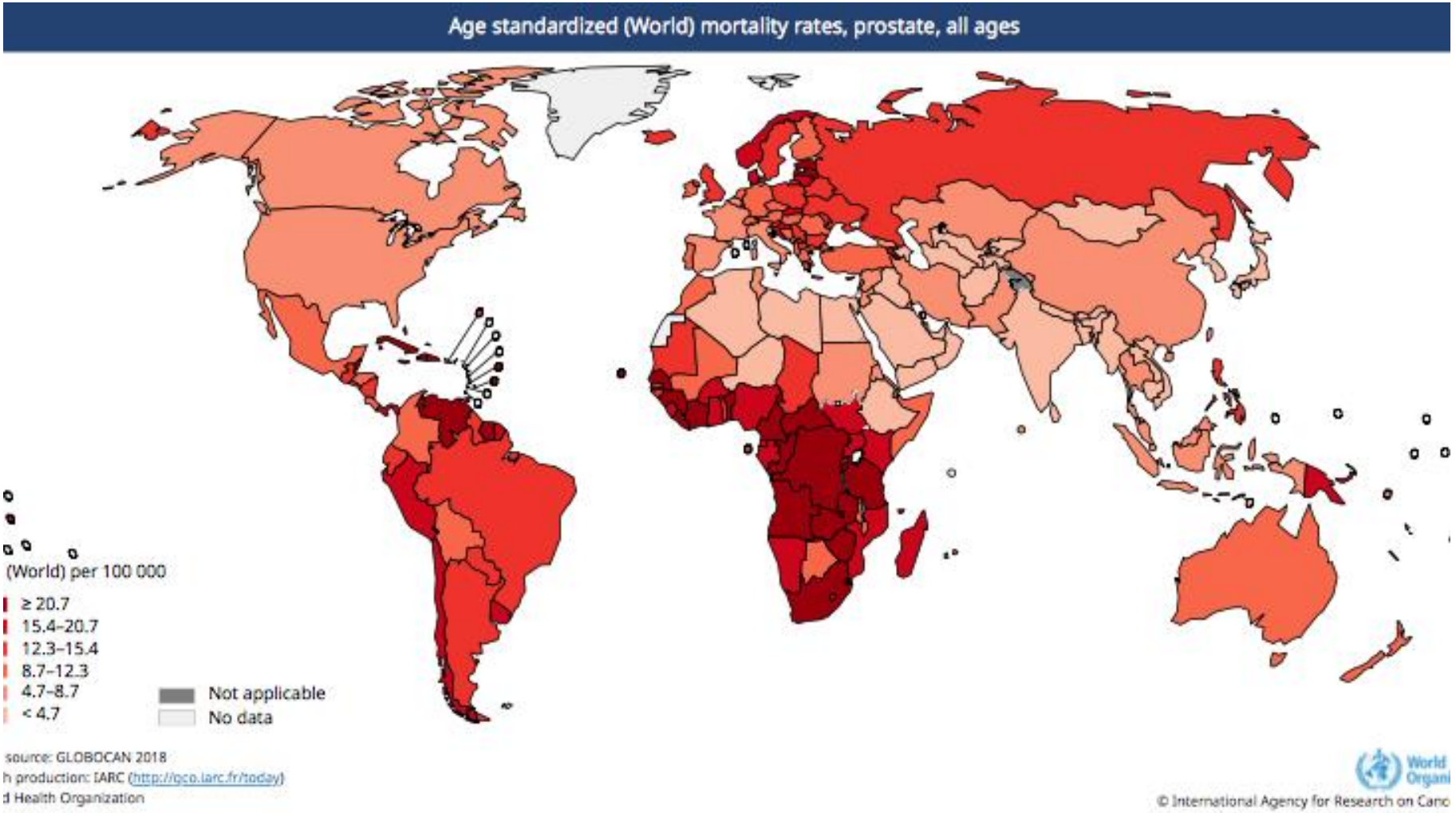


Cancer Incidence & Mortality in Males - 2018

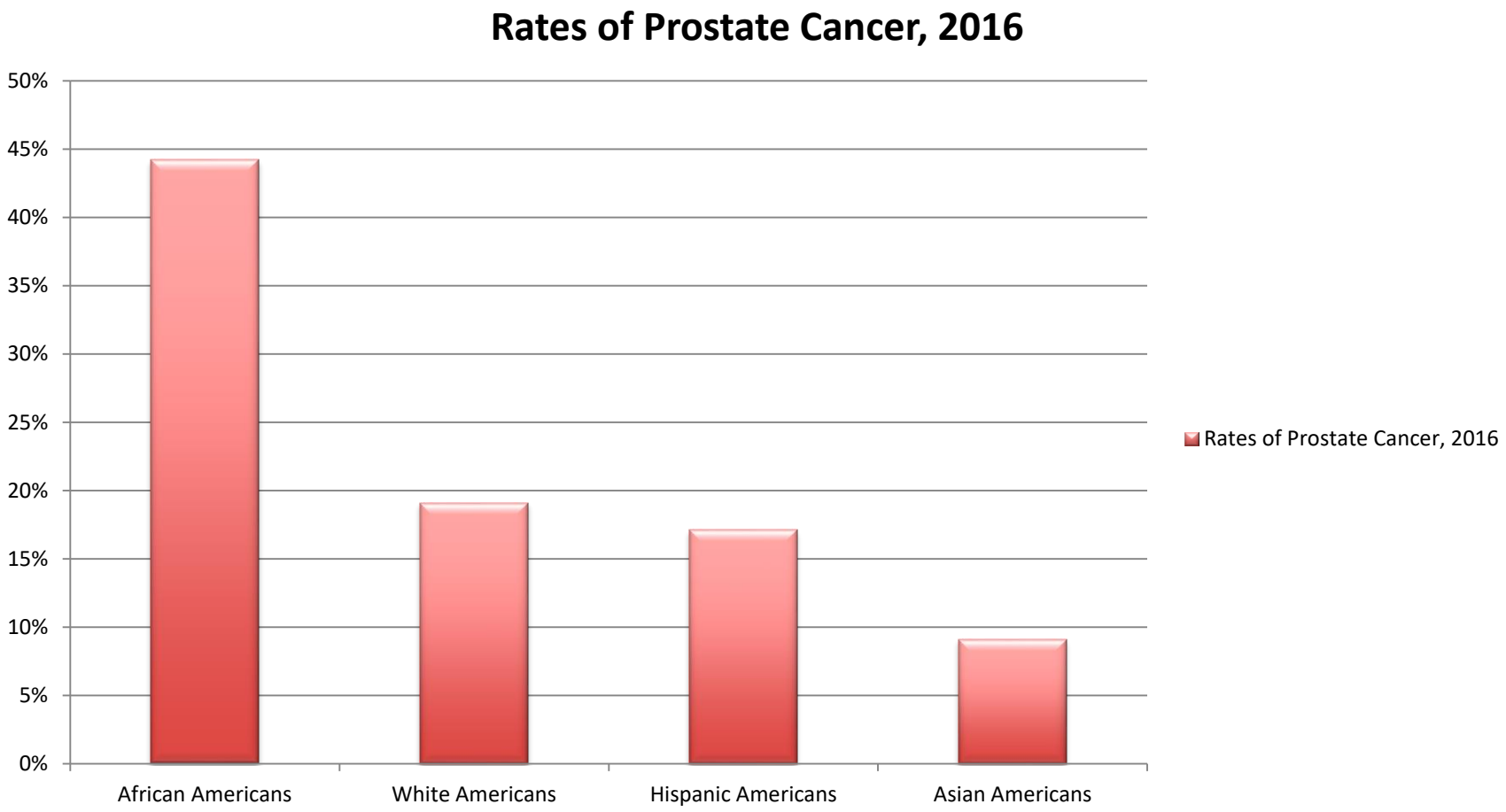
World Incidence



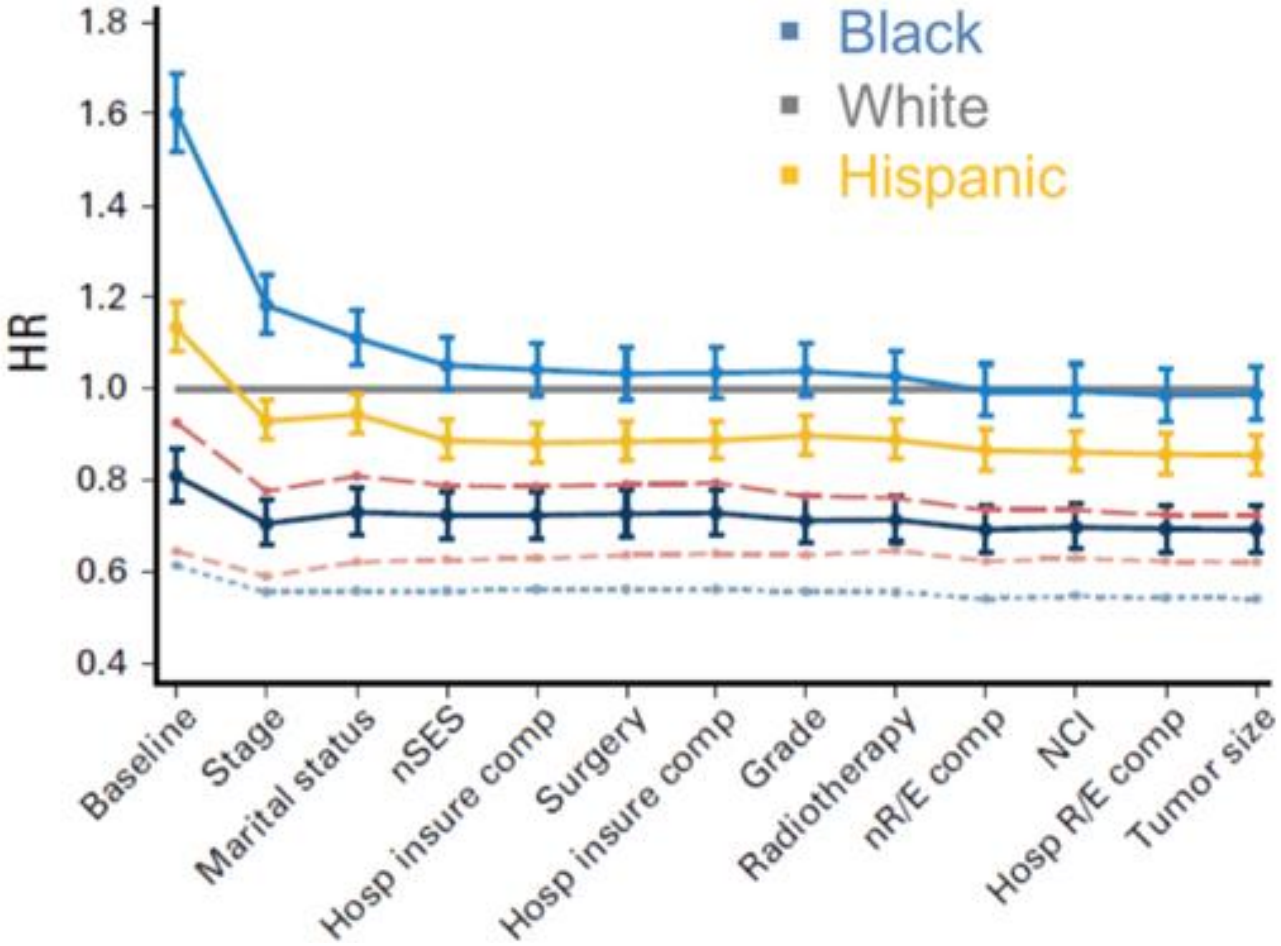
World Mortality



Racial Disparities

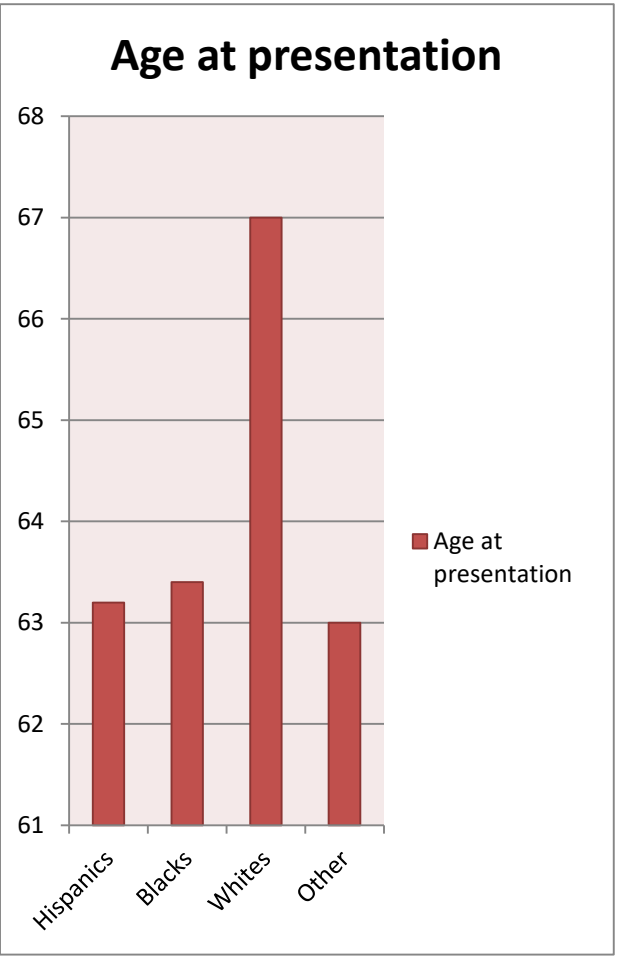


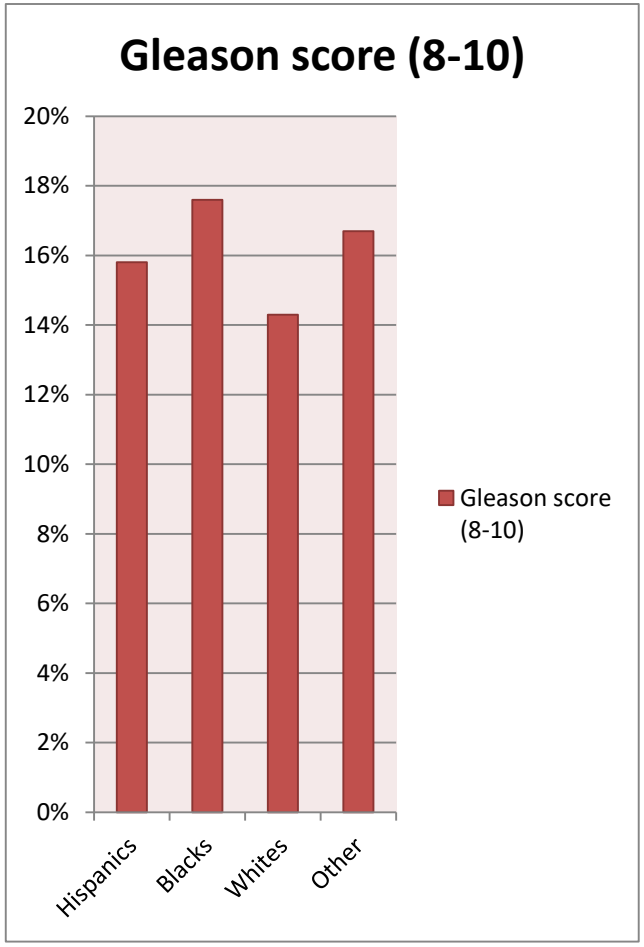
Racial Disparity – Prostate Cancer

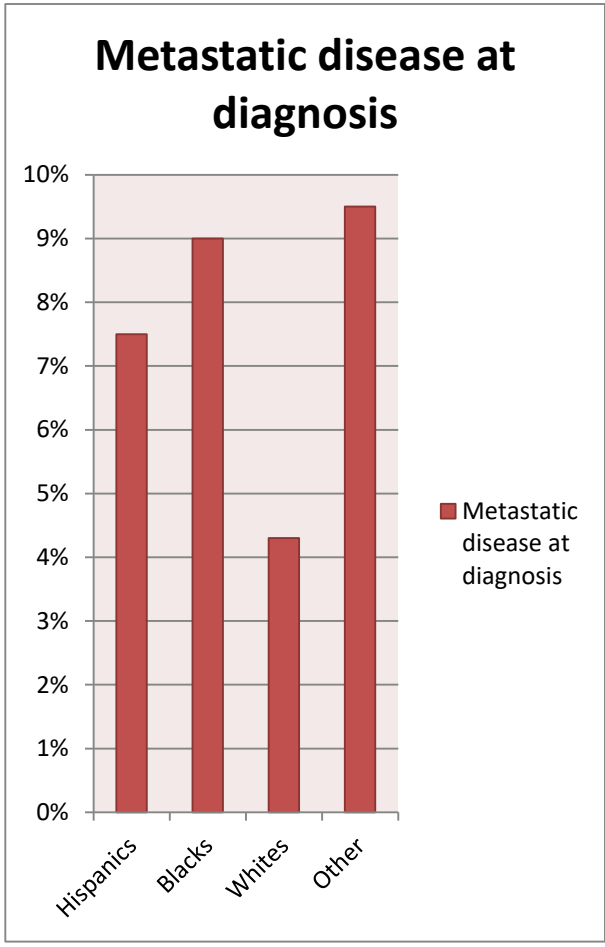


Ellis L. JCO, 2018

Racial Disparities, cont'd

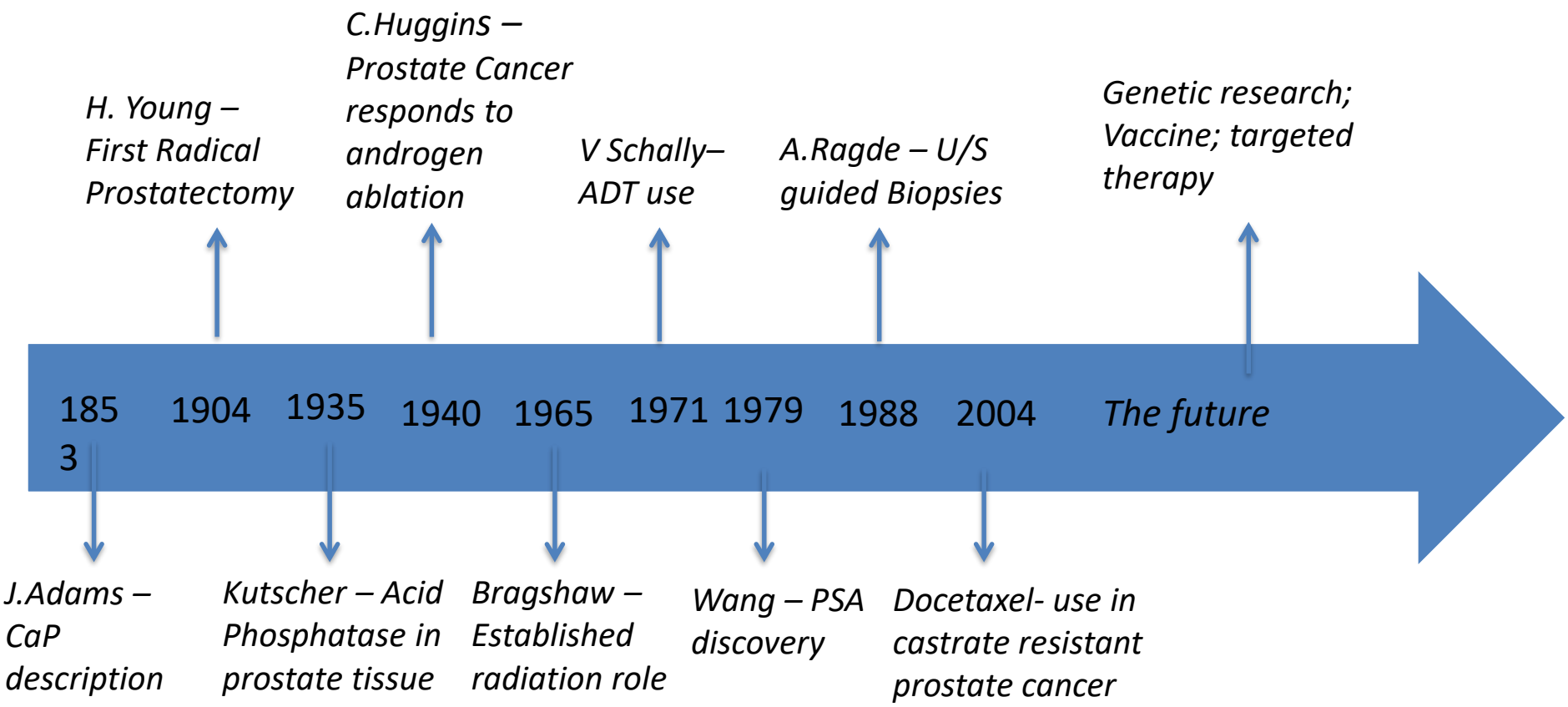




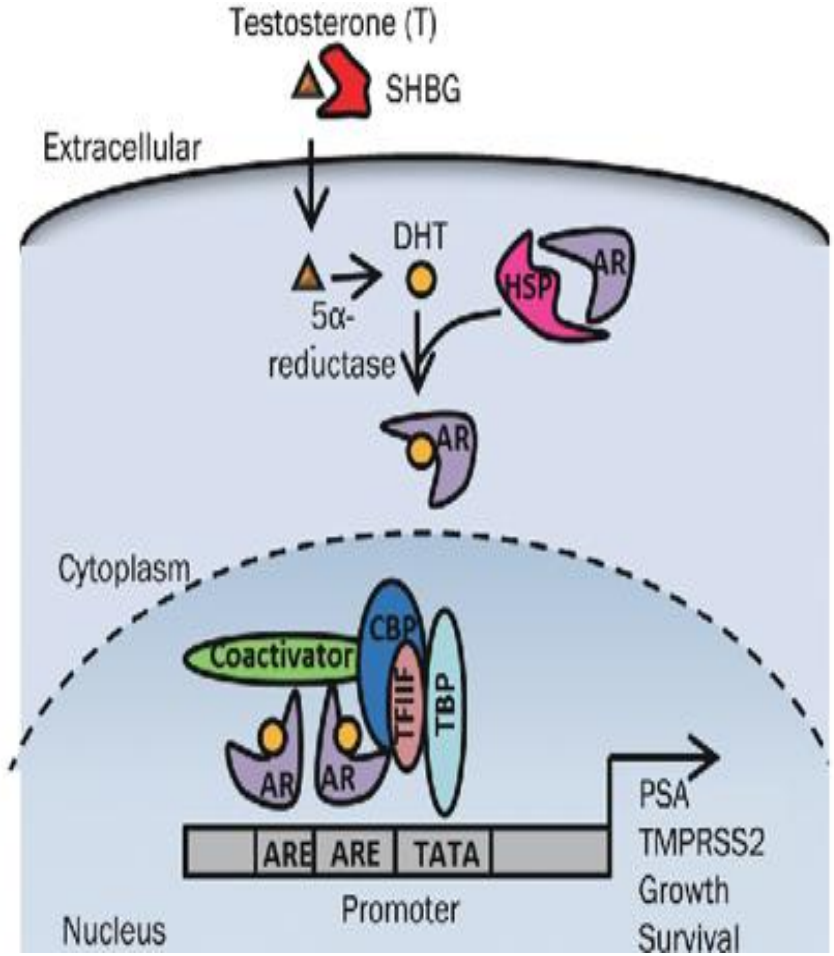


Suresh T, CGC, 2018

Historical Perspective – Prostate Cancer

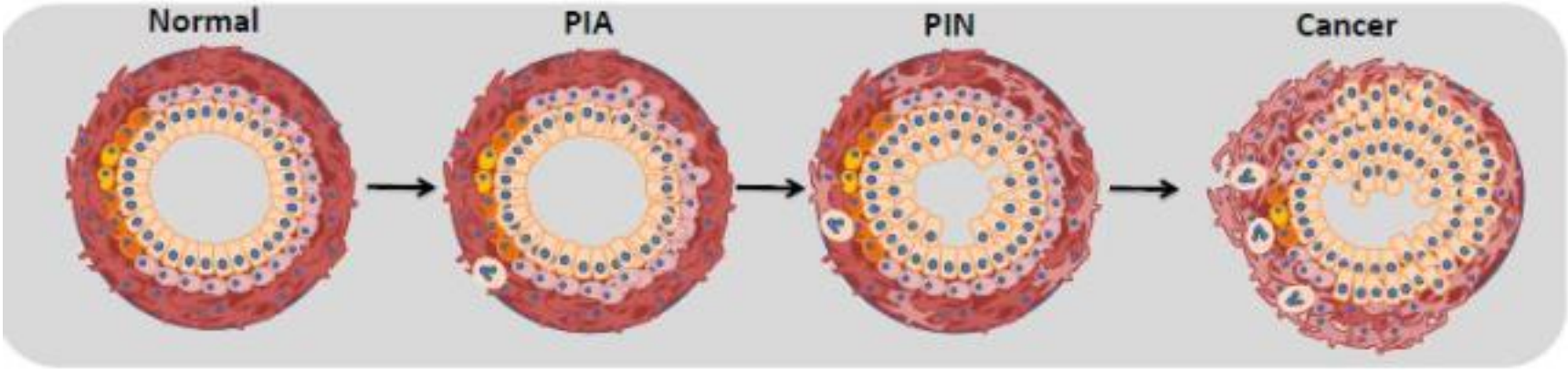


Androgen Receptors - Summary



Normal Prostate – balance between proliferation & apoptosis

Natural Evolution – Prostate Cancer



Processes:
Oxidative stress, Inflammation, luminal and basal proliferation

Molecular Changes:
Upregulation of Bcl-2 and GSTP1
Downregulation of NKX3.1, PTEN and CDKN1B

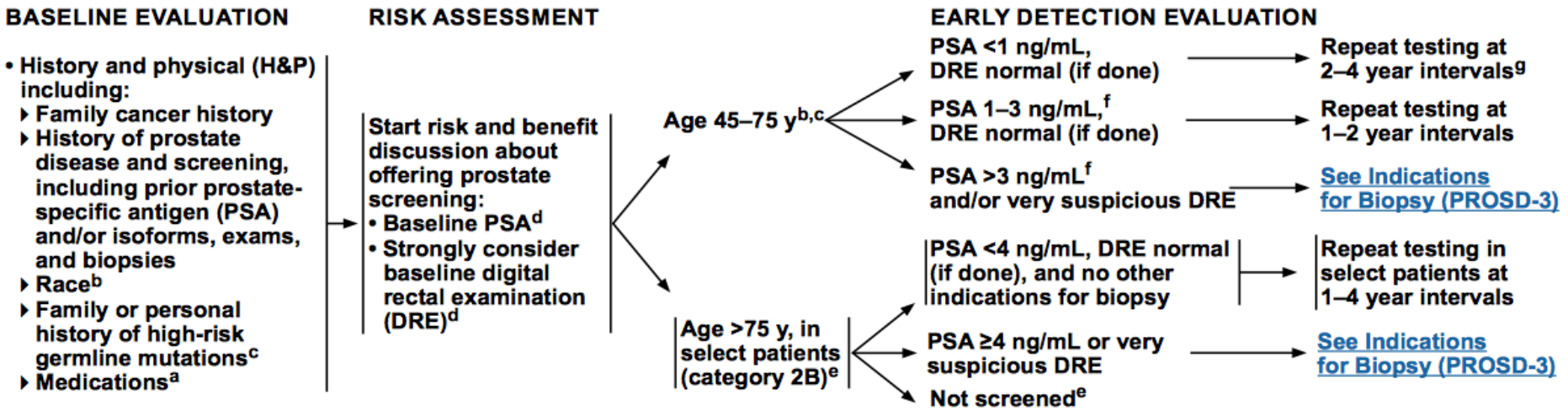
Processes:
Luminal cell hyperproliferation, Telomere shortening, Stromal reactivity

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

Guidelines - Screening



Risk Groups

Risk Group	Clinical/Pathologic features
Very Low Risk	-T1c AND -Gleason score ≤6/grade group 1 AND -PSA <10 ng/mL AND Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND -PSA density <0.15 ng/mL/g
Low Risk	-T1 to T2a AND -Gleason score ≤6/grade group 1 AND -PSA <10 ng/mL
Favorable Intermediate	-T2b to T2c OR -Gleason score 3+4 = 7/grade group 2 OR -PSA 10 to 20 ng/mL AND -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

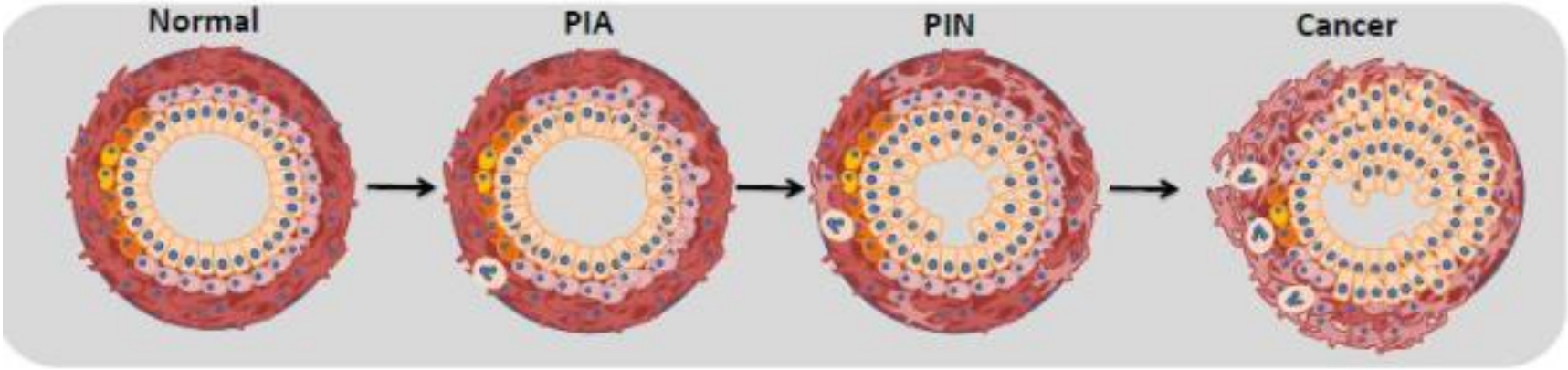
Established Treatment per risk groups

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 Prostatecomy 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 GSTP1
Downregulation of NKX3.1, PTEN and CDKN1B

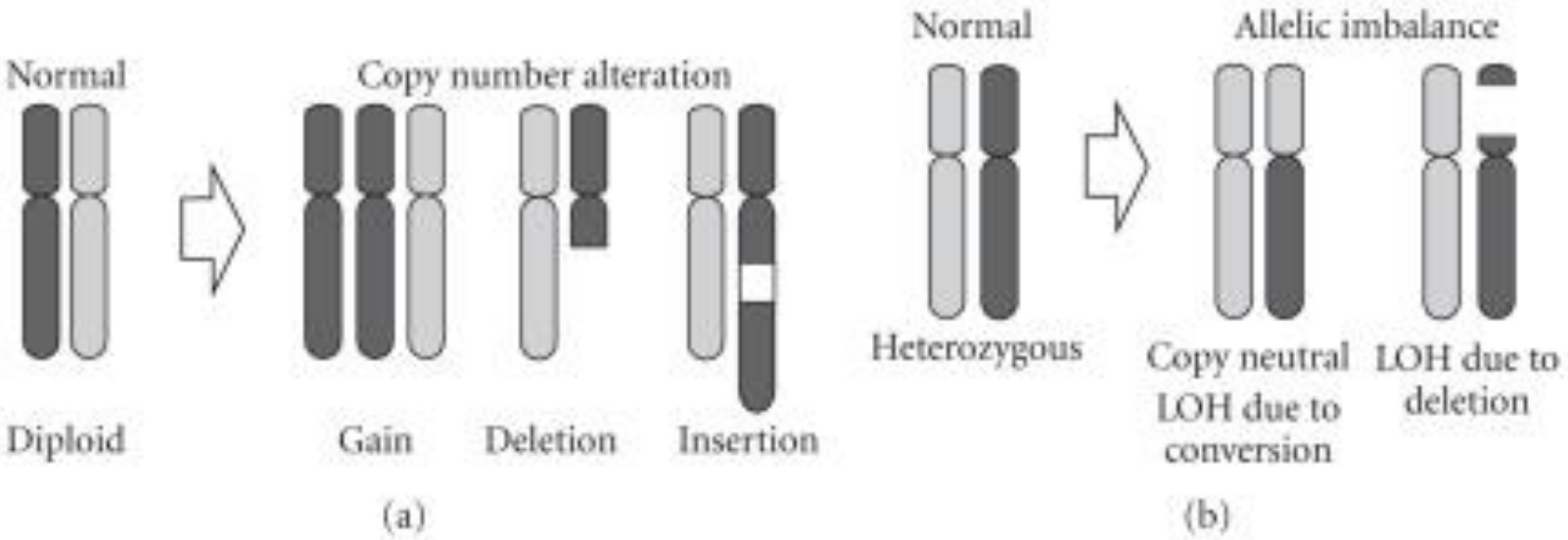
Processes:
Luminal cell hyperproliferation, Telomere shortening, Stromal reactivity

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

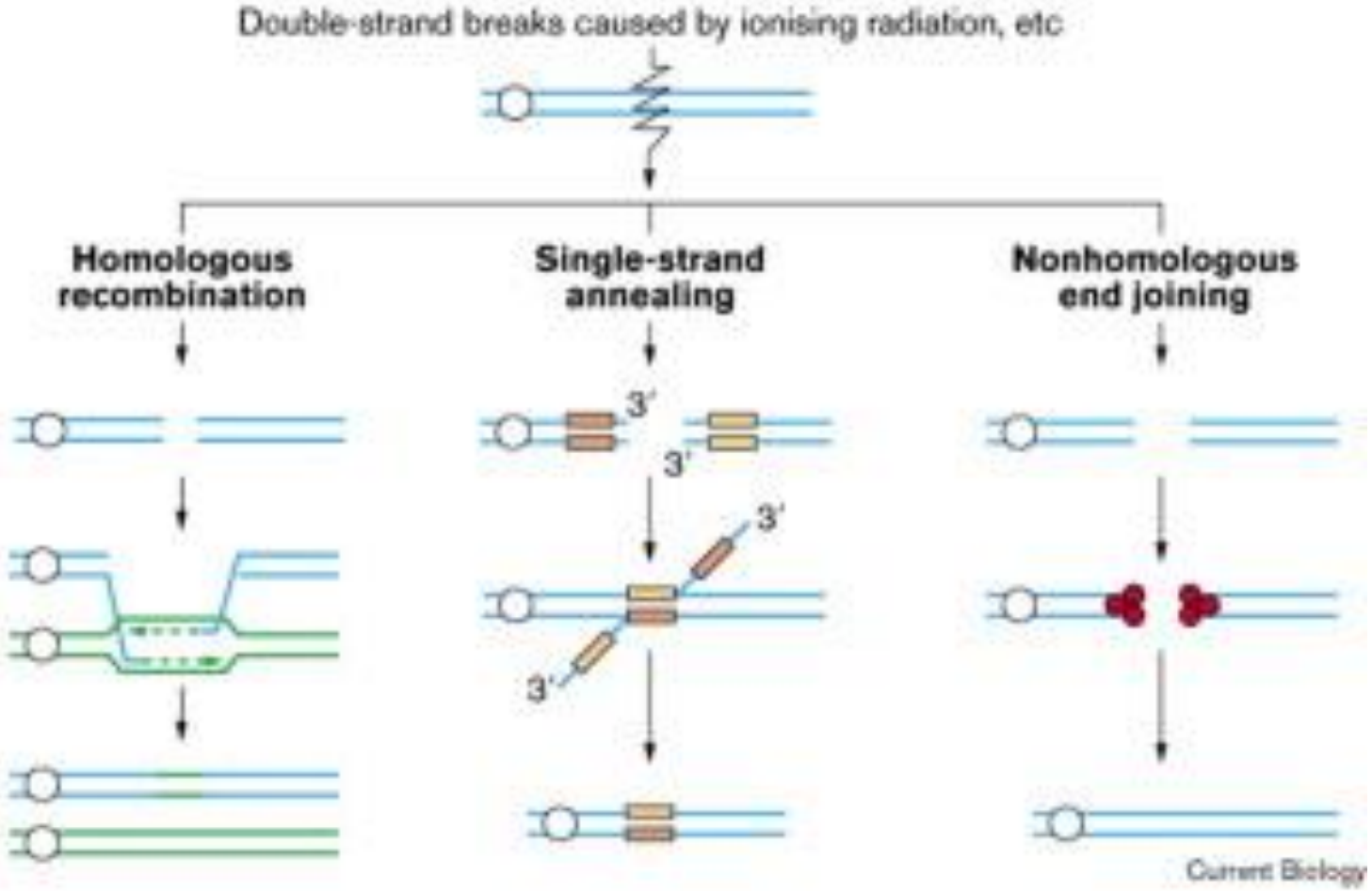
Processes:
Luminal cell hyperproliferation, loss of basal epithelia, basement membrane breakdown, immune cell infiltration, reactive stroma

Molecular Changes:
Telomerase activation, PTEN deletion, RB1 loss

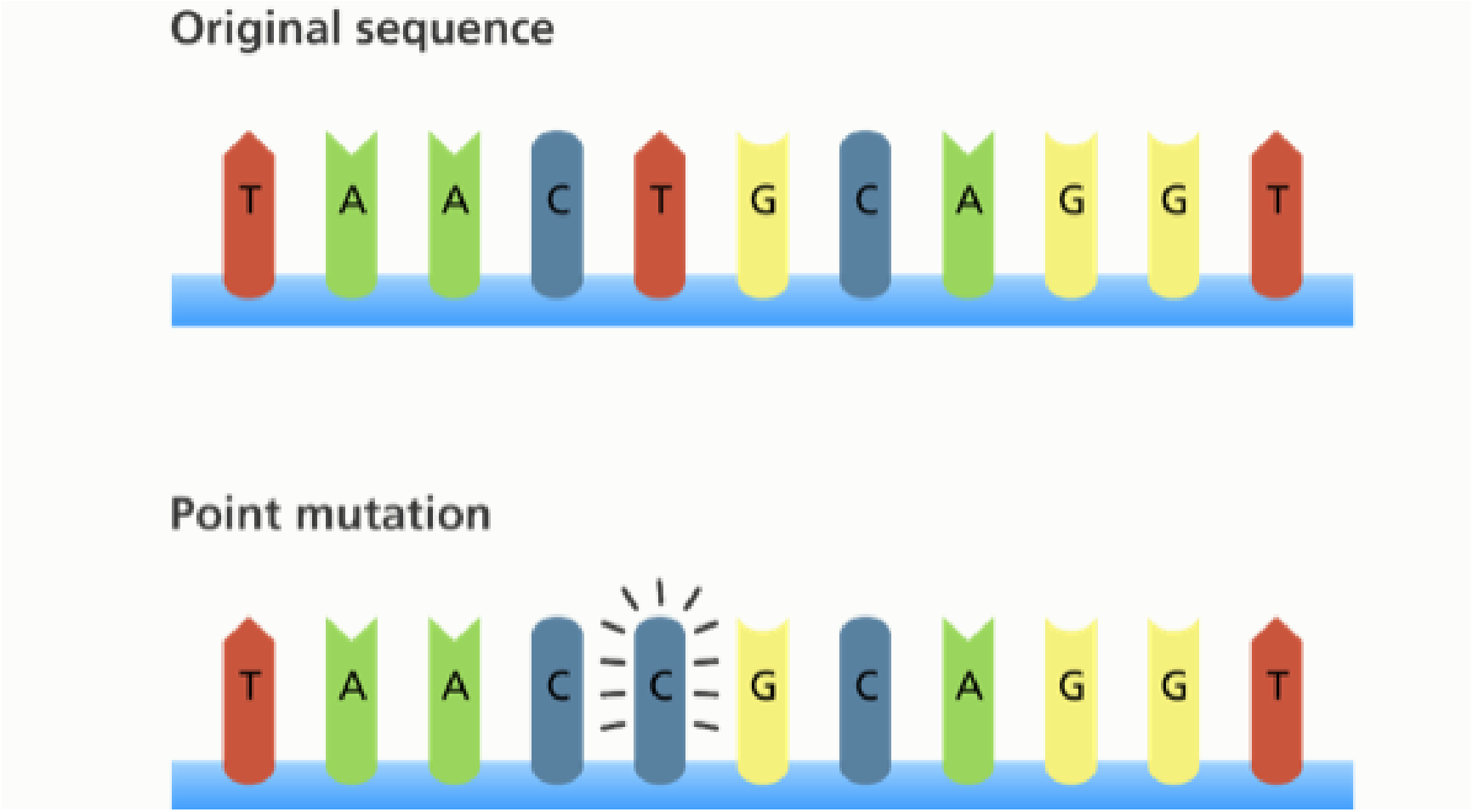
Somatic Copy number alterations



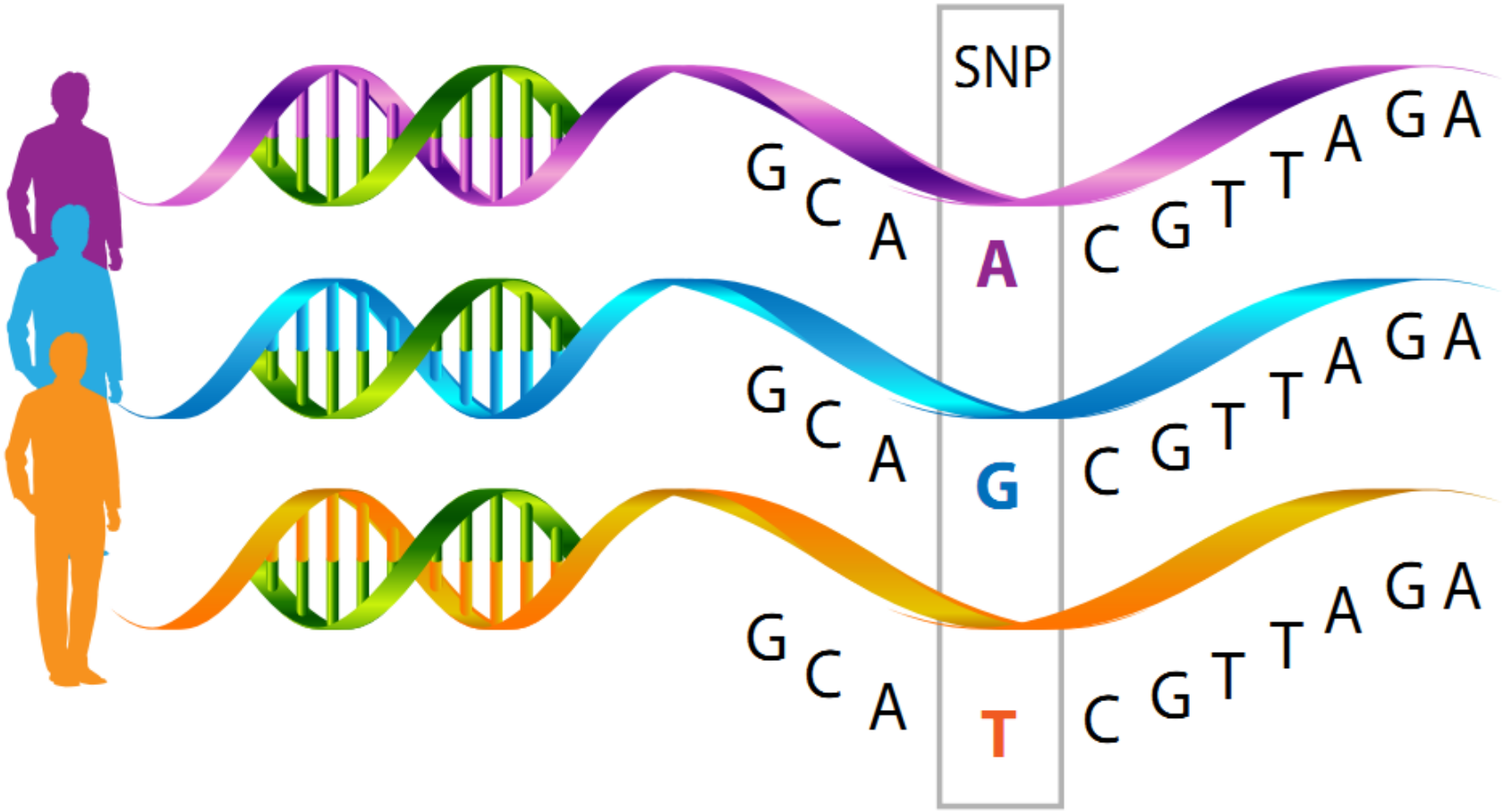
Structural Rearrangements



Point Mutation



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-transinduced neighboring cell)

END