



The Murtha Cancer Center
2nd Annual Cancer Research Seminar
Walter Reed National Military Medical Center
Bethesda, MD
June 23, 2014

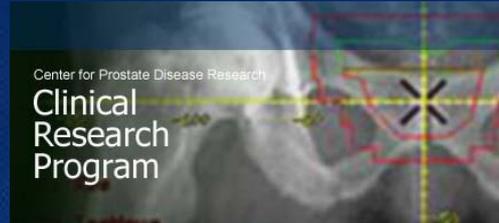
Center for Prostate Disease Research (CPDR)
Overview and Research Highlights





CENTER FOR PROSTATE DISEASE RESEARCH

“Commitment to Understanding the Biology, Genetics and Clinical Features of Prostate Cancer with the Ultimate Goal of Benefiting Patients”



DoD-Prostate Cancer Center of Excellence





Center For Prostate Disease Research Leadership

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Achieving the Mission

- Integration of clinical care and research at DoD medical centers improves early detection, prognostication, and new treatments for prostatic diseases with unparalleled clinical and translational research track record (23 yrs and nearly 400 publications).
- **Focus:**
 - Natural history and outcomes research in high risk patient groups; e.g., African American men
 - Discovery and development of precise biomarkers and therapeutic targets for personalized medicine
 - Innovative clinical trials for DOD health care beneficiaries
 - Training in translational and clinical research for DoD physicians, scientists, medical and graduate students
 - High impact collaborative research efforts related to prostate disease with other leading medical centers and biotechnology/pharmaceutical companies

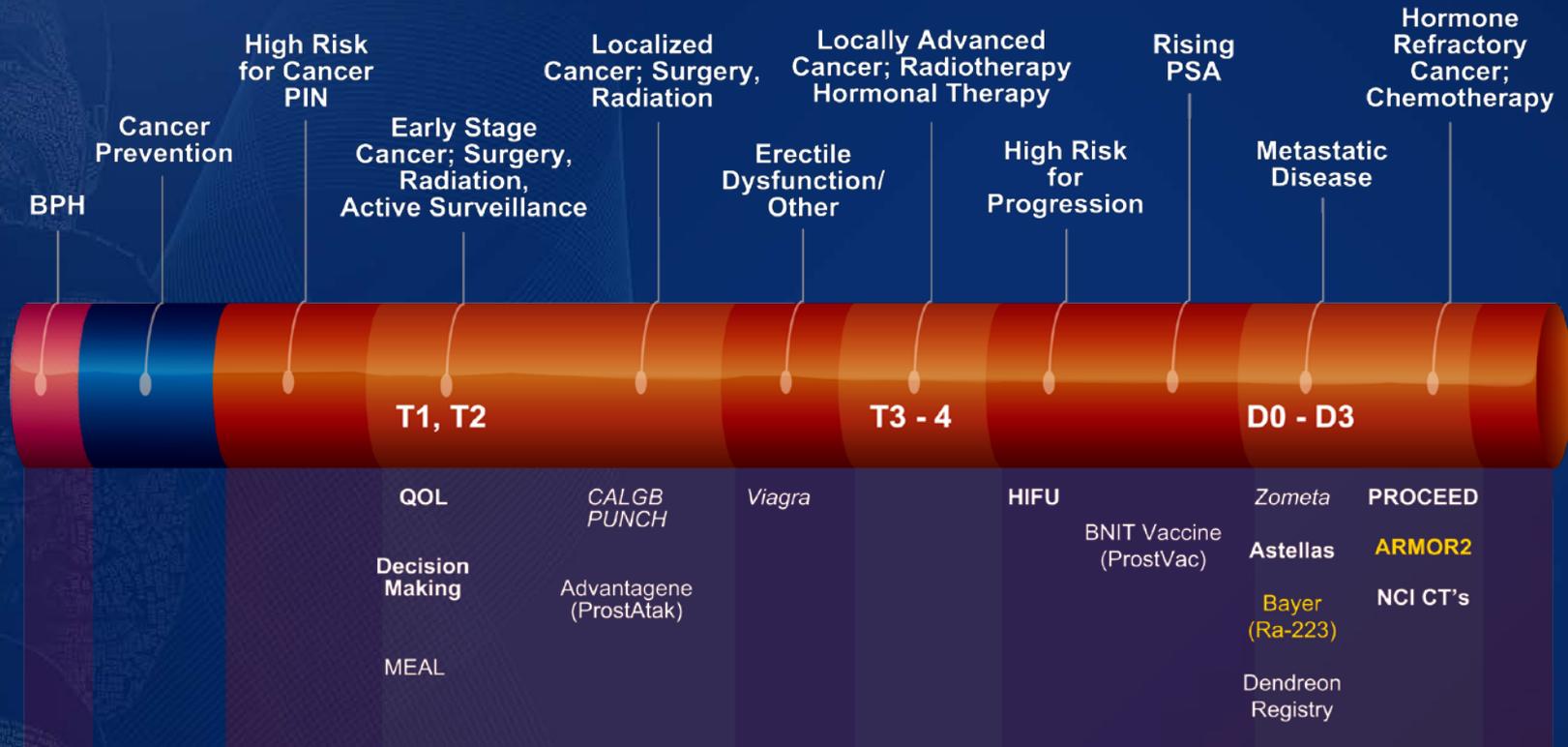


Locations of CPDR Sites





Center For Prostate Disease Research (CPDR)
 Clinal Research Center - Walter Reed National Military Medical Center
 Clinical Trials Portfolio Treating All Stages of Prostate Disease



Legend

- Enrolling Now
- Pending Approval/Site Initiation

Lab Studies

Biospecimen Bank: Collects Blood, Urine, Serum, Prostatic Secretions





CPDR National Database Program

- Established in 1991 as one of 3 main arms of CPDR
- 27,000+ subjects enrolled to date
- Eligibility for enrolment is based on suspicion for prostate cancer
- Comprehensive prospective and retrospective data collection, along the continuum of care, including health-related quality of life information
- Five nationally distributed medical centers contribute subjects
- Military & civilian subjects are enrolled with an over-representation of African American subjects
- Standardized data points are abstracted by trained staff and entered into a secure Oracle relational database





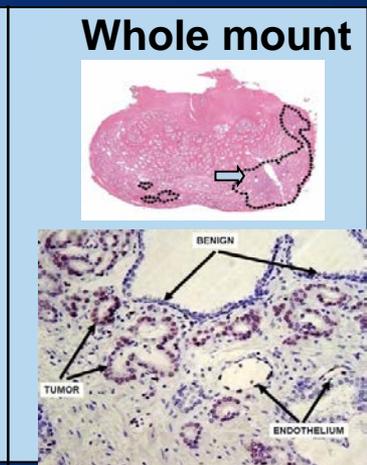
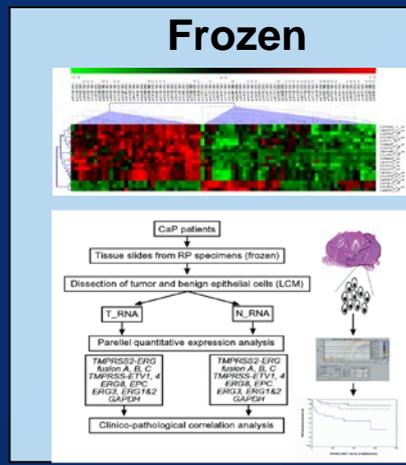
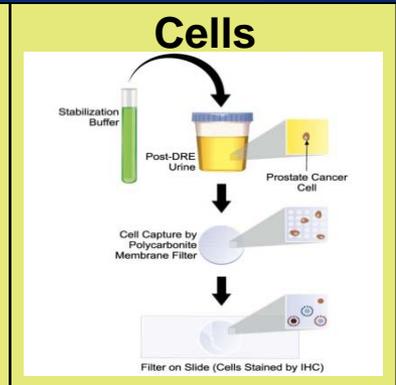
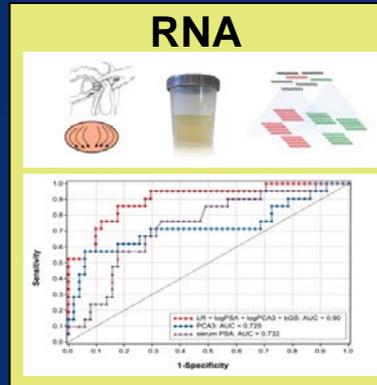
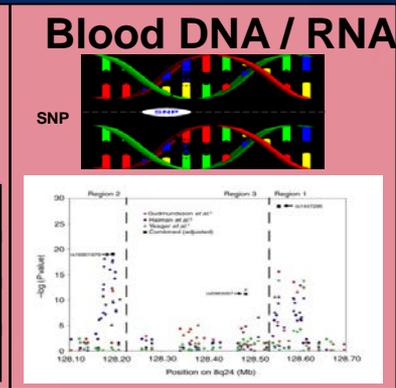
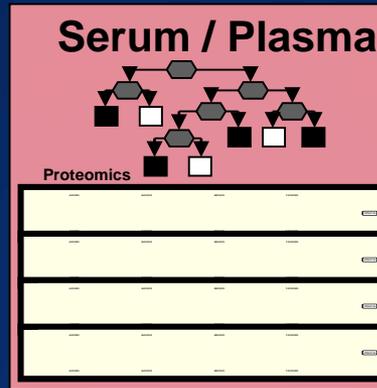
CPDR Biospecimen Banks : Multidisciplinary Collaborations



Clinical
information



Database



Long term biospecimen banks
(7,000+ patients; 200,000+ aliquots)
120+ publications
16+ grant awards
15+ patent applications





Prostate Cancer Progression

Tumor Biology, Biomarker and Treatment

Normal prostate

SNPs

Germ line

Pre-invasive stage (HGPIIN)
GSTP1+ERG+?

Localized CaP
GSTP1+ERG+NKX3.1+
C-MYC+PTEN+?

Metastatic CaP
Castration sensitive
GSTP1+NKX3.1+ERG+
C-MYC+PTEN+?

CaP-Genes: therapeutic targets

AR, ERG, C-MYC, GSTP1, NKX3.1, PTEN, p53

Metastatic CaP
Castration resistant
GSTP1+NKX3.1+ERG+C-MYC
+PTEN+AR+p53+BCL2+?

Develop new strategies for targeted therapy in CaP by treating early and effectively

ERG is a promising therapy target

Clonal selection and progression of CaP

Prevention

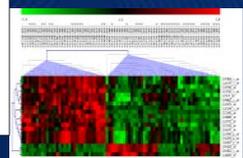
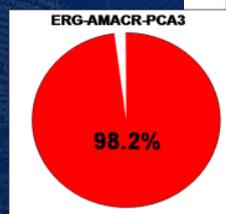
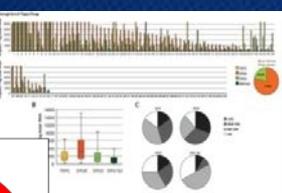
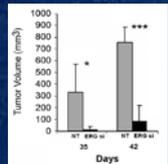
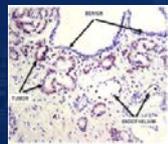
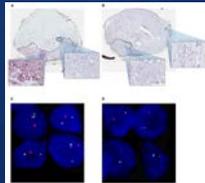
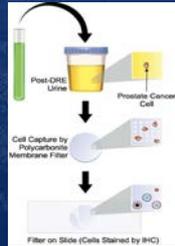
Surgery, Radiation
Active surveillance

Androgen axis
inhibitors

Chemotherapy
and vaccines



ERG Discovery, Biology and Translation

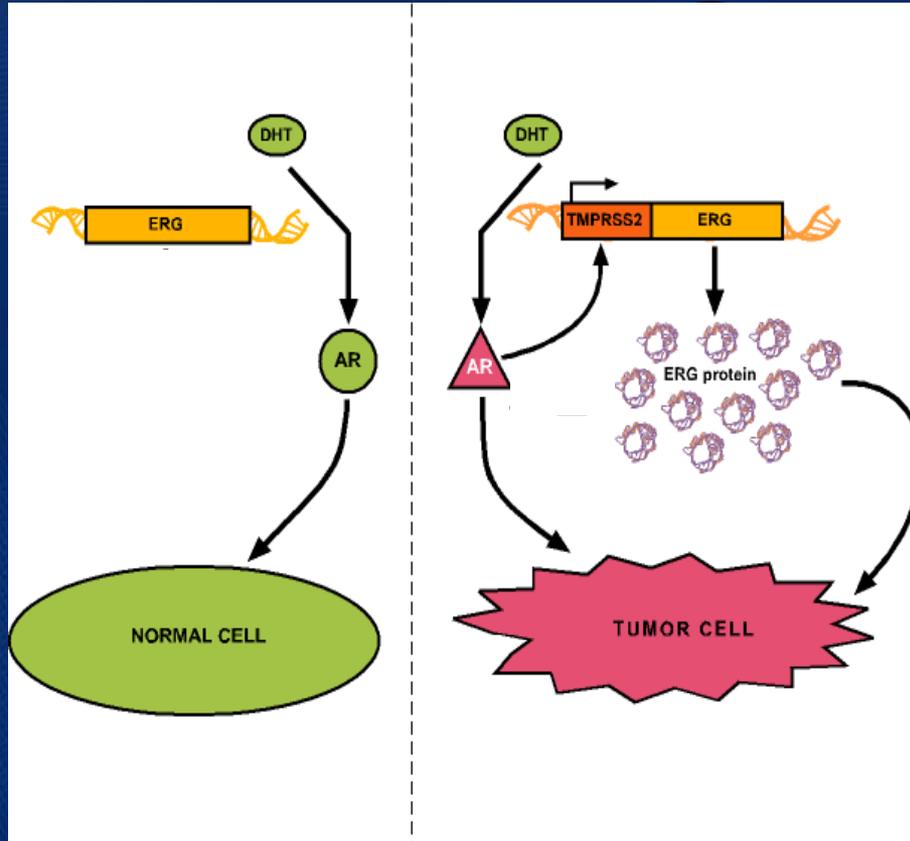


- 2014 — Evaluations of AA and CA prostate cancer genomes towards personalized medicine (patent application); Collaborations for **ERG** targeted therapy
- 2013 — Definitive studies establishing ethnic differences of **ERG** in prostate cancer (Rosen et al., Urology; Farrell et al., IJMS; DoD-PCR grant)
- 2012 — Detection of prostate tumor cells in urine (Patent application; 20+ **ERG** MAb collaborations; AUA awards; Rosen et al., Nature Rev Urol)
- 2011 — Cell specific signatures in prostate cancer: NIH RO1; NCI-Early Detection Research Network -Biomarker Reference Laboratory
- 2010 — First evaluations of **ERG** oncoprotein in **ARFI** prognostic panel: DoD-PCR grant; **ERG** Antibody Licensing: Biocare
- 2009 — Development of the first clinically useful **ERG** monoclonal antibody (Furusato et al., PCPD; patent application)
- 2008 — **ERG** as a novel prostate cancer therapeutic target (Sun et al., Oncogene; patent application)
- 2007 — Studies of **ERG** structure, expression & function (Prostate Cancer Foundation Award; Hu et al., Clin Cancer Res)
- 2006 — **ERG** splice forms and prognostic potential (DoD-PCR grant; patent application)
- 2005 — **ERG** discovery (Petrovics et al., Oncogene; Licensing: GenProbe)
- 2004 — Cell specific signatures of prostate cancer (NIH RO1 grant) **ERG/PCA3/AMACR** Panel (patent application)



AR Regulated ERG Oncogenic Activation is a High Frequency Causal Alteration in Prostate Cancer

Biologic function of *ERG* in early stages of prostate cancer



Diagnosis
Biological classification

ERG as therapeutic target

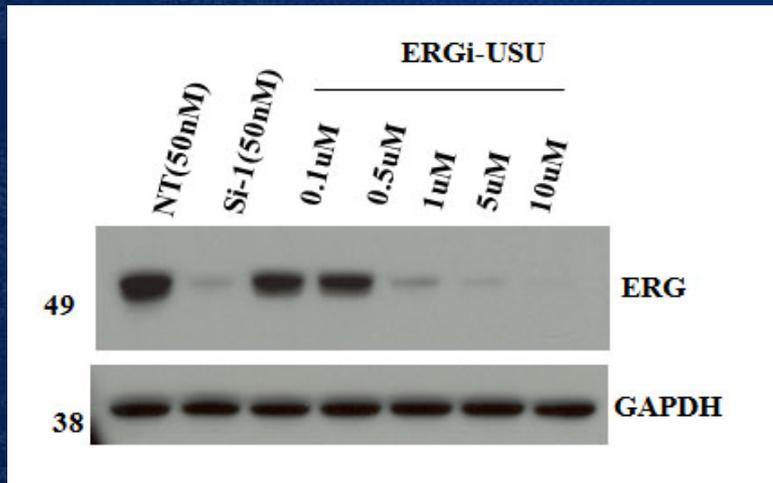
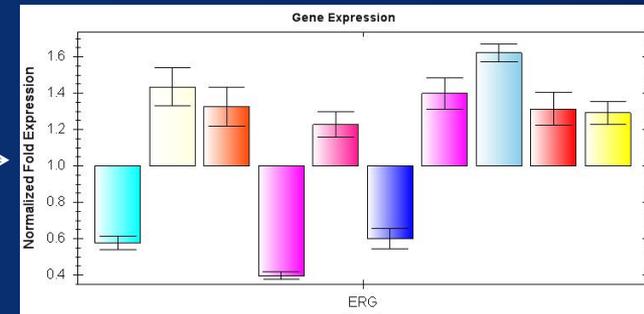
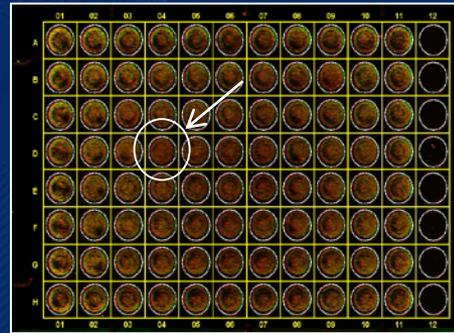
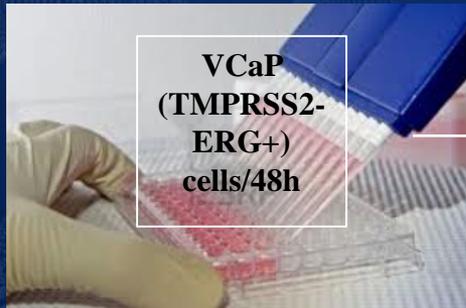
ERG MAb based screening and identification of small molecule inhibitors of the ERG oncoprotein expression

NCI-DTP Small
Molecule Library
Screening

Primary Screen by In-
cell western analysis
using ERGMab and
dual DNA stain

Secondary Screen by In-
cell western analysis
using ERGMab and
tetrazolium dye WST-8

Qualification of
candidate ERG
molecules using qPCR



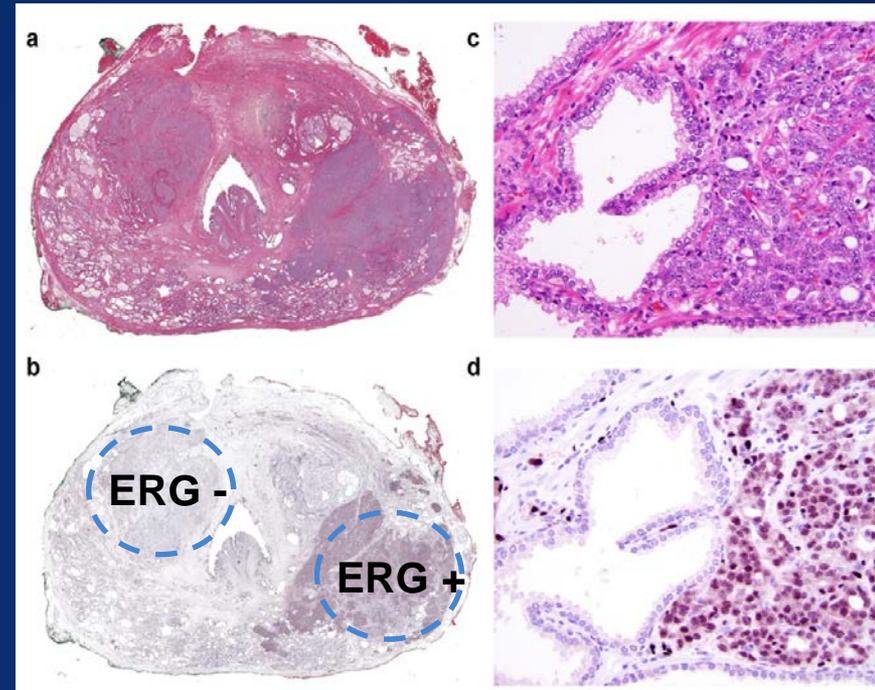
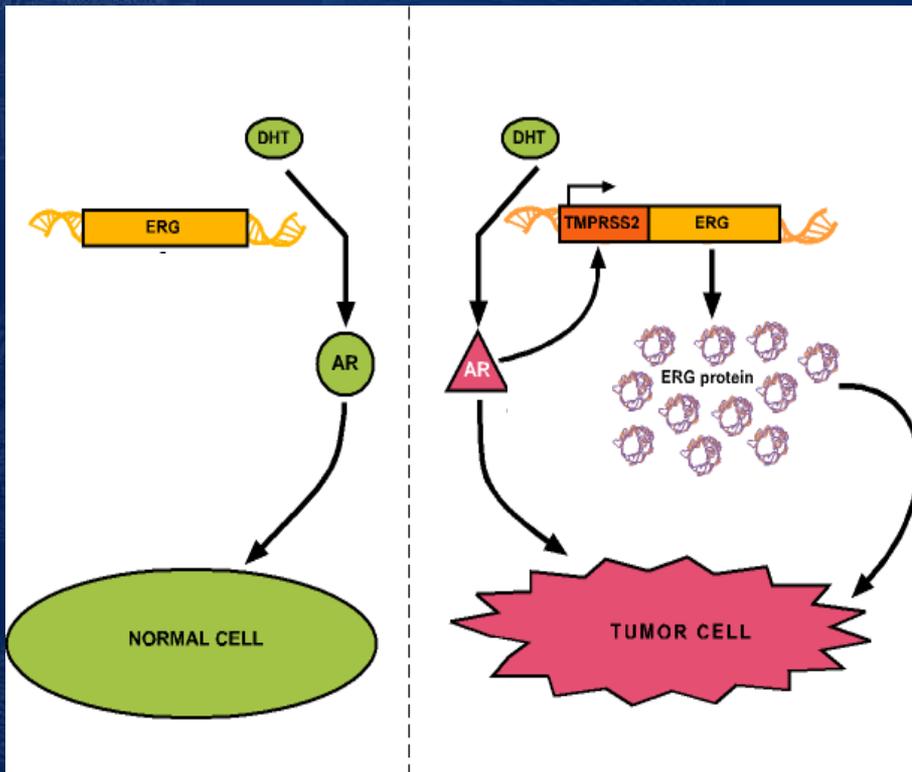
Validation of Lead
Compounds by Western
Blot

ERG I-1
ERG I-2
ERGi-USU

Evaluation of ERG Oncoprotein in the Multi-focal Context of Prostate Cancer

TMPRSS2-ERG (ERG) is a causal gene alteration in CaP with biomarker potential in diagnosis, prognosis and in targeted therapy

ERG-MAb distinguishes tumor foci from benign glands with **99.9%** specificity (**N=1,200+**)



Rosen et al., Nat Rev Urol, 2012

Highly specific ERG MAbs have streamlined the rapid evaluation of ERG alterations in clinical specimens
Dr. Isabell A. Sesterhenn



Ethnic Differences of ERG in Prostate Cancer





Comprehensive analyses of ERG in a CPDR cohort (N=909)

- Significant differences of ERG between CA and AA patients
- Prevalence of ERG negative cancers in high grade tumors of AA patients
- Increased association of ERG in younger patients

ERG racial disparities

| Race | ERG- | ERG+ | P value |
|------|------------|------------|---------|
| AA | 300 (71.8) | 118 (28.2) | <.0001 |
| CA | 240 (48.9) | 251 (51.1) | |

Association of ERG with Gleason sum

| Gleason sum | Overall | | | AA | | | CA | | |
|-------------|------------|------------|--------|------------|-----------|--------|------------|------------|--------|
| | ERG- | ERG+ | P | ERG- | ERG+ | P | ERG- | ERG+ | P |
| 6 or less | 253 (55.8) | 200 (44.2) | 0.1234 | 135 (66.2) | 69 (33.8) | 0.0319 | 118 (47.4) | 131 (52.6) | 0.7459 |
| 7 | 199 (62.6) | 119 (37.4) | | 114 (75.0) | 38 (25.0) | | 85 (51.2) | 81 (48.8) | |
| 8 to 10 | 66 (62.9) | 39 (37.1) | | 36 (83.7) | 7 (16.3) | | 30 (48.4) | 32 (51.6) | |

Association of ERG with age

| Age at RP | Overall | | | AA | | | CA | | |
|-----------|------------|-----------|--------|-----------|-----------|--------|-----------|-----------|--------|
| | ERG- | ERG+ | P | ERG- | ERG+ | P | ERG- | ERG+ | P |
| <50 | 85 (47.8) | 93 (52.2) | <.0001 | 48 (55.8) | 38 (44.2) | 0.0017 | 37 (40.2) | 55 (59.8) | 0.0209 |
| 50-54.99 | 88 (48.9) | 92 (51.1) | | 44 (66.7) | 22 (33.3) | | 44 (38.6) | 70 (61.4) | |
| 55-59.99 | 120 (68.6) | 55 (31.4) | | 76 (82.6) | 16 (17.4) | | 44 (53.0) | 39 (47.0) | |
| 60-64.99 | 126 (64.3) | 70 (35.7) | | 60 (72.3) | 23 (27.7) | | 66 (58.4) | 47 (41.6) | |
| 65-69.99 | 79 (69.3) | 35 (30.7) | | 52 (78.9) | 14 (21.2) | | 27 (56.2) | 21 (43.8) | |
| ≥70 | 31 (60.8) | 20 (39.2) | | 16 (80.0) | 4 (20.0) | | 15 (48.4) | 16 (51.6) | |

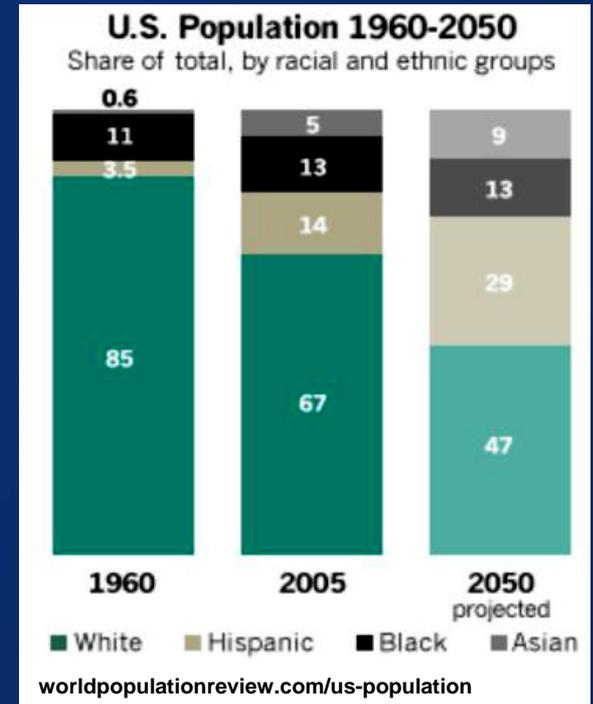
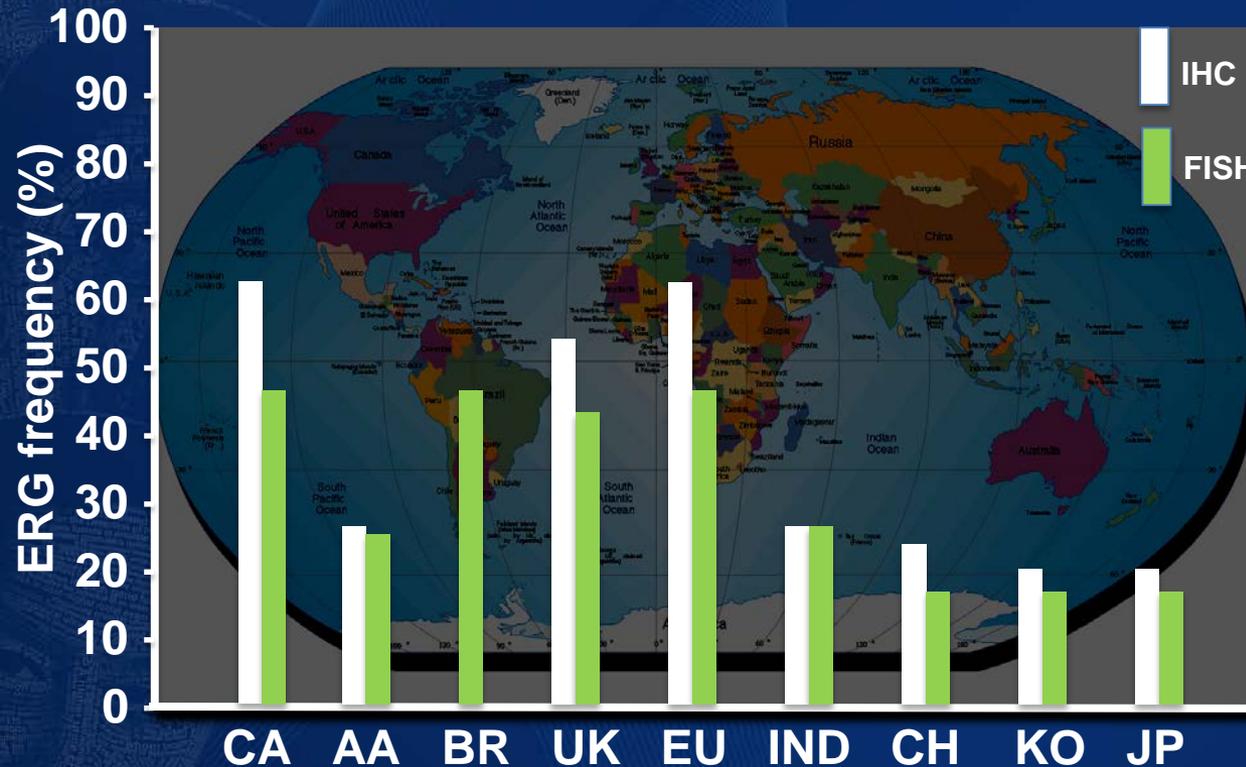


Potential Impact of Ethnic Differences in Biomarker Development

Focused evaluation of biomarkers representative of ethnic groups will enhance personalized medicine and targeted therapy

Ethnic difference of ERG frequencies in prostate cancer

Projected shift in the ethnic distribution of the US population





Collaboration Highlights

- **NCI-Walter Reed prostate cancer research initiatives**
- **CPDR as a biomarker reference laboratory of the NCI-Early Detection Research Network : USU-NCI Inter-Agency Agreement**
- **Validation studies of Oncotype DX-Prostate Cancer Assays- Genomic Health Inc**
- **Genomic mechanisms of ethnic differences of prostate cancer- Genomatix and Harvard Medical School**
- **Prostate cancer prognostic markers and therapy targets-Berg Pharma**





Thanks!

Patients and their families

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collaborating partners**

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CPDR team and collaborators

