PRINCIPLES FOR THE INTRODUCTION OF POPULATION SCREENING IN PROSTATE CANCER

IN THE NAME OF GOD

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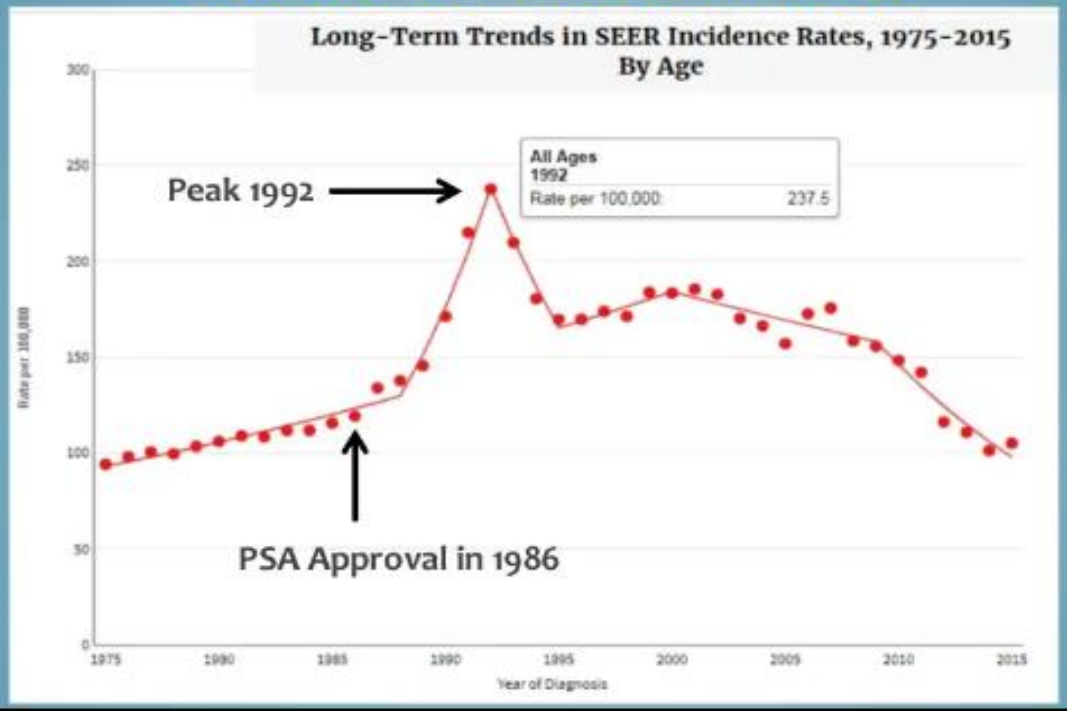
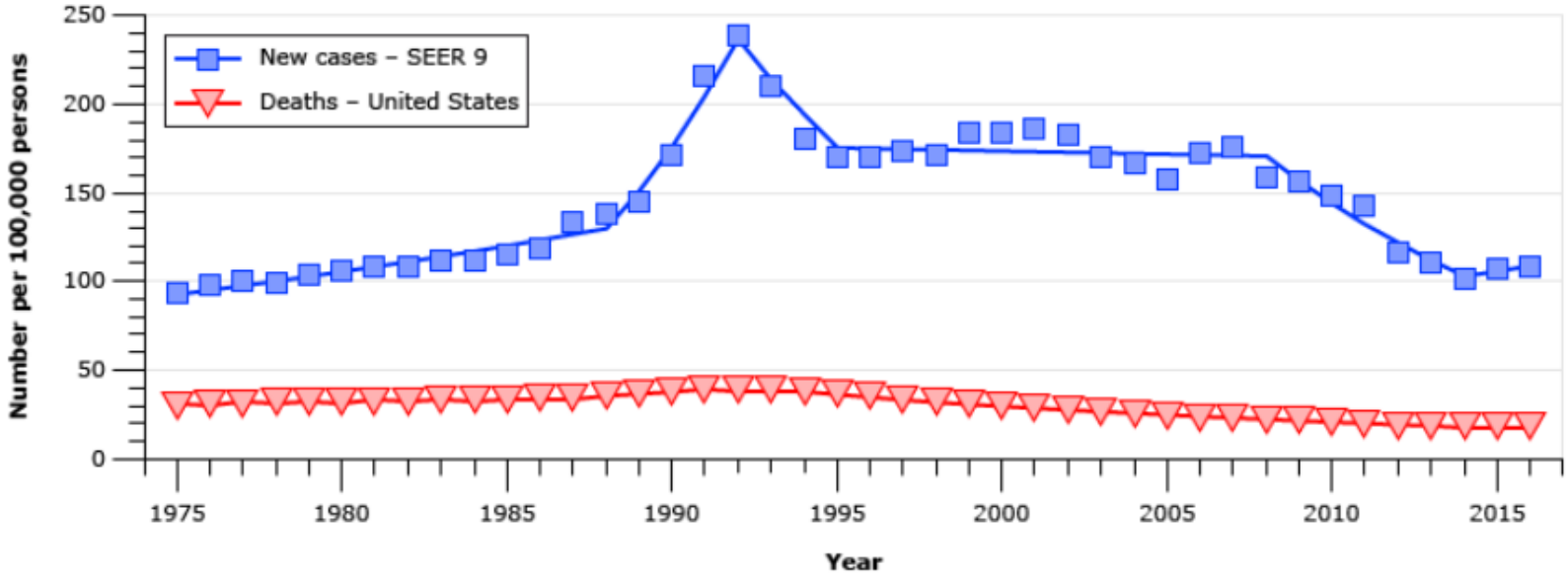
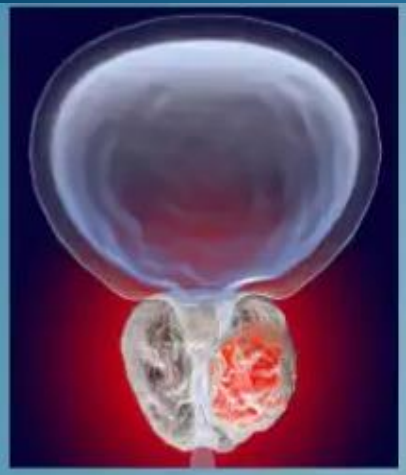
Prostate Cancer Incidence in the US.



Changes over time in average annual age-adjusted incidence and mortality rates in the United States, 1975 to 2016





Prostate Cancer Screening…. Why so controversial?

1. Prostate Cancer is very common but in most cases does not affect survival
2. Screening with PSA greatly increased the number of cases being diagnosed with very little survival benefit
3. Treatment options have significant side effects and expense

Changing Guidelines from the US Preventive Task Force

Table 1. Recommendations on Prostate-Specific Antigen (PSA)–Based Screening for Prostate Cancer.

Organization	Recommendation	Year
U.S. Preventive Services Task Force[1]	Recommend against routine screening at any age	2012
Canadian Task Force on Preventive Health Care[2]	Recommend against screening at any age	2014
American College of Preventive Medicine[3]	Recommend against screening at any age	2016
American Academy of Family Physicians[4]	Recommend against screening at any age	2012
American Urological Association[5]	Implement shared decision making for men 55 to 69 yr of age and proceed on the basis of men's values and preferences; recommend against screening for other ages	2013
American College of Physicians[6]	Discuss benefits and harms for men 50 to 69 yr of age and order screening only if clear preference is expressed for screening; recommend against screening for other ages	2015
National Comprehensive Cancer Network[7]	Offer screening after a discussion of risks and benefits for men 45 to 75 yr of age; screening for men older than 75 yr should be done cautiously and only in very healthy men	2016

Big change in 2012 and change again in 2018

BENEFITS AND HARMS OF SCREENING

MORTALITY
INCIDENCE
DISTANT STAGE REDUCTION

VS

Overdiagnosis of prostate cancer
False-positive PSA
Anxiety
Risks of prostate cancer therapy
Risks of prostate biopsy

BENEFITS AND HARMS OF SCREENING

- **Effect on incidence**

In a meta-analysis of four randomized trials including 675,232 participants, cancer was diagnosed more often in men who were screened

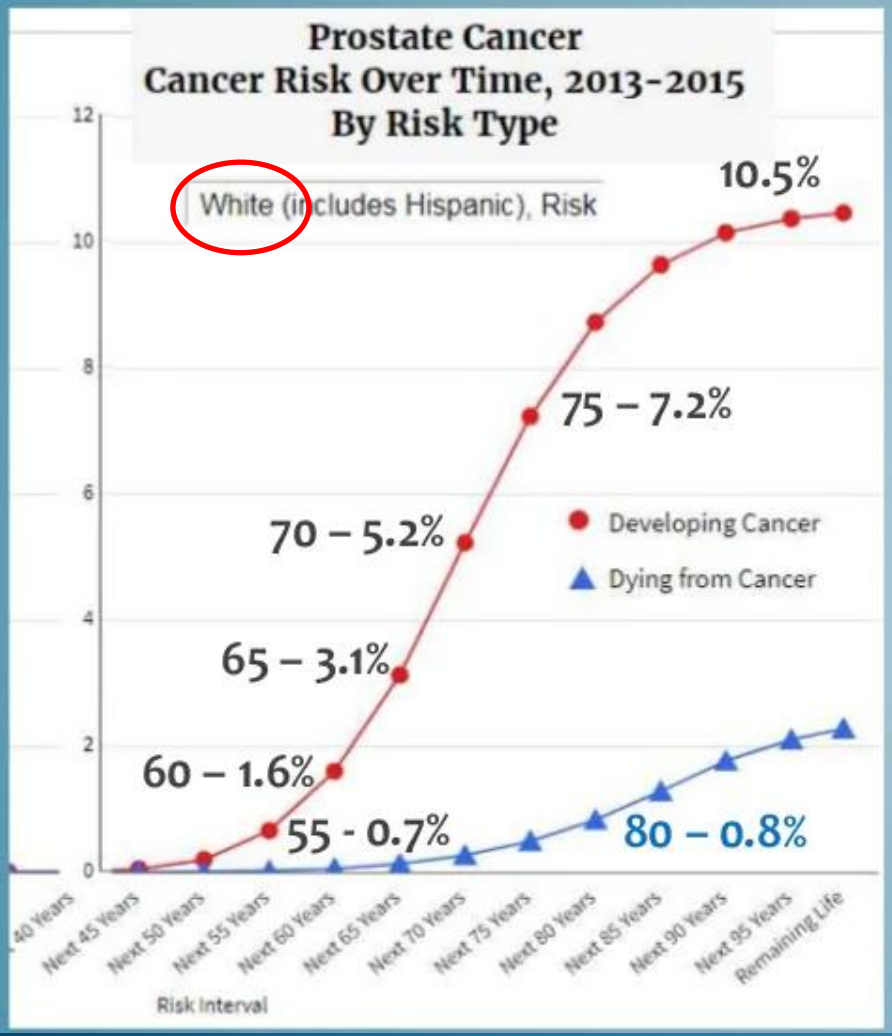
The incidence rate ratio was higher for screen-detected localized prostate cancers

ERSPC: Screening may reduce the risk for distant-stage prostate cancer
The absolute risk reduction of metastatic disease was 3.1 per 1000 men randomized

- **Effect on mortality**

EFFECT OF MORTALITY

- European Randomized Study of Screening for Prostate Cancer (ERSPC)
  found a small absolute survival benefit with PSA screening; at 13 years
- The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening TriaL:
  did not report a mortality benefit. ⊗
- GUTEBORS STUDY (sweden)



SEER*Explorer

Updated April 16, 2018 (Revision History)

Lifetime Risk of Developing Prostate Cancer 10.5%

Lifetime Risk of Dying from Prostate Cancer 2.3%

seer.cancer.gov/explorer

NIH NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

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U.S. Preventive Services
TASK FORCE

2018

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Prostate Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE In the United States, the lifetime risk of being diagnosed with prostate cancer is approximately 11%, and the lifetime risk of dying of prostate cancer is 2.5%. The median age of death from prostate cancer is 80 years. Many men with prostate cancer never experience symptoms and, without screening, would never know they have the disease. African American men and men with a family history of prostate cancer have an increased risk of prostate cancer compared with other men.

OBJECTIVE To update the 2012 US Preventive Services Task Force (USPSTF) recommendation on prostate-specific antigen (PSA)–based screening for prostate cancer.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the benefits and harms of PSA-based screening for prostate cancer and subsequent treatment of screen-detected prostate cancer. The USPSTF also commissioned a review of existing decision analysis models and the overdiagnosis rate of PSA-based screening. The reviews also examined the benefits and harms of PSA-based screening in patient subpopulations at higher risk of prostate cancer, including older men, African American men, and men with a family history of prostate cancer.

FINDINGS Adequate evidence from randomized clinical trials shows that PSA-based screening programs in men aged 55 to 69 years may prevent approximately 1.3 deaths from prostate cancer over approximately 13 years per 1000 men screened. Screening programs may also prevent approximately 3 cases of metastatic prostate cancer per 1000 men screened. Potential harms of screening include frequent false-positive results and psychological harms. Harms of prostate cancer treatment include erectile dysfunction, urinary incontinence, and bowel symptoms. About 1 in 5 men who undergo radical prostatectomy develop long-term urinary incontinence, and 2 in 3 men will experience long-term erectile dysfunction. Adequate evidence shows that the harms of screening in men older than 70 years are at least moderate and greater than in younger men because of increased risk of false-positive results, diagnostic harms from biopsies, and harms from treatment. The USPSTF concludes with moderate certainty that the net benefit of PSA-based screening for prostate cancer in men aged 55 to 69 years is small for some men. How each man weighs specific benefits and harms will determine whether the overall net benefit is small. The USPSTF concludes with moderate certainty that the potential benefits of PSA-based screening for prostate cancer in men 70 years and older do not outweigh the expected harms.

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Author Audio Interview
Animated Summary Video
Related article page 1914 and JAMA Patient Page page 1946
CME Quiz at jamanetwork.com/learning
Related articles at jamaoncology.com jamasurgery.com jamainternalmedicine.com

Table. Estimated Effects After 13 Years of Inviting Men Aged 55 to 69 Years in the United States to PSA-Based Screening for Prostate Cancer[a]

Effect	No. of Men
Men invited to screening	1000
Men who received at least 1 positive PSA test result	240
Men who have undergone 1 or more transrectal prostate biopsies	220[b]
Men hospitalized for a biopsy complication	2
Men diagnosed with prostate cancer	100
Men who initially received active treatment with radical prostatectomy or radiation therapy	65
Men who initially received active surveillance	30
Men who initially received active surveillance who went on to receive active treatment with radical prostatectomy or radiation therapy	15
Men with sexual dysfunction who received initial or deferred treatment	50
Men with urinary incontinence who received initial or deferred treatment	15
Men who avoided metastatic prostate cancer	3
Men who died of causes other than prostate cancer	200
Men who died of prostate cancer despite screening, diagnosis, and treatment	5
Men who avoided dying of prostate cancer	1.3

US Preventive Services Task Force Recommendation Statement
May 8, 2018
Screening for Prostate CancerUS Preventive Services Task Force Recommendation Statement

JAMA. 2018;319(18):1901-1913

Is Prostate Cancer Screening Right for You?

Understanding the Potential Benefits vs. Risks for Men 55–69

The prostate-specific antigen (PSA) screening test is the most common method clinicians use to screen for prostate cancer. The PSA test measures the amount of PSA, a type of protein, in the blood. When a man has an elevated PSA level, it may be caused by prostate cancer, but it could also be caused by other conditions too. Studies show that PSA-based screening in men 55–69 comes with potential benefits and harms over a period of 10–15 years.

The U.S. Preventive Services Task Force recommends that for men 55–69, the decision to receive PSA-based screening should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening and to incorporate their values into the decision. (C grade)

Of 1,000
Men Offered PSA-Based Screening

240
Get a Positive Result
which may indicate prostate cancer

Many of these men will learn they have a **false-positive result** after getting a biopsy.

Potential side effects of biopsy:
- Pain
- Bleeding
- Infection

Of those,
100
Get a Positive Biopsy
showing definite cancer

20%–50%
of these men will be diagnosed with cancer that never grows, spreads, or harms them, also known as overdiagnosis.

80*
Choose Surgery or Radiation Treatment

Treatment could be immediate or after a period of active surveillance.*

Erectile dysfunction **50**
Urinary incontinence **15**
Number of men who will experience negative outcomes**

3** **Avoid Cancer Spreading to Other Organs**
1** **Avoids Death From Prostate Cancer*****
5** **Die From Prostate Cancer Even After Surgery or Treatment**

Recommendation Summary

Population	Recommendation	Grade
Men aged 55 to 69 years	For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.	C
Men 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.	D

Clinician Summary

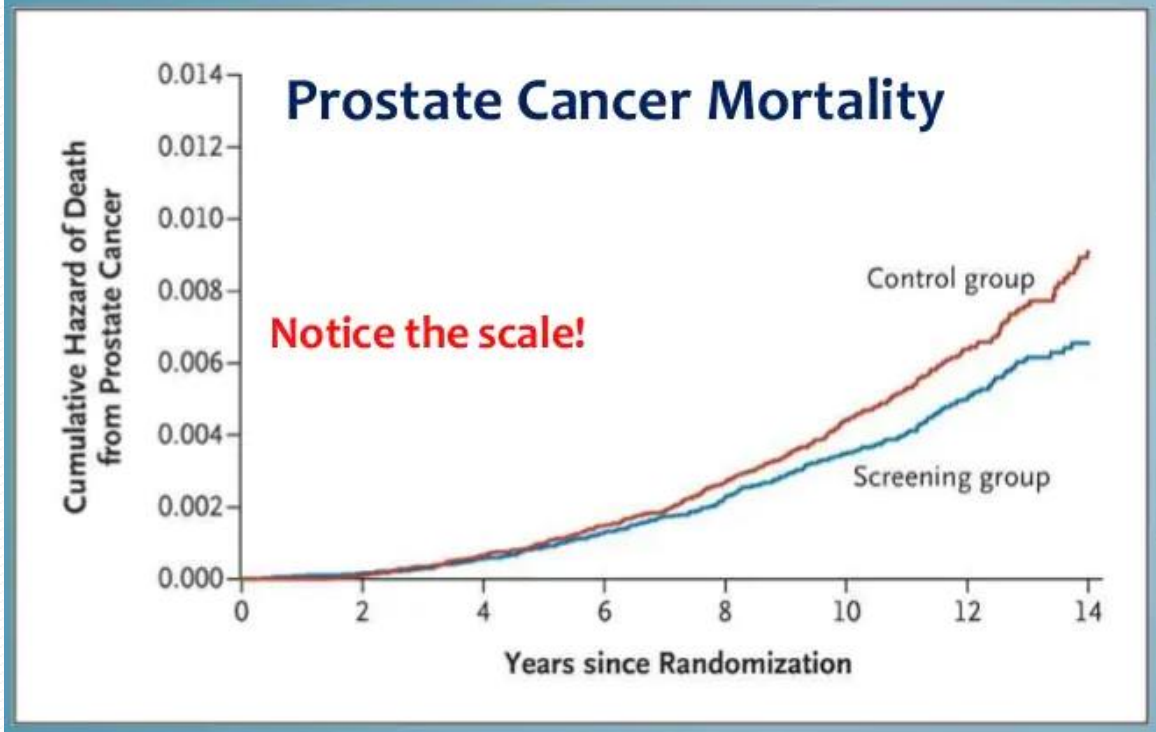
Expand All

Population	Men aged 55 to 69 y	Men 70 y and older
Recommendation	The decision to be screened for prostate cancer should be an individual one.	Do not screen for prostate cancer. Grade: D

U.S. Preventive Services TASK FORCE

Age 55 – 69:	Discuss it
70 or older:	Don’t

Prostate-Cancer Mortality at 11 Years of Follow-up . Schroder NEJM 2012:366, 981. European Randomized Study of Screening for Prostate Cancer (ERSPC)



Relative reduction in prostate cancer mortality was 29% but absolute reduction was 1.07 deaths per 1000 men screened.

To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected. There was no significant between-group difference in all-cause mortality.

Evidence Synthesis
Number 154

Prostate-Specific Antigen–Based Screening for Prostate Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

- Screening may reduce the risk of prostate cancer mortality, but is associated with harms including false-positive biopsy results, biopsy complications, overdiagnosis in 20 – 50%
- Early, active treatment may reduce the risk of metastatic disease, although the long-term impact of early active treatment on prostate cancer mortality remains unclear
- Active treatment is associated with sexual and urinary difficulties.

AHRQ Publication No. 17-05229-EF-1
May 2018

http://myprostatecancerrisk.com

Characteristics

Race

African American

Age

70

PSA [ng/ml]

6

Family History of Prostate Cancer

Yes

Digital rectal examination

Normal

Prior biopsy

Never had a prior biopsy

Risk of prostate cancer if biopsy were to be performed

Based on the provided risk factors a prostate biopsy performed would have a:

27% chance of high-grade prostate cancer,

23% chance of low-grade cancer,

51% chance that the biopsy is negative for cancer.

About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

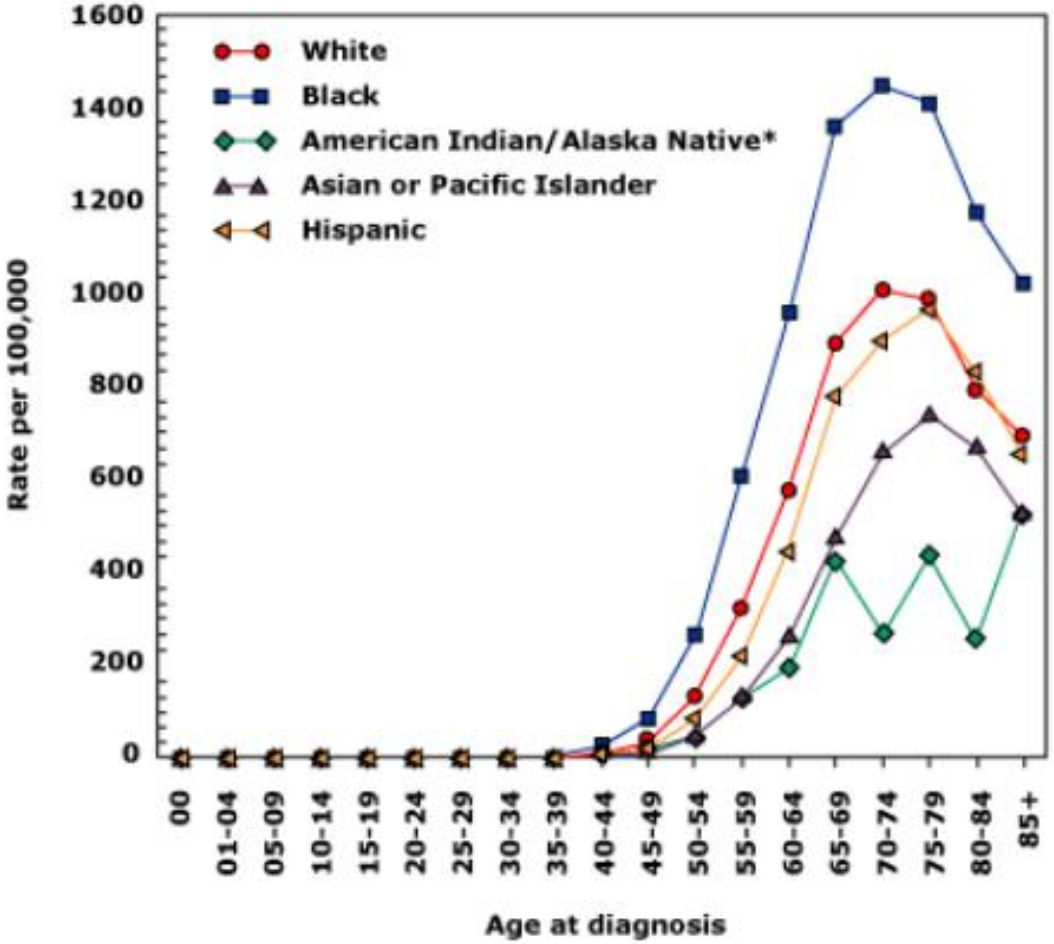
Please consult your physician concerning these results.

Click here to watch a video overview of these results.

High grade cancer has doubled by race, from 12% to 27%

Risk-adjusted approach:

We use Race, Age, and Family history to identify whether a man is at higher or average risk for prostate cancer


White
Black
American Indian/Alaska Native*
Asian or Pacific Islander
Hispanic
Rate per 100,000
1600
1400
1200
1000
800
600
400
200
0
00
01-04
05-09
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Age at diagnosis

Risk-adjusted approach:

Average-risk men:.(ERSPC)

- suggest initiating discussion of screening for prostate cancer at age 50 years for average-risk men as long as life expectancy is at least 10 years.
- some variability in the age at which expert guidelines recommend initiating discussion about screening for prostate cancer, mostly at age 50 or 55 years

higher-risk men:(should be informed potential benefits and risks of early screening are uncertain)

- screening at age 40 to 45 years with other men at higher risk for prostate cancer, including:

-Black men

-Men with a family history of prostate cancer, particularly in a first-degree relative who was diagnosed at age <65 years

Risk-adjusted approach:

BRCA carriers:

Men known or likely to carry *BRCA1 or BRCA2* genetic mutations are at increased risk. Discussing screening for prostate cancer may begin as early as age 40 years

Risk-adjusted approach:

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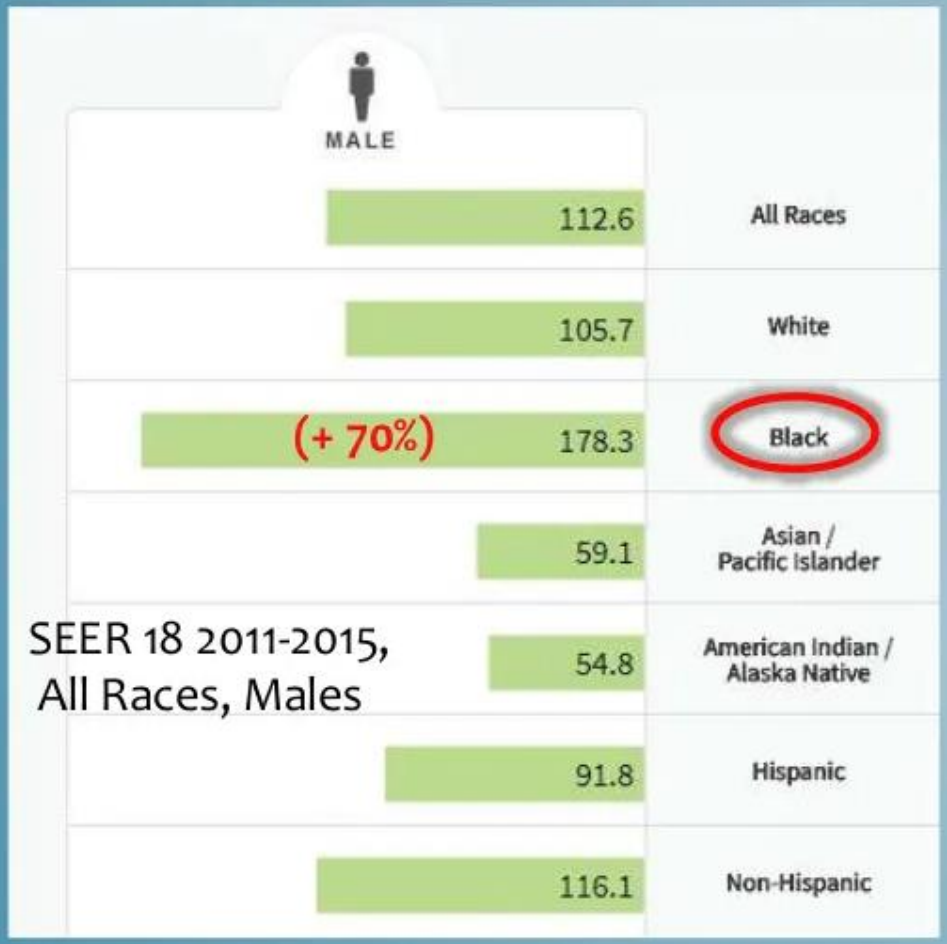
New Cases (per 100.000) by Race



SEER 18 2011-2015,
All Races, Males

Deaths (per 100,000) by Race

American Cancer Society®

Testing for
Prostate Cancer

American Cancer Society Recommendations for Prostate Cancer Early Detection

The American Cancer Society (ACS) recommends that men have a chance to make an informed decision with their health care provider about whether to be screened for prostate cancer. The decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. **Men should not be screened unless they have received this information.** The discussion about screening should take place at:

- **Age 50 for men who are at average risk** of prostate cancer and are expected to live at least 10 more years.
- **Age 45 for men at high risk** of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father or brother) diagnosed with prostate cancer at an early age (younger than age 65).
- **Age 40 for men at even higher risk** (those with more than one first-degree relative who had prostate cancer at an early age).

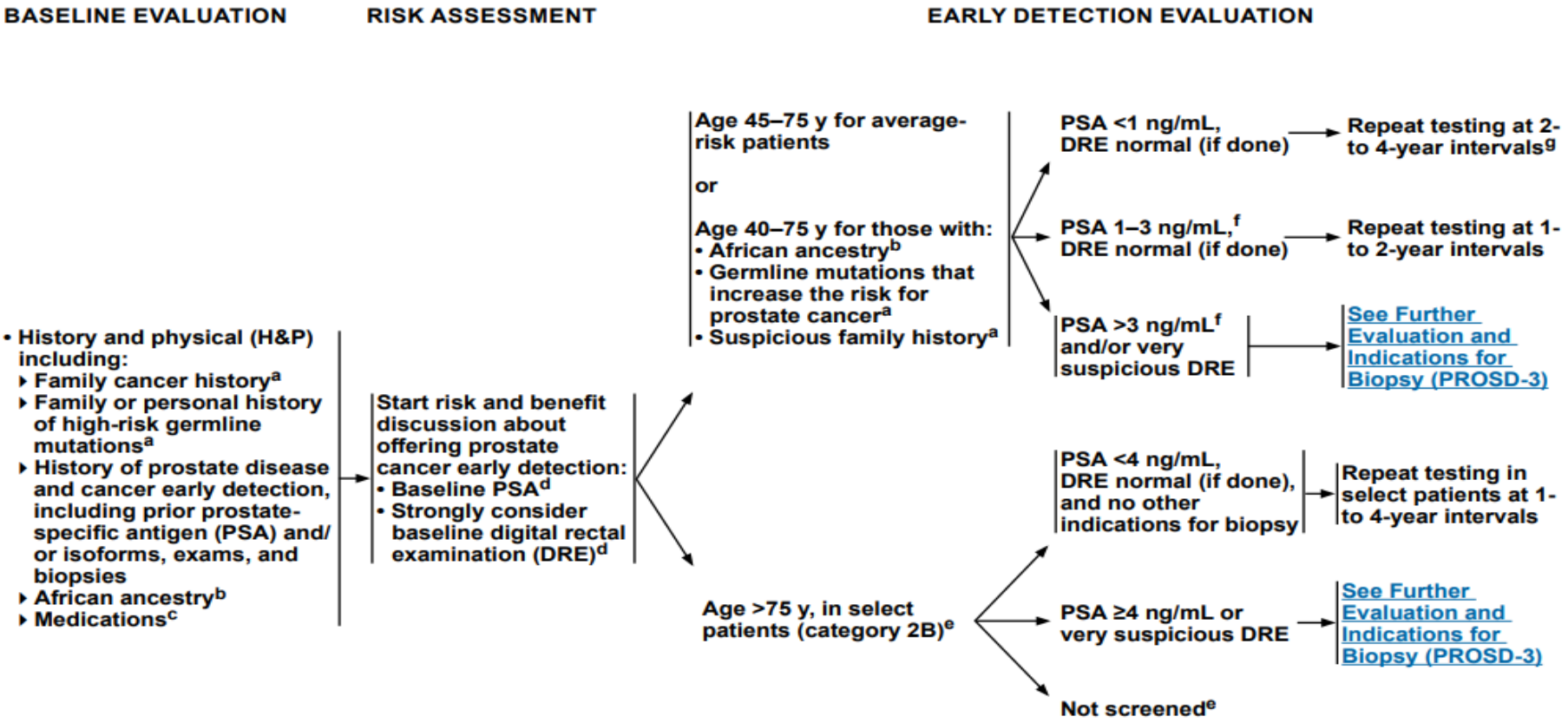
After this discussion, men who want to be screened should get the prostate-specific antigen (PSA) blood test. The digital rectal exam (DRE) may also be done as a part of screening. (See Screening Tests for Prostate Cancer.)

If, after this discussion, a man is unable to decide if testing is right for him, the screening decision can be made by the health care provider, who should take into account the man's general health preferences and values.

If no prostate cancer is found as a result of screening, the time between future screenings depends on the results of the PSA blood test:

- Men who choose to be tested who have a PSA of less than 2.5 ng/mL may only need to be retested every 2 years.
- Screening should be done yearly for men whose PSA level is 2.5 ng/mL or higher.

NCCN Guidelines Version 2.2021
Prostate Cancer Early Detection



See footnotes on PROSD-2A.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

APPROACH TO SCREENING

Shared decision-making

Although the randomized trials of screening all have important methodological limitations, the best available evidence suggests that screening confers a small absolute benefit for reducing prostate cancer mortality and the risk of developing metastatic disease. However, the potential harms from screening that arise from false-positive tests (eg, prostate biopsy, anxiety, overdiagnosis, and treatment complications) are common.

For average-risk men, many clinicians do not specifically advise in favor of or against screening. Men who are candidates for screening should be engaged in shared decision-making about whether they choose to be screened. Individual patient preferences for specific health outcomes are a deciding factor in determining whether to screen for prostate cancer. Decision aids may help patients receive consistent, complete, objective information.

Men who are being screened for prostate cancer should have a life expectancy of at least 10 years.

BENEFITS AND HARMS OF SCREENING

MORTALITY
INCIDENCE
DISTANT STAGE REDUCTION

VS

Overdiagnosis of prostate cancer
False-positive PSA
Anxiety
Risks of prostate cancer therapy
Risks of prostate biopsy

Characteristics

Race

African American

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PSA [ng/ml]

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Take home message:

- The best available evidence from randomized trials found that screening has at most a **small** benefit in reducing prostate cancer mortality and the risk of developing metastatic disease.

- The potential **benefits** of screening must be balanced against the potential **harms** to quality of life, including the risks of false-positive tests, prostate biopsy, anxiety, overdiagnosis, and treatment complications.

- Without screening, many cases of prostate cancer do not ever become clinically evident.

- At autopsy of men who died of other causes, prostate cancer detection rates (approximately 30 percent for men in their fifties and up to 70 percent for men in their seventies), are higher than the lifetime incidence of diagnosed prostate cancer in the population

Take home message:

- We do not perform digital rectal examination (DRE) as part of screening However, if a DRE is performed, men with a nodule, induration, or asymmetry on prostate examination should be referred to a urologist, regardless of the PSA level.

Take home message:

- For a man being screened for prostate cancer who is taking a 5-alpha reductase inhibitor (ARI) for benign prostatic hyperplasia (BPH), the PSA result needs to be corrected prior to interpretation. Additionally, a man taking *finasteride* or *dutasteride* for BPH with a confirmed PSA level rise >0.5 ng/mL (over any time frame) should be considered for urology referral.
- Men with a PSA level above 7 ng/mL should be referred, without further testing, to a urologist for evaluation.
- For men with a PSA level between 4 and 7 ng/mL, we repeat the PSA testing in six to eight weeks. Factors known to transiently increase PSA should be addressed prior to repeating the PSA test. Men with a repeat PSA level >4 ng/mL should be referred to a urologist for evaluation.

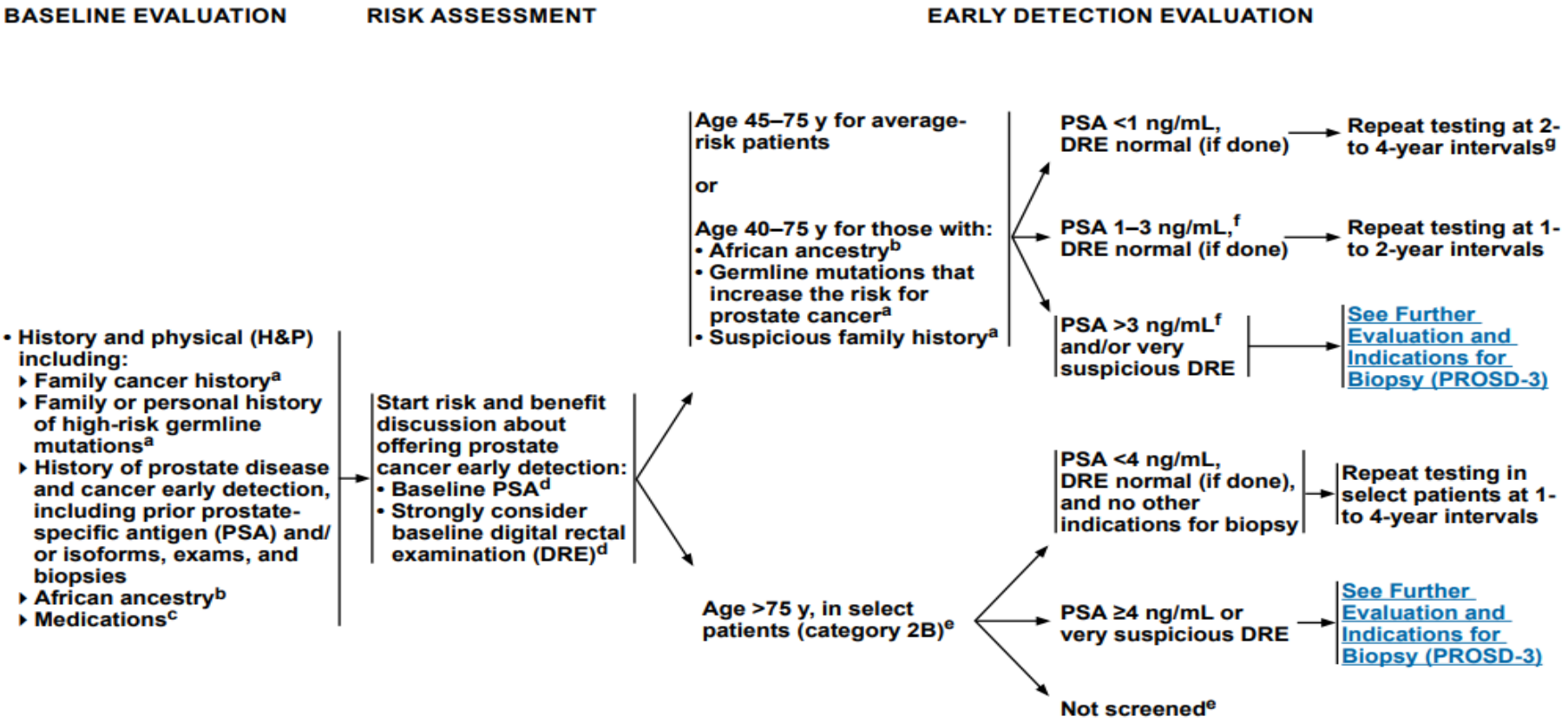
Take home message:

- lowering the PSA cutoff worsens specificity and overdiagnosis. A PSA cutoff of 3.0 ng/mL has a specificity of about 85 percent for detection of any prostate cancer It has been projected that if the PSA cutoff was lowered to 2.5 ng/mL, the number of men whose PSA is defined as abnormal would double.
- Additionally, many of the cancers that would be detected at these lower PSA levels may never have become clinically evident, so detecting them by using a lower PSA .cutoff would lead to overdiagnosis and overtreatment

SCREENING:

- There should be a suitable test or examination.
- Has a high level of accuracy (High sensitivity, specifity, PPV)
- Disease with High incidence
- The screening test must be acceptable to the population and cause minimal discomfort.
- Screening should lower specific morbidity and increase survival.
- cost of screening (including diagnosis and treatment of patients diagnosed) should be economically balanced.

NCCN Guidelines Version 2.2021
Prostate Cancer Early Detection



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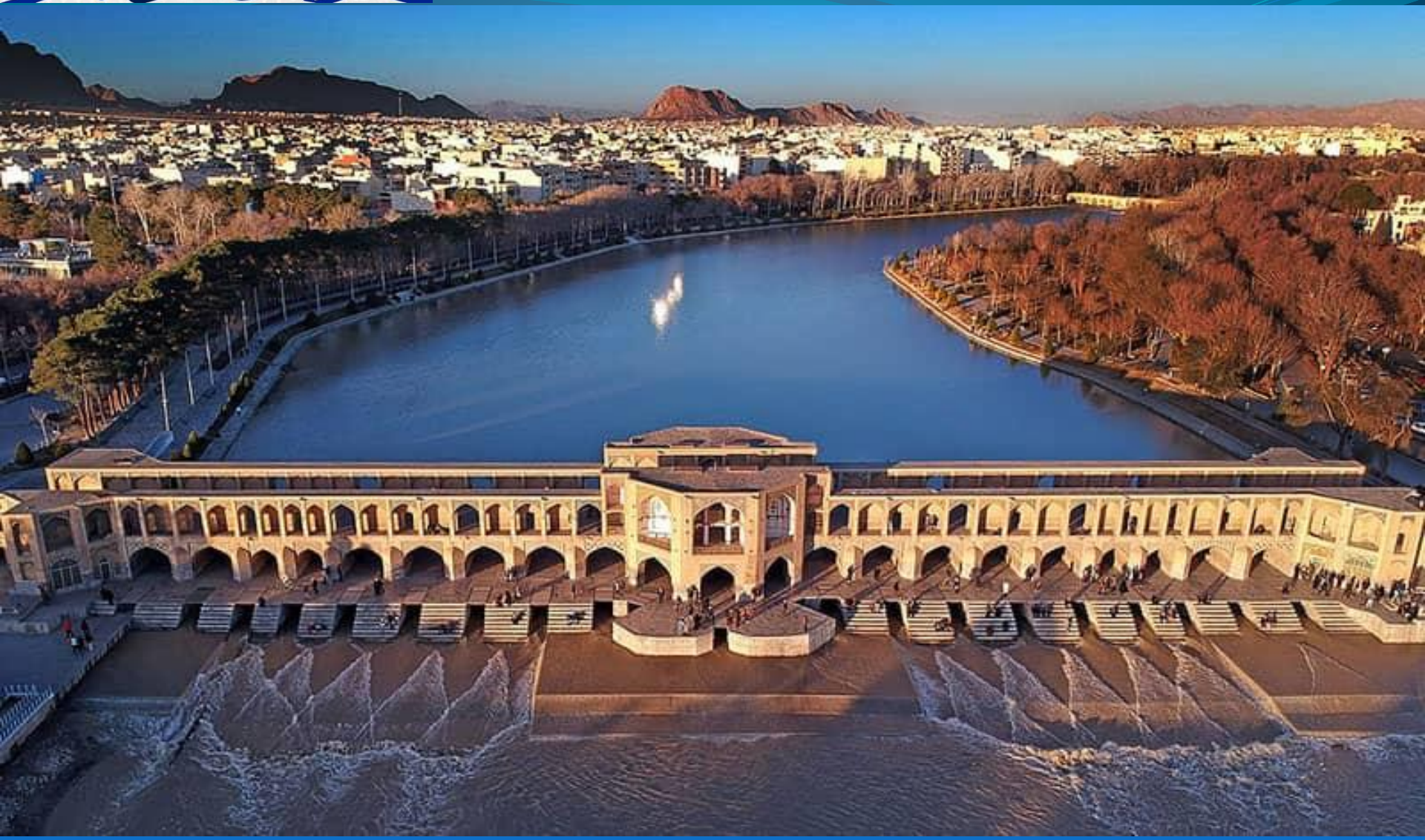
Where do we go from here…..

- Utilizing psa better
- New biomarkers aid selection for biopsy
- Prostate MRI fusion biopsy
- New Genomic testing



The changes need to be changed