PSA SCREENING AND DIAGNOSIS

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DISCLOSURE SLIDE

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Research grant: Astellas, Takeda, Sanofi
In 1838, Juntendo started with the founding of first private medical school in Japan
Now, Juntendo is the largest university hospital groups in Japan.
Introduction

• The prostate-specific antigen (PSA) test was shown early during the 1990s to enable diagnosis of the disease at an early stage.

• As screening using PSA prevailed, apparent morbidity rate of prostate cancer increased. However, the main weakness of screening is a high rate of over-diagnosis and over-treatment. The PSA test remains controversial.

• Demonstrating the advantages and problems of the PSA screening test and the current state of the recommended level in each country, we discuss how to further improve prostate cancer screening more effectively.
Prostate-specific antigen (PSA)

• **Prostate-specific antigen (PSA)** (γ-seminoprotein or kallikrein-3 (KLK3)), is a glycoprotein enzyme encoded in humans by the *KLK3* gene and is secreted by the epithelial cells of the prostate gland.

• PSA is produced for the ejaculate, where it liquefies semen in the seminal coagulum and allows sperm to swim freely.

• The blood level of PSA is often elevated in men with prostate cancer. However, number of benign conditions, such as prostatitis or benign prostatic hyperplasia (BPH), can cause a man’s PSA level to rise.

**Factors influencing the PSA value**
prostate cancer, BPH, inflammation, ejaculation, urinary retention, external stimulation(digital rectal exam.), 5α-reductase inhibitor, ketoconazole(antifungal drug), age, ...
**Additional factors related to PSA screening**

- **PSA thresholds** > 4 ng/mL, age- and race-specific PSA reference ranges
- **Age at onset screening** Age 50 has traditionally been for starting to consider
- **Frequency of screening** 1 yr, 2 yrs or 5 yrs, depending on age, PSA value, race...

- **PSA Density** PSA / prostate volume > 0.15, but insufficient sensitivity
- **PSA f/t ratio** free(unbound)/total PSA, < 20-25% cutoff (PSA 4-10)
- **PSA Velocity** > 0.35 ng/ml/yr (PSA < 4), > 0.75 ng/ml/yr (PSA 4-10)
- **PHI(Prostate Health Index)** combination of tPSA, fPSA, and proPSA (PSA 4-10)

- **Threshold for biopsy** > 3.0 or 4.0 ng/mL?
- **Age to stop screening** Expected life expectancy < 10 yrs, overdiagnosis

Other screening tools for prostate cancer: digital rectal exam.(DRE), transrectal US(TRUS), MRI,...
Screening for Prostate Cancer
With the Prostate-Specific Antigen Test
A Review of Current Evidence

- Recommended level is different depending on each country and academic society.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Who Should Be Screened</th>
<th>Screening Interval</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Services Task Force, 2012</td>
<td>Screening should not be offered</td>
<td>Consider 2-y interval over annual screening; may individualize intervals based on initial PSA</td>
<td>Systematic review</td>
</tr>
<tr>
<td>American Urological Association, 2013</td>
<td>Men aged 55-69 y or ≥70 y with &gt;10- to 15-y life expectancy: use shared decision-making approach</td>
<td>Men at higher risk &lt;55 y: individualize approach</td>
<td>Systematic review and meta-analysis of the literature, 1995-2013</td>
</tr>
<tr>
<td>American Society of Clinical Oncology, 2012</td>
<td>Men with life expectancy &gt;10 y: use shared decision-making approach</td>
<td></td>
<td>Updating of Agency for Healthcare Research and Quality literature review; PubMed search through 2012; expert opinion</td>
</tr>
<tr>
<td>American Cancer Society, updated 2010</td>
<td>Men aged ≥60 y at average risk with &gt;10-y life expectancy: use shared decision-making approach</td>
<td>Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y</td>
<td>Systematic review of the literature and consensus process</td>
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<td></td>
<td>Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y</td>
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<tr>
<td></td>
<td>Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y</td>
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<tr>
<td>American College of Physicians, 2013</td>
<td>Men aged 50-69 y with life expectancy &gt;10-15 y: use shared decision-making approach</td>
<td>Consider longer intervals than 1 y between screening PSAs</td>
<td>Review of available guidelines</td>
</tr>
<tr>
<td></td>
<td>Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y</td>
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<tr>
<td></td>
<td>Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y</td>
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<tr>
<td>Canadian Urologic Society, 2011</td>
<td>Men ≥50 y with a 10- y life expectancy: use shared decision-making approach</td>
<td>Consider intervals up to every 4 y</td>
<td>Systematic literature search 2004-2010</td>
</tr>
<tr>
<td></td>
<td>Men ≥40 y at high risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider baseline PSA in men 40-49 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Association of Urology, 2013</td>
<td>Baseline PSA≥40-45 y</td>
<td>Risk-adapted strategy based on initial PSA in men with life expectancy &gt;10 y</td>
<td>Systematic literature review and meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Screening intervals every 2-4 y for men with serum PSA ≥1.0 µg/L at 45-59 y and up to 8 y in men with serum PSA &lt;1 µg/L</td>
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<td></td>
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</table>
Screening for Prostate Cancer With the Prostate-Specific Antigen Test: A Review of Current Evidence

**Prostate Cancer Incidence and Mortality in the 2 randomized trials**
- European Randomized Study of Screening for Prostate Cancer (ERSPC)
- Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial in the USA

<table>
<thead>
<tr>
<th>Site</th>
<th>Follow-up, Median, y</th>
<th>No./Total (Cumulative Incidence %)</th>
<th>Rate Ratio (95% CI)</th>
<th>No./Total (Cumulative Incidence %)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC</td>
<td></td>
<td>896/17390 (5.2)</td>
<td>2028/17443 (11.6)</td>
<td>97/17390 (0.56)</td>
<td>69/17443 (0.40)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>11.1</td>
<td>311/4255 (7.3)</td>
<td>420/4307 (9.8)</td>
<td>25/4255 (0.48)</td>
<td>22/4307 (0.51)</td>
</tr>
<tr>
<td>Sweden</td>
<td>14</td>
<td>507/5951 (8.5)</td>
<td>759/5901 (12.9)</td>
<td>70/5951 (1.18)</td>
<td>39/5901 (0.66)</td>
</tr>
<tr>
<td>Finland</td>
<td>11</td>
<td>3175/48409 (6.6)</td>
<td>2838/31970 (8.9)</td>
<td>237/48409 (0.49)</td>
<td>139/31970 (0.43)</td>
</tr>
<tr>
<td>Italy</td>
<td>10.7</td>
<td>257/7251 (3.5)</td>
<td>374/7266 (5.1)</td>
<td>22/7251 (0.30)</td>
<td>19/7266 (0.26)</td>
</tr>
<tr>
<td>Spain</td>
<td>10.7</td>
<td>24/1141 (2.1)</td>
<td>69/1056 (6.5)</td>
<td>1/1141 (0.088)</td>
<td>2/1056 (0.19)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>8.2</td>
<td>226/4955 (4.6)</td>
<td>475/4948 (9.6)</td>
<td>10/4955 (0.02)</td>
<td>9/4948 (0.18)</td>
</tr>
<tr>
<td>All sites</td>
<td>11.0</td>
<td>5396/89352 (6.0)</td>
<td>6963/72891 (9.6)</td>
<td>1.63 (1.57-1.69)</td>
<td>462/89352 (0.52)</td>
</tr>
</tbody>
</table>

**PLCO in USA**

<table>
<thead>
<tr>
<th>No. / Total (Cumulative Incidence %)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Screening</td>
</tr>
<tr>
<td>3815/38345 (9.9)</td>
<td>1.12 (1.07-1.17)</td>
</tr>
</tbody>
</table>

**ERSPC**: level B evidence for prostate cancer mortality reduction
**PLCO**: No cancer-specific mortality benefit to PSA screening after 13-yr follow-up
After adjustment for non-participation, the rate ratio of prostate cancer mortality in men screened was 0.73 (95% CI 0.61–0.88).

**The European Randomised study of Screening for Prostate Cancer (ERSPC)**

(Belgium, The Netherlands, Spain, Switzerland, Finland, Sweden, Italy, and France)

- ERSPC confirms a substantial reduction in prostate cancer mortality attributable to testing of PSA, with a substantially increased absolute effect at 13 years compared with findings after 9 and 11 years.
PSA screening, ESMO guideline

• Population-based screening of men aged between 55 and 69 years, using PSA testing, has been evaluated in the 2 randomized trials, the ERSPC and PLCO.
• After a median follow-up of 13 years, the European screening trial demonstrated a relative reduction in the risk of prostate cancer mortality of 21% (29% if adjusted for non-compliance).
• However, 781 men needed to be invited for screening and 27 patients needed to be treated to prevent one death from prostate cancer.
• The baseline PSA at or before the age of 50 years is associated with the risk of prostate cancer mortality over the subsequent 25 years.

Recommendations
• Population-based PSA screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended [I, C].
• Testing for prostate cancer in asymptomatic men should not be done in men over the age of 70 years [I, B].
The ERSPC reported a 29% reduction in prostate-cancer mortality among men who underwent screening for PSA.

- Per **1000 men** of all ages who were followed for their entire life span, annual screening of men between the ages of 55 and 69 years would result in
  - **9 fewer deaths** from prostate cancer (28% reduction),
  - **14 fewer men receiving palliative therapy** (35% reduction),
  - **a total of 73 life-years gained** (average, 8.4 years per prostate-cancer death avoided).

- The number of **QALYs** (quality adjusted life-years) that were gained was **56**.
  (23% reduction from unadjusted life-years gained)
- Screening of all men between the ages of 55 and 74 would result in
  - **more life-years gained (82 yrs)**
  - but **the same number of QALYs (56 yrs)**.

- The benefit of PSA screening was diminished by loss of QALYs owing to post-diagnosis long-term effects.
In 2012, The US Preventive Services Task Force (USPSTF) released a highly controversial recommendation against PSA screening in men regardless of age.

In 2018, The USPSTF recommends that
- **For men aged 55 - 69 yrs,** the decision to undergo periodic PSA screening should be an individual one and should include discussion of the potential benefits and harms of screening with their clinician.
- **For men 70 yrs and older,** against PSA-based screening for prostate cancer.
Inverse stage migration related to USPSTF-recommended reduced PSA screening

Leyh-Bannurah SR, W J Urol 2018

Inverse stage migration patterns in North American patients undergoing local prostate cancer treatment: a contemporary population-based update in light of the 2012 USPSTF recommendations

Proportions of newly diagnosed PCAs

- High-risk (HR)
- Intermediate-risk (IR)
- Low-risk (LR)

Stage Migration: Improved detection of illness leads to the movement of people from the set of healthy people to the set of unhealthy people.

- All age, Epidemiology and End Results (SEER) database over the time period 2009–2014
- USPSTF-recommended reduced PSA screening.

- Inverse stage migration with increase of unfavorable PCa continues in most contemporary pts. in the USA.
- A paradigm shifted to treat LR pts. with less invasive methods. Contrary, HR pts. increasingly undergo RRP or RT.
- inverse stage migration vs. treatment trends translate into different mortality rates vs. proposed non-local treatment benefits.
PSA screening, AUA (American Urological Association) guideline

1. **Under age 40 yrs:** Recommends against PSA screening. (Recommendation; Grade C)

2. **Ages 40 - 54 yrs at average risk:** Does not recommend routine screening. (Recommendation; Grade C)

3. **Younger than age 55 years at higher risk:** Decisions regarding screening should be individualized: African American race, a family history of metastatic or lethal cancer spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.

4. **Ages 55 - 69 years:** Strongly recommends shared decision-making that involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. (Standard; Grade B)
   1. The greatest benefit of screening appears to be in men ages 55 to 69 years.
   2. The use of multiple tools approach subsequent to a PSA test can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.
   3. To reduce the harms of screening, a routine screening interval of 2 years or more may be preferred since it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives as compared to annual screening. (Option; Grade C)

5. **Age 70+ years or any man with less than a 10 to 15 year life expectancy:** Does not recommend routine PSA screening (Recommendation; Grade C)
• The NCCN Guidelines focus on minimizing unnecessary procedures and limiting the detection of indolent disease.

• The NCCN Prostate Cancer Early Detection Panel 2016's most significant discussions included issues surrounding screening in high-risk populations (ie, African Americans, BRCA1/2 mutation carriers.)
PSA screening, JUA (Japanese Urological Association) guideline

**Strongly recommend**

• “In all of the latest and highly reliable studies, PSA screening proved to have a large mortality reduction effect is also good for screening efficiency, and it is strongly recommended also in objective comparison with other existing cancer screening. It can be said to be a cancer screening examination.”

• “Currently in Japan, the spread of PSA screening has been be delayed. We should put more effort so that we can offer better PSA screening to citizens. All clinicians will understand the latest research results and the current situation that the prostate cancer mortality rate is increasing to disperse the PSA examination.”

• “It is not appropriate to apply the recommendation of USPSTF in USA to our Japan now. We defuse a good understanding of prostate cancer screening and the characteristics, diagnosis, treatment methods of prostate cancer to men who are generally > 50 years old or who have an opportunity to have a PCa screening in a medical checkup by each local government. We strongly recommend checking medical examinations from the age of 40, if possible.”
Characteristics of Men at Higher Risk for Prostate Cancer

Since relatively young age (40s), active annual PSA screening is recommended

• African-American race
• Family history, particularly if relation diagnosed before age 65 yrs.
• Known or suspected BRCA1 or BRCA2 mutation
Consideration of biopsy indication for PSA-positive men

• The true significance of PSA screening is not to detect and diagnose prostate cancer for all men, but to diagnose a clinically significant cancer.

Further information for selecting biopsy indication

• Multi-parametric MRI (mpMRI)
• PCA3 (prostatecancergene3) urine test
• PHI (Prostate Health Index) combination of tPSA, fPSA, and proPSA
• 4K score® total, free, and intact PSA and kallikrein-related peptidase 2 (hK2)
• ConfirmMDx® the epigenetic status of GSTP1, APC, and RASSF1 genes
• Genetic signature for high risk of Pca SNPs, GWAS,..
Multi-parametric MRI (mpMRI), PI-RADS score

PI-RADS: the Prostate Imaging–Reporting and Data System

The European Society of Urogenital Radiology (ESUR) proposed a numeric system called the PI-RADS, for prostate cancer detection by 3T multiparametric MRI (mpMRI). It is based on an earlier system for breast imaging.

• Level One:
  Each parameter that shows up in an image
  T2WI (T2-weighted imaging)
  DWI (Diffusion-weighted imaging)
  DCE (Dynamic contrast-enhancement)
  MRS (MRI spectroscopy)
  and assign a numerical value, with 1 being most probably benign and 5 being highly suspicious of malignancy.

• Level Two:
  The values are added together. In centers that don’t analyze for MRS, only T2, DWI and DCE are added together.
  In centers that analyze for all four parameters, those values are summed.
  The total determines whether the PI-RADS classification is Level I, II, III, IV, or V.
Assignment of a PI-RADS assessment category differs depending on the zone, PZ or TZ.

<table>
<thead>
<tr>
<th>Score</th>
<th>Peripheral Zone (PZ)</th>
<th>Peripheral Zone</th>
<th>Transition Zone (TZ)</th>
<th>Transition Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uniform hyperintense signal intensity (normal)</td>
<td></td>
<td>1</td>
<td>Homogeneous intermediate signal intensity (normal)</td>
</tr>
<tr>
<td>2</td>
<td>Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin</td>
<td></td>
<td>2</td>
<td>Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)</td>
</tr>
</tbody>
</table>
| 3     | Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity  
Includes others that do not qualify as 2, 4, or 5 | | 3 | Heterogeneous signal intensity with obscured margins  
Includes others that do not qualify as 2, 4, or 5 |
| 4     | Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension | | 4 | Lenticular or non-circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension |
| 5     | Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic extension/invasive behavior | | 5 | Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic extension/invasive behavior |

PI-RADS score

<table>
<thead>
<tr>
<th>PI-RADS classification</th>
<th>Definition</th>
<th>Total T2 + DWI + DCE score</th>
<th>Total T2 + DWI + DCE + MRS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Most probably benign</td>
<td>3 - 4</td>
<td>4 - 5</td>
</tr>
<tr>
<td>II</td>
<td>Probably benign</td>
<td>5 - 6</td>
<td>6 - 8</td>
</tr>
<tr>
<td>III</td>
<td>Indeterminate</td>
<td>7 - 9</td>
<td>9 - 12</td>
</tr>
<tr>
<td>IV</td>
<td>Probably malignant</td>
<td>10 - 12</td>
<td>13 - 15</td>
</tr>
<tr>
<td>V</td>
<td>Most probably malignant</td>
<td>13 - 15</td>
<td>17 - 20</td>
</tr>
</tbody>
</table>
MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

A total of 500 men underwent randomization to the MRI-targeted biopsy group or standard TRUS biopsy.

Clinically significant cancer was detected in 95 men (38%) in the MRI-targeted biopsy group, as compared with 64 of 248 (26%) in the standard-biopsy group.

- The use of risk assessment with MRI and MRI-targeted biopsy was superior to standard TRUS–guided biopsy in men at clinical risk for Pca.
Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci

Meta-analyzed genotype data from a custom high-density array of 46,939 PrCa cases and 27,910 controls of European ancestry with previously genotyped data of 32,255 PCa cases and 33,202 controls of European ancestry.

The analysis identified 62 novel loci associated ($P < 5.0 \times 10^{-8}$) with PCa and one locus significantly associated with early-onset PCa ($\leq 55$ yrs).

- These findings improve risk prediction, enhance fine-mapping, and provide insight into the underlying biology of PCa.
This finding accounts for a portion of the ‘missing heritability’ of Pca and has important implications for clinical risk profiling and management of patients.
Conclusion

Recommendations for Screening With PSA

• Focus screening discussions on men aged 55 to 69 years
• Use PSA screening every other year as the default frequency
• Consider a higher biopsy threshold
• MRI and genetic signature are useful information for selecting biopsy indication
• Consider surveillance or watchful waiting
• Strongly recommends “shared decision-making” that involves weighing the benefits and harms of PSA screening