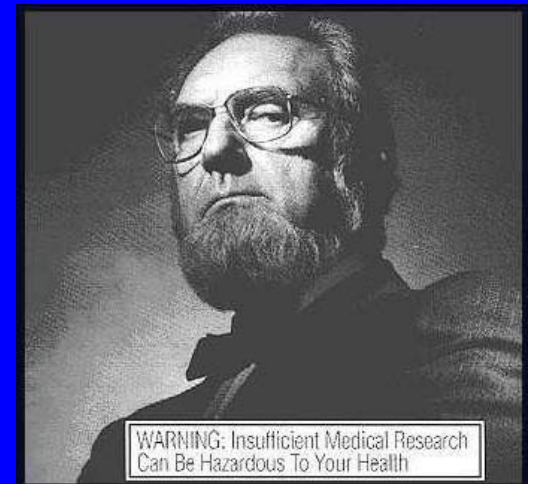


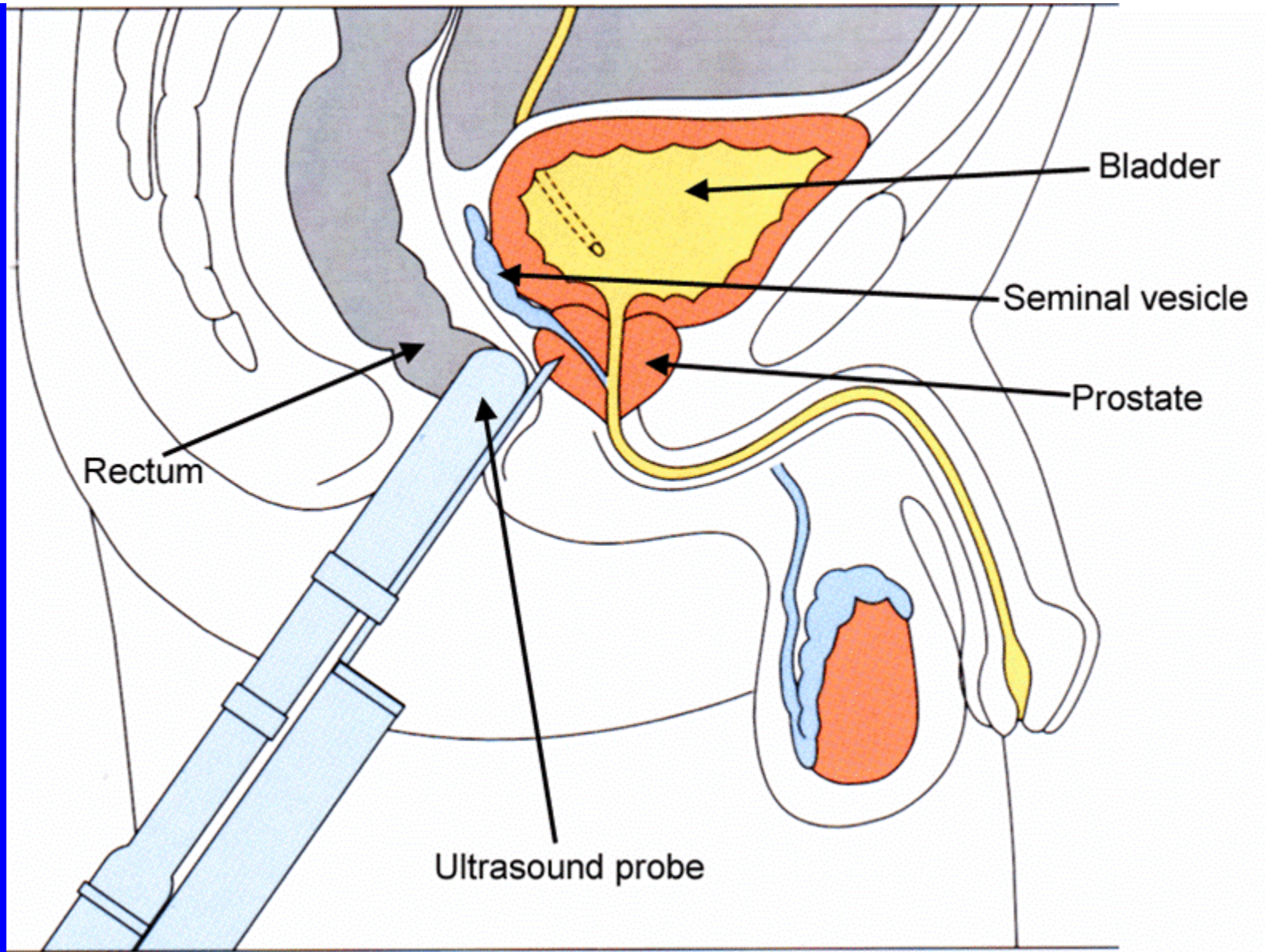
Biomedical Engineering for Global Health

Lecture Twelve



Prostate Cancer

Early Detection



Prostate gland contributes enzymes, nutrients and other secretions to semen.

Prostate Cancer: Statistics

■ United States:

- 230,110 new cases in US
- 29,900 deaths in US
- 2nd leading cause of cancer death in men

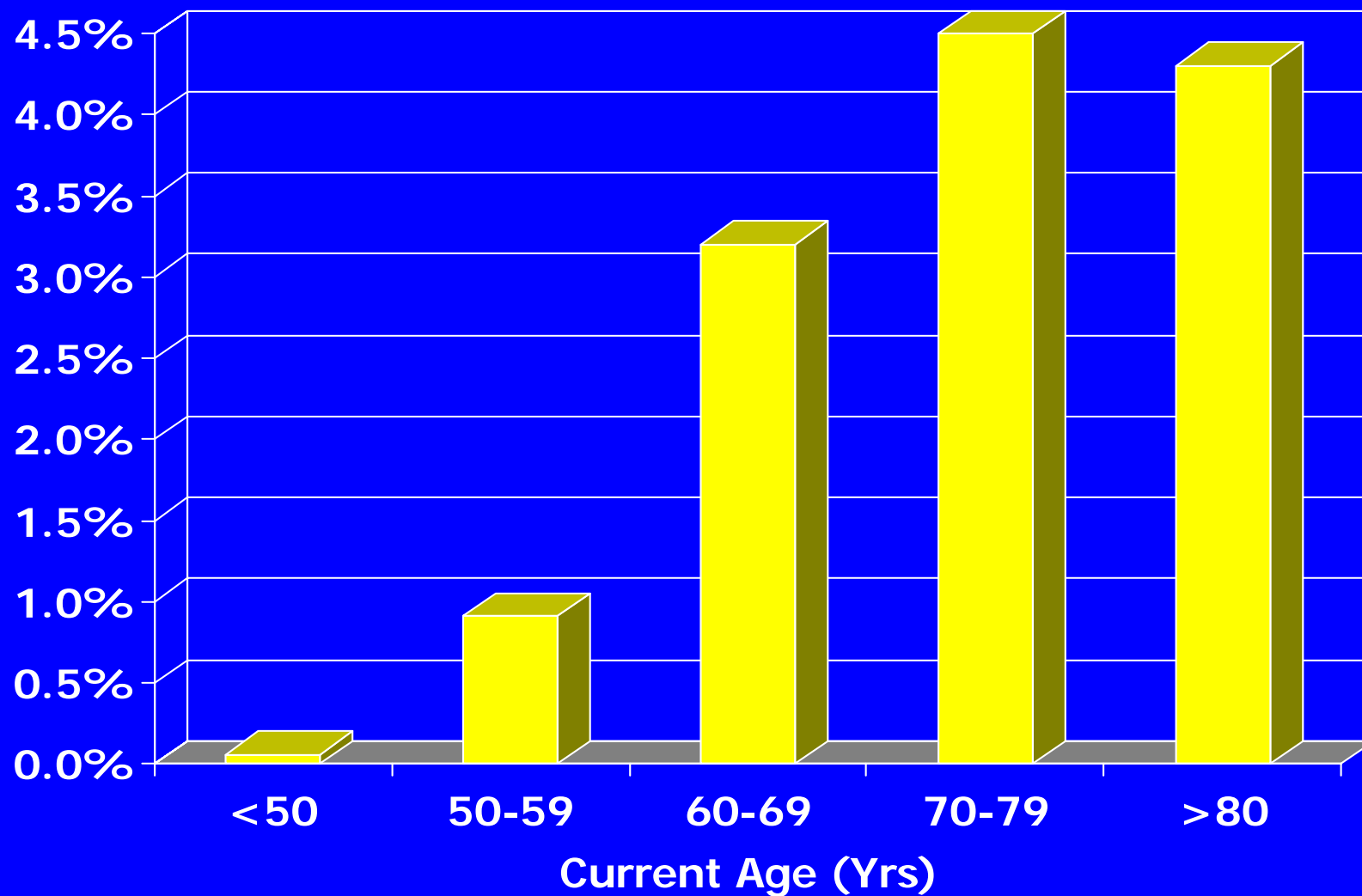
■ Worldwide:

- 543,000 new cases each year
- Third most common cancer in men

■ Risk Factors:

- Age
- Race (incidence 3X higher in African Americans)
- Family history of prostate cancer

Risk of Prostate Cancer in Next 5 Yrs



Development of Prostate Cancer

■ Prostate Cancer:

- Slow, but continuously growing neoplasia
- Preclinical form develops at age 30
- Remains latent for up to 20 years
- Can progress to aggressive, malignant cancer

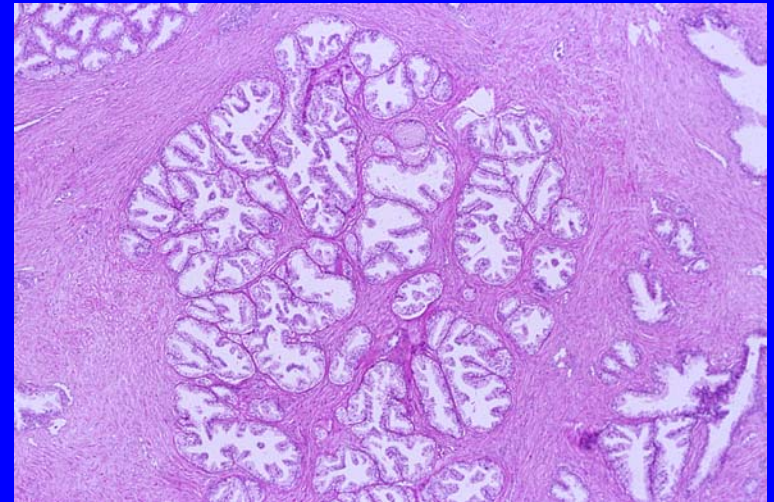
■ Peak incidence: 7th decade of life

■ Signs and symptoms:

- Often asymptomatic in early stages
- Weak or interrupted urine flow
- Inability to urinate
- These are symptoms of prostate enlargement

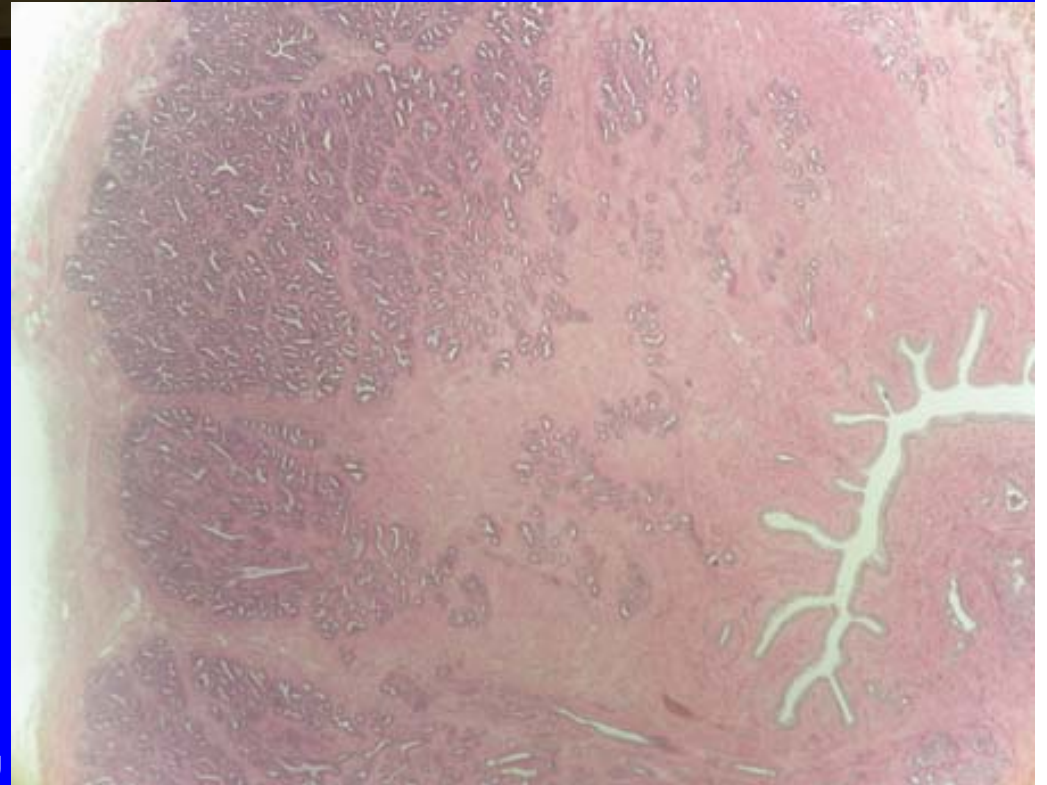


Bostwick Laboratories, Inc

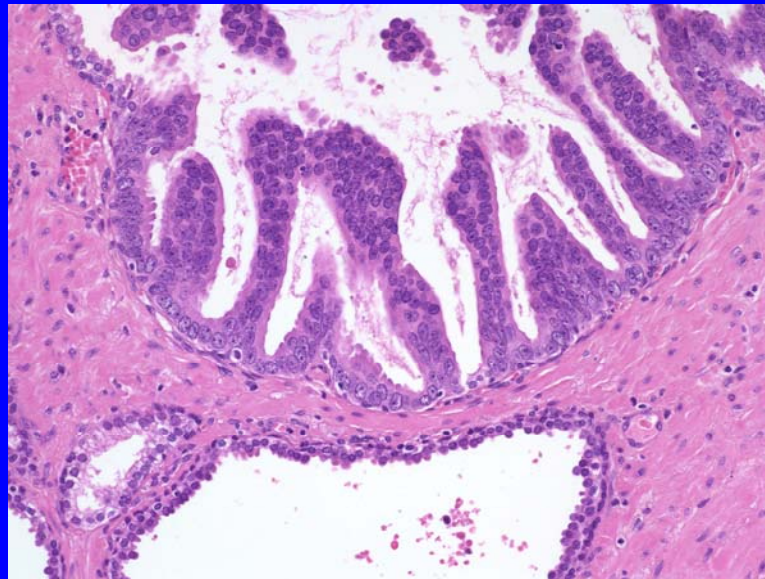


Laura P. Hale, MD, PhD, Duke University Medical Center

Normal Prostate



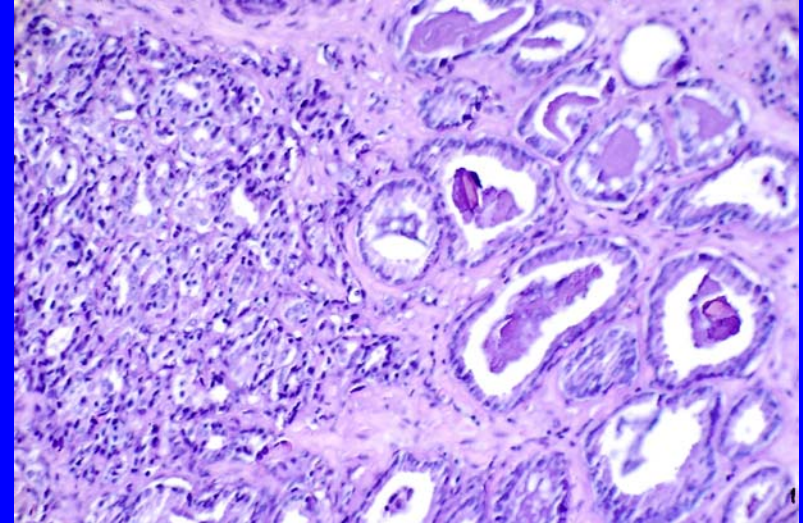
Pre-cancerous Gland



Dharam M. Ramnani, MD; WebPathology.com



Department of Pathology,
Washington University



NCI/Otis Brawley

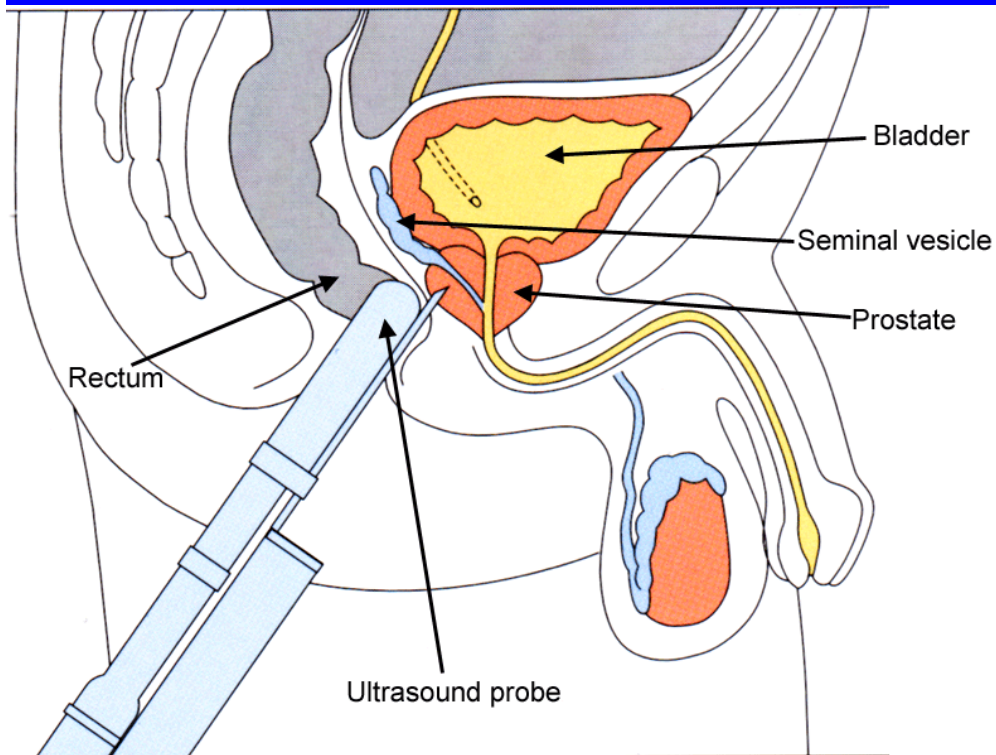
Prostate Cancer

Prostate Cancer (2005)

- **Screening (American Cancer Society recs):**
 - Annual serum PSA test beginning at age 50
 - Annual digital rectal exam at age 50
- **Treatment:**
 - Surgery, radiation therapy, hormone therapy, chemotherapy
- **5 year survival**
 - All stages: 98%
 - Localized disease: 100%
 - Distant metastases: 31%

What happens if DRE & PSA are +?

- Biopsy of prostate (\$1500)
 - Insert needle through wall of rectum into prostate
 - Remove fragments of prostate
 - Examine under microscope



Rx for Localized Prostate Cancer

- Radical prostatectomy (remove prostate)
 - Usually curative
 - Serious side effects:
 - Incontinence (2-30%)
 - Impotence (30-90%)
 - Infertility
- Conservative management
 - Just watch until symptoms develop

Does Early Detection Make a Δ ?

- 10 Yr Survival Rates for Localized Prostate CA:
 - Grade I:
 - Surgery 94%
 - Conservative Rx 93%
 - Grade II:
 - Surgery 87%
 - Conservative Rx 77%
 - Grade III:
 - Surgery 67%
 - Conservative Rx 45%
- Makes a difference only for high grade disease

Challenges of Screening

- Prostate cancer is a slow-growing cancer
 - Not symptomatic for an average of 10 years
- Most men with prostate cancer die of other causes
- Treatment has significant side effects
- 50 year old man:
 - 40% chance of developing microscopic prostate cancer
 - 10% chance of having this cancer diagnosed
 - 3% chance of dying of it

Should we screen?

■ Yes:

- Localized prostate cancer is curable
- Advanced prostate cancer is fatal
- Some studies (**not RCTs**) show decreased mortality in screened patients

■ No:

- False-positives lead to unnecessary biopsies
- Over-detection of latent cancers
 - We will detect many cancers that may never have produced symptoms before patients died of other causes (slow growing cancer of old age)
- No RCTs showing decreased mortality

Clinical Evidence

- Three case-control studies of DRE
 - Mixed results
- One completed RCT of DRE & PSA
 - Found no difference in # of prostate cancer deaths between groups randomized to screening and usual care

Randomized Clinical Trials Underway

- Prostate Cancer vs. Intervention Trial (US)
- Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (US)
- European Randomized Study for Screening for Prostate Cancer
 - 239,000 men
 - 10 countries
 - Will be complete in 2008

Do All Countries Screen with PSA?

- United States:

- Conflicting recommendations

- Europe:

- No
- Not enough evidence that screening reduces mortality

Conflicting Recommendations in US

- Guide to Clinical Preventive Services
 - Do NOT screen using DRE or serum PSA
- American College of Preventive Medicine
 - Men aged 50 or older with >10 yr life expectancy should be informed and make their own decision
- American Cancer Society (and others)
 - Men aged 50 or older with > 10 yr life expectancy should be screened with DRE and serum PSA

USPSTF Recommendation

■ The USPSTF found:

- good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes.
- Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies and potential complications of treatment of some cancers that may never have affected a patient's health.

■ The USPSTF concludes:

- that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.

American Cancer Society (2008):

- PSA and DRE should be *offered* annually, beginning at age 50, to men who have at least a 10-year life expectancy.
- Information should be provided about what is known and what is uncertain about benefits, limitations, and harms of early detection and treatment of prostate cancer so they can make an informed decision.
- Men who ask their doctor to make the decision on their behalf should be tested. Discouraging testing is not appropriate. Also, not offering testing is not appropriate.

PSA Test

Details

The PSA Test

- **What is PSA?**
 - Prostate-specific antigen
 - A glycoprotein responsible for liquefaction of semen
 - Highly specific for prostate (only made by the prostate)
- **PSA test is a blood test to measure PSA levels**
- **Why measure PSA to screen for cancer?**
 - PSA levels are closely (but not definitively) associated with prostate cancer
 - May be elevated in benign conditions (BPH, Prostatitis)
 - Not always high in cancer
- **Cost:**
 - \$30-\$100

PSA Levels

■ Normal PSA Levels:

- < 4 ng/ml
- Can vary by age
 - 40-49 yo < 2.5 ng/ml
 - 50-59 yo < 3.5 ng/ml
 - 60-69 yo < 4.5 ng/ml
 - 70-80 yo < 6.5 ng/ml

■ Cancer Patients:

- 20-25% have PSA < 4 ng/ml
- 20-25% have 4 ng/ml < PSA < 10 ng/ml
- 50-60% have PSA > 10 ng/ml

Sensitivity and Specificity of PSA

- How to determine
 - Trial: Serum PSA → Biopsy (Gold standard)
 - If BX is positive and PSA is positive: get TP
 - If BX is positive and PSA is negative: get FN
 - If BX is negative and PSA is negative: get TN
 - If BX is negative and PSA is positive: get FP
 - BUT: if BX is negative:
 - Did BX just fail to sample area with cancer?
 - Hard to calculate Specificity - $TN/(TN+FP)$
- Cutpoint of 4 ng/ml
- Sensitivity = 63-83%
- Specificity = 90%

Predictive Value Calculation

- Screening Performance:
 - Se = 73%; Sp = 90%
- Number Tested:
 - N=1,000,000; Prevalence = 2%
- Costs:
 - Screening = \$30; Follow up biopsy = \$1500
- What are PPV & NPV?
- What is screening cost?
- What is biopsy cost?
- What is cost/cancer found?

PSA Example – Predictive Value

	Test Positive	Test Negative	
Disease Present	14,600	5,400	# with Disease = 20,000
Disease Absent	98,000	882,000	#without Disease = 980,000
	# Test Pos = 112,600	# Test Neg = 887,400	Total Tested = 1,000,000

$$\text{PPV} = 14,600 / 112,600 = 13\%$$

$$\text{NPV} = 882,000 / 887,400 = 99\%$$

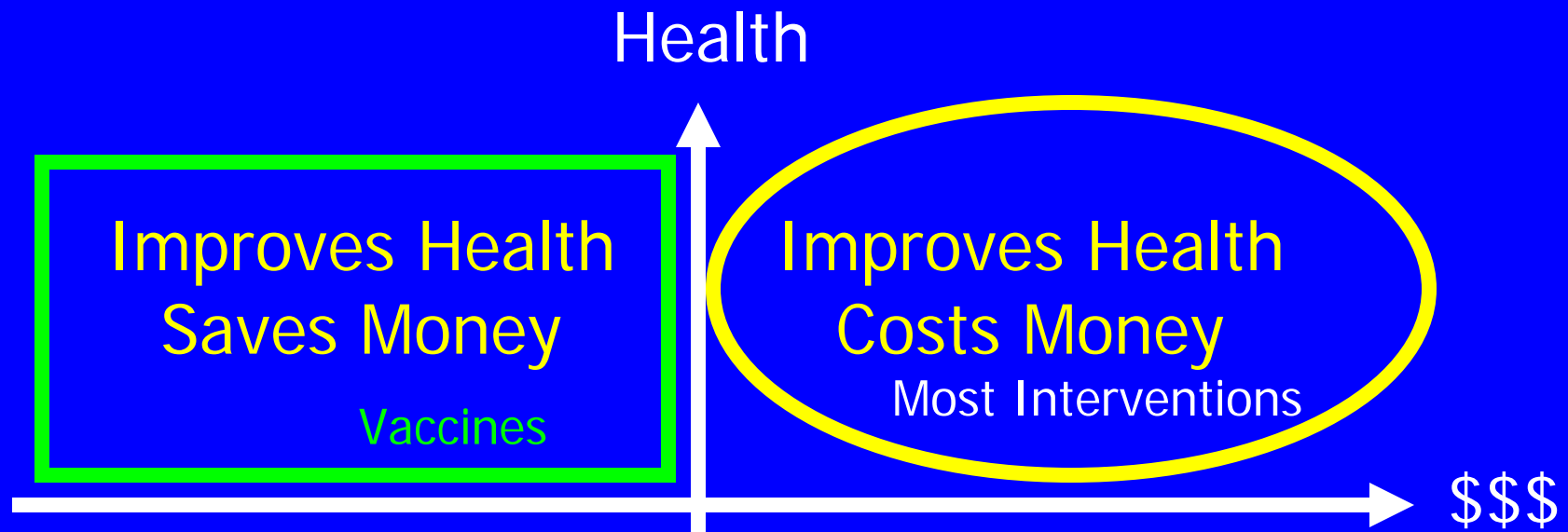
PSA Example – Cost

	Test Positive	Test Negative	
Disease Present	14,600	5,400	# with Disease = 20,000
Disease Absent	98,000	882,000	#without Disease = 980,000
	# Test Pos = 112,600	# Test Neg = 887,400	Total Tested = 1,000,000

Cost to Screen = $\$30 * 1,000,000 + \$1500 * 112,600 = \$168,900,000$

Cost/Cancer = $\$168,900,000 / 14,600 = \$13,623$

Health – Policy Space



<http://www.npr.org/templates/story/story.php?storyId=93313794>

New Technologies: Improved Screening

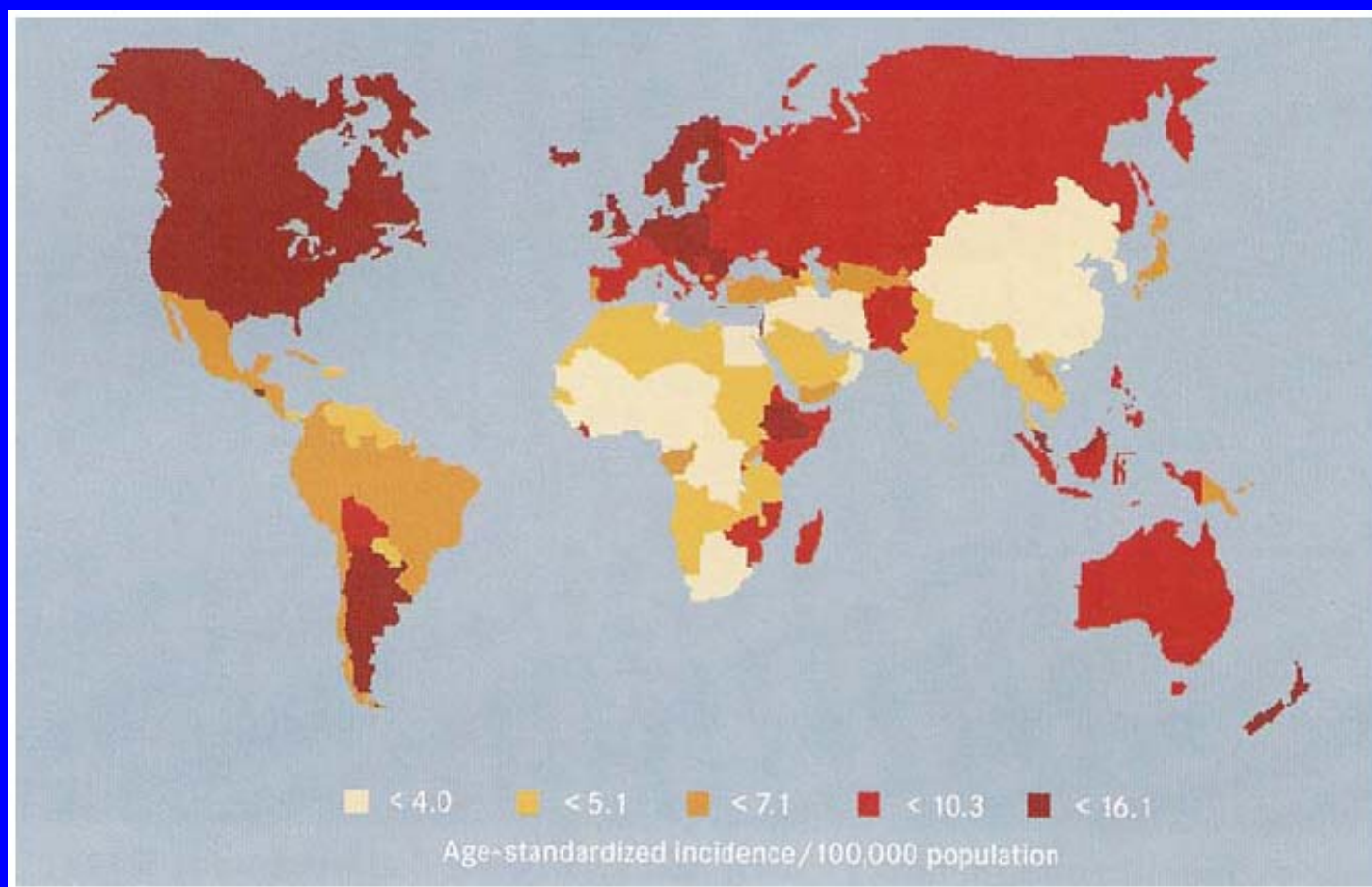
- Additional serum markers → Improve Sp
 - Free PSA
 - PSA density
 - PSA velocity
- Predict those cancers which will progress to advanced disease
 - Gene chips

Ovarian Cancer

Statistics on Ovarian Cancer

- **United States:**
 - Incidence: 22,430
 - Mortality: 15,280
- **Worldwide:**
 - Incidence: 190,000
 - Mortality: 114,000

Global Burden of Ovarian Cancer

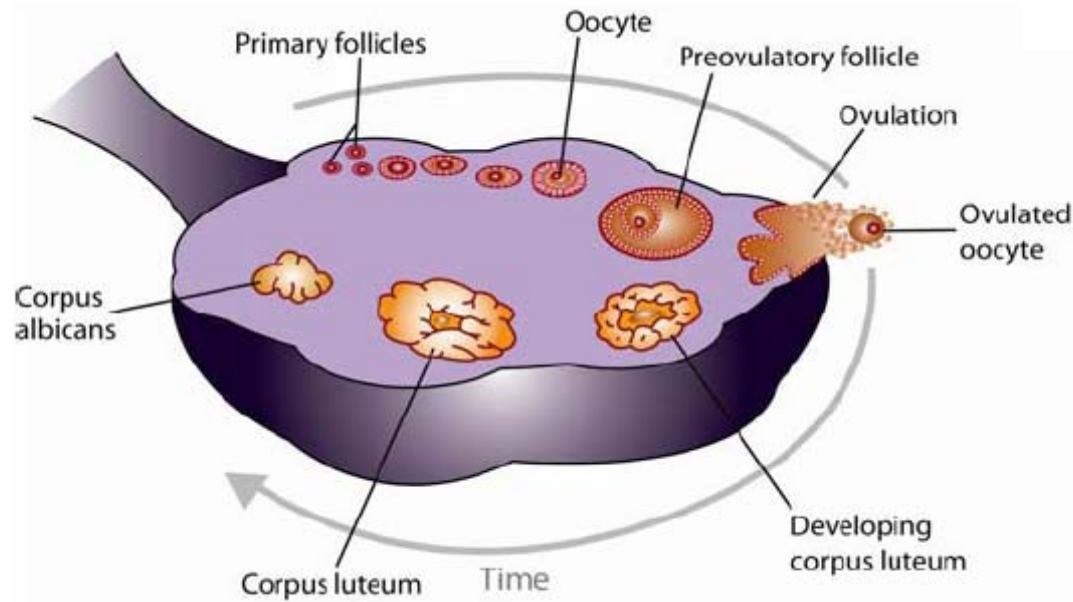
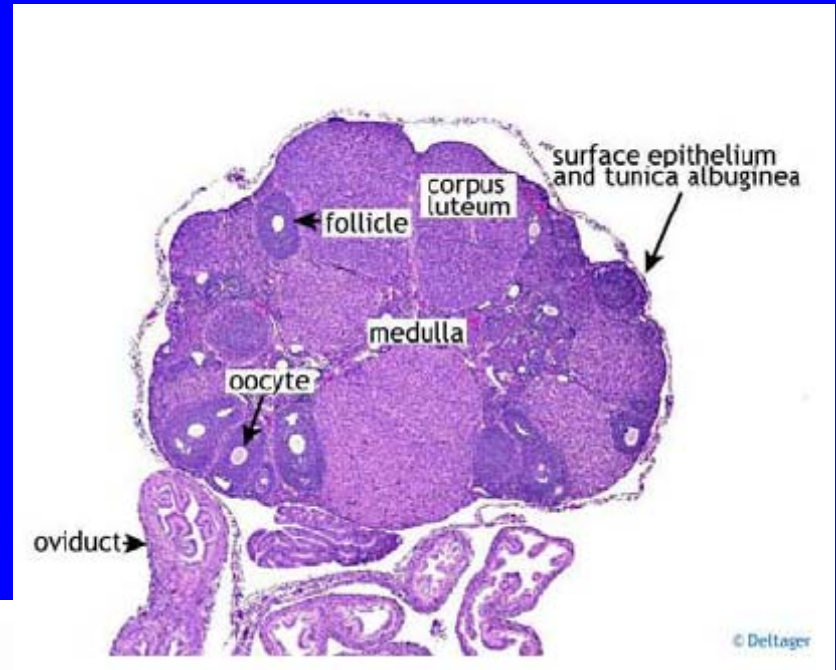
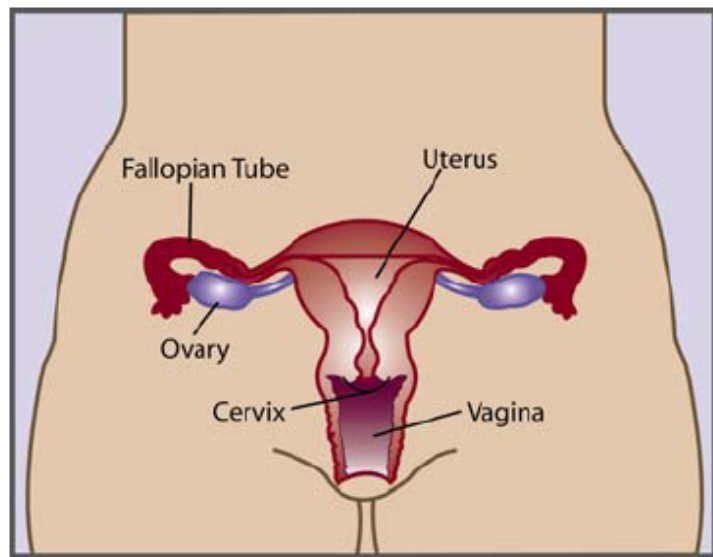


Risk factors

- Age
 - Most ovarian cancers develop after menopause
- Personal or family history of breast, ovarian, endometrial, prostate or colon cancer.
- Reproductive history

Increases with the more lifetime cycles of ovulation that a woman has undergone. Thus, women who have undergone hormonal treatment for infertility, never used birth control pills, and who never became pregnant are at higher risk for ovarian cancer

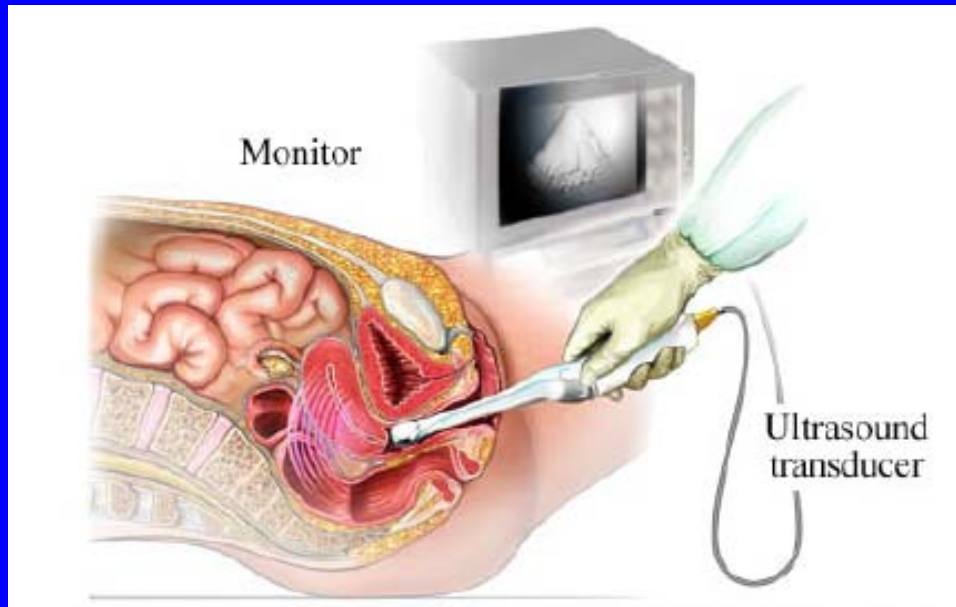
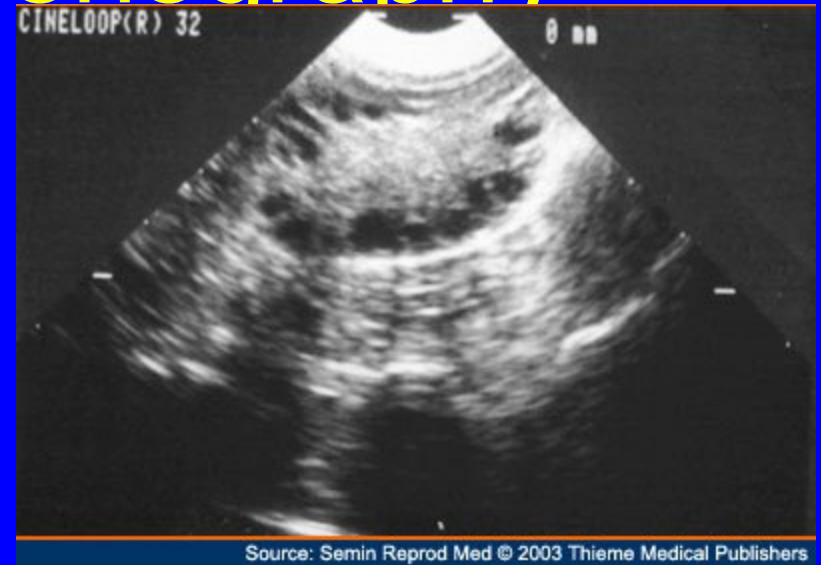
Pathophysiology



Screening of Ovarian Cancer

- Pelvic and rectal exam
- CA125 test
- Transvaginal sonography

Transvaginal Sonography



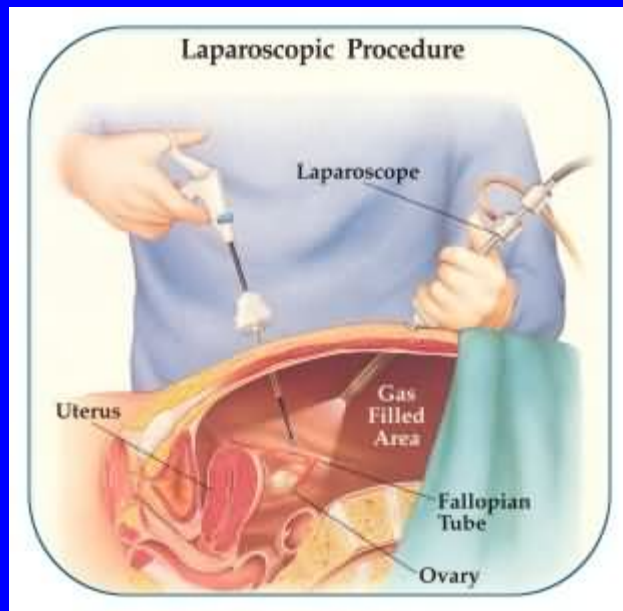
Nucleus Medical Art



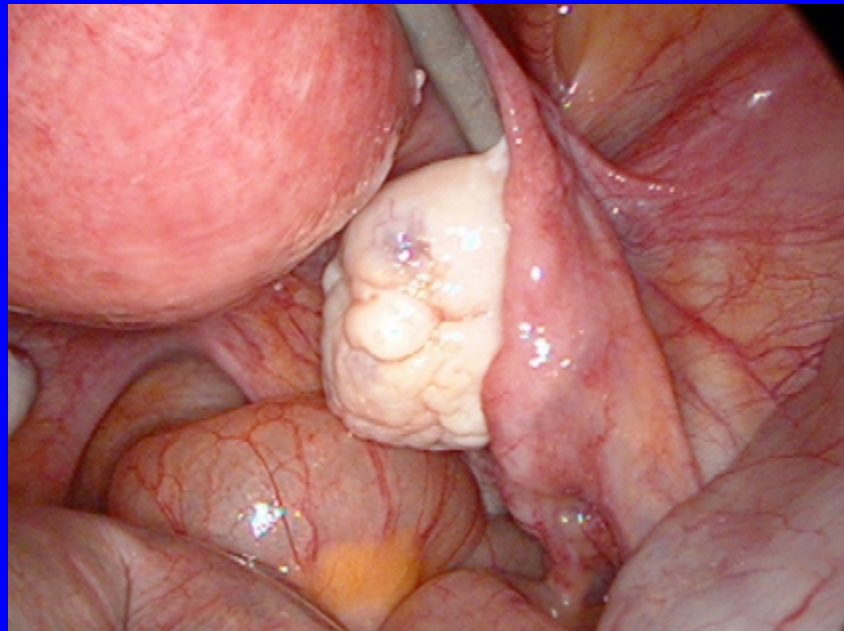
www.ivf-infertility.com

Diagnostic Laparoscopy

Complication Rate = 0.5



Allon Health Center - Center for Women's Medicine



John P.A. George, M.D., Washington Hospital Center

Detection and Treatment

■ Screening

- Pelvic exam
- CA125 test
- Transvaginal ultrasound

■ Diagnosis

- Diagnostic laparoscopy

■ Treatment:

- Surgery, radiation therapy, chemotherapy

■ 5 year survival

- Localized disease: 93% (20% diagnosed at this stage)

Screening Scenarios

- Scenario #1:
 - Screen 1,000,000 women with CA125
 - $p = .0001$ (100 cancers)
 - $Se=35\%$, $Sp=98.5\%$
 - Cost = \$30
 - Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
- TP=35 FP=14,999 Complications=150
- PPV =0.23% NPV =99.99%
- Cost per cancer found = \$1,716,200

Screening Scenarios

- Scenario #2:
 - Screen 1,000,000 women with transvaginal US
 - $P = .0001$ (100 cancers)
 - $Se=100\%$, $Sp=96\%$
 - Cost = \$150
 - Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
- $TP=100$ $FP=39,996$ $Complications=401$
- $PPV = 0.25\%$ $NPV = 100\%$
- Cost per cancer found = \$300,672

Screening Scenarios

■ Scenario #3:

- Screen 1,000,000 women >age 50 with TVUS
 - P = .0005 (500 cancers)
 - Se=100%, Sp=96%
 - Cost = \$150
- Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
- TP=500 FP=39,980 Complications=405
- PPV =1.24% NPV =100%
- Cost per cancer found = \$60,670

Screening Scenarios

■ Scenario #3 cont.:

- Screen 1,000,000 women > age 50 with TVUS
 - $P = .0005$ (500 cancers)
 - $Se = 100\%$, $Sp = ??\%$
 - Cost = \$150
- How high does Sp need to be for PPV to reach 25%?
 - $Sp = 99.985\%$

Does Ultrasound Screening Work?

- Two studies of over 10,000 low-risk women:
 - The positive predictive value was only 2.6%
 - Ultrasound screening of 100,000 women over age 45 would:
 - Detect 40 cases of ovarian cancer,
 - Result in 5,398 false positives
 - Result in over 160 complications from diagnostic laparoscopy
 - Jacobs I. Screening for early ovarian cancer. Lancet; 2:171-172, 1988.

Ongoing Clinical Trials

■ United Kingdom

- 200,000 postmenopausal women
 - CA 125 level plus transvaginal ultrasound examination
 - Transvaginal ultrasound alone
 - No screening

■ United States:

- 37,000 women (aged 55–74)
 - Annual CA 125 level and transvaginal ultrasound examination
 - No screening

■ Europe:

- 120,000 postmenopausal women
 - No screening,
 - Transvaginal ultrasound at intervals of 18 months
 - Transvaginal ultrasound at intervals of 3 years

http://www.mja.com.au/public/issues/178_12_160603/and10666_fm.pdf

Ovarian Cancer

Risk factors

Detection

Treatment

Challenges

New technologies

Challenge

Better screening methods to detect early stages of ovarian cancer

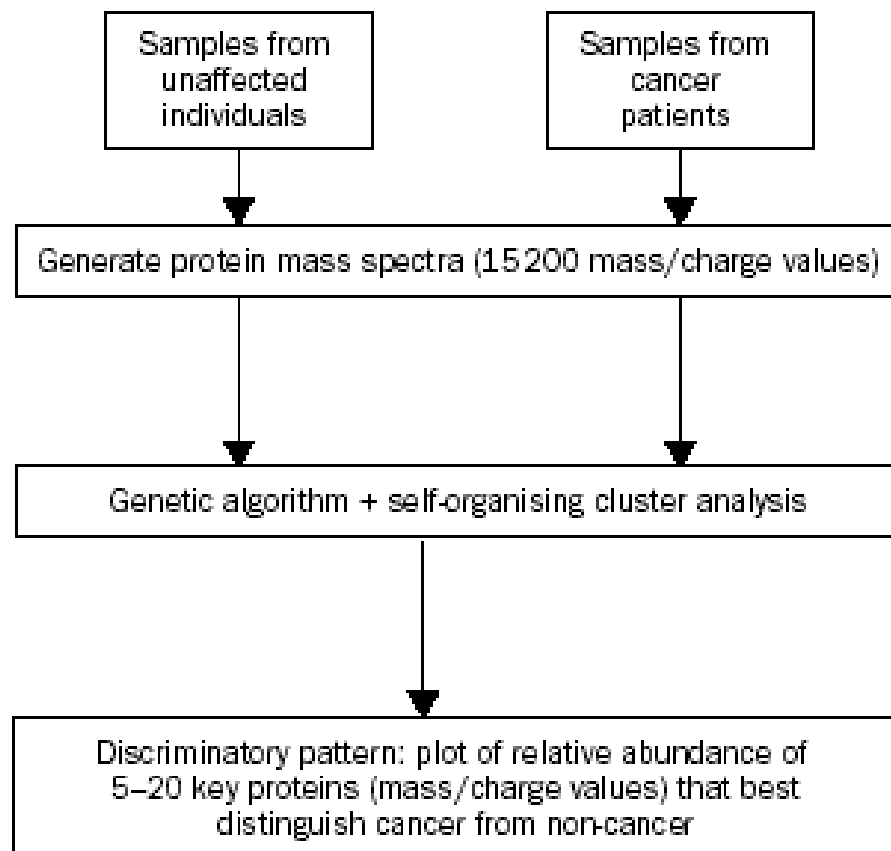
Cancer Screening Exams

- Cellular/Morphological Markers
 - Pap smear
- Serum protein markers
 - PSA
 - CA125
- DNA markers
 - HPV DNA

Data Analysis

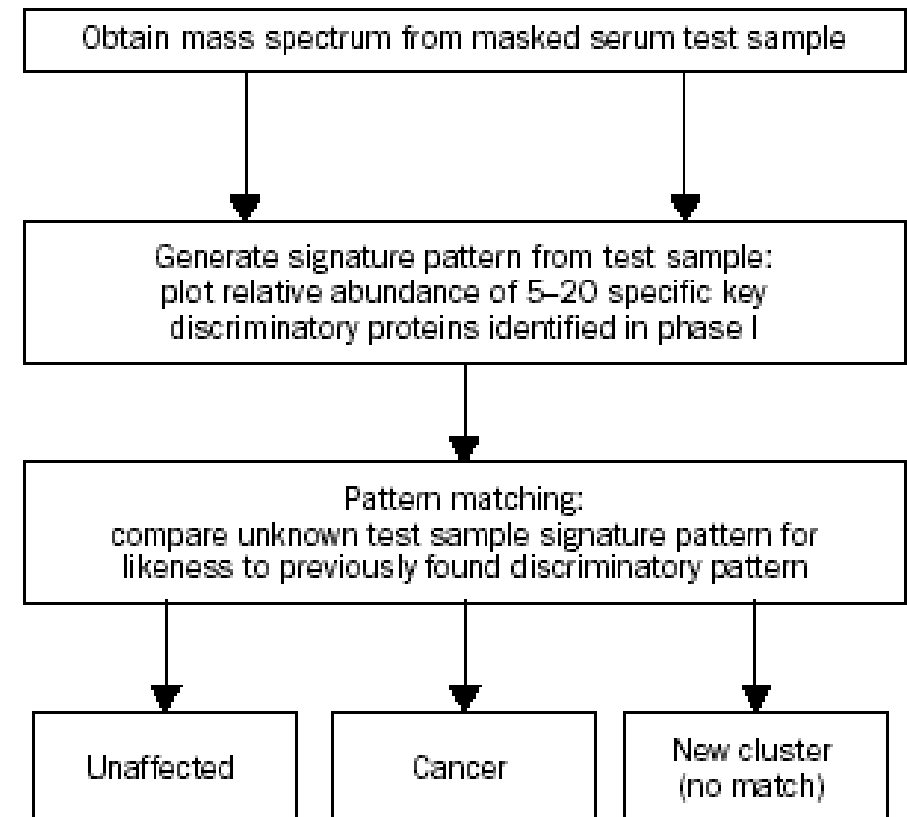
Training

Phase I: pattern discovery



Validation

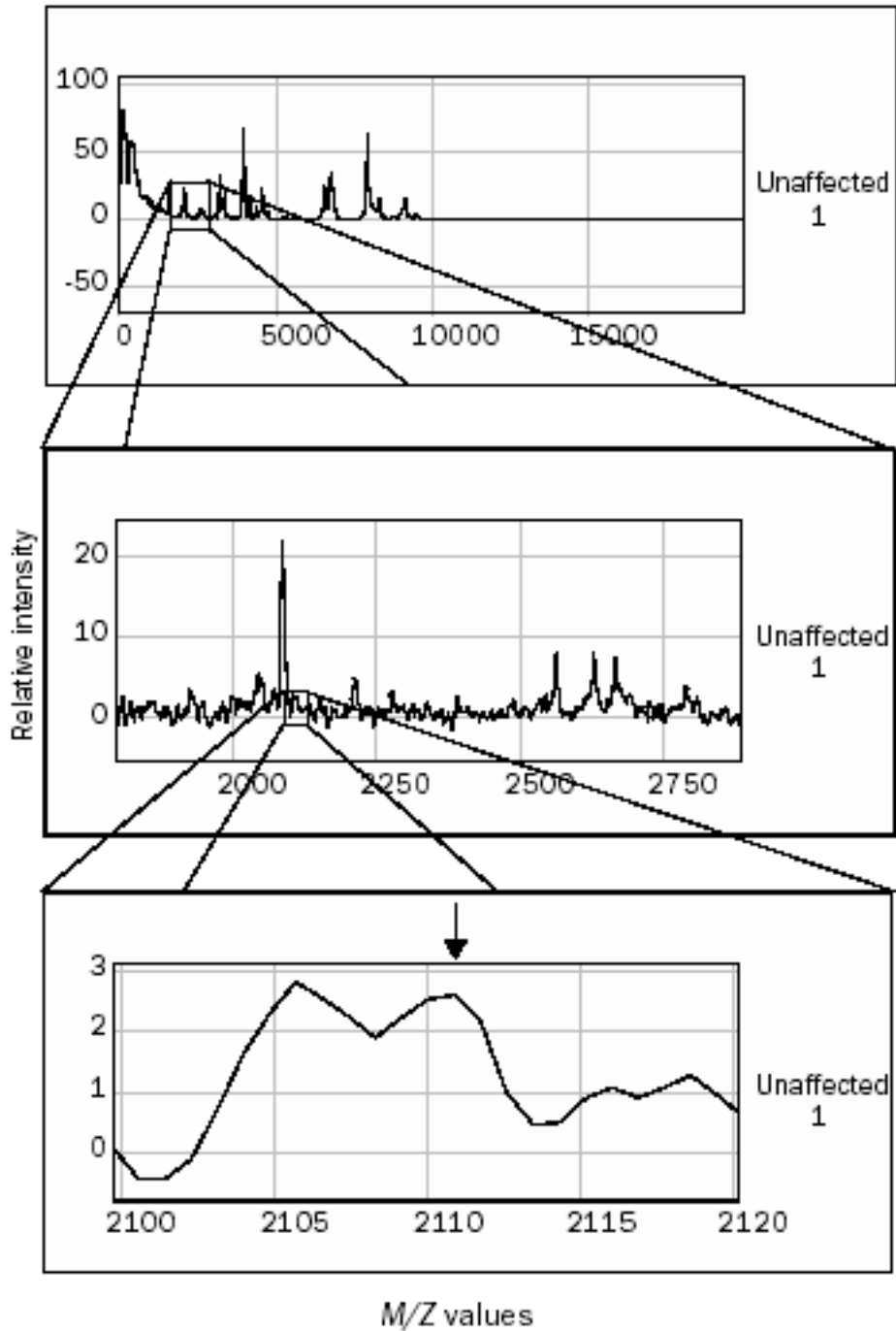
Phase II: pattern matching



OvaCheck

- Quest Diagnostics and LabCorp:
 - Will analyze blood samples sent by doctors, rather than sell test kits to doctors and hospitals
 - Tests performed at a central location do not require F.D.A. approval
 - Cost: \$100-\$200

Chromatogram



Useful M/Z:

534

989

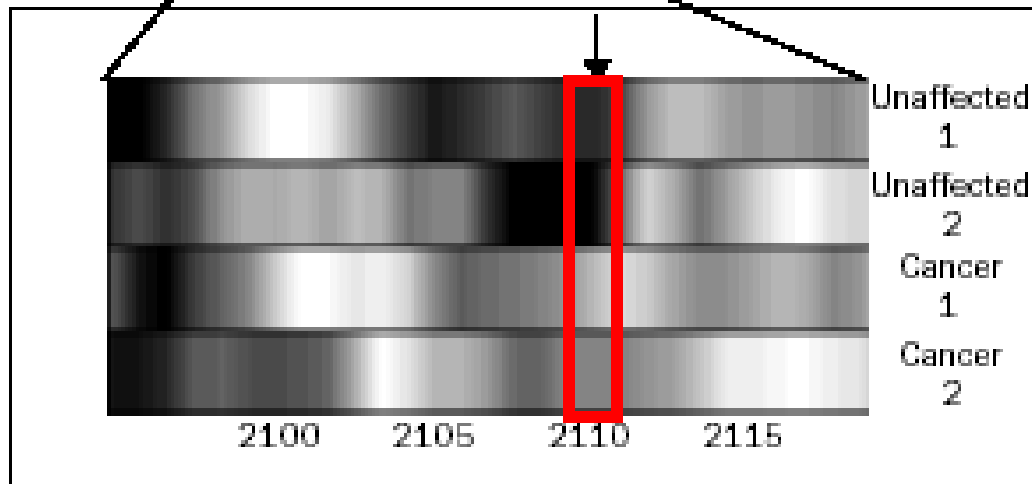
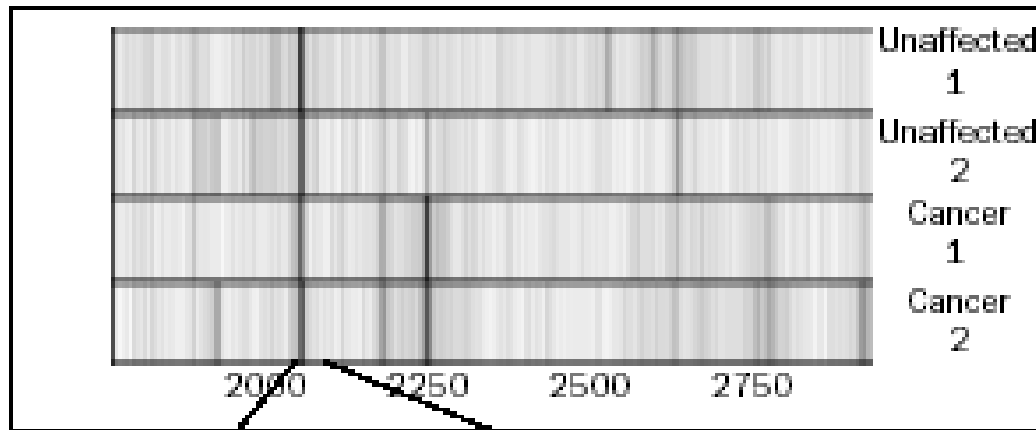
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Comparative Analysis

Density plot



M/Z values

Useful M/Z:

534

989

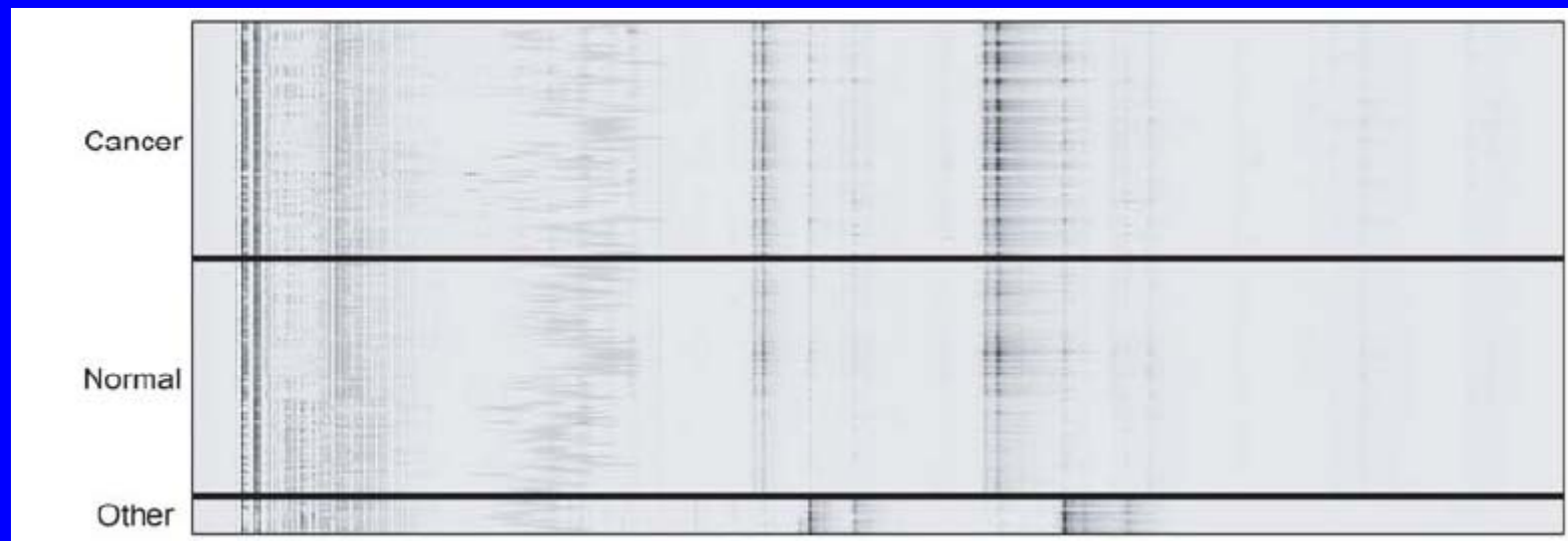
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Lance Liotta, lead author:

"The most important next goal is validating the promise of these results in large, multi-institutional trials."



Response

- Dr. Eleftherios P. Diamandis, head of clinical biochem at Mount Sinai Hospital in Toronto.
 - "If you don't know what you're measuring, it's a dangerous black-box technology... They are rushing into something and it could be a disaster."
- Dr. Nicole Urban, head of gynecologic cancer research at the Fred Hutchinson Cancer Research Center in Seattle.
 - "Certainly there's no published work that would make me tell a woman she should get this test."
- Dr. Beth Karlan, director of gynecologic oncology at Cedars-Sinai Medical Center
 - "Before you mass-market to the uninformed, fearful population, it should be peer-reviewed,"
 - When asked whether she would recommend her patients not get tested, she said: "It doesn't matter what I recommend. They are going to do it anyway."

New screening technologies

- New screening technologies
 - Proteomics
 - DNA microarrays
 - Optical technologies