Biomedical Engineering for Global Health

Lecture Thirteen

Outline

- The burden of cancer
- How does cancer develop?
- Why is early detection so important?
- Strategies for early detection
- Example cancers/technologies
  - Cervical cancer
  - Ovarian cancer
  - Prostate cancer

Statistics on cervical cancer

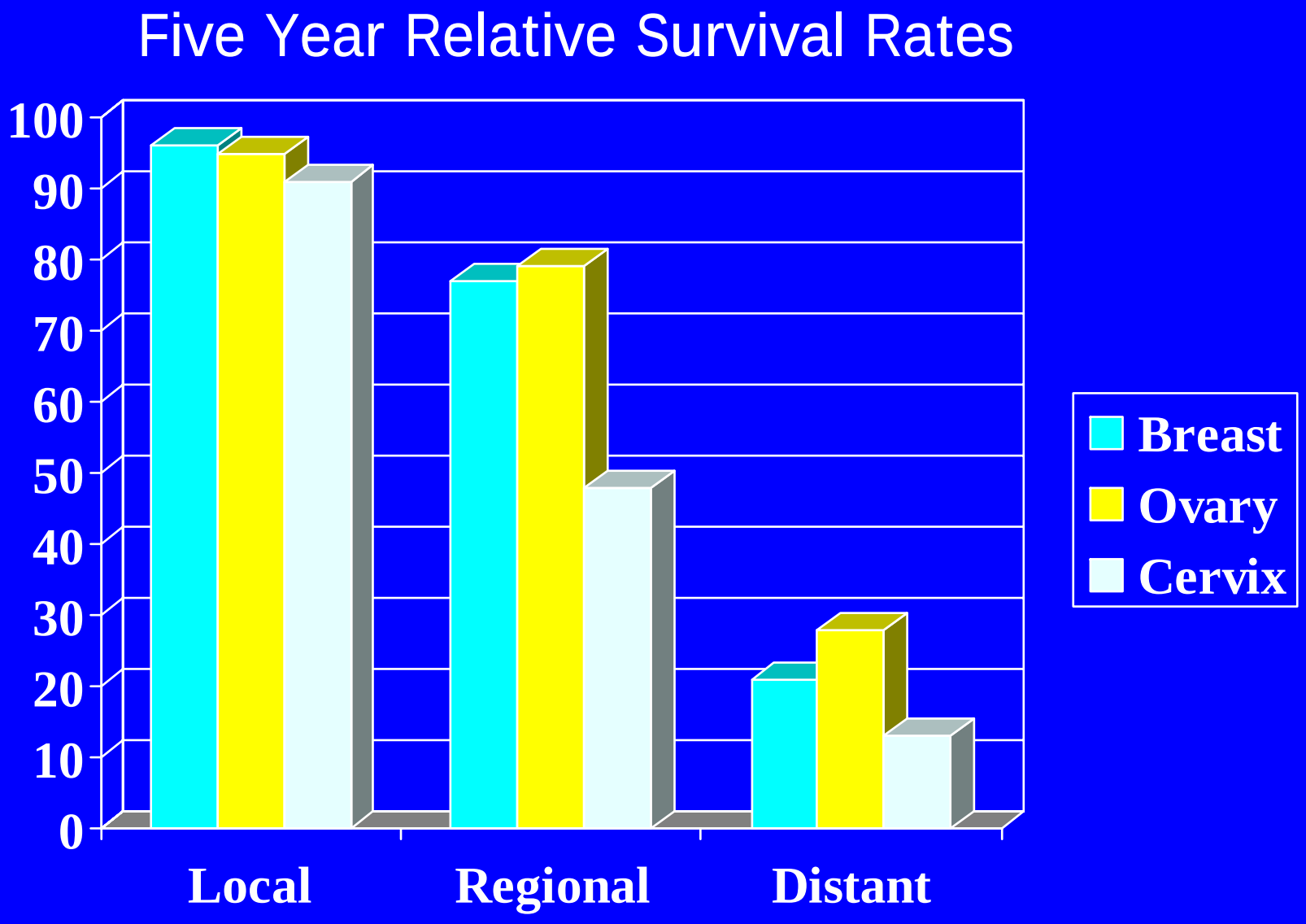
US data (2007)

- Incidence: 11,150
- Mortality: 3,670

World data (2004)

- Incidence: 510,000 (80% developing world)
- Mortality
  - 288,000 deaths per year worldwide

Importance of Early Detection



Screening

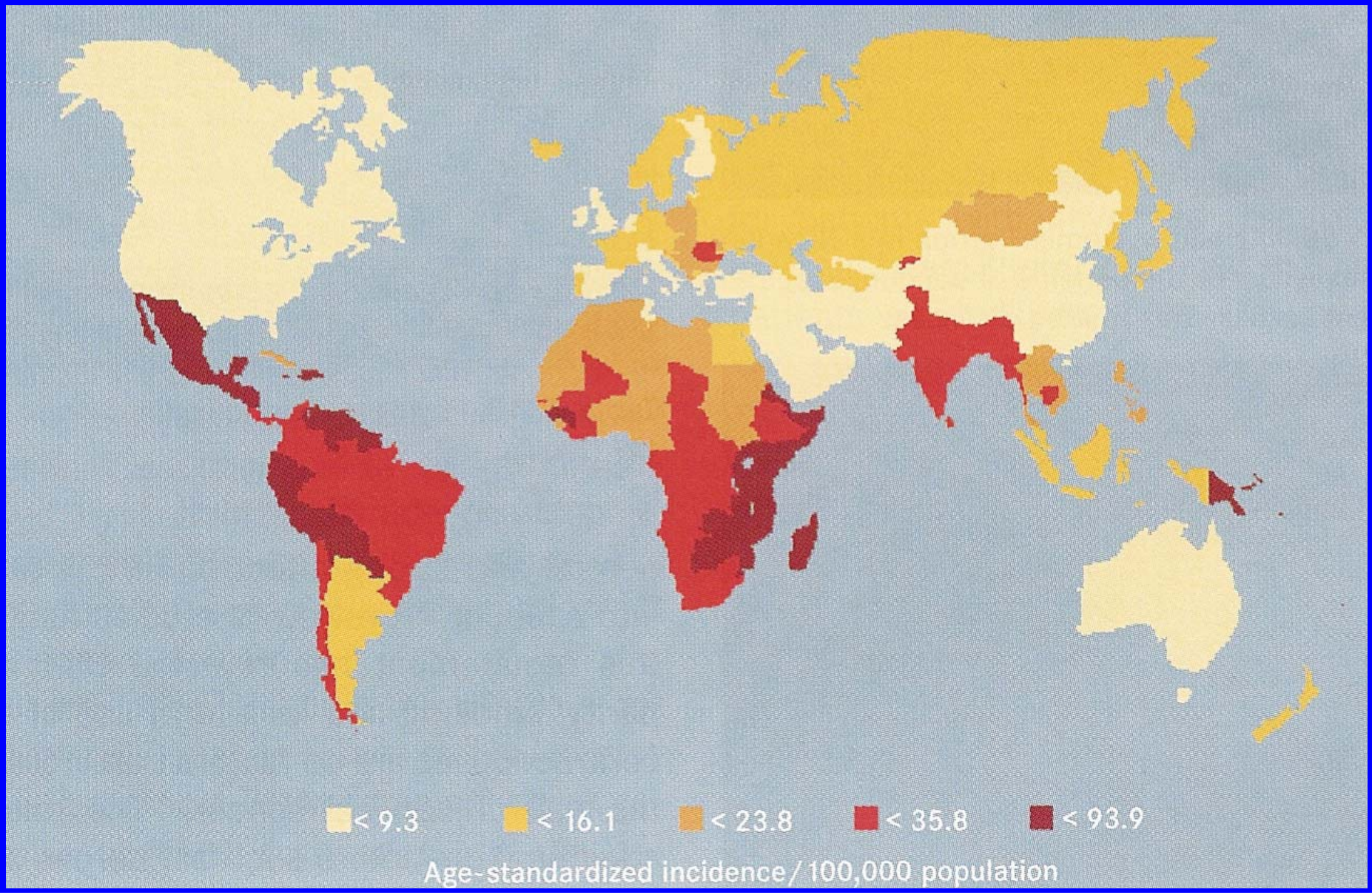
- Use of simple tests in a healthy population
- Goal:
  - Identify individuals who have disease, but do not yet have symptoms
- Should be undertaken only when:
  - Effectiveness has been demonstrated
  - Resources are sufficient to cover target group
  - Facilities exist for confirming diagnoses
  - Facilities exist for treatment and follow-up
  - When disease prevalence is high enough to justify effort and costs of screening

How do we judge efficacy of a screening test?

Sensitivity/Specificity

Positive/Negative Predictive Value

Global Burden of Cervical Cancer

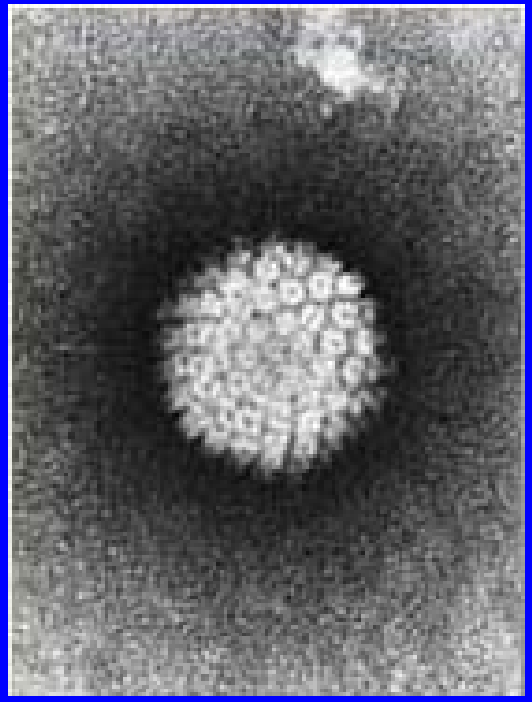


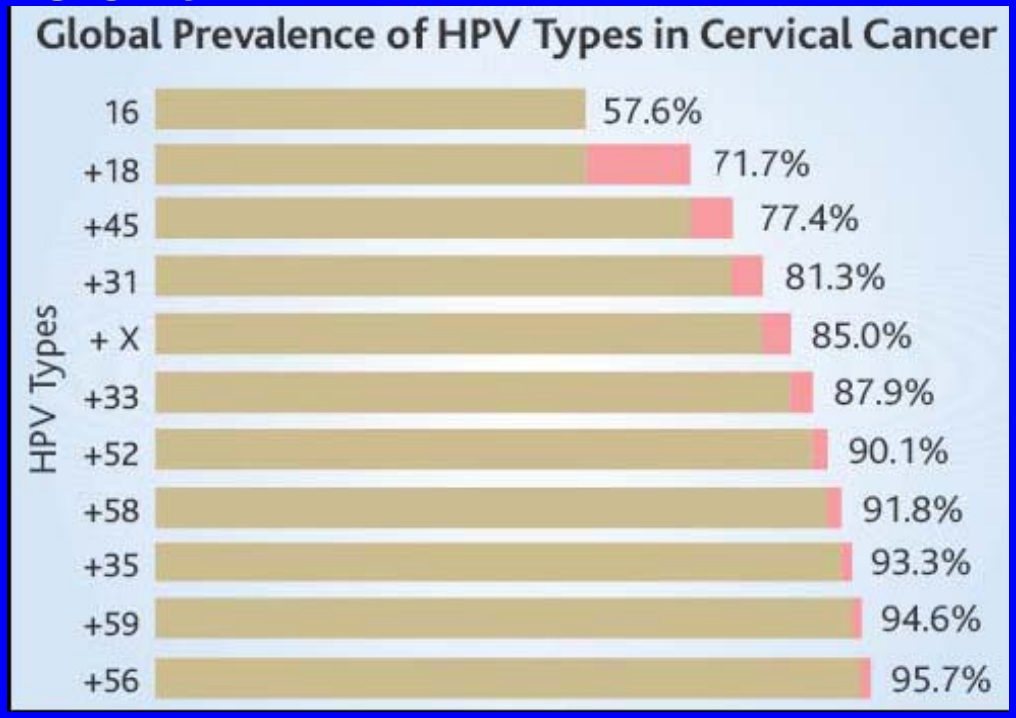
Risk factors

- HPV infection
  - HPV infection is the central causative factor in squamous cell carcinoma of the cervix
- Sexual behaviors
  - Sex at an early age
  - Multiple sexual partners
- Cigarette smoking

Human papilloma virus (HPV)

- Most common STD
- >70 subtypes
- Asymptomatic infections in 5-40% of women of reproductive age
- HPV infections are transient

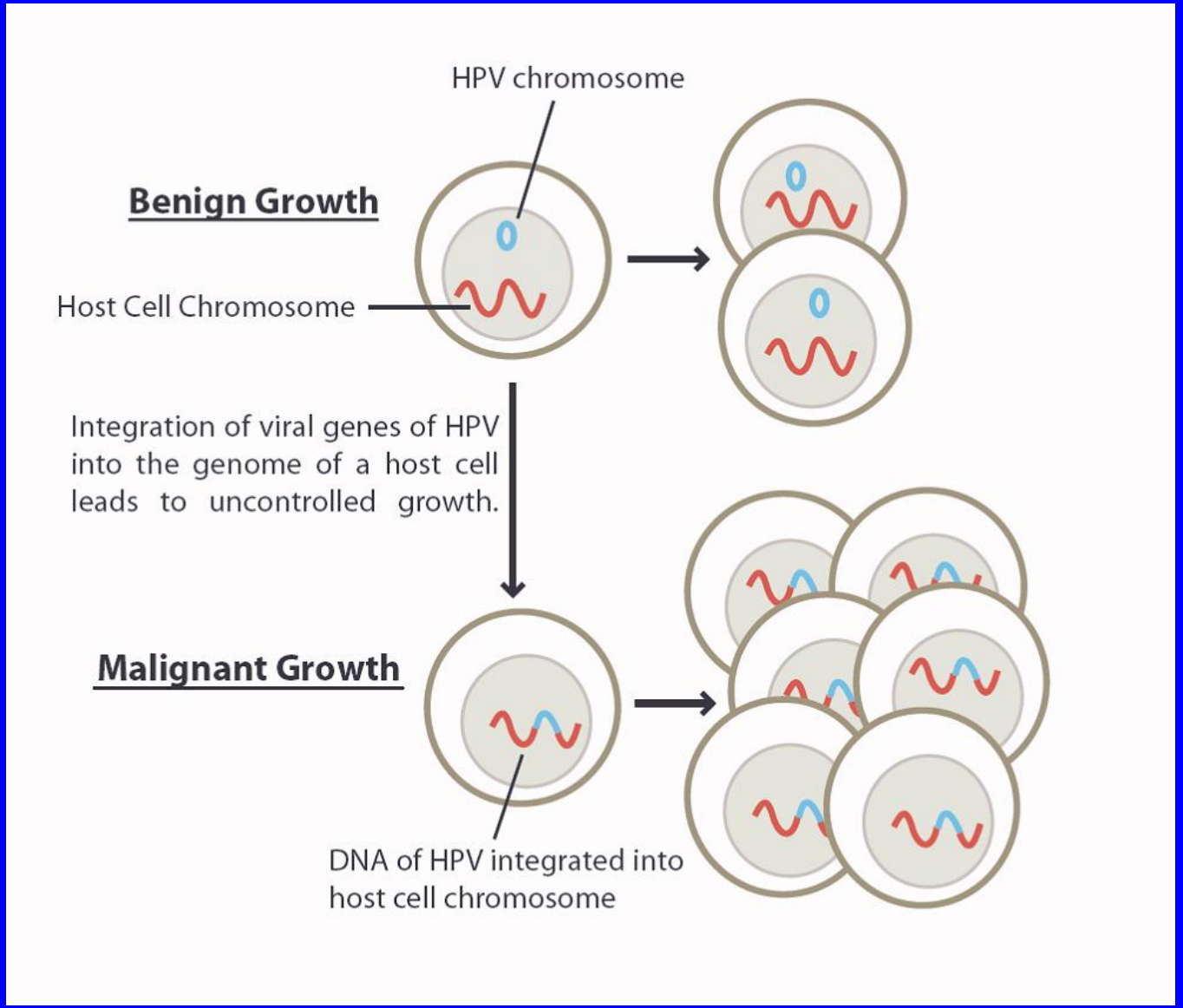




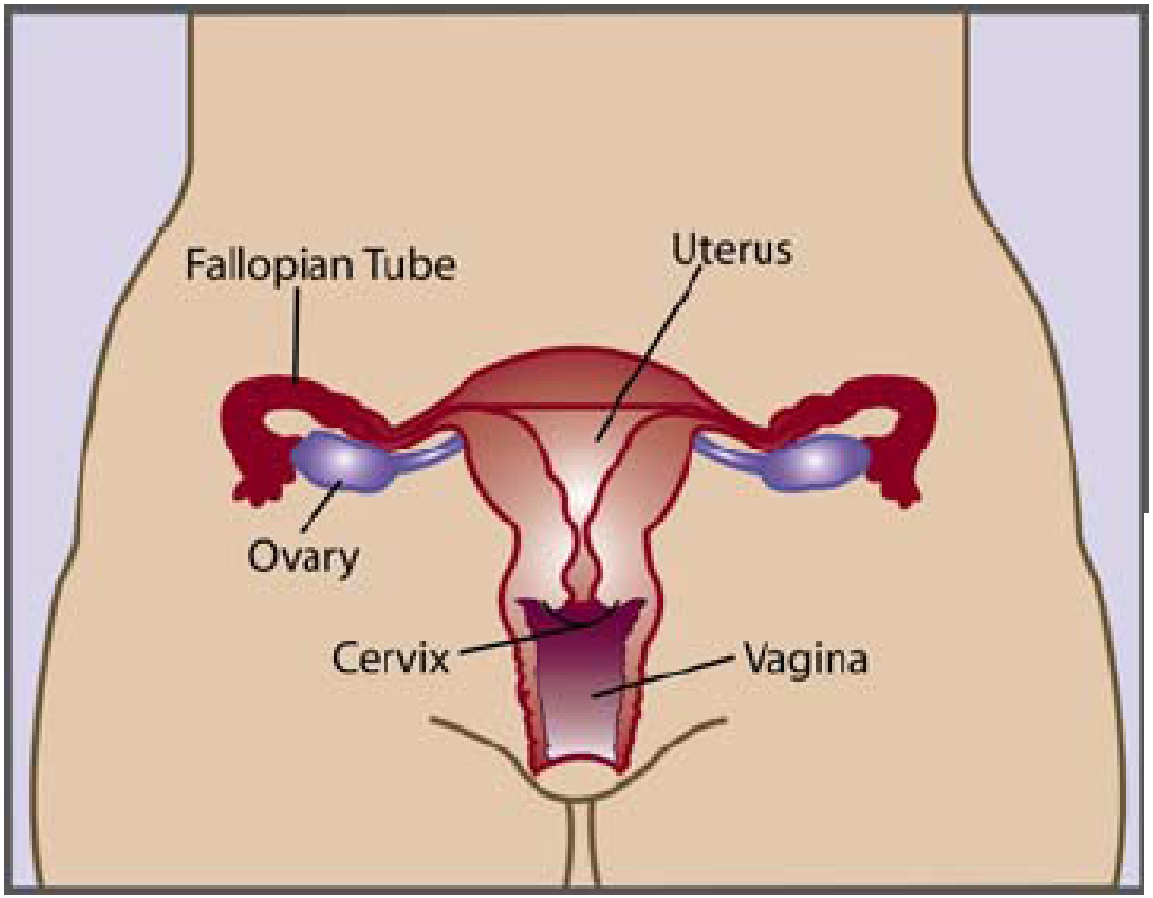
X. Bosch And N. Munoz/Iarc, Ibsccs, And Multicentric Studies (N = 3045). From Science *29 April 2005: Vol.* ***308****. no. 5722, pp. 618–621.*

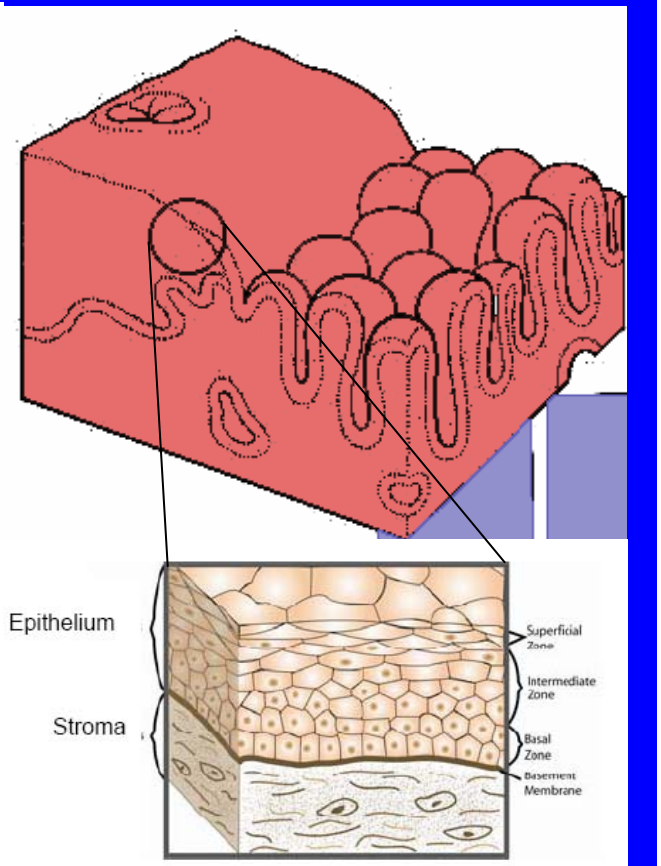
HPV and cervical cancer

What Initiates Transformation?

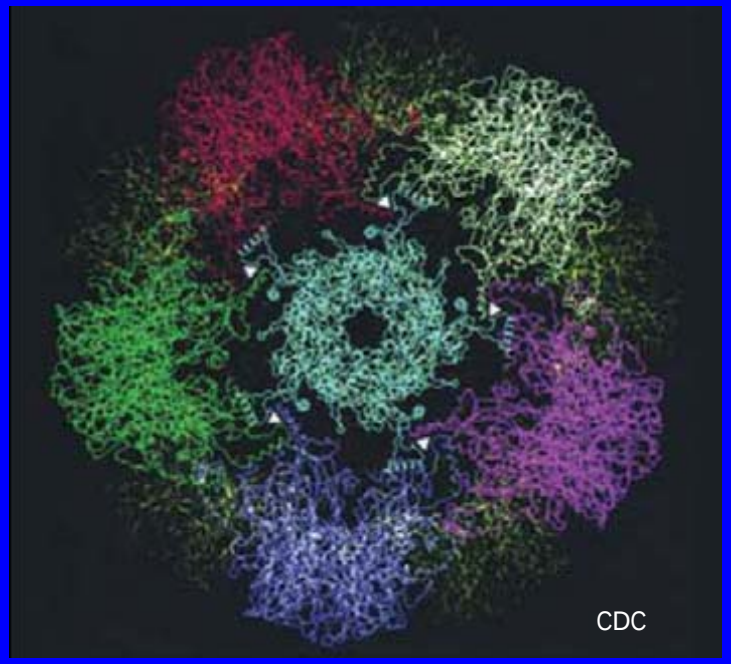


Pathophysiology





HPV vaccine

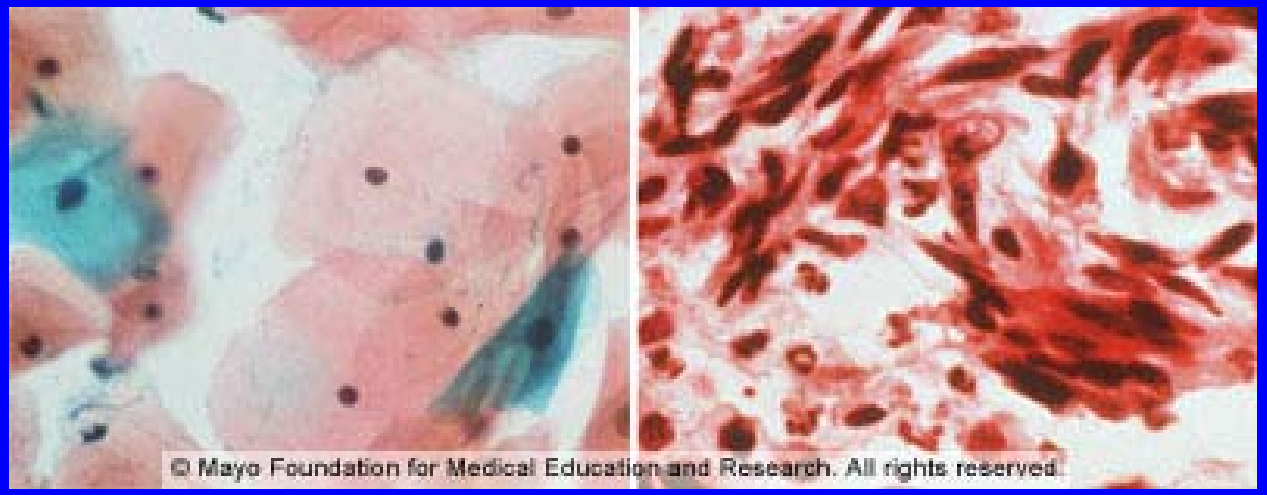


Virus-like particles (VLP) made from the L1 protein of HPV 16

- approved for use in girls and women aged 9 to 26 years in the US
- not effective to women already exposed to HPV
- Effective on 4 HPV isotypes
- Recombinant technology
- Alternative prevention technique to screening?

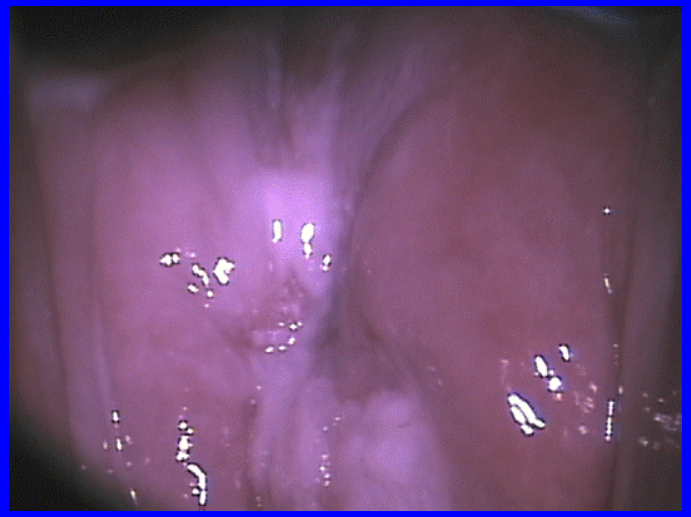
How Do We Detect Early Cervical Cancer?

Pap Smear



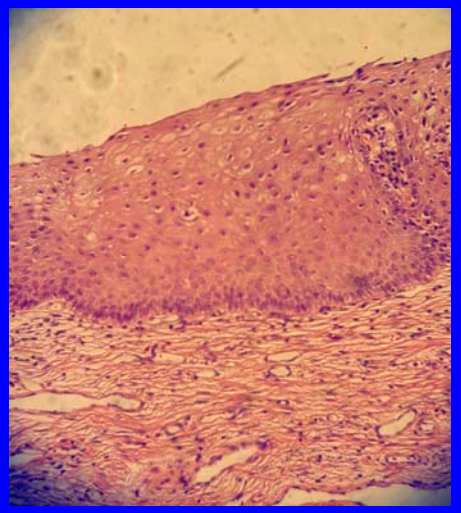
- 50,000-300,000 cells/per slide
- Cytotechnologists review slides (<100/day)
- Se = 62% → 3%
- Sp = 78% → $6B

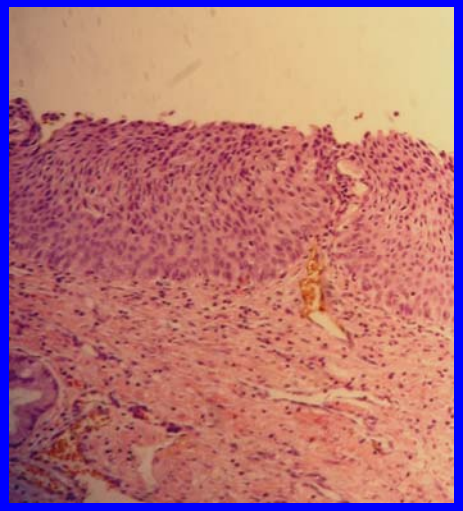
Colposcopy and Biopsy



Colposcope

Se = 95%
Sp = 44%

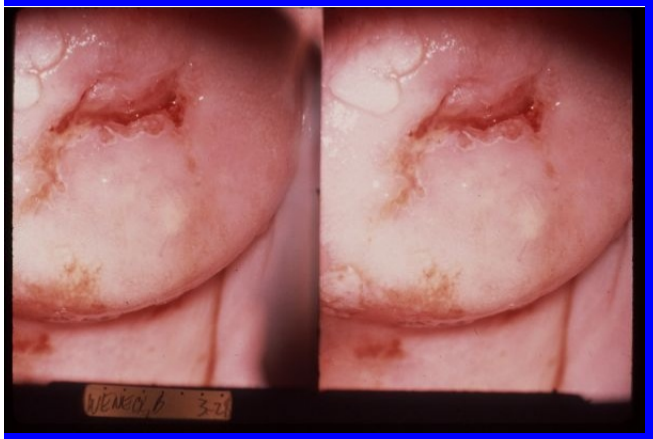




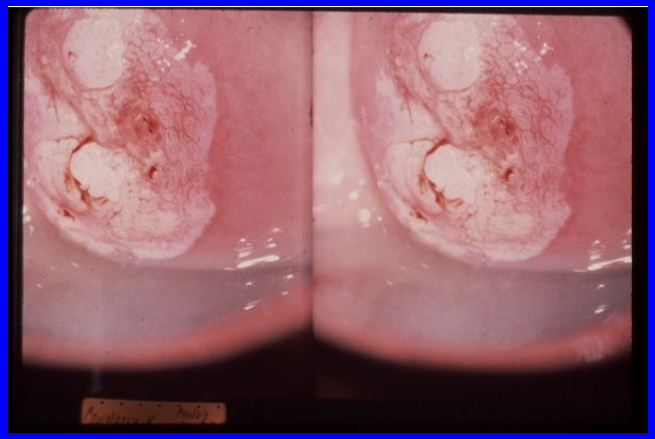
Biopsy sections

Colposcopy and Treatment

CIN 1/LGSIL



CIN 2/HGSIL

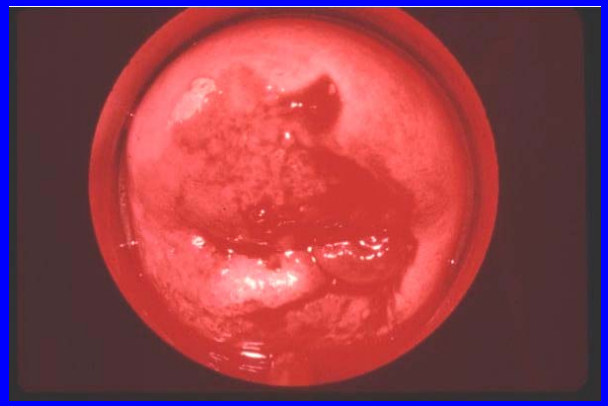


CIN 3/HGSIL

Microinvasive CA

Invasive CA

Invasive CA



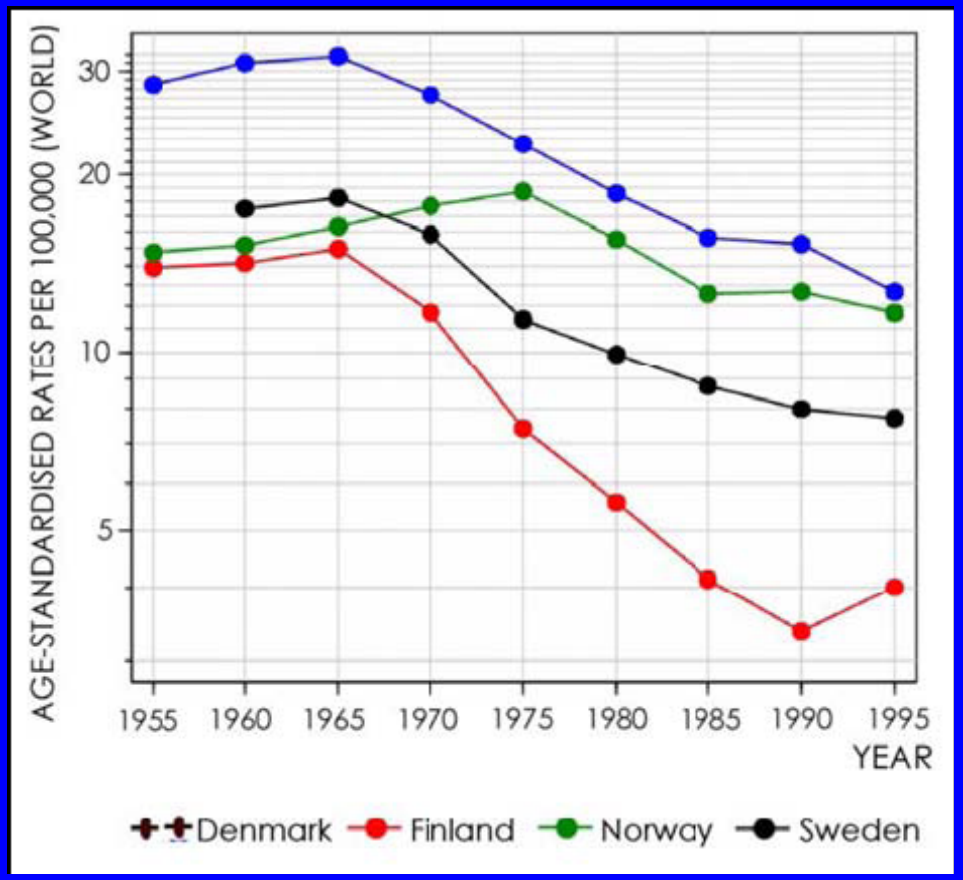
Detection and Treatment

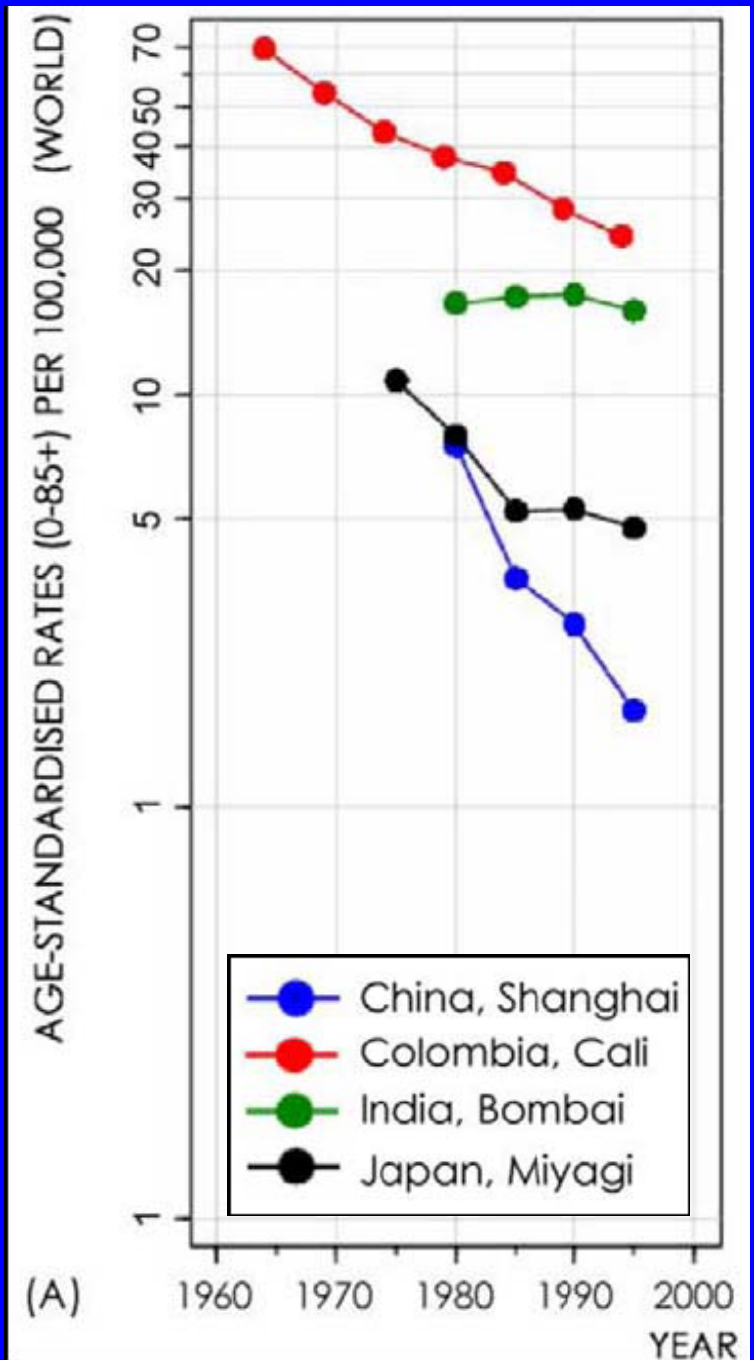
- Screening:
  - Pap smear
- Diagnosis:
  - Colposcopy + biopsy
- Treatment:
  - Surgery, radiotherapy, chemotherapy
- 5 year survival
  - Localized disease: 92% (56% diagnosed at this stage)

Screening Guidelines, ACS

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years with either the conventional (regular) or liquid-based Pap test.
- Option for women over 30 is to get screened every 3 years with either the conventional or liquid-based Pap test, *plus* the HPV DNA test.

Trends in Screening Cervical Cancer





Challenge

- Developed and developing world
- Cost and infrastructure requirements for screening
- Need for appropriate technologies

New Detection Technologies

Aims:

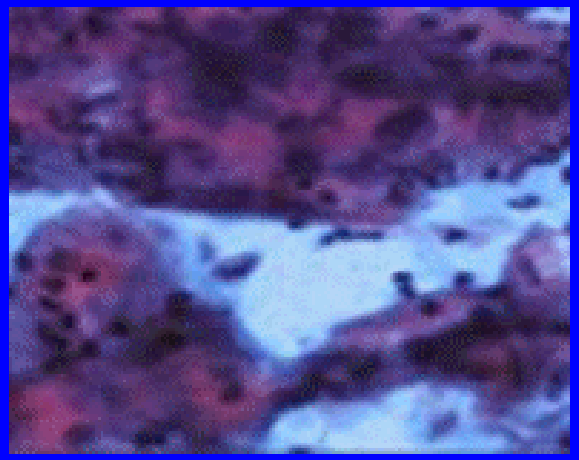
- Reduce the false positive and false negative rates
- Give instantaneous results
- Reduce the costs

New Technologies for Cervical Cancer

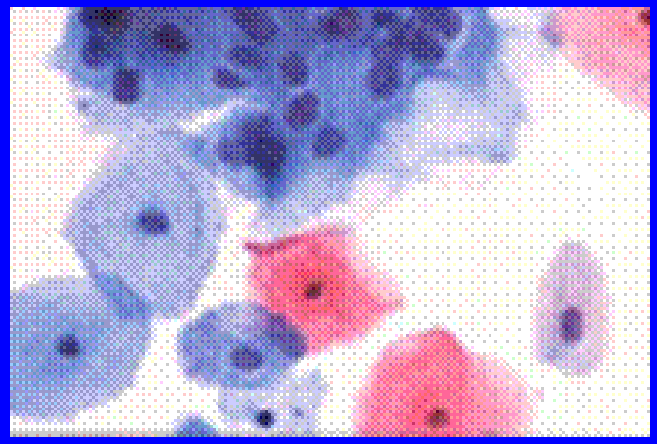
- Liquid Based Pap testing
- Automated Pap smear screening
- HPV Testing
- VIA
- HPV Vaccine

Liquid Based Pap Smear

- Rinse collection device in preservative fluid
- Process suspension of cells to deposit a monolayer of cells on a microscope slide



Conventional Pap

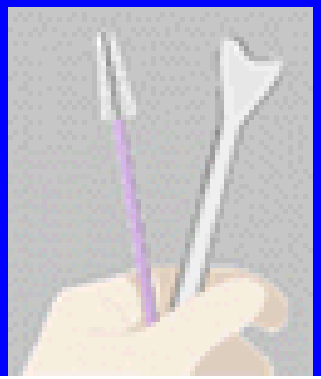


Liquid Based Pap

http://www.prlnet.com/ThinPrep.htm

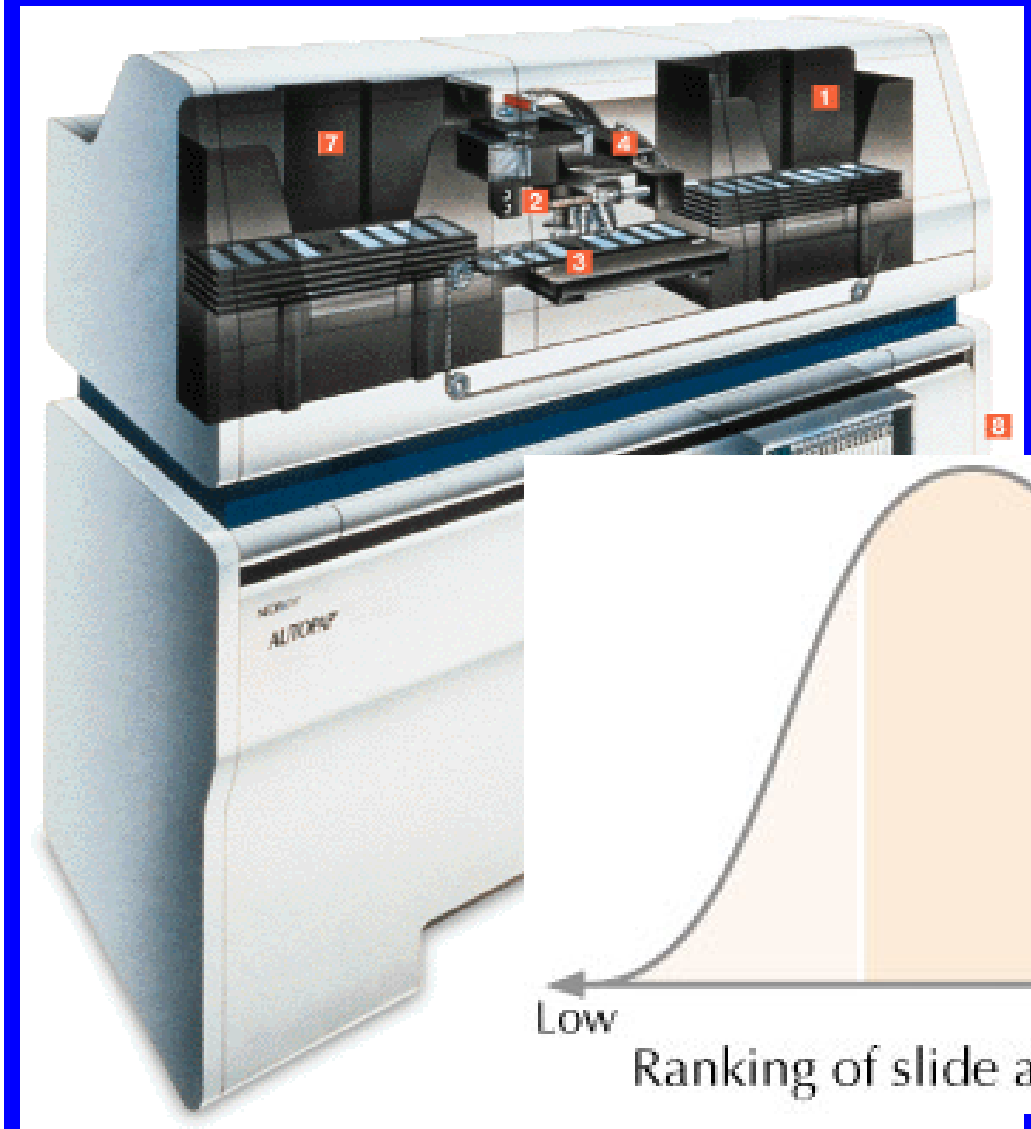
Liquid Based Pap Smear

- Gentle dispersion breaks up blood, mucous, non-diagnostic debris, and mixes sample
- Negative pressure pulse draws fluid through filter to collect a thin, even layer of cells
- Monitor flow through filter during collection to prevent cells from being too scant or too dense
- Cells then transferred to a glass slide

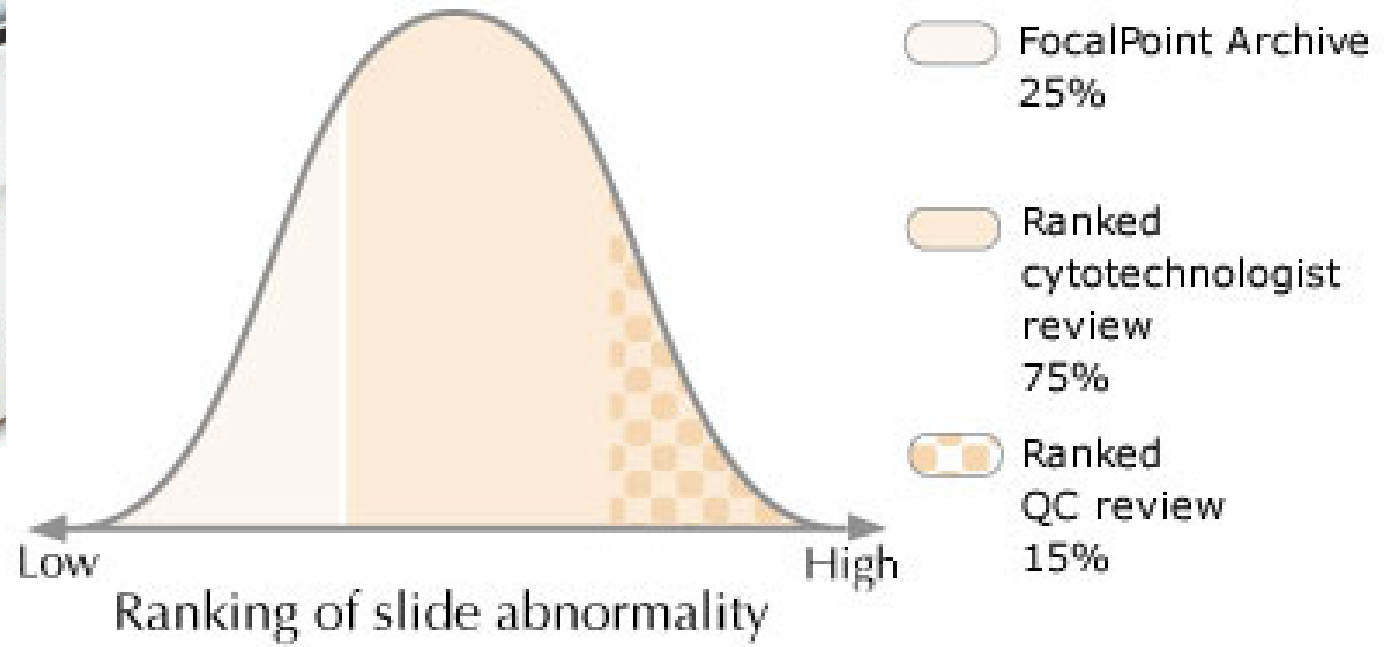



Automated Pap Smear Screening

http://www.tripathimaging.com/images/cutaway.gif



- TriPath Care Technologies
  - http://www.tripathimaging.com/usproducts/index.htm



The Lancet Oncology, *2001, Vol.* ***2*** *No. 1, pp. 27–32*

HPV Testing

- The DNAwithPap Test is FDA-approved for routine adjunctive screening with a Pap test for women age 30 and older.
- Digene
  - http://www.digene.com

http://www.digene.com/PapXYLC-5301-30%20VER%20X.mpg

1. Release Nucleic Acids

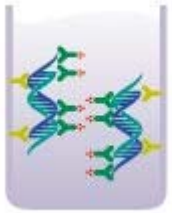
Clinical specimens are combined with a base solution which disrupts the virus or bacteria and releases target DNA. No special specimen preparation is necessary.

2. Hybridize RNA Probe with Target DNA

Target DNA combines with specific RNA probes creating RNA:DNA hybrids.

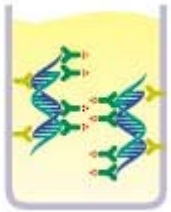
3. Capture Hybrids

Multiple RNA:DNA hybrids are captured onto a solid phase coated with universal capture anbtibodies specific for RNA:DNA hybrids.



4. Label for Detection

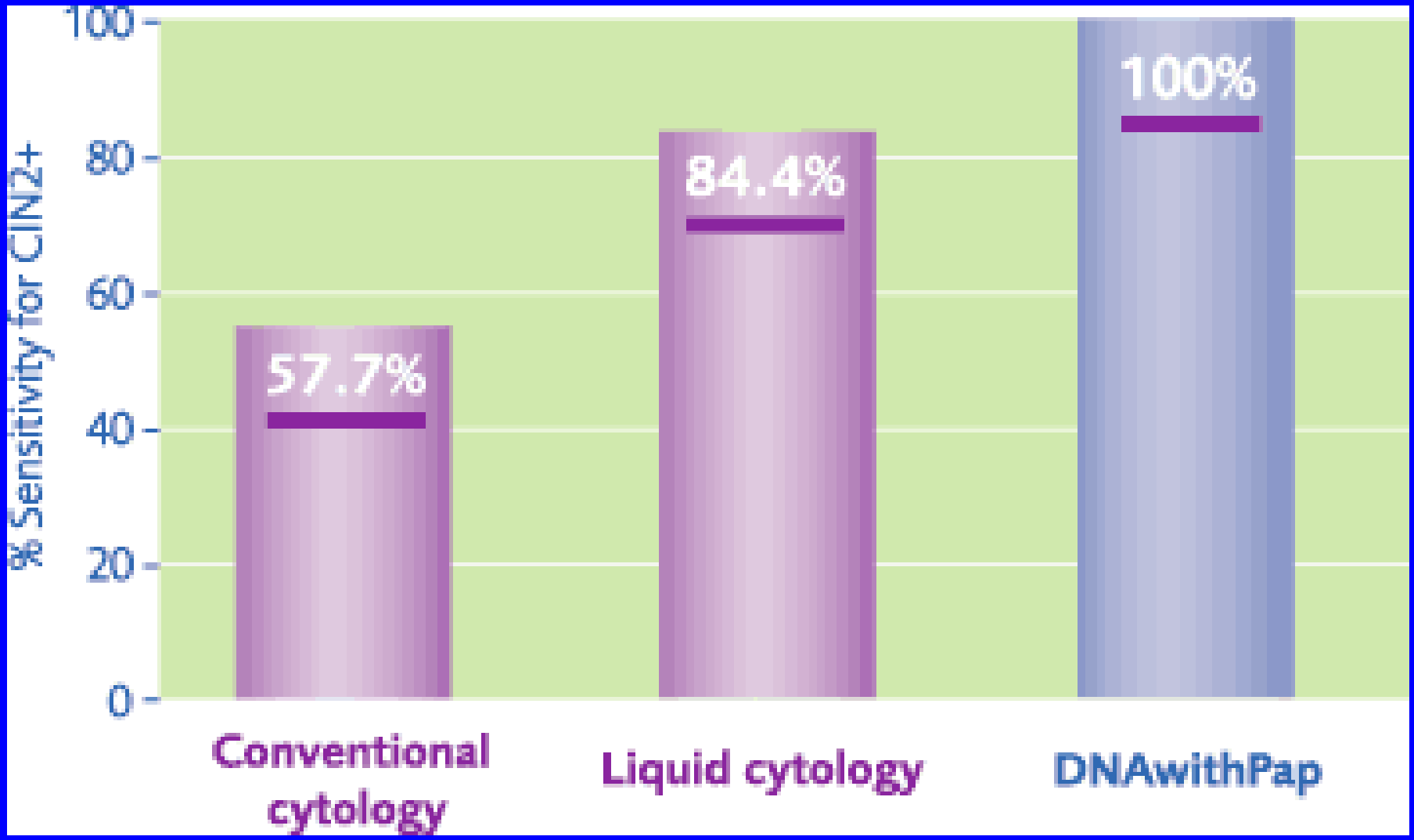
Captured RNA:DNA hybrids are detected with multiple antibodies conjugated to alkaline phosphatase. Resulting signal can be amplified to at least 3000-fold.



5. Detect, Read and Interpret Results

The bound alkaline phosphatase is detected with a chemiluminescent dioxetane substrate. Upon cleavage by alkaline phosphatase, the substrate produces light that is measured on a luminometer in Relative Light Units (RLUs).

Sensitivity of HPV Testing



http://www.digene.com/images/sens.gif

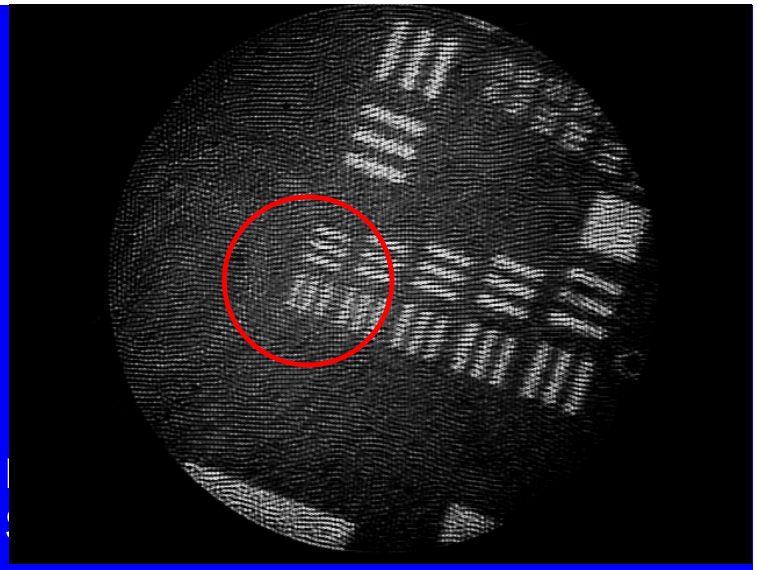
Study of 5,671 women age >30 years

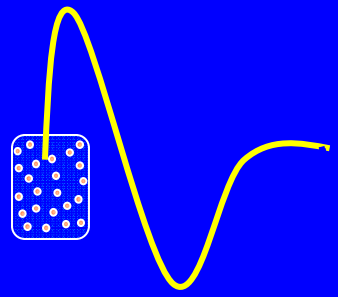
Comparison of Various Techniques

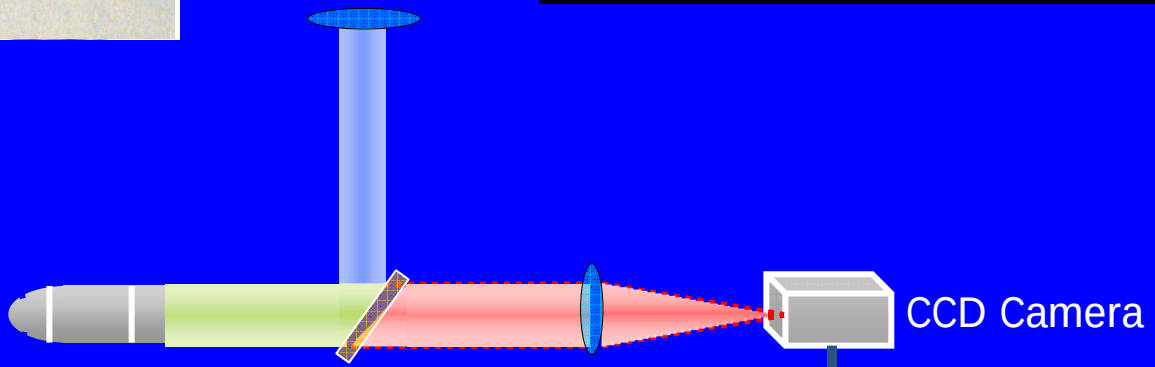
	Sensitivity	Specificity
Pap smear	60-80%	45-70%
Colposcopy	90-100%	20-50%
Digene HPV Test	80-90%	57-89%
VIA	67-79%	49-86%

Costs

Pap Test	$10-20
Liquid-based Pap	$50
Automated Pap Smear Screening	$20-60
HPV DNA test	$90
HPV vaccine	$360







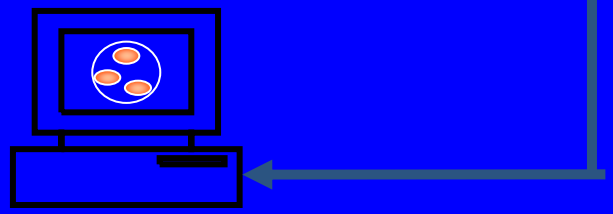


Image Guide

10X UPLAPO Objective

Dichroic Mirror

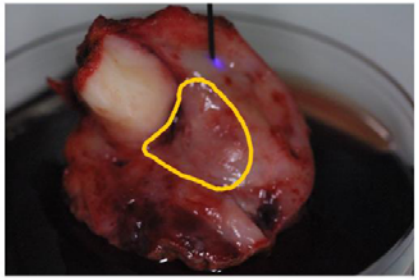
Tube Lens

CCD Camera

Frame Grabber

Needle Biopsy

Needle Biopsy



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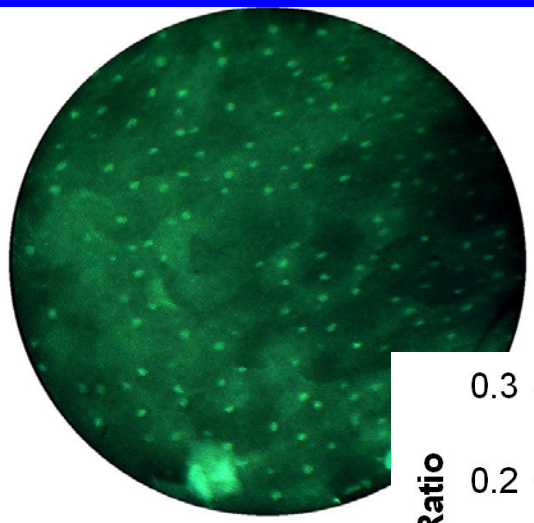

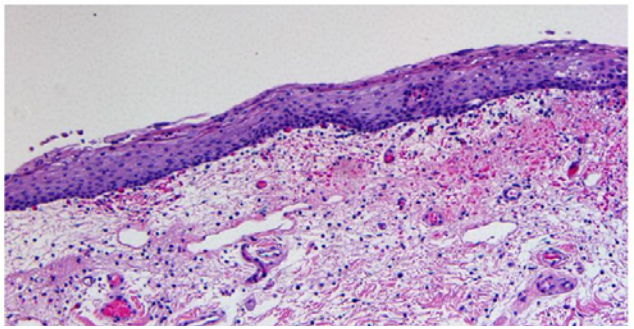

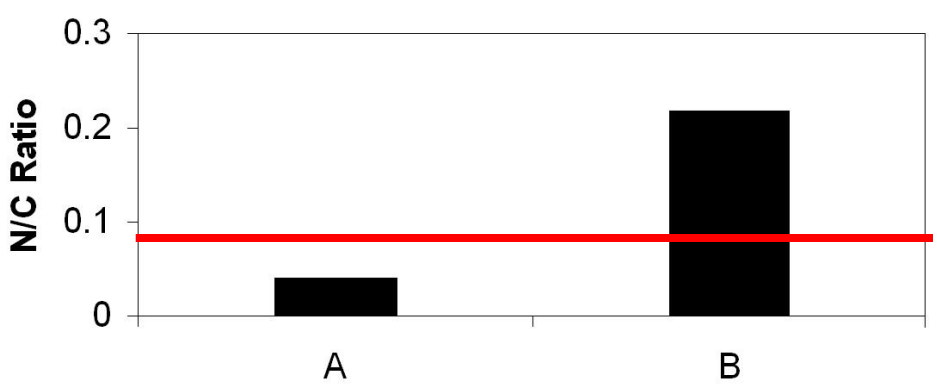

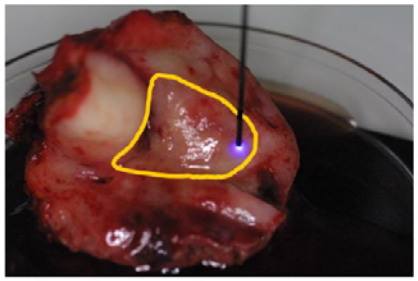

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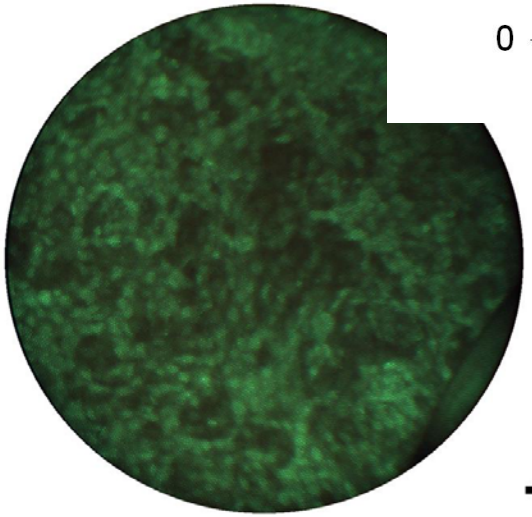
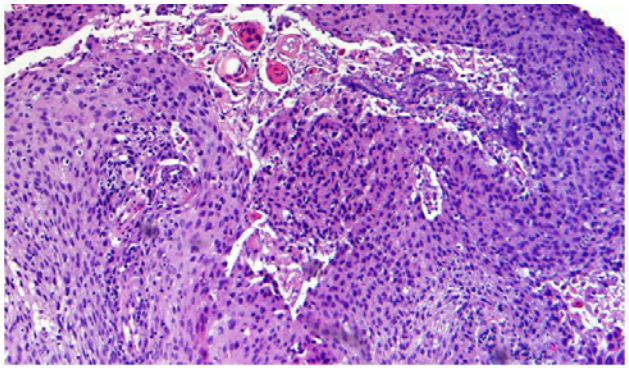
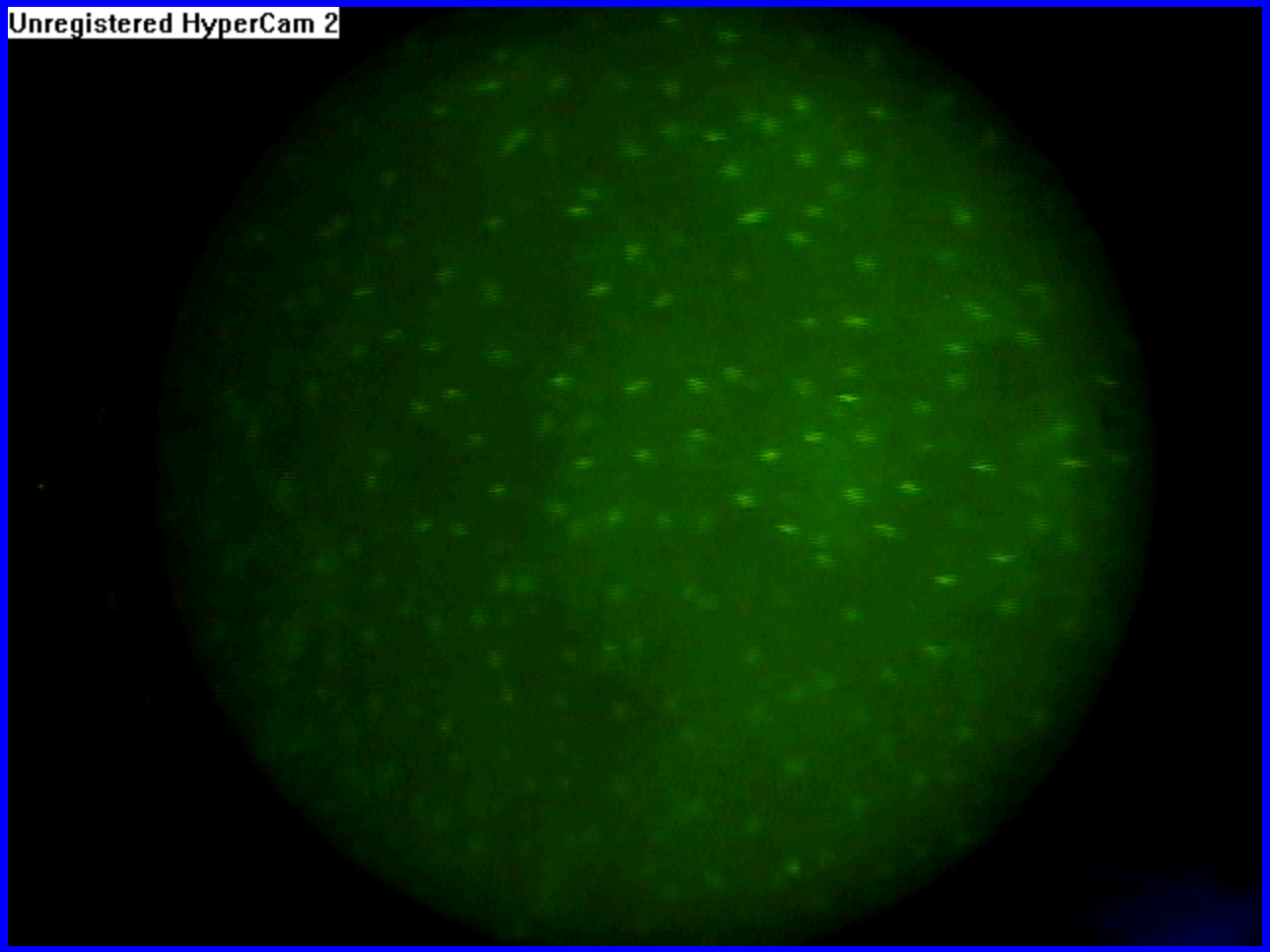





MICRO
5mm

Needle Biopsy



Summary of Cancer

- The burden of cancer
  - Contrasts between developed/developing world
- How does cancer develop?
  - Cell transformation → Angiogenesis → Motility → Microinvasion → Embolism → Extravasation
- Why is early detection so important?
  - Treat before cancer develops → Prevention
- Accuracy of screening/detection tests
  - Se, Sp, PPV, NPV

Summary of Cervical Cancer

- Cervical cancer
  - 2nd Leading cause of cancer death in women in world
  - Caused by infection with HPV
  - Precancer→cancer sequence
  - Precancer is very common
- Screening & Detection
  - Pap smear; colposcopy + biopsy
  - Reduces incidence and mortality of cervical cancer
  - Insufficient resources to screen in developing countries
- New technologies
  - Automated reading of Pap smears → reduce FN rate
  - HPV testing
  - VIA

Global Inequities in Cancer Prevention