Four Questions

- What are the major health problems worldwide?
- Who pays to solve problems in health care?
- How can technology solve health care problems?
- How are health care technologies managed?
Three Case Studies

- Prevention of infectious disease
  - HIV/AIDS
- Early detection of cancer
  - Cervical Cancer
  - Ovarian Cancer
  - Prostate Cancer
- Treatment of heart disease
  - Atherosclerosis and heart attack
  - Heart failure
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
The Burden of Cancer: U.S.

- Cancer:
  - 2nd leading cause of death in US
  - 1 of every 4 deaths is from cancer

- 5-year survival rate for all cancers:
  - 62%

- Annual costs for cancer:
  - $172 billion
    - $61 billion - direct medical costs
    - $16 billion - lost productivity to illness
    - $95 billion - lost productivity to premature death
U.S. Cancer Incidence & Mortality 2004

- New cases of cancer:
  - United States: 1,368,030
  - Texas: 84,530

- Deaths due to cancer:
  - United States: 563,700

www.cancer.org, Cancer Facts & Figures
Estimated US Cancer Cases in 2009*

**Women: 713,220**
- Breast: 27%
- Lung & Bronchus: 14%
- Colon & Rectum: 10%
- Uterine Corpus: 6%
- Non-Hodgkin Lymphoma: 4%
- Skin Melanoma: 4%
- Thyroid: 4%
- Kidney: 3%
- **Ovary**: 3%
- Pancreas: 3%
- All Other Sites: 22%

**Men: 766,130**
- Prostate: 25%
- Lung & Bronchus: 15%
- Colon & Rectum: 10%
- Urinary Bladder: 7%
- Skin Melanoma: 5%
- Non-Hodgkin Lymphoma: 5%
- Kidney: 5%
- Oral Cavity: 3%
- Leukemia: 3%
- Pancreas: 3%
- All Other Sites: 19%

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

American Cancer Society
Estimated US Cancer Deaths in 2009*

**Women: 269,800**
- Lung & Bronchus: 26%
- Breast: 15%
- Colon & Rectum: 9%
- Pancreas: 6%
- **Ovary**: 5%
- Non-Hodgkin Lymphoma: 4%
- Leukemia: 3%
- Uterine Corpus: 3%
- Liver & Intrahepatic Bile Duct: 2%
- Brain/ONS: 2%
- All Other Sites: 25%

**Men: 292,540**
- Lung & Bronchus: 30%
- **Prostate**: 9%
- Colon & Rectum: 9%
- Pancreas: 6%
- Leukemia: 4%
- Liver & Intrahepatic Bile Duct: 4%
- Esophagus: 4%
- Urinary Bladder: 3%
- Non-Hodgkin Lymphoma: 3%
- Kidney: 3%
- All Other Sites: 25%

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

American Cancer Society
Worldwide Burden of Cancer

- **Today:**
  - 11 million new cases every year
  - 6.2 million deaths every year (12% of deaths)

- **Can prevent 1/3 of these cases:**
  - Reduce tobacco use
  - Implement existing screening techniques
  - Healthy lifestyle and diet

- **In 2020:**
  - 15 million new cases predicted in 2020
  - 10 million deaths predicted in 2020
  - Increase due to ageing population
  - Increase in smoking
Worldwide Burden of Cancer

- 23% of cancers in developing countries caused by infectious agents
  - Hepatitis (liver)
  - HPV (cervix)
  - H. pylori (stomach)
- Vaccination could be key to preventing these cancers
Table 10.4. The number of estimated cancer deaths worldwide in 2002 [6].

### Estimated Worldwide Cancer Deaths in 2002*

<table>
<thead>
<tr>
<th></th>
<th>Women: 2,927,896</th>
<th>Men: 3,795,991</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Lung</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Stomach</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Colon &amp; Rectum</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Ovary</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>28%</td>
<td>23%</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers
What is Cancer?

- Characterized by uncontrolled growth & spread of abnormal cells
- Can be caused by:
  - External factors:
    - Tobacco, chemicals, radiation, infectious organisms
  - Internal factors:
    - Mutations, hormones, immune conditions
Squamous Epithelial Tissue

- Epithelium
- Stroma
- Superficial Zone
- Intermediate Zone
- Basal Zone
- Basement Membrane
Precancer ➔ Cancer Sequence
Histologic Images

Normal

Cervical Pre-Cancer
Progression of Malignant Cancer

1. Normal Cells
2. Abnormal Cells
3. Abnormal Cells Multiply
4. Malignant / Invasive Cancer

Primary Cancer
Local Invasion
Angiogenesis: Tumors grow their own blood vessels
Lymph Vessel
Boundary
Blood Vessel
Metastasis: Cells move away from primary tumor and invade other parts of the body via blood vessels and lymph vessels

©Asbestos.com
The War on Cancer

- **1971 State of Union address:**
  - President Nixon requested $100 million for cancer research

- **December 23, 1971**
  - Nixon signed National Cancer Act into law
  - "I hope in years ahead we will look back on this action today as the most significant action taken during my Administration."
Change in the US Death Rates* by Cause, 1950 & 2001

<table>
<thead>
<tr>
<th>Cause</th>
<th>1950 Rate Per 100,000</th>
<th>2001 Rate Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Diseases</td>
<td>586.8</td>
<td>193.9</td>
</tr>
<tr>
<td>Cerebrovascular Diseases</td>
<td>180.7</td>
<td>48.1</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>245.8</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td>193.9</td>
<td></td>
</tr>
</tbody>
</table>

* Age-adjusted to 2000 US standard population.
Change in the US Death Rates* by Cause, 1950 & 2001

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf
Change in the US Death Rates* by Cause, 1950 & 2001

<table>
<thead>
<tr>
<th>Cause</th>
<th>1950</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Diseases</td>
<td>586.8</td>
<td>245.8</td>
</tr>
<tr>
<td>Cerebrovascular Diseases</td>
<td>180.7</td>
<td>57.5</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>194.4</td>
<td>48.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>193.9</td>
<td></td>
</tr>
</tbody>
</table>

* Age-adjusted to 2000 US standard population.
Change in the US Death Rates* by Cause, 1950 & 2001

* Age-adjusted to 2000 US standard population.
Change in the US Death Rates* by Cause, 1950 & 2001

<table>
<thead>
<tr>
<th>Cause</th>
<th>1950 Rate</th>
<th>2001 Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Diseases</td>
<td>586.8</td>
<td>245.8</td>
</tr>
<tr>
<td>Cerebrovascular Diseases</td>
<td>180.7</td>
<td>57.5</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>48.1</td>
<td>21.8</td>
</tr>
<tr>
<td>Cancer</td>
<td>193.9</td>
<td>194.4</td>
</tr>
</tbody>
</table>

* Age-adjusted to 2000 US standard population.

*Age-adjusted to the 2000 US standard population.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>66</td>
<td>51</td>
<td>55</td>
<td>68</td>
<td>40</td>
<td>41</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>24</td>
<td>29</td>
<td>35</td>
<td>23</td>
<td>28</td>
<td>34</td>
<td>27</td>
<td>33</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>89</td>
<td>76</td>
<td>80</td>
<td>91</td>
<td>62</td>
<td>65</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>65</td>
<td>52</td>
<td>60</td>
<td>66</td>
<td>46</td>
<td>50</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>5</td>
<td>10</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>18</td>
<td>3</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>74</td>
<td>79</td>
<td>86</td>
<td>74</td>
<td>80</td>
<td>87</td>
<td>71</td>
<td>75</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>51</td>
<td>56</td>
<td>67</td>
<td>51</td>
<td>56</td>
<td>67</td>
<td>50</td>
<td>54</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>67</td>
<td>64</td>
<td>67</td>
<td>67</td>
<td>66</td>
<td>64</td>
<td>59</td>
<td>53</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>51</td>
<td>36</td>
<td>43</td>
<td>52</td>
<td>34</td>
<td>34</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Liver*</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>11</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>82</td>
<td>87</td>
<td>92</td>
<td>82</td>
<td>87</td>
<td>92</td>
<td>60</td>
<td>70</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>26</td>
<td>29</td>
<td>35</td>
<td>25</td>
<td>27</td>
<td>35</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>65</td>
<td>48</td>
<td>54</td>
<td>66</td>
<td>49</td>
<td>48</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>53</td>
<td>55</td>
<td>60</td>
<td>55</td>
<td>57</td>
<td>62</td>
<td>36</td>
<td>36</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>46</td>
<td>37</td>
<td>39</td>
<td>45</td>
<td>43</td>
<td>41</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>99</td>
<td>70</td>
<td>77</td>
<td>99</td>
<td>61</td>
<td>66</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>67</td>
<td>49</td>
<td>58</td>
<td>67</td>
<td>45</td>
<td>46</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>16</td>
<td>18</td>
<td>25</td>
<td>15</td>
<td>18</td>
<td>23</td>
<td>16</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>83</td>
<td>93</td>
<td>96</td>
<td>83</td>
<td>93</td>
<td>96</td>
<td>82</td>
<td>87</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>93</td>
<td>94</td>
<td>97</td>
<td>93</td>
<td>94</td>
<td>97</td>
<td>91</td>
<td>90</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>74</td>
<td>78</td>
<td>81</td>
<td>75</td>
<td>79</td>
<td>82</td>
<td>51</td>
<td>61</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>70</td>
<td>68</td>
<td>73</td>
<td>71</td>
<td>70</td>
<td>74</td>
<td>65</td>
<td>58</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>88</td>
<td>84</td>
<td>84</td>
<td>89</td>
<td>85</td>
<td>86</td>
<td>61</td>
<td>58</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

*Survival rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 9 areas from 1975-1977, 1984-1986, and 1996-2004, and followed through 2005. †The difference in rates between 1975-1977 and 1996-2004 is statistically significant (p <0.05). ‡The standard error of the survival rate is between 5 and 10 percentage points. §The standard error of the survival rate is greater than 10 percentage points. #Includes intrahepatic bile duct.

Importance of Early Detection

Five Year Relative Survival Rates

Breast
Ovary
Cervix

American Cancer Society. Cancer Facts and Figures 2005
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
Cancer Screening

- We routinely screen for 4 cancers:
  - Female breast cancer
    - Mammography
  - Cervical cancer
    - Pap smear
  - Prostate cancer
    - Serum PSA
    - Digital rectal examination
  - Colon and rectal cancer
    - Fecal occult blood
    - Flexible sigmoidoscopy, Colonoscopy
Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.

A clinical breast exam should be part of a periodic health exam, about every three years for women in their 20s and 30s, and every year for women 40 and older.

Women should know how their breast normally feel and report any breast changes promptly to their health care providers. Breast self-exam is an option for women starting in their 20s.

Women at increased risk (e.g., family history, genetic tendency, past breast cancer) should talk with their doctors about the benefits and limitations of starting mammography screening earlier, having additional tests (i.e., breast ultrasound and MRI), or having more frequent exams.
How do we judge efficacy of a screening test?

Sensitivity/Specificity

Positive/Negative Predictive Value
Sensitivity & Specificity

**Sensitivity**
- Probability that given DISEASE, patient tests POSITIVE
- Ability to correctly detect disease
- 100% - False Negative Rate

**Specificity**
- Probability that given NO DISEASE, patient tests NEGATIVE
- Ability to avoid calling normal things disease
- 100% - False Positive Rate
**Possible Test Results**

<table>
<thead>
<tr>
<th></th>
<th>Test Positive</th>
<th>Test Negative</th>
<th># with Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Present</td>
<td>TP</td>
<td>FN</td>
<td>TP+FN</td>
</tr>
<tr>
<td>Disease Absent</td>
<td>FP</td>
<td>TN</td>
<td>FP+TN</td>
</tr>
</tbody>
</table>

# Test Pos = TP+FP

# Test Neg = FN+TN

Total Tested = TP+FN+FP+TN

Se = TP/(# with disease) = TP/(TP+FN)

Sp = TN/(# without disease) = TN/(TN+FP)
Amniocentesis Example

- **Amniocentesis:**
  - Procedure to detect abnormal fetal chromosomes

- **Efficacy:**
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive

- **Calculate:**
  - Sensitivity & Specificity
### Possible Test Results

<table>
<thead>
<tr>
<th></th>
<th>Test Positive</th>
<th>Test Negative</th>
<th># with Disease = 28</th>
<th># without Disease = 972</th>
<th>Total Tested = 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Present</td>
<td>25</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Absent</td>
<td>7</td>
<td>965</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Se = \frac{25}{28} = 89\%  Sp = \frac{965}{972} = 99.3\%
As a patient:

What Information Do You Want?
Predictive Value

- **Positive Predictive Value**
  - Probability that given a POSITIVE test result, you have DISEASE
  - Ranges from 0-100%

- **Negative Predictive Value**
  - Probability that given a NEGATIVE test result, you do NOT HAVE DISEASE
  - Ranges from 0-100%

- Depends on the prevalence of the disease
## Possible Test Results

<table>
<thead>
<tr>
<th></th>
<th>Test Positive</th>
<th>Test Negative</th>
<th># with Disease = TP+FN = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Present</strong></td>
<td>TP 25</td>
<td>FN 3</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Absent</strong></td>
<td>FP 7</td>
<td>TN 965</td>
<td>#without Disease = FP+TN = 972</td>
</tr>
<tr>
<td><strong>Total Tested</strong></td>
<td># Test Pos = TP+FP = 32</td>
<td># Test Neg = FN+TN = 968</td>
<td>Total Tested = TP+FN+FP+TN = 25+3+7+965 = 1000</td>
</tr>
</tbody>
</table>

\[
PPV = \frac{TP}{(# \text{ Test Pos})} = \frac{TP}{(TP+FP)} = \frac{25}{(25+7)} = .781
\]

\[
NPV = \frac{TN}{(# \text{ Test Neg})} = \frac{TN}{(FN+TN)} = \frac{965}{(3+965)} = .997
\]
Amniocentesis Example

- **Amniocentesis:**
  - Procedure to detect abnormal fetal chromosomes

- **Efficacy:**
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive

- **Calculate:**
  - Positive & Negative Predictive Value
Dependence on Prevalence

- Prevalence – is a disease common or rare?
  - \( p = \frac{\text{# with disease}}{\text{total #}} \)
  - \( p = \frac{TP+FN}{TP+FP+TN+FN} = \frac{25+3}{25+7+965+3} = 28/1000 = .028 \)

- Does our test accuracy depend on \( p \)?
  - \( Se/Sp \) do not depend on prevalence
  - \( PPV/NPV \) are highly dependent on prevalence

- \( PPV = \frac{pSe}{[pSe + (1-p)(1-Sp)]} = .781 \)
- \( NPV = \frac{(1-p)Sp}{[(1-p)Sp + p(1-Se)]} = .997 \)
Is it Hard to Screen for Rare Disease?

- **Amniocentesis:**
  - Procedure to detect abnormal fetal chromosomes

- **Efficacy:**
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive

- **Calculate:**
  - Prevalence of chromosomal abnormalities
Is it Hard to Screen for Rare Disease?

- **Amniocentesis:**
  - Usually offered to women > 35 yo

- **Efficacy:**
  - 1,000 20-year-old women given the test
  - Prevalence of chromosomal abnormalities is expected to be 2.8/1000

- **Calculate:**
  - Sensitivity & Specificity
  - Positive & Negative Predictive Value
  - Suppose a 20 yo woman has a positive test. What is the likelihood that the fetus has a chromosomal abnormality?
Cervical Cancer

Early Detection
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
Global Burden of Cervical Cancer

Age-standardized incidence / 100,000 population
What Initiates Transformation?

**Benign Growth**
- Host Cell Chromosome
- Integration of viral genes of HPV into the genome of a host cell leads to uncontrolled growth.

**Malignant Growth**
- DNA of HPV integrated into host cell chromosome
Pathophysiology
How Do We Detect Early Cervical Cancer?

- Pap Smear (The most successful cancer-screening test in medical history)
- Coposcopy + Biopsy
Pap Smear

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

Courtesy of Mayo Foundation for Medical Education and Research. All rights reserved.
Screening Guidelines for the Early Detection of Cervical Cancer, American Cancer Society 2006

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. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.

Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test.

Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or a weakened immune system should continue to have screening as long as they are in good health.

Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or precancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.
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
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

- TriPath Care Technologies

![Automated Pap Smear Screening Diagram](Image)

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
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>Release Nucleic Acids</strong>&lt;br&gt;Clinical specimens are combined with a base solution which disrupts the virus or bacteria and releases target DNA. No special specimen preparation is necessary.</td>
</tr>
<tr>
<td>2.</td>
<td><strong>Hybridize RNA Probe with Target DNA</strong>&lt;br&gt;Target DNA combines with specific RNA probes creating RNA:DNA hybrids.</td>
</tr>
<tr>
<td>3.</td>
<td><strong>Capture Hybrids</strong>&lt;br&gt;Multiple RNA:DNA hybrids are captured onto a solid phase coated with universal capture antibodies specific for RNA:DNA hybrids.</td>
</tr>
<tr>
<td>4.</td>
<td><strong>Label for Detection</strong>&lt;br&gt;Captured RNA:DNA hybrids are detected with multiple antibodies conjugated to alkaline phosphatase. Resulting signal can be amplified to at least 3000-fold.</td>
</tr>
<tr>
<td>5.</td>
<td><strong>Detect, Read and Interpret Results</strong>&lt;br&gt;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).</td>
</tr>
</tbody>
</table>
## Comparison of Various Techniques

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear</td>
<td>60-80%</td>
<td>45-70%</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>90-100%</td>
<td>20-50%</td>
</tr>
<tr>
<td>Digene HPV Test</td>
<td>80-90%</td>
<td>57-89%</td>
</tr>
<tr>
<td>VIA</td>
<td>67-79%</td>
<td>49-86%</td>
</tr>
</tbody>
</table>
## Comparison of Various Techniques

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap Test</td>
<td>$10-20</td>
</tr>
<tr>
<td>Liquid-based Pap</td>
<td>$50</td>
</tr>
<tr>
<td>Automated Pap Smear Screening</td>
<td>$20-60</td>
</tr>
<tr>
<td>HPV DNA test</td>
<td>$90</td>
</tr>
<tr>
<td>HPV vaccine</td>
<td>$360</td>
</tr>
</tbody>
</table>
HPV vaccine

- 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?

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