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Reasons for This Presentation

• Cervical Cancer Screening = Moving from Simple to Complex Approaches

• Cervical Cancer has not been eradicated despite recent discoveries and improvements in testing/screening

• Controversy and Disagreement regarding Screening Intervals and Follow-up

Goals

• Start with a Few Questions and End with: +/- Questions > Answers?

• Focused Look at the Factors and Forces shaping this Evolution

• Reveal lesser known realities which will be obstacles in the future
The Evolution of Cervical Cancer Screening in the United States

• The First Pap Test, or the “Pap Smear”
• The Role of HPV in Carcinogenesis
• The Improved Pap Test, or Liquid Based Cytology
• The Role of Molecular Diagnostic Testing for High Risk HPV Detection
  ➢ As a Reflex Test
  ➢ As a Primary Screening Test
• The Development of Preventative HPV Vaccines

➤ Will Complex Tests, Vaccines and Surveillance = Eradication of Cervical Carcinoma and Decrease Surgical Interventions?
A Brief Historical Overview of The PAP “Smear”

• The most effective cancer screening test in history of medicine

• The Pap Test has dramatically lowered Cervical Cancer Incidence and Mortality by over 75% in Developed countries including the US

• Cervical Cancer was a leading Killer of women in 1920 (and remains so in most of the world without quality screening programs)

• In 1923 Dr George Papanicolaou made the discovery of cancer cells under the microscope while studying the effects of hormones on the cervical-vaginal epithelium

• He postulated that there must be a series of precursor steps(lesions) which can be detected microscopically and possibly preventing the development of Invasive Cancer, if patients are *sampled repeatedly*

• Through the efforts of Dr. Papanicolaou and other Physicians he collaborated with during the 1930s and 1940s, they eventually developed the microscopic criteria which have been shown to represent a spectrum of precursor lesions which range from **LGSIL(CIN I)** to **HGSIL (CIN II and CINIII Carcinoma In – Situ)**
Dr. George Papanicolaou (1883-1962)

1904 – MD, U of Athens
1910 – PhD, Zoology U of Munich
1914 – 1961 Cornell University

Made the discovery and developed the test that made him famous

Early Work:
Reproductive Endocrinology

Later Work:
Transferred the Cytologic Method to Medicine
Reproductive Endocrinology

Early work of the 1920s focused on

- Testing the theory of sex determination by the X, Y Chromosomes
- Study the effects of hormones on the FGT epithelium
- Used vaginal samples from rodents collected with suction pipette via a nasal speculum
- Microscopic examination of “exfoliated cells” in the vaginal pool secretion became the cytologic sampling method
Application to Medicine

• Cytologic method was used to evaluate the effects of hormones on the vaginal epithelium of women

• The High Prevalence of FGT Cancer in the 1920s = good odds of accidently seeing cancer cells

“In the field of observation, chance favors the prepared mind”
Louis Pasteur

• James Ewing – Chair of Pathology, New York Memorial Hospital

➢ Probably assisted in the positive ID of the cancer cells but was very much against the use of cytology in cancer detection and diagnosis

➢ Rationale: Histology already confusing and difficult with thousands of cells, cytology would be unreliable in obtaining consensus agreement in diagnosis
Early Opposition

- The cytologic method of evaluation was initially met with overwhelming skepticism as it was poorly received by pathologists and clinicians.

- Dr. Papanicoloau was eventually at the Right Place at the Right Time with the Right People to support this revolutionary idea.

- Dr. Joseph Hinsey became the Chair of Anatomy in 1939, and pledged his full support of cytology in the detection and diagnosis of cancer.

- Arranged key collaborations with interested physicians at New York Hospital/Cornell University:
  
  - **Herbert Traut** – A gynecologist trained in Pathology
  - **Andrew Marchetti** – Chair of the OB Gyn clinic

- Collaboration provided a wealth of study material and data = All women admitted to the OB GYN clinic were required to have a vaginal smear collected for evaluation.
The 3 Step Program

Together, Dr. Pap and his colleagues outlined a plan to move cytology screening forward:

(1) Establish the validity of the cytologic method
(2) Train others to use it
(3) Educate the medical community and the public in what the cytologic method has to offer

They also recognized their need for financial support and applied for 3 different cancer research funding grants = all denied

1940 – Lester Evans, Medical Director of the Commonwealth Fund pledged $124,000 for 10 years

1945 – Charles Cameron, Director of the newly organized American Cancer Society, became a major voice and advocate of “Pap Smears” as a core focus of cancer research, prevention and intervention
The 1st Cohort Study of the Cytologic Method: Cornell University and New York Hospital 1939-1942

Diagnosis of Uterine Cancer by the Vaginal Smear. By George N. Papanicolaou and Herbert F. Traut. The Commonwealth Fund, New York, 1943. x + 46 pp., 11 plates. $5.

This work describes a new approach to the diagnosis of uterine cancer and is of essential interest because its use promises to be of signal value in the recognition of early uterine cancer, especially that of the cervix. The method is based upon the recognition of exfoliated abnormal cells characteristic of carcinoma which may be found in the study of the stained vaginal smear. During the three years covered by the study 3014 women have been intensively studied and among these 179 were found to have cancer which was primary in the uterus. Of these, 127 were cervical cancer. In the latter group, 7 were found to be early intradermal types of squamous carcinoma and nearly all were invisible on close inspection of the cervix.

The authors state that the method is not recommended as a means of ultimate diagnosis, but rather as a preliminary or sorting procedure to be confirmed by biopsy and tissue diagnosis. They also emphasize that the evaluation of the stained smear requires a greater knowledge of cytology than that necessary for diagnosis in tissue preparations.

The colored illustrations in this work are a fine exposition of the printer’s art and show in a splendid manner the cytological differences that exist in the various cell types which may be found in the stained vaginal smear. The authors are to be congratulated not only upon a study which promises to be of great significance, but also upon the clearness and beauty of its presentation in this volume.

—Herbert Thoms.
The Cytologic Method

- FGT Carcinoma was Highly Prevalent and was a Major Public Health problem in the 1940s

- Postulated that a series of precursor lesions could be detected and described microscopically before invasion occurs

- A screening procedure in Asymptomatic women

- Early Diagnosis and Treatment = Higher Percentages of cured patients

- Success is dependent upon Regular, Repeated Sampling
The Earliest Pap Smears: Vaginal Pool Samples

Patient Sample was the random accumulation of cells in the vaginal pool

Collected using a Suction Bulb attached to a glass pipette

Sample for examination Dependent entirely on spontaneous exfoliation of both normal and abnormal cells

Wet Fixation in an Ether-Alcohol Solution to preserve well visualized cellular detail
An Early Improvement of the Pap Test

Dr. J Ernest Ayre - Canadian Gynecologist

Dr. Ayre was a pioneer in refining and promoting the Pap test for women

Sometimes a great idea usually begins with subsequent growth and development required:

Mechanical Exfoliation vs Spontaneous Exfoliation?

Direct mechanical sampling with a better collection instrument – The Ayre Spatula

Founded The National Cancer Center in 1953, a non-profit organization committed to research and education about cancer
In 1944 Canadian Gynecologist J. Ernest Ayre developed the idea that more cervical disease could be detected with a direct, Instrumented sampling of the cervix.

Why have Screening Programs been so Successful?

Success was realized with High Disease Prevalence in an Unscreened Population

The development of reliable cytologic criteria by Pathologists and Cytotechnologists has lead to accurate and reliable histologic correlation on biopsy and surgical resection specimens

After Dr. Papanicoloau and other physicians developed the sampling technique and microscopic criteria, the credibility and validity of Pap testing caught on in the medical community in the 1950s

Screening programs were established across the US and become a public health initiative that has been very effective

The establishment of quality Cytopathology training programs over the last 75 years also accommodated this new public health measure

Repeated Annual Screening

The Pap Test has been the focus of continuous quality improvement
Number of New Cases and Deaths per 100,000: The number of new cases of cervix uteri cancer was 7.7 per 100,000 women per year.

The number of deaths was 2.3 per 100,000 women per year.

These rates are age-adjusted and based on 2008-2012 cases and deaths.
“Nothing is so powerful as an idea whose time has come”

Victor Hugo
Illustrations of Cells Found in Cancer Patients

Pap Test Limitations

- **Sampling Dependent Test**: The sampling instrument must sample the lesion. Many CIN I and CIN II are not grossly evident.

- **Represents a Blind sampling**: There usually isn’t any certainty that the Transformation Zone is being sampled as its location varies in each woman based upon age and unique anatomy.

- **A Labor Intensive Process**: Conventional Smear Preparations usually contain anywhere from 100,000 to 300,000 cells which must be analyzed quickly = humans making unavoidable errors under pressure.

- **Suboptimal Samples**: Often have air drying artifact, thick obscuring areas of cells, blood and inflammation which can interfere with interpretation or hide abnormal cells.
Conventional Pap Smear Sampling
Conventional Smear Slide: Obscuring Inflammation
Conventional Smear Slide:
Obscuring Blood and Air Drying Artifact

Figure 3: Conventional Pap smear, Pap stain, 40X
Not all Screeners are Created Equal

• Some Women had a series of “Negative” Pap Smears and then an abrupt Cervical Cancer

• Women with Negative Pap Smears are rarely biopsied

• Clinicians and laboratories were unaware of how much disease was being missed by screening tests

• Precursor lesions and cancer develop slowly

• Unfortunately, some labs were motivated by volume and profit, not performing quality cancer detection at the microscope

Lax Laboratories
The Pap Test Misses Much Cervical Cancer Through Labs’ Errors
Cut-Rate ‘Pap Mills’ Process Slides Using Screeners With Incentives to Rush
Misplaced Sense of Security?

By WALT BOGDANICH 11-2-87
Staff Reporter of The Wall Street Journal
The Pap smear. Over the past three decades, it has sharply reduced deaths from cervical cancer. Women and physicians trust it, so much so that the Pap smear has become one of the most common laboratory tests in America. It is also one of the most inaccurate. No one knows how many women die because a lab botches the analysis or a doctor takes an inadequate specimen. The test, as it is being done today, fails to detect roughly one in every four cases of cancer or precursor cell abnormalities.
The Perfect Storm: CLIA 1988

- A lack of oversight and regulation allowed for instances of negligence and gross errors in Pap Smear screening in laboratories during the 1970s and 1980s.

- The Clinical Laboratory Improvement Acts of 1988 (CLIA) resulted from Litigation and Increased public awareness due to Negative Press Reports.

- Occult Cancers –
  - Some cases were due to sampling inadequacies and/or poor quality slides which made accurate interpretation impossible.
  
  - Other cases were due to negligent screening practices and the failure to detect abnormal cells microscopically, which should have lead to further clinical investigation for the patients.

- This lead to the unrealistic expectations that Pap Tests are Perfect and should result in the 100% detection of Precursor Cervical lesions and Carcinoma.

- Focused efforts to improve every part of the Pap Test Process emerged starting in the late 1980s.
“Knowledge and Wisdom You Seek...”
An Overview of All the Changes Since the 1990s

• Greater understanding of the Biology of HPV Virus and its role in Cervical Carcinogenesis

• Liquid Based Cytology and the improvement of the Pap Test as a result

• Image Guide Screening Technology as a tool for assisting cytotechnologists with locating the cells that are diagnostic of precursor lesions

• Molecular Diagnostic Testing technology used for detecting High Risk HPV DNA infection

• Preventive HPV Vaccines: Bivalent Cervarix, 4 – Valen Gardisil and 9 – Valen Gardisil

• Approaches in Patient Screening and Follow-up Management of precursor lesions
Liquid-Based Cytology

Physician Office

Sample Collected

Laboratory

- Representative sample
- Even distribution of cells
- Minimal obscuring material

Dispersion / Collection / Transfer
Liquid Based Cytology Samples

2 Purposes in 1 specimen collection:

• Microscopic screening of cellular samples from Cervix

• HPV HR DNA Testing can be performed as collection vials contain an ideal preservative medium
Anatomy of the Female Genital Tract
Histology of the Transformation Zone (T-Zone)

The Vaginal Wall and Ectocervix
- Lined by Stratified Non Keratinizing Squamous Epithelium

The Transformation Zone
- Area of Squamous Metaplastic Cells

The Endocervical Canal
- Columnar glandular cells

Mature squamous cells

Immature squamous cells
The Transformation Zone

The T ZONE = The most common site for the development of:

• **Precancerous Lesions**
  – Low Grade and High Grade Squamous Intraepithelial Lesions (Cervical Dysplasia)

• **Invasive Carcinoma**
Histology of Vaginal Mucosa and Ectocervix

II.1
a. Normal histology; b. Basal cells [C]; c. Parabasal cells [C]; d. Intermediate cell [C]; e. Superficial cell [C]
Sample Collection

• A Speculum is inserted into the Vagina and is used to expose the Cervix – Transformation Zone

• Procedure is basically a blind sampling of cells
The Goal of the Cytotechnologists: Finding Waldo
Glass Slide Preparations

• Samples are placed into fixative containers

• Centrifugation creates a thin monolayer of cells concentrated into a circular area

• Glass slides are stained with the Papanicoloau method which includes Hematoxylin, Eosin and Orange G Dyes
The Results are a Huge Improvement
The Discovery of HPV Types 16 and 18

Carcinogenic (High Risk) HPV

- Harold Zur Hausen
  “Condylomata Accuminatum and Cervical Cancer”

- HPV16: PNAS 1983; 80: 3812-5
- HPV18: EMBO 1984; 3: 1151-7
- 2000: FDA approval of Digene Hybrid Capture 2 reflex test with ASCUS cytology
- 2003: FDA approval of HPV and Pap cotesting women ≥30
- 2008 Nobel prize in Medicine
The Strong Association of HPV and Cervical Cancer

**High Risk HPV Testing**

- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7% \(^1\)
- “Virtually all cervical cancers” commonly claimed to be due to persistent carcinogenic hrHPV infections. \(^2\)
- Long interval of 8 to 50 years \(^3\) from initial HPV infection to most invasive disease.

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Profile of the HPV Virus

- Member of Papovavirus Family

- There are approximately 150 HPV Types, with about 40 HPV types causing genital lesions

- HPV is the most common Sexually Transmitted Pathogen

- HPV is very prevalent, with 50% or more of the general population eventually exposed to various viral types

- Only a small percentage of women (5 – 10%) develop genital lesions from persistent infection

- Most women clear the virus with strong cell mediated immunity in 1-2 years following exposure
HPV Pathogenesis I

- HPV Virus requires a live host cell for replication

- Trauma to the epithelium exposes the basement membrane

- HPV Virus targets squamous epithelial cells at the **basal layer (reserve cells)** which are capable of fully differentiating

- Genetic material is a circular DNA strand with 6 Early E Genes (code for Viral Replication) and 2 Late L genes (code for Capsid Proteins)

- Viral Integration into host cell DNA disrupts and inactivates E2 Gene

- Leads to overexpression of E6 and E7 gene protein products

- E6 and E7 bind to the p53 and pRb (Retinoblastoma) proteins respectively, blocking their normal cell cycle regulation activity

- Without the protection of Rb and p53, Infected cells grow wildly with the accumulation of damaged DNA
HPV General Structure

HPV genome organization

URR
Promoter and enhancer elements
Viral ORI

L1
Major capsid protein

L2
Minor capsid protein

Early genes
E1–Replication
E2–Replication and transcription
E4–Viral release
E5–Immune evasion
E6–Binds p53
E7–Binds pRB

Late genes
E5

Non Enveloped DNA Virus
HPV Pathogenesis II

• HPV viral infection and integration in the cell produces E6 and E7 proteins, which are **Virulence Factors** which selectively target p53 and pRb

• Rb and p53 are **Tumor Suppressor Genes**, 2 main “security guards” of cell

• Normal Function of p53
  – Activate DNA Repair Proteins
  – Arrest cell growth when DNA damage is recognized
  – Promote Apoptosis when DNA damage is beyond repair

• Normal Function of pRb
  – Prevent excessive cell growth by regulating the cell cycle

• Their normal activities within the cell stop the proliferation and progression of potential precancerous dysplasia and carcinoma

• Disruption of Rb and p53 causes blocked apoptosis and cell cycle arrest, leading to **Intraepithelial Lesions**, AKA “Dysplastic Cells”

Zur Hausen, H. Papillomaviruses and Cancer: From Basic Studies to Clinical Application
## Risk Factors for Acquiring HPV Infection

### Strong Association
- Beginning sexual activity at an early age (16 years or younger)
- Having many sex partners (the greater the number, the greater the probability of exposure to viral types, the greater the uncertainty)
- Having a sex partner who has had many sex partners (Even more uncertainty as How do you really know your risk?)
- Having a male sex partner who has not been circumcised (the penile foreskin often harbors HPV Virus for reasons which are unclear)

### Probable Association
- Cigarette Smoking
- Long term Oral Contraceptive use
- Increased Parity
- Other Sexually Transmitted Diseases such as Chlamydia, Gonorrhea and Herpes
• May or may not be grossly evident

• If present, may appear as raised, red or gray papules
Low Risk HPV

- Condyloma Acuminata
  "Genital Warts"

- HPV Types 6 and 11 cause about 90% of all genital warts

- Corresponds to CIN I or LGSIL
LGSIL – Cin I
“The Koilocyte”

- Clear perinuclear vacoule with well defined border
- Nuclear enlargement at least 3 times the size of an intermediate cell nucleus
- Intense staining of nuclear chromatin “Hyperchromasia”
- Irregular Nuclear Membranes
- Infected squamous cells which are actively producing viral particles and are sequestered in the vacoule
- Cells can be multinucleated
LGSIL

- Largest Dysplastic cells
- Largest Nuclei
- Lowest NC Ratio due to high amount of cytoplasm
- Can be caused by both Low Risk and High Risk HPV Virus
High Risk HPV

- Types 16 and 18 are the most common

- Responsible for approximately 70% of all cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma respectively

- Average time for progression from CINI (LGSIL) to Invasive Carcinoma is 12 – 25 years

- Most HGSIL (CIN II and III) lesions **will regress** and not progress to Invasive Carcinoma if untreated

- 14 other High Risk Types account for an additional 20% of Cervical Carcinomas (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and 82)

- HPV Testing targets all of the above High Risk Types for detection except Types 73 and 82
Precursor Lesions of Squamous Cell Carcinoma of the Cervix

<table>
<thead>
<tr>
<th>L SIL</th>
<th>H SIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
<td>CIN II</td>
</tr>
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</table>

Normal | Mild dysplasia | Moderate dysplasia | Severe dysplasia | Carcinoma in situ

Stanley, M. Pathology and Epidemiology of HPV Infection in Females. Gynecologic Oncology 117 (2010) S5-S10
HGSIL – CIN II Moderate Dysplasia

- Hyperchromasia
- Increased Nuclear Cytoplasmic Ratio
- Variation in Nuclear Size and Shape
- Decreasing overall cell size compared to LGSIL – CIN I
HGSIL CIN III Severe Dysplasia

- High NC Ratio
- Nuclear Hyperchromasia
- Irregular Nuclear Membranes
- Immature Metaplastic Type Cells
- Dense Basophilic cytoplasm
HGSIL CIN III Carcinoma In – Situ

- Highest NC Ratio with indistinct cell borders

- Hyperchromatic Crowded Groups = 3 Dimensional cellular aggregates
  “Syncytium”

- Coarse Nuclear Chromatin
  “Salt and Pepper”

- Clean Background with no nucleoli present in the nuclei

- *Carcinoma In – Situ is contained by the Basement Membrane subjacent to basal layer*
Variable Regression of Precursor Lesions

- **CIN I**: Usually clears spontaneously in 60% of cases and progresses to Carcinoma 1% of cases untreated.

- **CIN II and III**: Usually clears spontaneously 30-40% of cases and progresses to cancer in 12-15%(CIN II) and 30-40%(CIN III) of cases untreated.

- HPV Carcinogenesis is considered a long term process that takes from 10-30 years to develop.
Invasive Carcinoma

When precursor Cervical Dysplastic cells *invade through the underlying Basement Membrane*, the lesion becomes malignant carcinoma.
Cervical Carcinoma “Exophytic”
Cervical Carcinoma “Endophytic” with Ulceration and Erythema
Squamous Cell Carcinoma

- Keratinizing and Non Keratinizing Types
- Prominent “Cherry Red” Nucleoli
- Coarse, Unevenly distributed nuclear chromatin
- Cell In Cell Arrangements and Pearl Formation
Squamous Cell Carcinoma

- Tumor Diathesis
- Dyscohesive, isolated single cells
- Giant Tadpole and Spindle shaped cells “Pleomorphism”
- Brilliant orange cytoplasm with bizarre nuclear shapes
- Most often associated with HPV Type 16
Endocervical Adenocarcinoma
In – Situ

- HPV Infection in glandular columnar epithelial cells of the endocervical canal
- Elongated overlapping nuclei “feather edge” cell clusters
- Nuclear hyperchromasia
- Rosette formation
- Difficult to detect on cytology
Endocervical Adenocarcinoma Gross
Endocervical Adenocarcinoma

- Malignant cell groups form glandular structures
- Prominent cherry red nucleoli
- Disordered, overlapping nuclei “loss of polarity”
- Variation in nuclear size
- Most often associated with HPV Type 18
- While overall incidence of cervical carcinoma has been declining
- Endocervical Adenocarcinoma has been rising (now 25% of all cases)
If the microscopic criteria for LGSIL, HGSIL and Carcinoma are well defined, why is HPV High Risk DNA Testing important?
Who is that girl?
Now You Have the Whole Picture
There is more than meets the eye

“Absence of Proof may not mean Proof of Absence”

- Liquid based cytology screening and HPV tests are **sampling dependent** tests

- For LB cytology, the patient may have a lesion that has not been sampled and/or the location of TZ is higher up beyond reach of sampling instrument

- Sometimes only the edge of lesion is sampled which may be less severe and not totally representative

- The Limitations of the Microscope: What is seen is only partial or incomplete diagnostic criteria
  
  - The “ASCUS”, “ASC – H” and “AGUS” Diagnoses

- For HPV testing, the patient may be infected by one of the **less common HPV** types not tested in routine test panels

- Recall 90% of Cervical Cancer and Precursors caused by HR Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 which are targeted for detection in Molecular Testing Methods

- The **mystery 10%** not included in the above

- There may be **undiscovered viral types** which contribute to precursor lesions

- **Routine screening is vitally important** as it increases the probability that a previously undetected lesion will be discovered

- Has the patient developed increasing risk factors over the years...... lifestyle choices and elevated risk factors
ASCUS and AGUS

Atypical Squamous Cells of Undetermined Significance

Atypical Glandular Cells of Undetermined Significance
Factors Influencing Sample Collection and Interpretation

- Location of lesion in relationship to the Transformation Zone = lesion not sampled

- Coexistent STDs such as HSV, Chlamydia/ Pelvic Inflammatory Disease, Gonnorrhea, Trichomonas Vaginalis can cause intense cytologic atypia in epithelial cells

- Small number of atypical cells present in sample not adequate for definitive diagnosis

- Some, but not all microscopic criteria for LGSIL or HGSIL are present
The Role of HPV Testing

• Identify patients who harbor persistent infection

• Better predict the probability of patients who will develop CIN III and possibly progress to Invasive Carcinoma

• Clarify the nature of borderline cytology screening diagnosis such as ASCUS, “Atypical Squamous Cells of Undetermined Significance”
HPV High Risk DNA Testing: Complex Molecular Techniques

• **In – Situ Hybridization:**
  HPV DNA is visualized in cells under microscope using an antigen- antibody reaction – an old technique that is now obsolete

• **Hybrid Capture:**
  HPV DNA is measured using liquid Nucleic Acid Hybridization method

• **Polymerase Chain Reaction:**
  Detection of HPV DNA is done using amplification of gene copies
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<th>Test</th>
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<td>Digene Hybrid Capture HC2</td>
<td>Digene Corporation Gaithersburg, MD, USA</td>
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Digene Hybrid Capture via liquid Nucleic Acid Hybridization Method

- Approved by the FDA for clinical use

- Detects 13 high risk types in one “Pooled” test

- HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68

- Results are reported as + or – and does not specify or separate the types

**Hologic Cervista** is a similar HPV Test which can detect the above 13 HPV Types plus Type 66, offering a 14 pool test
HPV Genotyping via Polymerase Chain Reaction
Roche Cobas System

Molecular Diagnostics

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HPV DNA (HIGH RISK)

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<tr>
<td>HPV 16 DNA</td>
<td>NEGATIVE</td>
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HPV type 16 DNA was undetectable or below the pre-set threshold.

| HPV 18 DNA      | NEGATIVE   |

HPV type 18 DNA was undetectable or below the pre-set threshold.

| HPV OTHER RESULTS | NEGATIVE   |

HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 were undetectable or below pre-set threshold.

SOURCE PAP

CLINICAL INFORMATION ABNORMAL PAP
Aptima HPV Test

- Test identifies High Risk HPV Infections by targeting E6/E7 Oncogene mRNA, demonstrating evidence of active, persistent infection.
- Genotyping for HPV Types 16/18 and 45 is also an option.
“You Never Know What the Future Holds”
2 Big Women’s Health Questions

• How often should women be screened?

• How should patient follow-up be managed as a result of screening tests?

➤ Late 1980s to early 2000s = Fear of litigation and missing even minor abnormalities
The Annual Screening Model

Review of large population studies (mostly Multicenter Randomized Clinical Trials) evaluating the follow-up and treatment of precursor cervical lesions have demonstrated that Annual screening has resulted in

- **Excessive overtreatment** of early precursor lesions ASCUS, LGSIL, HGSIL CIN II (which have a high probability of resolution/clearance by immune system)

- **Unneccessary Risks** for patient Reproductive Health
  
  This has amounted to **Greater Harms from Treatment than Benefits from Screening** for many patients

- Examples include Incompetent Cervix, Scarring, Cervical Stenosis, Infection, Low Birth Weight Babies, Preterm Delivery and PPROM

- Both Screening and Follow Up Guidelines have been thoroughly explored by the medical community with Recommendations for “Average Risk” patients developed based upon Consensus Opinion

The ASCUS-LGSIL Triage Study aka ALTS Trial

Screening and Follow-Up for Precursor Cervical Lesions

**Screening Guidelines**

- American Cancer Society Symposium Guidelines
  Released in 2012

- Evolved over the last 15 years due to results of large population studies

- Involved data collection, literature review and analysis of Cytology screening, HPV Testing and Treatment Outcomes

- Focused collaboration by multiple professional medical specialty organizations ACS, ASCP, ASCCP, NCI and CAP

- Newest Guidelines (2012) suggest **3 or 5 year screening intervals with Cytology alone or HPV co-testing based upon patient age**

- Women age population subsets 21-24, 25-29 and 30-65

**Follow-up Guidelines**

- American Society For Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines

- First published in 2001 with revisions in 2006 and **2012**

- Panel of experts from 23 medical specialties

- Goal was to develop Evidence Based Practice Guidelines for the management and followup of women with abnormal cervical cytology

- Findings were based upon literature review and several large population studies of over 1.4 million patients

- *Newest Guidelines determined by patient age populations*

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2012 ACS, ASCCP and ASCP Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

Infection Prevalence and Cervical Cancer Incidence

![Graph showing HPV prevalence and cervical cancer incidence by age](graph.png)
Cervical Cancer Screening Guidelines Summary For Average Risk Women

<table>
<thead>
<tr>
<th>AGE Group</th>
<th>Recommended Screening Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21</td>
<td>No Screening by any modality</td>
</tr>
<tr>
<td></td>
<td><strong>Evidence Based Rationale:</strong> HPV infection is highly prevalent in adolescents with most infections (&gt;90%) spontaneously clearing without treatment in 1-2 years. The Incidence of CA is very low and has not changed after 4 decades of screening studies</td>
</tr>
<tr>
<td>21 – 29</td>
<td>Screening by Cervical Cytology every 3 Years alone</td>
</tr>
<tr>
<td></td>
<td><strong>Evidence Based Rationale:</strong> With a High Prevalence of HPV Infection in this age group, the use of HPV testing is not recommended due to Low PPV which could lead to excessive colposcopies and overtreatment. Risk of CA is low as patients in this group are usually 10-20 years away from the development of Invasive CA</td>
</tr>
<tr>
<td>30 – 65</td>
<td>Screening by Both Cervical Cytology and HPV HR DNA Testing every 5 years</td>
</tr>
<tr>
<td></td>
<td><strong>Evidence Based Rationale:</strong> Cotesting with HR HPV Testing increases the Sensitivity in detecting HGSIL (CIN II and III) while providing a much lower risk for the development of CA after a Cytology (–) and HPV (–) Cotest, Justifying a longer interval between screens. Provides a balance of benefits from effective screening while minimizing the potential harms associated with colposcopy/biopsy</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>Discontinue Screening by all modalities if patient has extended prior history of HR HPV(-) and/or Cytology(–) test results (3 Pap – or 2 Cotest – in last 10 years)</td>
</tr>
<tr>
<td></td>
<td><strong>Evidence Based Rationale:</strong> Based upon the natural history of HPV Carcinogenesis, any newly discovered HPV infection after age 65 will have insufficient time to develop into Cervical CA in the remainder of a women’s lifetime. The potential harms associated with the overtreatment of False Positive test</td>
</tr>
</tbody>
</table>
Key Facts

• In 2015, there will be an estimated 12,900 new cases of Cervical Carcinoma, with 4,100 cases resulting in death

• 50% of all new Invasive Cervical Carcinomas occur in women who have never been screened at all (no cervical cytology and/or HPV testing)

• Another 10% have not been screened for at least 5 years at time of diagnosis

• Cervical Cancer Screening programs are not reaching all women in the US

• Will this improve/change with the Affordable Care Act?
The Evolution of Screening, Management and Treatment of Cervical Cancer and its Precursors I

1940s – Early 1990s

Annual Conventional Pap Smear → If Abnormal

Repeat Conventional Pap Smear @ 6-12months → If Abnormal

Colposcopy +/- Biopsy

If Normal

Routine Annual Screening

If Negative
Mid 1990s – 2003

Annual LB Cytology → If Abnormal

Reflux to HR HPV DNA Pool Test

or

Repeat LB Cytology @1 Year

If Negative

If Negative

Routine Annual Screening

If Abnormal

Colposcopy +/− Biopsy

If Negative
The Evolution of Screening, Management and Treatment of Cervical Cancer and its Precursors III

2003 – 2014: Depends on Age Population and “Average Risk”

Cotesting at 3 Years or Cotesting 5 Years or Cytology 3 years alone

If Cytology – HPV +

If Cytology + HPV –

If Cytology – And HPV –

If Cytology + HPV –

Repeat Cotest 1 Year

HPV Genotype 16 and 18

If +

If –

Colposcopy +/- Biopsy

If Cytology + And/or HPV +

Routine Screening at 3 or 5 years
Controversial Newsflash

• April 24, 2014 – The FDA approves The Roche Cobas System for Primary Stand Alone Cervical Cancer Screening in the United States

• Is Molecular Pathology testing going to replace the Pap Test for Primary Screening?

• This decision is not in compliance with the aforementioned 2012 Consensus Guidelines
The Evolution of Screening, Management and Treatment of Cervical Cancer and its Precursors IV

2015: Primary Screening with HPV Testing Alone?

Use of Primary High Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidance
**Patient Follow – up I**

<table>
<thead>
<tr>
<th>Available Options</th>
<th>Factors to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat LB Cytology</td>
<td>Follow - up for each individual patient is often employs a unique approach</td>
</tr>
<tr>
<td>HPV HR DNA Testing alone</td>
<td>Initial sampling unsatisfactory ?</td>
</tr>
<tr>
<td>Repeat LB Cytology and HPV HR DNA Cotesting</td>
<td>Age</td>
</tr>
<tr>
<td>Colposcopy with or without biopsy</td>
<td>Risk Factor profile / history of other STDs</td>
</tr>
<tr>
<td>Biopsies include Cervical LEEP and Ablation of T Zone</td>
<td>Reproductive status, future plans</td>
</tr>
<tr>
<td>Excisional procedures - Cold Knife Conization</td>
<td>Prior and current cervical cytology or biopsy results</td>
</tr>
<tr>
<td>Hysterectomy for Carcinoma</td>
<td>Clinical Symptoms and will the patient come back?</td>
</tr>
</tbody>
</table>
Followup for HGSIL and Carcinoma

- Colposcopy with Biopsy for HGSIL (CIN II and CIN III) 
  LEEP, Ablation or Conization

- Early Stage I and II Cervical Carcinoma is usually treated surgically with Radical Hysterectomy.

- Lymph Node removal included

- Cisplatin or Bevacizumab based Chemotherapy and/or radiation treatments with Direct Beam/Brachytherapy may also be indicated
Colposcopy of The Transformation Zone

Before the Application of Acetic Acid

After the Application of Acetic Acid:
White, Intensely Opaque Lesional Area with Well Demarcated Borders localized to the T-Zone = CIN

J Cuzick et al. Overview of Human Papillomavirus - Based and Other Novel Options for Cervical Cancer Screening in Developed and Developing Countries Vaccine 265(2008) K29-K41
5 Year Risk of HGSIL and Cervical CA With Suggested Management

<table>
<thead>
<tr>
<th>Result on Cytologic Testing or Cotesting</th>
<th>Frequency of Screening Result §</th>
<th>Risk of Histologic HSIL and Cancer ‡</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>0.0048</td>
<td>84</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/HSIL</td>
<td>0.20</td>
<td>71</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.21</td>
<td>69</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV-/HSIL</td>
<td>0.013</td>
<td>49</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/AGC</td>
<td>0.054</td>
<td>45</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/ASC-H</td>
<td>0.12</td>
<td>45</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>ASC-H</td>
<td>0.17</td>
<td>35</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/LSIL</td>
<td>0.81</td>
<td>19</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/ASC-US</td>
<td>1.1</td>
<td>18</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>LSIL</td>
<td>0.97</td>
<td>16</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>AGC</td>
<td>0.21</td>
<td>13</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV-/ASC-H</td>
<td>0.051</td>
<td>12</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV+/Pap-</td>
<td>3.6</td>
<td>10</td>
<td>Repeat testing in 6 to 12 mo</td>
</tr>
<tr>
<td>ASC-US</td>
<td>2.8</td>
<td>6.9</td>
<td>Repeat testing in 6 to 12 mo</td>
</tr>
<tr>
<td>HPV-/LSIL</td>
<td>0.19</td>
<td>5.1</td>
<td>Repeat testing in 6 to 12 mo</td>
</tr>
<tr>
<td>HPV-/AGC§</td>
<td>0.16</td>
<td>2.2</td>
<td>Immediate colposcopy</td>
</tr>
<tr>
<td>HPV-/ASC-US</td>
<td>1.8</td>
<td>1.1</td>
<td>Repeat testing in 3 yr</td>
</tr>
<tr>
<td>Pap-</td>
<td>96</td>
<td>0.68</td>
<td>Repeat testing in 3 yr</td>
</tr>
<tr>
<td>HPV-/Pap-</td>
<td>92</td>
<td>0.27</td>
<td>Repeat testing in 5 yr</td>
</tr>
</tbody>
</table>

Schiffman, M et al. Cervical Cancer Screening with Human Papillomavirus and Cytologic Cotesting
HPV Vaccines I

• Vaccines are intended for use in protecting girls/young women ages 9 -25 years old (Cervarix) and 9 -26 Years old (Gardasil)

• Ideally administered before the onset of first sexual experience

• Will not confer protection in patients who have already been exposed/infected with:

  ➢ High Risk Viral Types 16 and/or 18 previous to vaccination with 4 – Valent Gardisil
  ➢ High Risk Viral Types 16, 18, 31, 33, 45, 52 and 58 previous to vaccination with 9 – Valent Gardisil

• Administered Intramuscularly as 3 separate 0.5ml injections, with the second Dose 2 months after the first Dose and the third Dose 6 months after the first Dose
HPV Vaccines II

**Cervarix** (2 – Valent) Vaccine targets

- HR HPV Types 16 and 18 only

**Gardisil** (4 – Valent) Vaccine targets

- LR HPV Types 6 and 11
- HR HPV Types 16 and 18

**Gardisil** (9 – Valent) Vaccine targets

- LR HPV Types 6 and 11
  - (to prevent condyloma acuminata)
- HR HPV Types 16, 18, 31, 33, 45, 52, 58

FDA Approved for use in the United States
12/10/2014
HPV Vaccines III: Preliminary Reports

- HPV Vaccines showed 96- near 100% efficacy in the reduction of HPV Vaccine Type (16 and 18) CIN II + in women who are HPV Naïve

- Approximately **9 years of Data** is reported from 7 Randomized Control Trials of women who had a limited number sex partners

- Modeling studies suggest that vaccination coverage from 70-80% is expected to result in a 47-95% reduction of Precursor CIN II, CIN III – AIS and CA.

- This reduction is likely not to occur until 15 – 17 years after vaccination programs have reached 70% coverage in the US Population

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Compliance: Latest Data from CDC shows that 33.4% of targeted females youth (age 9-26) have received the necessary 3 doses of the Vaccine

Vaccination is Opportunistic: does not specifically target girls/women before the onset of sexual activity

Vaccination is administered to mostly lower risk young women (Just as Cytology Screening is not reaching many high risk women)

The future appears promising although there are many unanswered questions due to the lack of long term Evidence/Data

The absence of a centralized database precludes the collection of complete and accurate data for epidemiological outcomes assessment

Vaccines Have only been available for ~ 10 years ....... Carcinogenesis is usually a long term process lasting 20 – 40+ years

Experts agree that an estimated 10 – 20 years will be needed to see the full impact of vaccination:
HPV Vaccines:  
Key Considerations for the Future

• Since the 1\textsuperscript{st} and 2\textsuperscript{nd} Generation Vaccines only targets HPV Types 16, 18, 31, 33, 45, 52 and 58, there will be approx. 15 % of cervical cancer still occurring from other HPV Types

• Some of which are still yet to be discovered: Viral Mutation

• Will rarer HPV Types which are etiologic agents for Cervical Cancer emerge as more virulent (causative) in the future as a result of vaccination against the 7 targeted types?

• A need to report screening results and follow-up based upon documented vaccination status

• The lack of screening test performance in light of new cervical cancer precursor management and treatment guidelines which utilizes Cotesting at 3 or 5 Year Intervals, or Primary HPV Testing alone
The HPV Vaccines and Questions

- Do the Vaccines actually prevent Cervical Cancer?

- What is the **Duration of Protection** from HPV Vaccination?

- How effective will screening tests be in the vaccinated cohort?

- What are the possible **Long Term Health Risks** which may result from the various vaccines?
HPV Vaccines: 
Potential Serious Health Risks?

The Vaccine Adverse Events Reporting System (VAERS) Database online:

http://vaers.hhs.gov/index

Co sponsored by the CDC and the FDA

As of Dec 13, 2013 there were 29,918 Reported events, which include –

Death  Facial Palsy
Paralysis  Convulsions
Paraesthesia  Chronic fatigue syndrome
Guillain Barre Syndrome  Autoimmune disorders
Anaphylaxis  Cervical Cancers
Deep Vein Thrombosis

Coincidence or are these outcomes caused by the Vaccines?
HPV Vaccine Quick Facts

• The National Vaccine Information Center

• http://www.nvic.org/Vaccines-and-Diseases/HPV.aspx
Cervical Cancer Screening in 2015

Primary Prevention = Vaccination

Secondary Prevention = HPV Testing and Cervical Cytology

Screening of Vaccinated and Unvaccinated women will continue for the foreseeable future in the US
Developing Cervical Cancer is a Low Probability Event

Lifetime Risk = A woman in the United States has 0.6% chance of developing Cervical Cancer as per 2012-2013 SEER Data

Question:

Is the unknown risk of illness or harm from HPV Vaccination greater than the risk of developing cervical cancer?
Cervical Cancer Screening in the United States: Lesser Known Realities
Obstacles to Cervical Cancer Eradication I

50% of all new Cervical Cancers occur in Women who have never been screened with any testing at all, including Cytology or HPV Testing.

An additional 10% of all new Cervical Cancers occur in women who have not been screened in 5 years or longer.

- Screening by any modality is not being performed on a lot of women in the United States.
- The above 2 facts are important as the 2012 ASCCP Guidelines recommend Screening at 3-5 year Intervals instead of Annually.

Low HPV Vaccination Coverage in the United States

- All required 3 doses not being administered (33.4% as of 2012).
Significant numbers of Cervical Squamous and Adenocarcinoma are HR HPV DNA – by routine Molecular Diagnostic Test Methods

- This is really important since there is a controversial push to implement Primary Cervical Cancer Screening utilizing HR HPV Testing alone without Cytologic screening
- 4/24/2014 FDA approves the Roche Cobas HPV Test for Primary Screening

Significant numbers of Cervical Cancers are difficult to detect with Screening

The most difficult Cervical Cancer to Prevent/Detect is markedly on the rise

- Endocervical Adenocarcinoma has increased from 5% up to 20% of all Cervical Cancer cases since 1975 in the US
- Incidence rates have increased by 32.2% from 1973-2007
Obstacles to Cervical Cancer Eradication III

Some Cervical Cancers are Rapidly Developing in only a matter of a few months up to a few years in a mysterious, unknown progression

- This is in stark contrast to the majority, which take 20 – 40 years to progress from CIN I to invasion
- Tend to be HPV 16+ or HPV 18+

Documented cases of Cervical Cancer and its precursors are occurring in young women who have received the HPV Vaccines

How can HPV Naïve status be confirmed in young women who are not being screened with Cytology or Pelvic Exam?

Some cases of cervical cancer are caused by the untested viral types (i.e. Types 73 and 82), and perhaps undiscovered or mutated viral types

Current screening strategies utilize expensive testing approaches (liquid based cytology and HR HPV molecular testing) that present a cost barrier for effective screening across the US population
“Peace and Time Out”
Two Types of Cervical Carcinoma

Cytopathology 2012; 23: 6-12

Type I Cervical Cancers (Slow-Growing)

EXTENSIVE CIN3

Limited Superficial Invasive Cancer

Type II Cervical Cancers

LIMITED, NONDIAGNOSTIC, OR HIDDEN CIN3/AIS

Subsurface Invasive Cancer may remain asymptomatic until cervical rupture

Used by Permission of Author – R. Marshall Austin, MD PhD
UPMC Medical Center, Pittsburgh, PA
Type I Cervical Carcinoma

• Comprises the majority of Cervical Cancers

• Slow Growing neoplasms that follow the accepted model of HPV Carcinogenesis involving 20-40+ years of CINI-III/CIS before Invasion

• Tend to occur in older women in the 50-70 age group
Type II Cervical Carcinoma

• Comprise a smaller subset of Cervical cancers whose incidence is increasing

• Includes Endocervical Adenocarcinomas and Glandular Neoplasms which originate away from the cervical Transformation Zone, often high in the Endocervical canal

• Tend to occur in women as young as teenagers up through age 40

• Also occur in older postmenopausal women age 75+
High Risk HPV (−) Cervical Carcinomas

Data from multiple Large Population Studies have shown that, despite using routine molecular diagnostic test methods:

- From 5 up to 15% of Cervical Squamous Cell Carcinomas are HPV –
- From 8 up to 25% of Cervical Adenocarcinomas are HPV –

Possible contributing factors for these results may be due to inadequate sampling of infected, abnormal tissue and cells:

- Neoplasm originates away from the T-Zone, such as the upper Endocervical Canal, and is not accessible to the sampling instrument
- Neoplasm is not grossly visible to the clinician performing the sampling
- Neoplasm is growing underneath a relatively intact mucosa before rupturing as a fungating mass
- Low Viral Load Neoplasms whose copy number falls below the detection threshold of the test assay
The Barrel-Shaped Invasive Cervical Carcinoma
What is the Best Screening Approach for Average Risk Women?

Co-testing at 3 year intervals

HPV Testing: Higher Sensitivity and Lower Specificity
Cervical Cytology: Lower Sensitivity and Higher Specificity

The combined advantages of using both tests provides the best protection against the risk of Developing Cancer between screening rounds while minimizing the Harms of Overtreatment for Precursor lesions that may resolve on their own. If a lesion persists after several rounds of screening, intervention can be initiated before Cancer develops.
Will Cervical Cancer and Surgical Specimens From the Cervix Become An Endangered Species?

- Until screening programs reach more women, Cervical Cancer at all stages will remain a public health concern (60% of new Cervical Cancer in unscreened or infrequently screened patients)

- No laboratory test is a perfect performer and problems with sample collection and processing will always exist, not to mention the variability of human error at each step of the testing process

- There are high risk HPV types which are not tested for (approx 10%) via molecular test methods or are undiscovered which cause cervical cancer

- Low coverage of HPV vaccination across the US population is reported as 33.4% in 2012, so until vaccines become more available...
Undetected Cervical Cancers

There are Cervical Cancer Precursors and Invasive Carcinomas **which harbor low viral loads** that may escape detection of molecular test methods.

- A Quest Diagnostics Health Trends Study of 3,727,894 women age 30-65 found that 14.3% of these women (533,088) had a Pap Test that was HGSIL CIN III or Carcinoma.

- 4.6% of women with CIN III or Carcinoma on Pap Test (24,522) were HR HPV –

- Almost 25% of the women who were CIN III on Pap Test and HPV – (6,130) developed CA within 5 years.

- For unknown reasons, Late HPV integration into the host cell DNA can results in decreased viral load neoplasms.
HPV: The Unpredictable Virus

• Mystery still surrounds the HPV Virus in terms of its potential for mutation into new higher virulence types

• The influence of patient lifestyle choices have the strongest influence on
  Likelihood of exposure to High Risk HPV Viral Types
  Willingness to comply with Vaccination – Screening – Followup

• With longer screening intervals, Will this = Fewer LEEP and CONE Biopsy procedures across screening population?

• Will the Affordable Care Act create a Bigger screening population to increase surgical specimen volume?

• This may offset volume loss from Vaccine Efficacy and Improved Screening/Detection?)
Will the Affordable Care Act = Quality?

Decrease system costs or Provide the best possible healthcare screening approaches?

Pathologists Workforce Shortage Emerging?

- (Supply) Arch Pathol Lab Med Vol 137 Dec 2013
- (Demand) Arch Pathol Lab Med Vol 139 Nov 2015

Annual Screening or Extended Screening Intervals at 3 or 5 years?

Cytology alone or Cytology + HPV Testing?
The Bottom Line

Cervical Cytology used in combination with High Risk HPV Molecular Testing provides the best surveillance and detection approach for women that comply with regular screening programs aka “Cotesting”

If more women were screened = more precancerous and cancerous lesions detected = save more lives

Early Stage Ia and Ib Cervical Carcinoma that is caught and treated = Patient has 92% 5 year survival rate

Too Early to draw reliable conclusions on the efficacy of HPV Vaccines in preventing Cervical Cancer

➢ An increasing % of Cervical Cancer = High Risk HPV –
Questions?