Pap Smears
Where are we headed

Ian H. Thorneycroft  PhD,MD,FACOG
Where are we headed/

• Less frequent sampling.
• More use of DNA technology.
• Increase in cervical cancer.
History

• The test was invented by and named after the prominent Greek doctor Georgios Papanikolaou.

• Aurel Babeș of Romania independently made similar discoveries in 1927. However, it should be noted that Babeș method was radically different from Papanicolaou's.

• Papanicolaou's name was repeatedly submitted to the Nobel Committee and rejected every time. The Nobel Committee delegated the in-depth investigation of Papanicolaou's merits and demerits to the late Professor Santesson, who was at that time the head of pathology at the Stockholm Cancer Institute (the Radiumhemmet). The investigator discovered Babeș' contributions that had never been cited by Papanicolaou and duly reported this fact to the Committee, which then rejected Papanicolaou's Nobel award.
Pap Smears

• The Pap test, when combined with a regular program of screening and appropriate follow-up, can reduce cervical cancer deaths by up to 80%. [8]

• Failure of prevention of cancer by the Pap test can occur for many reasons, including
  – not getting regular screening,
  – lack of appropriate follow up of abnormal results,
  – sampling and interpretation errors. [26]
Latest Guidelines

http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm
ACOG guidelines summary

• Cervical cancer screening should begin at age 21 years.
• Pap cytology screening is recommended every 3 years for women between the ages of 21 years and 29 years.
• For women aged 30-65 years, co-testing with cervical cytology screening and HPV testing is preferred and should be performed every 5 years.
• For women aged 30-65 years, screening with cytology alone every 3 years is acceptable.
• Both liquid-based and conventional methods of Pap cytology are acceptable for screening.
• In women who have had a total hysterectomy and have never had CIN2 or higher, routine cytology screening and HPV testing should be discontinued and not restarted for any reason.
• Women who have a history of cervical cancer, have HIV infection, are immunocompromised, or were exposed to diethylstilbestrol in utero should not follow routine screening guidelines.

• Screening by any modality should be discontinued after age 65 years in women with evidence of adequate negative prior screening results* and no history of CIN2 or higher.

• *Adequate negative prior screening results are defined as three consecutive negative cytology results or two consecutive negative co-test results within the previous 10 years, with the most recent test performed within the past 5 years.
ACOG guidelines cont.

- In the US, over half of all invasive cancers occur in women that have never had a Pap smear; an additional 10 to 20% of cancers occur in women that have not had a Pap smear in the preceding five years. About one-quarter of US cervical cancers were in women that had an abnormal Pap smear, but did not get appropriate follow-up (woman did not return for care, or clinician did not perform recommended tests or treatment).
US Preventive Task Force

• http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm
• On the basis of that fair-quality evidence, the USPSTF recommended against routinely screening women older than 65 years for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer
• cancer
ASCUS

- HPV+
  - Consider colposcopy

- HPV-
  - Follow with Pap in 6 months.
LGSIL

• All should be HPV +
  – Age dependent treatment
  – Colposcopy
  – Follow Q 6 Months
HGSIL

- Colposcopy
  - LEEP depending on colpo results.
ECC positive

• Depending on path would perform a LEEP or cone.
Flower Children
48 year old

- 48 year old white female who had a normal Pap smear one year preceding.
- Pap: CIS suspicious for invasive cancer.
- Colpo: Microinvasive carcinoma.
- Cone: Microinvasive carcinoma margins free.
- Robotic TLH-BSO: No residual disease.
65 year old

• 65 year old S/P TAH-BSO referred by Family Practitioner for abnormal vaginal Pap.
• Colp: CIS
• Resection: CIS margins free.
• F/U clear of disease.
  – New boyfriend
  – 3 months later comes in with Herpes.
50 year old

• 50 y/o s/p TAH-BSO with Crohn’s disease.
• Pap: CIS
• Biopsy: CIS
• HPV: + HR and subtype 16 positive.
• Placed on Imuran for Crohn’s and compounded imiquimod (Aldara) and estradiol vaginal cream.
• Paps have remained HSIL.
• Now has inflammatory breast cancer.
66 year old

- Called with vaginal bleeding
- Listed a partner who had been dead for 6 years as her MD.
- Saw in ER: Fungating cervical lesion
- Stage IIIB Squamous cell carcinoma.
New Guidelines

• Will be very difficult to adapt
  – Many patients use gynecologists only
  – Need annual well patient exam
    • Mammograms
    • Pelvic for ovarian mass
    • Refill and evaluation of ERT
Future

• We have gone from smearing on a slide to liquid based Paps.
• Now have computers which scan slide and pick the worst looking cells for review.
  – Can work 24/7 and do not get fatigued.
• HPV High Risk subtyping—Most helpful to me with ASCUS.
• Techniques which detect changes in cells which are high risk for developing into cancer. Which are most likely to progress.
Cervical DNA Dtex®
The Molecular basis of Cancer

“Virtually every cancer cell has an abnormal chromosome component, whereas virtually every normal cell has the (normal) diploid number.”
- Bert Vogelstein (Johns Hopkins University)
Persistent high-risk HPV infection is a “necessary but NOT SUFFICIENT condition...”¹
90% of infections regress within 2 years²

“Only 1 in 10 to 1 in 30 HPV Infections are associated with abnormal cytology”

ACOG Practice Bulletin

2 – Dunne et al, JAMA 2007
Infections that clear cause NO DNA damage

2 – Dunne et al, JAMA 2007
But some infections cause DNA damage
DNA damage starts the progression to dysplasia
DNA damage is irreversible
The Cervical DNA Dtex® test identifies DNA damage to cervical cells.

The Cervical DNA Dtex® test uses FISH technology to identify DNA damage.
The Cervical DNA Dtexas® Test is based on biomarkers discovered at the National Cancer Institute.
The Cervical DNA Dtex® Test is based on biomarkers discovered at the National Cancer Institute.
DNA damage to 3q26 and 5p15 is irreversible
DNA damage to 3q26 and 5p15 is irreversible
Damage to 3q26 and 5p15 is present in over 95% of cervical carcinomas.

DNA damage to 3q26 and 5p15 is irreversible.
Case Studies - Advocate Algorithm
Knight Case Study

Profile

- Age: 26yo medical student
- Sexually Active: Occasional
- Regular Medical Care: Highly engaged

Pap/HPV Results

Historical: Consistently WNL
Current: ASCUS, High-risk HPV “positive”

Guidelines Recommendation

ASCCP and ACOG guidelines recommend conservative care for women under 30 although Colposcopy/biopsy should be considered
**Knight Case Study**

### The Cervical DNA Dtex® Test Result

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<tr>
<th>Total Cells</th>
<th>Abnormal Cells</th>
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**Test Result** **NEGATIVE**

### Reference Range

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**Actual Patient Images**

- **Cen7**: No DNA Damage
- **3q**: No DNA Damage
- **5p**: No DNA Damage
Knight Case Study

Colposcopy / biopsy
Colposcopy showed cervicitis
Biopsy showed CIN2

Physician’s Care
After discussing the results with the patient both agreed to hold-off on a LEEP procedure until the results of a 6 month follow-up visit. The follow-up visit showed WNL and HPV negative
Dittus Case Study: “Dtex saved this patient’s life”

Profile
- Age: 42yo with history of high-risk behavior
- Sexually Active: Highly active
- Regular Medical Care: Intermittent compliance
- Other: Long history of smoking

Pap/HPV Results
Historical: Abnormal Pap and High-risk HPV “positive”
Current: ASCUS, High-risk HPV “positive”

Guidelines Recommendation
Colposcopy/biopsy should be performed
Dittus Case Study: “Dtex saved this patient’s life”

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**Actual Patient Images**

- Cen7
- 3q
- 5p

![No DNA Damage](image1)

![DNA Damage](image2)

![DNA Damage](image3)
Dittus Case Study: “Dtex saved this patient’s life”

Colposcopy / biopsy  
Colposcopy showed visible lesions  
8 biopsies taken all CIN1  
ECC performed and was negative

Physician’s Care  
Dr. Dittus consulted with pathologist and agreed to order another Dtex given the conflicting test results and patient history
Dittus Case Study: “Dtex saved this patient’s life”

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**Test Result** POSITIVE

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**Actual Patient Images**

- Cen7 3q 5p

- No DNA Damage

- DNA Damage

- DNA Damage
Dittus Case Study: “Dtex saved this patient’s life”

Physician’s care
Performed a conization
AIS Adenocarcinoma
Follow-up Hysterectomy
Thank You!