From Pap smear to HPV testing?

BOSNIAN-TURKISH CYTOPATHOLOGY SCHOOL
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Sarajevo

Prof Dr Sıtkı Tuzlalı
Tuzlalı Pathology Laboratory


WHO CRITERIA FOR A GOOD SCREENING

- The condition to be screened should be important for the population
- There should be an acceptable therapy for the patients
- There should be diagnostic and therapeutic tools
- There should be a known latent or early symptomatic stage
- An appropriate test with a low false positivity (specific) and low false negativity (sensitivity)
- Test or evaluation should be acceptable for the society (population)
- The cost of the diagnosis and the following therapy should be economic regarding the total health expenses

Wilson and Jungner criteria for screening (World Health Organization)

Wilson Criteria

- Disease:
  - Common/important
  - Latent phase
  - Natural history
- Screening test:
  - Simple, cheap, Accessible, affordable
  - Accuracy (Specificity and Specificity)
  - Continuous
- Follow-up:
  - Facilities and manpower
  - Effective treatment
  - Policy of who to treat

Also called as positive predictive value (PPV).

Proportion of people actually having the disease among those who have tested positive on the test: i.e. “If one tests positive on screening, what are the chances that he really has the disease?”

$$PPV = \frac{true\ positives}{true\ positives + false\ positives}$$

Also, $$PPV = \frac{Sensitivity \times Prevalence}{Sensitivity \times Prevalence + (1 - Specificity) \times (1 - Prevalence)}$$

$$PPV$$  cost-effectiveness
Cervix Ca screening

- VIA (Visual Inspection with 3-5% Acetic acid)
- VIAM (VIA with low level (2-4X) magnification)
- VILI (Visual inspection with Lugol's iodine)
- Cytology
- HPV

2000: The Hybrid Capture 2 (HC2) HPV test had FDA approval for screening women with a cytological diagnosis of ASCUS.


April 2014: FDA approved the use of an HPV test (cobas HPV test) alone without Pap test in screening of women over 25 y.

Limitations of cytology

- Is relatively subjective with a considerable interlaboratory/intralaboratory variability
- Sensitivity in the detection of high grade precancerous lesions is relatively low.
- Can determine the women with precursor lesions but cannot determine the women with the risk of development of precursor lesions
Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in 20,514 women according to oncogenic human papillomavirus (HPV) status at enrollment.


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Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in 12,976 women 30 years old and older with negative cytology at enrollment, according to oncogenic human papillomavirus (HPV) status at enrollment.


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Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test

Thomas C. Wright, Mark H. Stoler, Catherine M. Behrens, Abha Sharma, Guili Zhang, Teresa L. Wright

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Table 1: Performance Comparison of the Candidate Algorithm and the Primary Comparator Algorithm in Detecting ≥CIN2

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Prevalence (%) of ≥CIN2</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PLR</th>
<th>NLR</th>
<th>N.N.R.</th>
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<tbody>
<tr>
<td>Candidate</td>
<td>66.42 (4.82)</td>
<td>96.68 (1.54)</td>
<td>86.14 (1.49)</td>
<td>65.50 (6.52)</td>
<td>86.43 (10.43)</td>
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<td>0.87</td>
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<td>Comparator</td>
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<td>Improvement</td>
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Table 2: Performance Comparison of the Candidate Algorithm and the Primary Comparator Algorithm in Detecting ≥CIN3

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Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test.

Gynecol Oncol. 2015 Feb;136(2):189-97.


A negative HPV result at baseline predicts one-half the risk of CIN3+ over 3 years than a negative cytology result.

HPV primary screening with triage using 16/18 genotyping and cytology increases sensitivity to detect CIN3+ 28% over cytology.

Cytology failed to detect approximately 50% of CIN3+ in women 25–29 years.

Clinical Commentary


The guidance panel was co-sponsored and funded by the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) and included thirteen experts that represented SGO, ASCCP, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology.

Is hrHPV testing for primary screening as safe and effective as cytology-based screening?

A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result.
• Can primary hrHPV screening be considered as an alternative to current US cervical cancer screening methods?

• Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening methods.
• Cytology alone and cotesting remain the screening options specifically recommended in major guidelines.

• What is the optimal interval for hrHPV screening?

• Re-screening after a negative primary hrHPV screen should occur no sooner than every 3 years.

• At what age should one initiate primary hrHPV screening?

• Primary hrHPV screening should not be initiated prior to 25 years of age.

• How does the performance of primary hrHPV screening compare to cotesting?

• Primary hrHPV testing with a negative result with a 3-year screening interval is at least as effective as five-year cotesting.

New FDA-approved Cervical Screening Options
FDA Microbiology Devices Panel of the Medical Devices Advisory Committee
March 2014

• Cytology
• Cytology with adjunctive reflex HPV testing after ASCUS
• Cytology with adjunctive reflex HPV testing of women 30 y or older
• HPV testing of women 25 y or older with 16-18 genotyping and reflex cytology for hrHPV +/- hrHPV 16-18 - patients
• Use of FDA-approved hrHPV test:

• As a triage in ASC-US

• Complementary to cytology in women >30 y co-testing)

• These two usage is adopted by many organizations (Including the United States Preventive Services Task Force (USPSTF))


• 176 464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening in Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC). We followed up these women for a median of 6-5 years (7 214 415 person-years) and identified 107 invasive cervical carcinomas by linkage with screening, pathology, and cancer registries, by masked review of histological specimens, or from reports. Cumulative and study-adjusted rate ratios (experimental vs control) were calculated for incidence of invasive cervical carcinoma.

• Detection of invasive cervical carcinoma was similar between screening methods during the first 2.5 years of follow-up (0.79, 0.46–1.36) but was significantly lower in the experimental arm thereafter (0.45, 0.25–0.81).

• HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years.
HPV SCREENING - Concerns

- Is it specific?
- Increase in colposcopies, overtreatment of lesions with no risk
- There isn’t any well evaluated and defined therapy strategy in hrHPV positive women
- The screening interval in hrHPV negative women is not known
- There is no data about the errors due to specimen inadequacy
- Is it cost effective?

- hrHPV screening is highly sensitive. But its specificity depends upon the subsequent evaluation strategies and screening intervals.

- A 2011 evidence-based review commissioned by the Agency for Healthcare Research and Quality for the United States Preventive Services Task Force (USPSTF) concluded that “numerous studies have confirmed that HPV testing is more sensitive than cytology”.
- Therefore in 2012 the American Cancer Society (ACS) recommended that cotesting become the preferred approach to screening women >30 years.
- This recommendation has also been adopted by the American College of Obstetricians and Gynecologists (ACOG).

- There is a tendency against cytology as a first-line screening test
- Most important limitation of HPV is its lower specificity compared to cytology. This can be overcome by triage methods in HPV-positive women (cytology and HPV 16/18 genotyping)
- There is considerable ≥CIN3 in ages 25-29, and efficacy of cytology in these cases is low. HPV screening is more effective in this group. Triage reduces overuse of colposcopy and transient HPV infection therapy

Summary of Results from 3-Year Follow-Up of ATHENA Study

- In the follow-up data for the Primary Screening population, a negative HPV result predicted a lower 5-year risk of ≥CIN3 than did a negative cytology result, validating that HPV as the primary test is superior to cytology for cervical cancer screening.
- The low 3-year CIR for a negative HPV result also confirmed the safety of a 3-year interval for HPV primary screening and offers clinicians and their patients more confidence in a negative HPV result than a negative Pap result.
- In addition, the follow-up study confirmed the continued high risk of HPV16 or HPV18 infection, with the observation that 1 in 4 women who tested HPV16+ at Baseline and 1 in 9 who tested HPV18+ at Baseline were diagnosed with ≥CIN3 within 3 years.
- These results demonstrate that the Candidate Algorithm, the cobas® HPV Test with genotyping for 16 and 18 in women 25 years and older can be used as a first-line, primary screening test when reflex to cytology is included.

• Point-Counterpoint: Cervical Cancer Screening Should Be Done by Primary Human Papillomavirus Testing with Genotyping and Reflex Cytology for Women over the Age of 25 Years.

• Mark H. Stoler, R. Marshall Austin, Chengquan Zhao

• University of Virginia Health System, Charlottesville, Virginia, USA; Magee-Women’s Hospital of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA


CONCLUSIONS:
Compared with HPV-only testing, cotesting was more sensitive for the detection of ≥ CIN3 in women ages 30 to 65 years. The current data suggest that approximately 19% of women with cervical cancer may be misdiagnosed by an HPV-only cervical screen. It is important to consider these data as the guidelines for cervical cancer screening undergo revision.

• Zaibo Li, MD, PhD; R. Marshall Austin, MD, PhD; Ming Guo, MD; Chengquan Zhao, MD: Screening Test Results Associated With Cancer Diagnoses in 287 Women With Cervical Squamous Cell Carcinoma. Arch Pathol Lab Med. 2012;136:1533–1540.

Among 31 SCC cases with liquid-based cytology and high-risk HPV cotest results less than 1 year before SCC diagnoses, 2 patients (6.5%) had Pap/HPV results, and 1 patient (3.2%) had Pap/HPV results. Polymerase chain reaction detected high-risk HPV DNA in tumor tissues of 3 SCC cases with recent HC2 results.


8 CIN 2/3 cases that are Cobas (-)
5 of them are negative for p16 staining and are negative for other hrHPV types
FDA advisory panel for use as a first-line cervical cancer screening test. Dr. R. Marshall Austin, Director of Cytopathology at Magee-Womens Hospital at the University of Pittsburgh, contacted me and informed me he was in attendance at the hearing and that Quest Diagnostics submitted comments that were very interesting.

Quest was kind enough to provide me with these comments, and I would like to share them, as they provide more data to support co-testing.

After Dr. Austin gave me the heads-up, I presumed the comments would be online, so I started looking. And looking. I never found them.

**Quest recommendation:** If new indication is approved, a statement should be made for cobas HPV that its results do not predict or diagnose the cervical cancer and despite in the presence of negative results Pap or other tests are needed.

**These indications are not approved by 5 medical associations recommending co-testing in ages 30-65**

**HPV infection is usually transient and its presence does not indicate the presence of cervical cancer or dysplasia.** A Quest Diagnostics Health Trends study (in 3.7 million women) revealed that 5% of women with high grade dysplasia or cancer (CIN3-carcinoma) are HPV negative.

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Re: Quest Diagnostics Inc. Comments Concerning the cobas® Human Papillomavirus (HPV) Test, sponsored by Roche Molecular Systems, Inc.

Dear Shanika Craig:

Quest Diagnostics submits these comments for consideration by the Microbiology Device Panel of the Medical Devices Advisory Committee of the U.S. Food and Drug Administration (FDA) for the meeting being held March 12, 2014, from 8 a.m. to 6 p.m. regarding the cobas® HPV Test, sponsored by Roche Molecular Systems, Inc. Quest Diagnostics is the world’s leading provider of diagnostic testing and information services. We believe we are the largest provider of laboratory services for cervical cancer screening in the United States, performing approximately ten million Pap and HPV tests annually. We have approximately 1,000 pathologists and cytotecnologists on staff.

**Disclosure Statement:**
We purchase equipment and reagents from numerous companies including Roche Molecular Systems, Inc. and Hologic, Inc., two of the leading providers of equipment and reagents for gynecologic pathology and human papillomavirus (HPV) testing. The comments made herein are based on the Quest Diagnostics experience performing HPV testing for more than a decade.

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**HPV False Negative Results in Years Before Cervical Cancer Diagnoses**

- 31% (27/87) HPV false-negative rate in baseline HC2 HPV tests performed ≤ 5 years before cervical cancer diagnoses (Lancet Oncology 2011; 12: 662-672)
- 42% (8/19) HPV false negative rate in baseline HC2 HPV tests performed ≥ 2.5-7 years before cervical cancer diagnoses (Lancet 2014; 383: 524-32)
• In 3,727,894 women 14.3% of them had a Pap smear test ≥CIN 3 orol (533,088); %4.6 % of these was HPV negative

• In follow up of women with Pap + HPV –: 25% developed cervix CA

• Extrapolating using US Census data, Quest notes 411,240 women in the US with CIN 3 or worse would therefore go unidentified if screening were limited to HPV testing alone.

• Quest further estimates, based on numbers from the American Cancer Society, screening using HPV testing alone could potentially miss 13.5% of women with invasive cervical cancer this year that would have been identified with co-testing.

• Again, based on our experience at Quest Diagnostics we would request that if the Panel recommends approval of the new indication for the cobas HPV Test, that the Panel and the FDA consider placing a Warning in the Labeling of the test to warn physicians and other diagnosicians that:
  • 1) the cobas HPV Test is not predictive or diagnostic of all causes or forms of cervical disease including cancer, and
  • 2) Pap testing and/or other follow up testing is required regardless of obtaining a negative result from the cobas HPV Test.

• Proposed Decision Memo for Screening for Cervical Cancer with Human Papillomavirus (HPV) Testing (CAG-00442N)

• IX. Conclusion

• The Centers for Medicare & Medicaid Services (CMS) proposes that the evidence is sufficient to cover a combined Human Papillomavirus (HPV) and Pap smear test once every five years as a cervical cancer screening for asymptomatic beneficiaries aged 30 to 65 years. CMS will cover screening for cervical cancer with the appropriate U.S. Food and Drug Administration (FDA) approved/cleared laboratory tests, used consistent with FDA approved labeling and in compliance with the Clinical Laboratory Improvement Act (CLIA) regulations.
SERVİKS KANSERİ TARAMASI ULUSAL STANDARTLARI

• Bu belge, Türkiye’de yürütülecek toplum tabanlı serviks kanser tarama çalışmalarının(saved) standartları belirlemektedir.

• GİRİŞ: Serviks kanseri tarama yöntemleri invazif kanser insidansını ve mortalitesini azalttığı düşünülen ve bu açıdan... 

• YÖNTEM: Ülkemizin altyapısı ve olanakları göz önünde alındığında ideal yöntem, serviks kanserini görüntüleyen pap smear testidir.

• SERVİKS KANSERİ TARAMA PROGRAMI ULUSAL STANDARTLARI

- TANIM: Türkiye Halk Sağlığı Kurumu tarafindan yürütülen toplum tabanlı serviks kanser tarama çalışmalarının(saved) standartları istenildi.

- GERÇEK: Serviks kanserinin tedavinin bir zamanlaması olarak kabul edilmektedir.

- HEDEF POPÜLASYON, TARAMANIN BAŞLANGIÇ VE BİTİŞ YAŞLARI, TARAMA SIKLIĞI: Taramada mutlak...
• The target to be screened should be at least 70% of the population for the quality and efficacy of the screening
• Screening interval should not be more than 2 years
• We may state that at least one smear in a lifetime between 30-65 years decreases the mortality of a woman from cervical cancer as X3

TARGET in SCREENING

• To reduce the mortality and morbidity of cervical cancer
• NOT to detect the HPV infection
• NOT to detect abnormal smears

Turkish data
33 centers 140334 women

• Overall, the prevalence of cervical cytological abnormalities was 1.8%;
• ASCUS: %1.07
• ASC-H: %0.07
• LSIL: %0.3
• HSIL: %0.17
• AGC: %0.08
• Invasive neoplasia: %0.06

Design cost-effectiveness analysis based on a Dutch simulation model. Base case analyses investigated the cost-effectiveness of more than 1,500 different screening policies using the microsimulation model. Subsequently, the policies were compared for five different scenarios that represent different possible scenarios (risk of cervical cancer, previous screening, quality associated test characteristics, costs of testing, and prevalence of HPV).

- Setting Various European countries.
- Main outcome measures Optimal screening strategy in terms of incremental cost-effectiveness ratios (costs per quality-adjusted life years gained) compared with different cost-effectiveness thresholds, for two levels of sensitivity and costs of the HPV test.

Results Primary HPV screening was the preferred primary test over the age of 30 in many considered scenarios.

- Primary HPV screening is preferred in many of the scenarios that would correspond to the cervical cancer screening situation of various European countries.
- In countries with high prevalence of HPV and high costs for the HPV test, primary cytology screening is preferred over primary HPV testing, indicating that it is important to organise primary HPV screening so that the costs of the test are low.

In the future cervical cancer screening may well begin with HPV testing with cytology as a triage for HPV-positive samples.

- On one hand, the absolute number of cervical cytology samples would decrease, but on the other hand, cytologic evaluation, in its new role as a method of triage, would become even more important and challenging.

Foreword by Robert Kurman, in

Science News from research organizations
Science news from research organizations
Scent-trained dog detects thyroid cancer in human urine samples
Date: March 7, 2015
Source: The Endocrine Society
Summary: A trained scent dog accurately identified whether patients' urine samples had thyroid cancer or were benign (noncancerous) 88.2 percent of the time, according to a new study.
A trained scent dog accurately identified whether patients’ urine samples had thyroid cancer or were benign (noncancerous) 88.2 percent of the time, according to a new study, to be presented Friday at the Endocrine Society’s 97th annual meeting in San Diego.

"Current diagnostic procedures for thyroid cancer often yield uncertain results, leading to recurrent medical procedures and a large number of thyroid surgeries performed unnecessarily," said the study’s senior investigator, Donald Bodenner, MD, PhD, chief of endocrine oncology at the University of Arkansas for Medical Sciences (UAMS) in Little Rock.

He said the dog’s diagnostic accuracy is only slightly less than that of fine-needle aspiration biopsies, the method generally used first to test thyroid nodules for cancer. Canine scent detection has the advantages of being noninvasive and inexpensive, he said.

Bodenner’s colleague at UAMS and a study-coauthor, Arny Ferrando, PhD, previously "imprinted," or scent-trained, a rescued male German Shepherd mix named Frankie to recognize the smell of cancer in thyroid tissue obtained from multiple patients. Ferrando, who noted that dogs have at least 10 times more smell receptors than humans do, said, "Frankie is the first dog trained to differentiate benign thyroid disease from thyroid cancer by smelling a person’s urine."

THANKS FOR YOUR ATTENTION