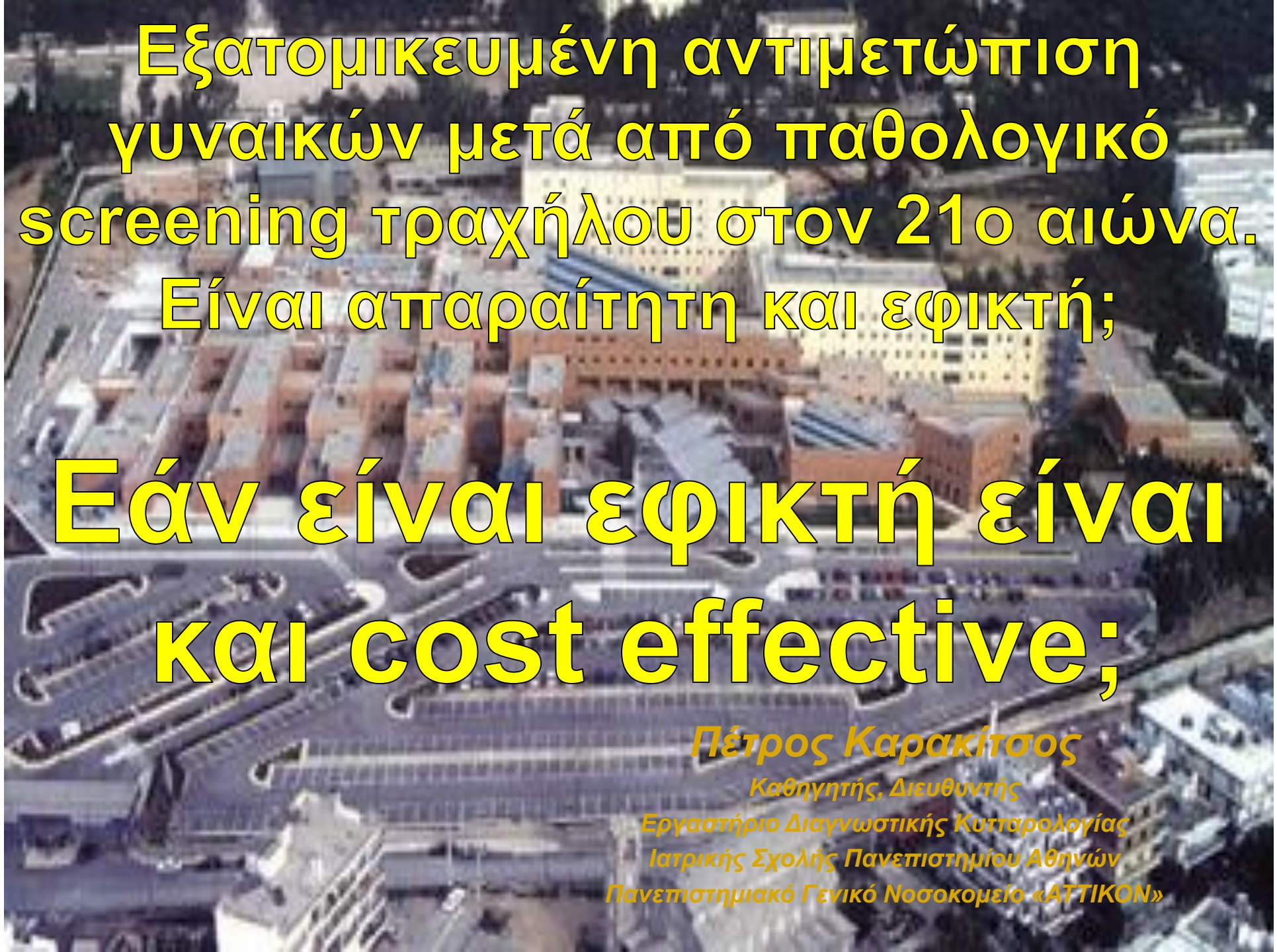


Εξατομικευμένη αντιμετώπιση γυναικών μετά από παθολογικό screening τραχήλου στον 21ο αιώνα. Είναι απαραίτητη και εφικτή;

Εάν είναι εφικτή είναι και cost effective;

Πέτρος Καρακίτσος

Καθηγητής, Διευθυντής

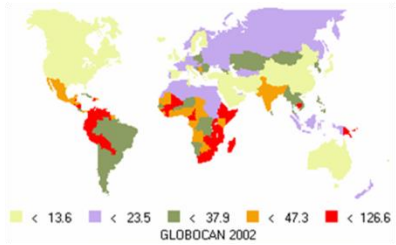
Εργαστήριο Διαγνωστικής Κυτταρολογίας

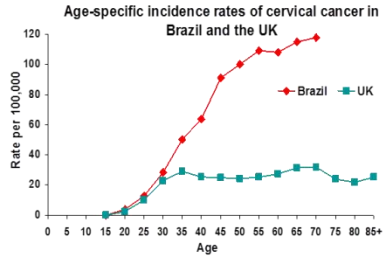
Ιατρικής Σχολής Πανεπιστημίου Αθηνών

Πανεπιστημιακό Γενικό Νοσοκομείο «ΑΤΤΙΚΟΝ»

500.000 νέα κρούσματα καρκίνου του τραχήλου διαγιγνώσκονται ετησίως

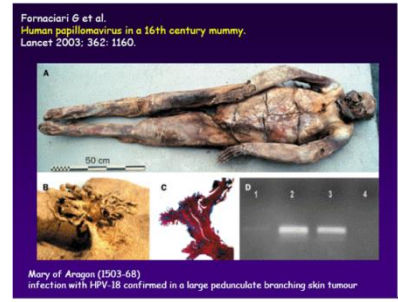
250.000 Θάνατοι από καρκίνο τραχήλου της μήτρας ετησίως





Υψηλή κοινωνική και ψυχολογική επίπτωση σε γυναίκες με παθολογικό test Pap

1. Cancer Research UK. UK Cervical Cancer mortality statistics.



JOURNAL OF PATHOLOGY
J. Pathol. 189: 12–19 (1999)

HUMAN PAPILLOMAVIRUS IS A NECESSARY CAUSE OF INVASIVE CERVICAL CANCER WORLDWIDE

JAN M. M. WALBOOMERS[1]*, MARCEL V. JACOBS[1], M. MICHELE MANOS[2], F. XAVIER BOSCH[3], J. ALAIN KUMMER[1], KIERTI V. SHAH[2], PETER J. F. SNIJDERS[1], JULIAN PETO[4], CHRIS J. L. M. MEIJER[1] AND NUBIA MUÑOZ[5]

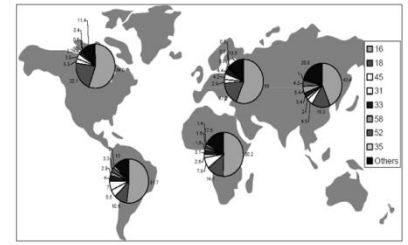
[1]*Department of Pathology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands*
[2]*Department of Molecular Microbiology and Immunology, Johns Hopkins University, Baltimore, MD, U.S.A.*
[3]*Institute Catala d'Oncologia, Barcelona, Spain*
[4]*Institute of Cancer Research, Belmont, Surrey, U.K.*
[5]*Unit of Field and Intervention Studies, IARC, Lyon, France*

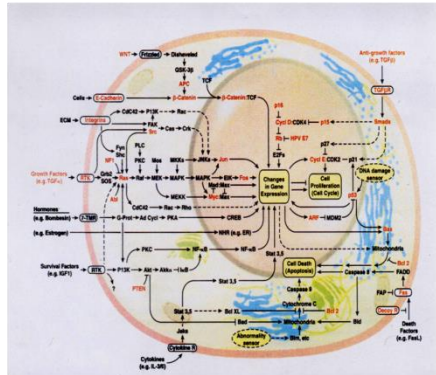
SUMMARY

A recent report that 93 per cent of invasive cervical cancers worldwide contain human papillomavirus (HPV) may be an underestimate due to sample inadequacy or integration events affecting the HPV L1 gene, which is the target of the polymerase chain reaction (PCR)-based test which was used. The formerly HPV-negative cases from this study have therefore been reanalysed for HPV serum antibodies and HPV DNA. Serology for HPV 16 VLPs, E6, and E7 antibodies was performed on 49 of the 86 cases which were HPV-negative and a sample of 48 of the 866 cases which were HPV-positive in the original study. Moreover, 55 of the 66 formerly HPV-negative biopsies were also reanalysed by a sandwich procedure in which the outer sections in a series of sections are used for histological review, while the inner sections are assayed by three different HPV PCR assays targeting different open reading frames (ORFs). No significant difference was found in serology for HPV 16 proteins between the cases that were originally HPV PCR-negative and -positive. Type-specific E7 PCR for 14 high-risk HPV types detected HPV DNA in 38 (69 per cent) of the 55 originally HPV-negative and amplifiable specimens. The HPV types detected were 16, 18, 31, 33, 39, 45, 52, and 58. Two (4 per cent) additional cases were only HPV DNA-positive by E1 and/or L1 consensus PCR. Histological analysis of the 55 specimens revealed that 21 were qualitatively inadequate. Only two of the 34 adequate samples were HPV-negative on all PCR tests, as against 13 of the 21 that were inadequate ($p<0{\cdot}001$). Combining the data from this and the previous study and excluding inadequate specimens, the worldwide HPV prevalence in cervical carcinomas is 99·7 per cent. The presence of HPV in virtually all cervical cancers implies the highest [illegible] cancers reinforces the rationale for HPV testing in addition to, or even instead of, cervical cytology in routine cervical screening.

Detection of HPV Types in Cervix Cancers from Different Regions of the World

adapted from Clifford Br J Cancer 2003;88:63





Ασθενείς με συστηματικό ερυθηματώδη λύκο

✓**Αυξημένο κίνδυνο λοίμωξης από HPV, κυρίως από υψηλού κινδύνου τύπους** (Klumb, Lyrio, Nath)

✓**Αυξημένη επίπτωση ενδοεπιθηλιακών αλλοιώσεων, κυρίως HGSIL** (Dugué, Klumb, Nath, Zard)**,**

✓**Αμφιλεγόμενα είναι τα σχετικά με το καρκίνωμα δεδομένα** (Dugué)

✓**Επιπτώσεις ενισχύονται λόγω της ανοσοκατασταλτικής αγωγής** (Klumb)

✓**Πρόσφατες αναφορές αυξημένης επίπτωσης ΣΕΛ μετά από εμβολιασμό για HPV εγείρουν πιθανότητες σταυροειδούς άτοπης αντίδρασης του ανοσιακού συστήματος** (Geier, Segal)

Αυξημένη επίπτωση ενδοεπιθηλιακών αλλοιώσεων

- **Ρευματοειδή αρθρίτιδα (Waldström)**
- **Σκληροδερμία (Colaci)**
- **Ελκώδη κολίτιδα**
- **Νόσος Crohn (Allegretti, Rungoe)**

Ρευματοειδής αρθρίτιδα

✓**Αμφιλεγόμενα αποτελέσματα για αυξημένο κίνδυνο εξέλιξης SIL (Cordtz [2015]) ή ανάπτυξη καρκινώματος τραχήλου (Cordtz [2016]) σε γυναίκες, που λαμβάνουν θεραπεία με βιολογικά τροποποιητικά της νόσου φάρμακα (biological disease-modifying anti-rheumatic drugs [bDMARD])**

✓**Γυναίκες που λαμβάνουν μη στεροειδή αντιφλεγμονώδη σκευάσματα εμφανίζουν μειωμένη επίπτωση καρκινώματος τραχήλου, πιθανόν λόγω καταστολής της επιτόπιας φλεγμονής (Mercer).**

✓**Αυξημένος κίνδυνος εμμένουσας λοίμωξης από HPV έχει αναφερθεί σε γυναίκες, που λαμβάνουν γλυκοκορτικοειδή (Stensen)**

✓**Ασχέτως υποκειμένου αιτίου, οι ανοσοκατεσταλμένες γυναίκες εμφανίζουν συχνότερα κερατινοποιημένη δυσπλασία στο Pap test (Boogs)**

HPV ένας διαφορετικός ιός

A Sophisticated Immune Evasion Mechanism[1-4]

Φτωχή έκθεση στα αντιγονοπαρουσιαστικά κύτταρα (APC). Δεν επάγει ικανοποιητική ανοσιακή απάντηση

Καθόλου ή ελεγχόμενη καμία έλξη των κυττάρων του ανοσιακού συστήματος

Χρησιμοποιεί το γονιδίωμα του κυττάρου ξενιστή μέσω του κυτταρικού κύκλ
απελευθερώνει νέους ιούς
Δεν προκαλεί κυτταρικό θάνατο[1-4]

Τοπική Ανοσοκαταστολή[1-4]

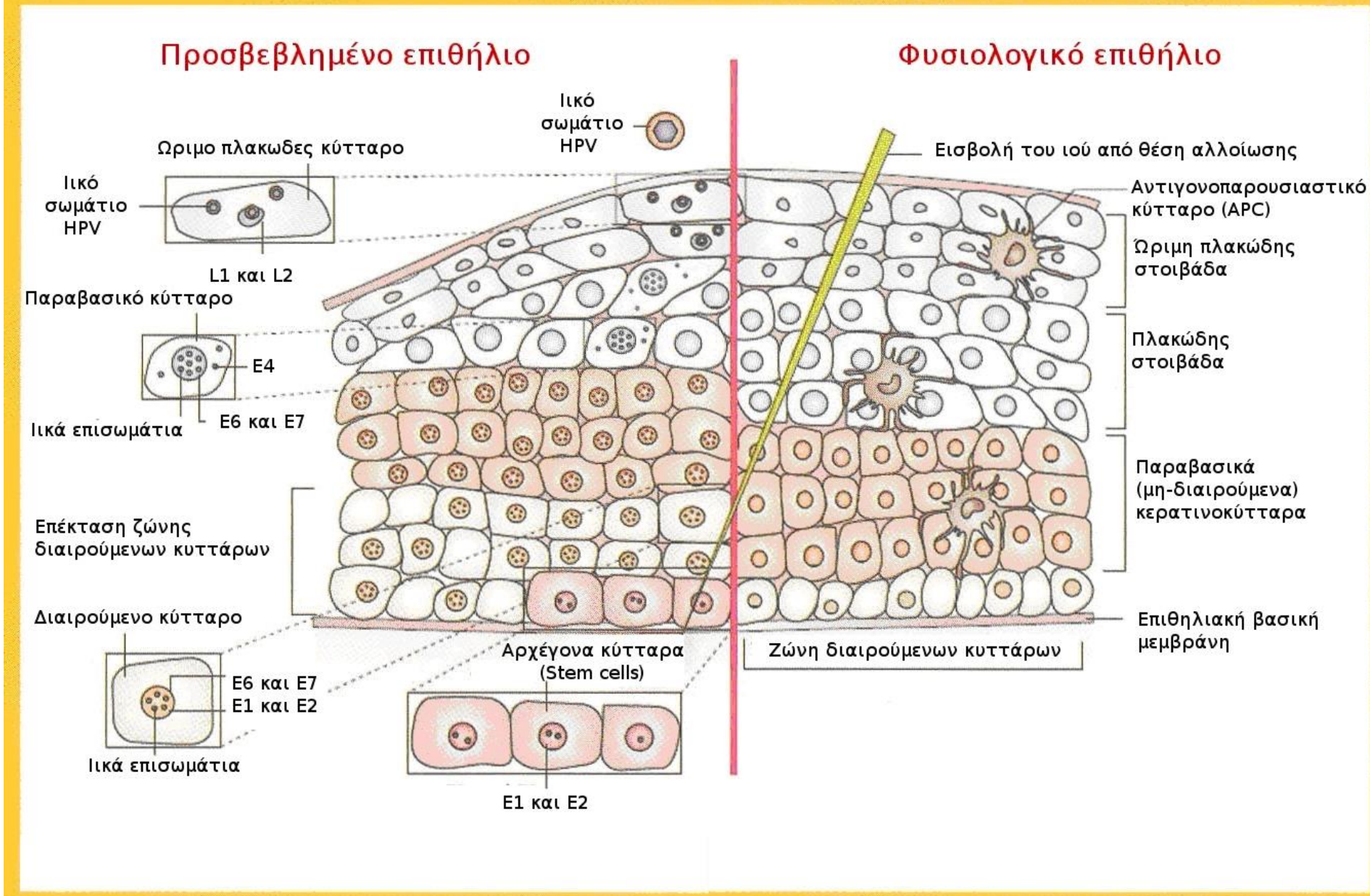
Εισέρχεται στο επιθηλιακό κύτταρο της βασικής στοιβάδας
και ενσωματώνεται στο DNA
Πολλαπλασιάζεται στο κύτταρο και παραμένει εξ ολοκλήρου ενδοεπιθηλιακά.[1-4]

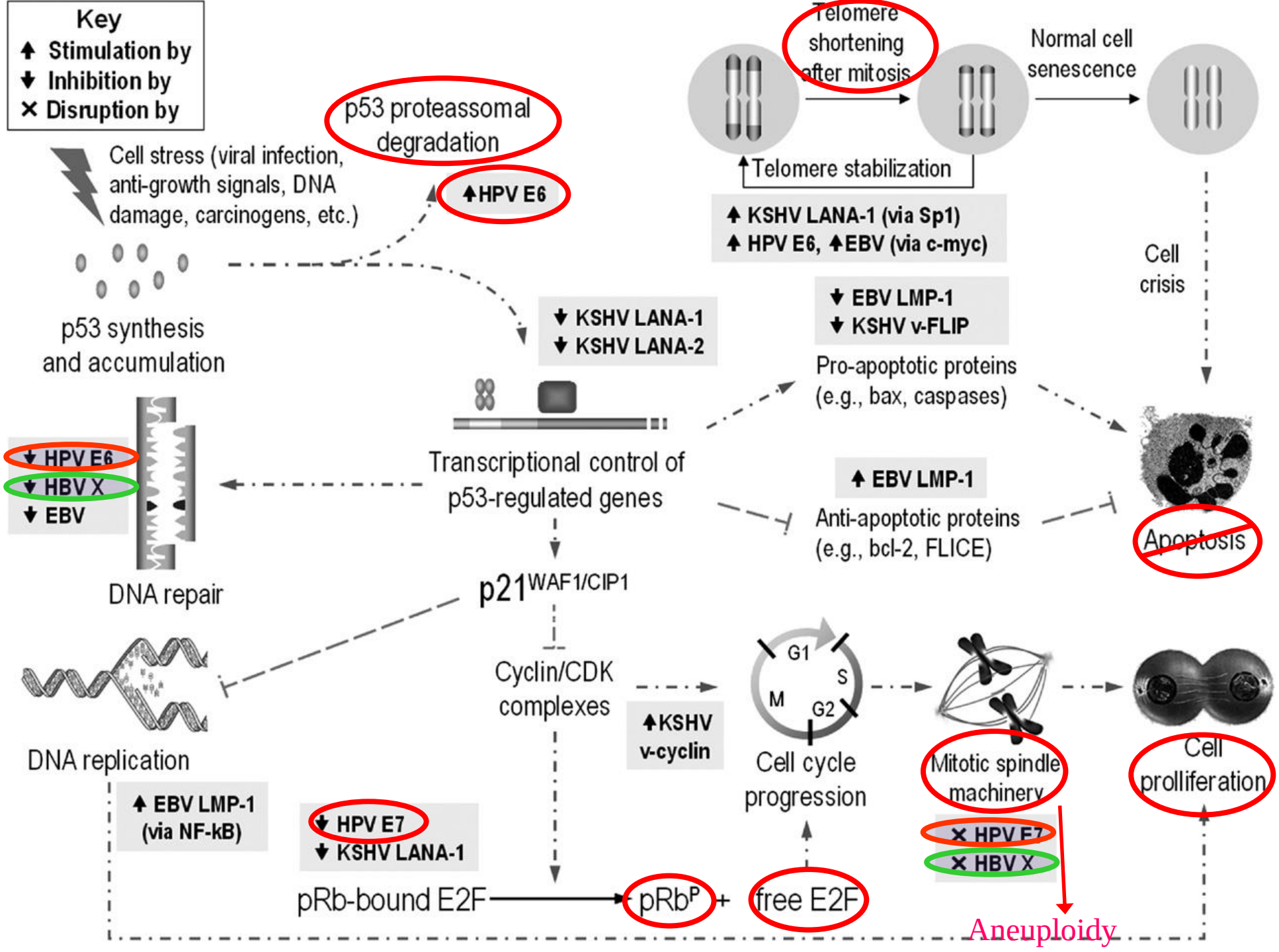
Οχι ιαμία (πχ Ηπατίτιδα)

Τοπική λύση[1-4]
Λοίμωξη επιθηλιακών κυττάρων λόγω εκδορών[1-4]

1.Stanley M. Vaccine 2006; 24: S106-13, 2.Tindle, Nat Rev Cancer 2002; 2, 59, 3.Stanley M. Vaccine 2006; 24: S16-22, 4. Stanley M. HPV Today 2007; 11: 1-16

ΣΧΗΜΑΤΙΚΗ ΑΝΑΠΑΡΑΣΤΑΣΗ ΤΩΝ ΚΥΡΙΩΝ ΣΤΑΔΙΩΝ ΤΟΥ ΚΥΚΛΟΥ ΖΩΗΣ ΤΟΥ HUMAN PAPILLOMA VIRUS (HPV) ΣΤΟ ΠΛΑΚΩΔΕΣ ΕΠΙΘΗΛΙΟ

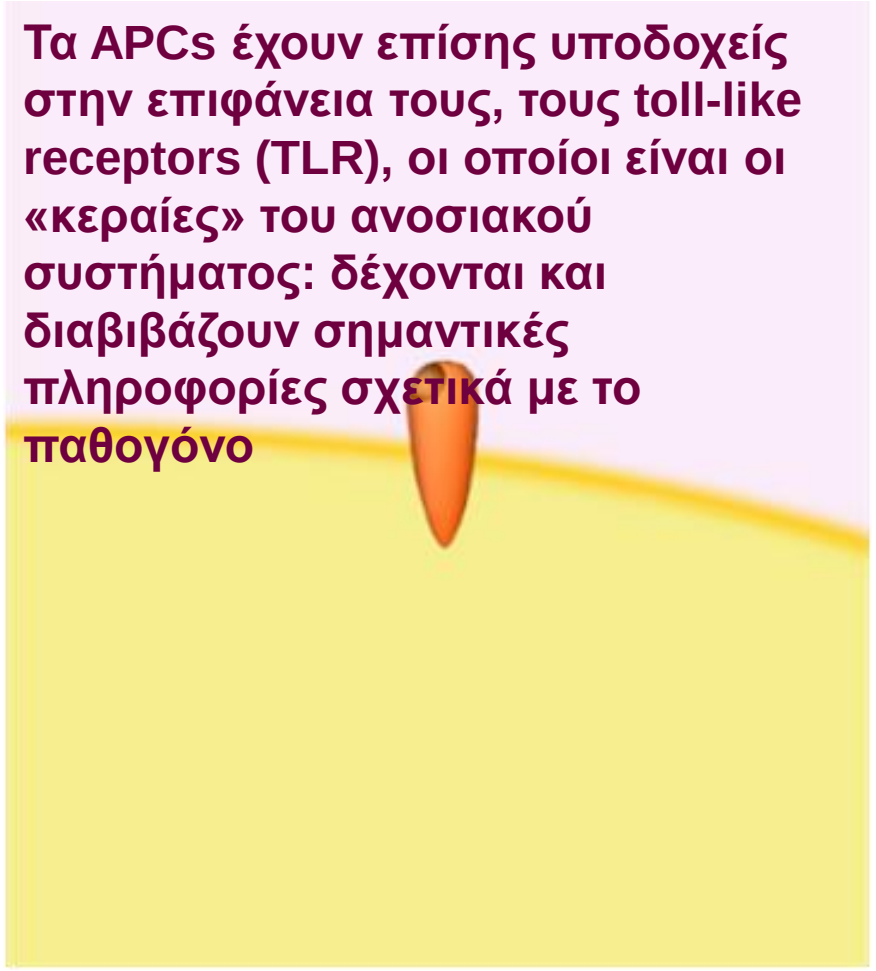



Key
Stimulation by
Inhibition by
Disruption by
Cell stress (viral infection, anti-growth signals, DNA damage, carcinogens, etc.)
p53 proteassomal degradation
HPV E6
p53 synthesis and accumulation
KSHV LANA-1
KSHV LANA-2
Transcriptional control of p53-regulated genes
HPV E6
HBV X
EBV
DNA repair
p21WAF1/CIP1
DNA replication
Cyclin/CDK complexes
KSHV v-cyclin
G1
S
M
G2
Cell cycle progression
EBV LMP-1 (via NF-kB)
HPV E7
KSHV LANA-1
pRb-bound E2F
pRbP
free E2F
Telomere shortening after mitosis
Normal cell senescence
Telomere stabilization
KSHV LANA-1 (via Sp1)
HPV E6, EBV (via c-myc)
Cell crisis
EBV LMP-1
KSHV v-FLIP
Pro-apoptotic proteins (e.g., bax, caspases)
EBV LMP-1
Anti-apoptotic proteins (e.g., bcl-2, FLICE)
Apoptosis
Mitotic spindle machinery
HPV E7
HBV X
Aneuploidy
Cell prolliferation

Ο ρόλος των αντιγονοπαρουσιαστικών κυττάρων (APCs)

Το APC προσλαμβάνει το VP και το αποδομεί σε μικρά θραύσματα, τα οποία παρουσιάζονται στην επιφάνεια του APC.

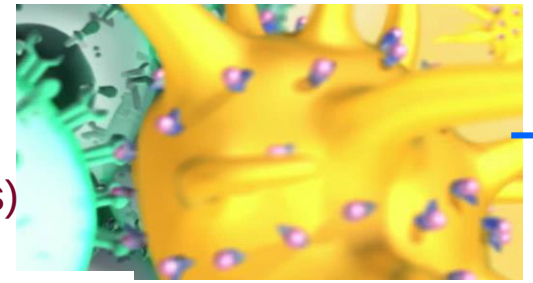
Τα APCs έχουν επίσης υποδοχείς στην επιφάνεια τους, τους toll-like receptors (TLR), οι οποίοι είναι οι «κεραίες» του ανοσιακού συστήματος: δέχονται και διαβιβάζουν σημαντικές πληροφορίες σχετικά με το παθογόνο

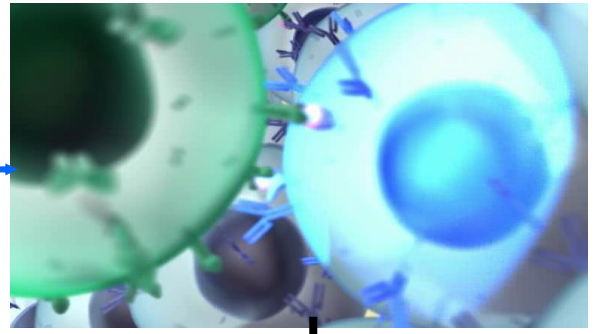


Kaisho T, Akira S. Biochimica et Biophysica Acta 1589 (2002) 1-13. De Becker G, Moulin V, Pajak B, Bruck C, Francotte M, Thiriart C et al. Int Immun 2000;12:807-15. Baldridge J, McGowan P, Evans J et al. Expert Opin Biol Ther (2004) 4(7):1129-1138.

Toll-like Receptors: Οι ανιχνευτές του «Bar Code»

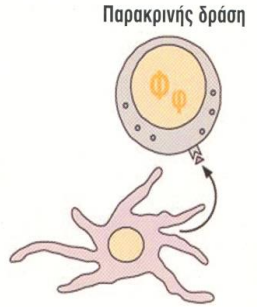
Τ-βοηθητικό κύτταρο





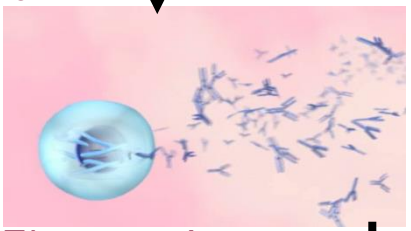
Β κύτταρο

Toll-like Receptors (TLRs)



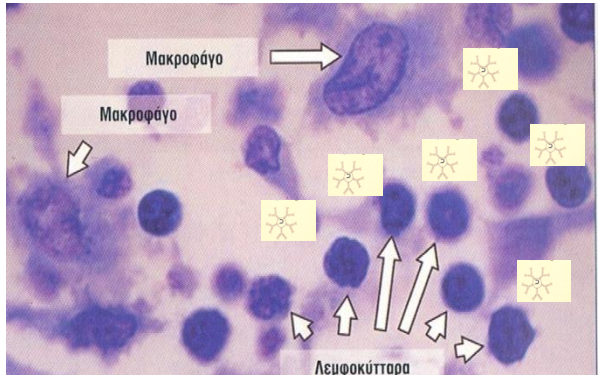
Δενδριτικό κύτταρο

IgG

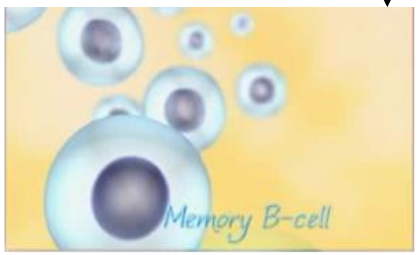


Πλασματοκύτταρο που παράγει αντισώματα

…και αναγκάζει το APC να μεταναστεύσει στο χόριο ή στον λεμφαδένα, όπου θα ξεκινήσουν τα βασικά βήματα για την ενεργοποίηση των λεμφοκυττάρων, την παραγωγή αντισωμάτων και την ανοσιακή απάντηση



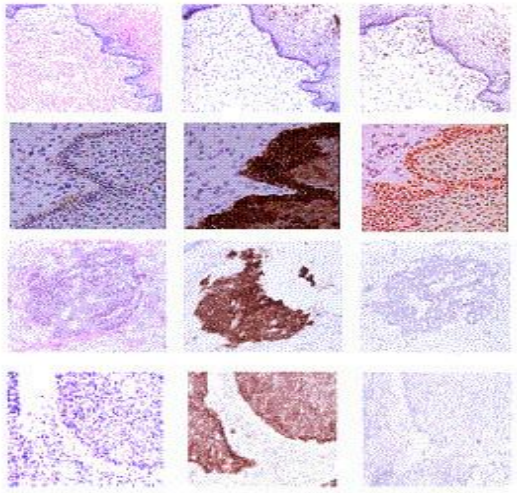
Β κύτταρο χορίου



Μνημονικό Β κύτταρο

HPV strategies to avoid immune recognition: suppression

Repression of TLR9 (signal pathways) by E6/E7



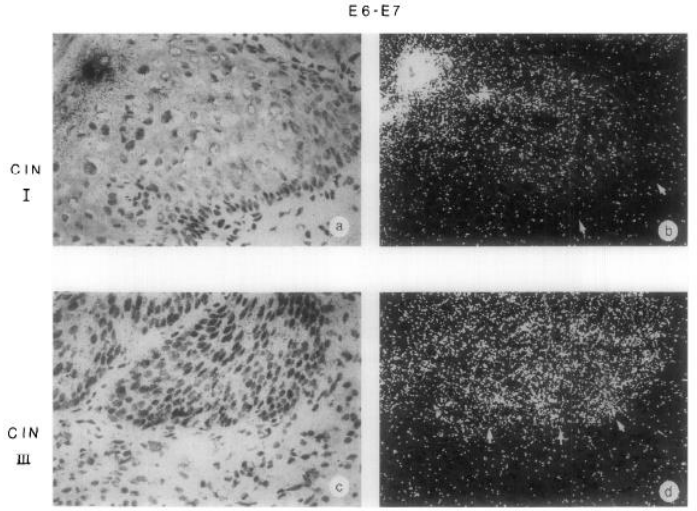
Normal x4

Normal x40

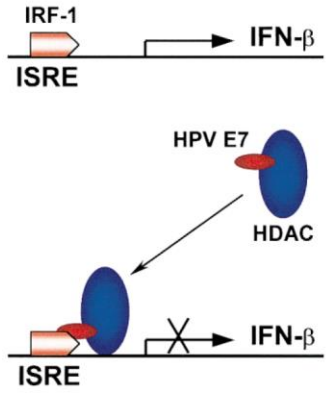
Patient a
HPV16 x20

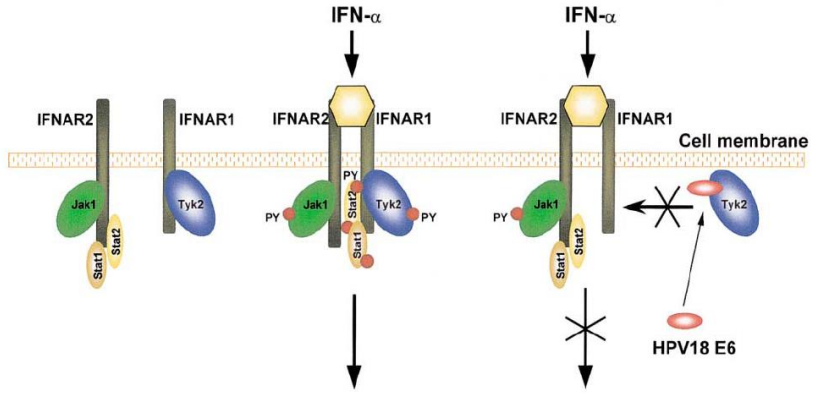
Patient b
HPV16 x20

pan keratin TLR9

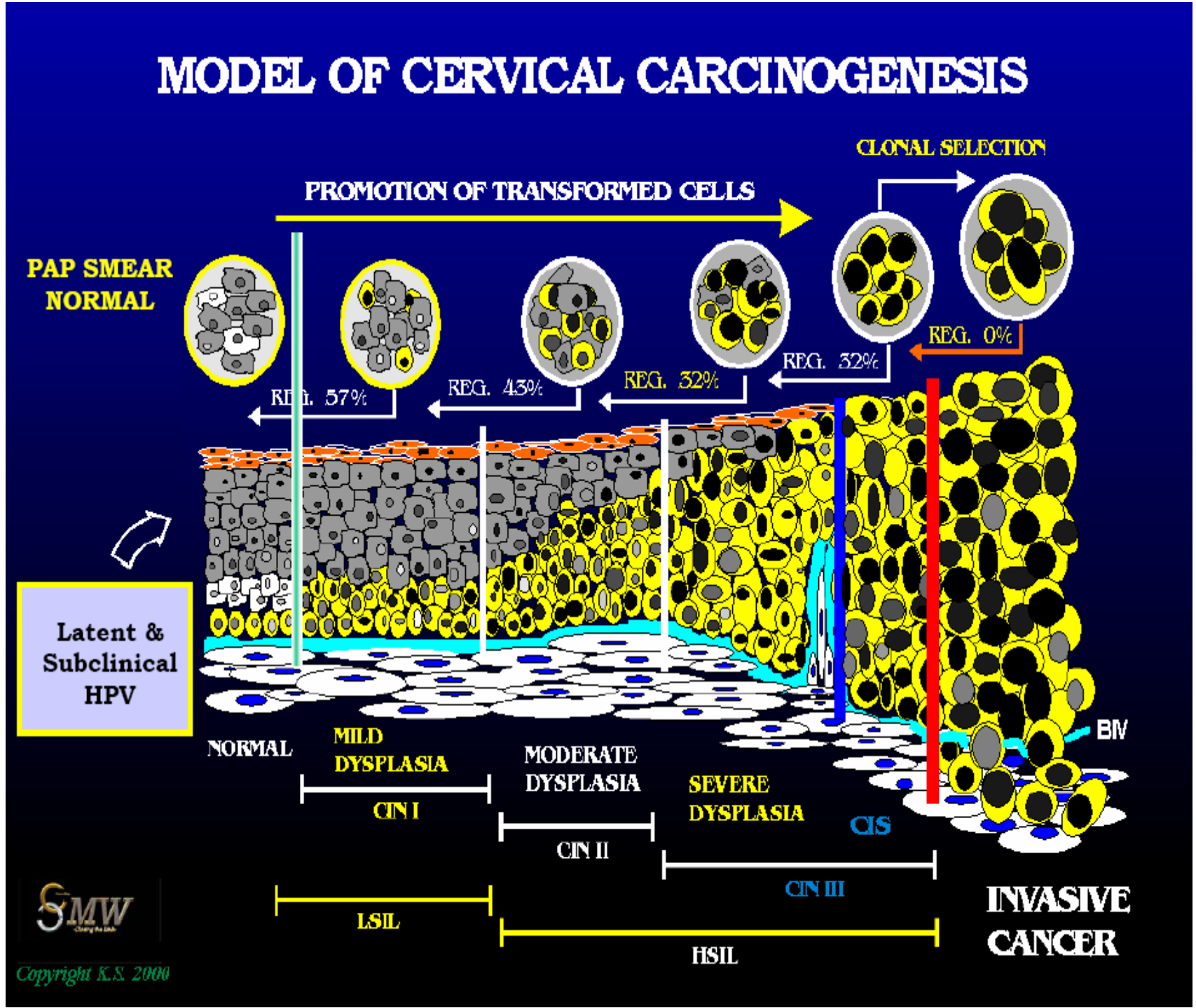


Reduction of migration of Langerhans cells (reduction of E-cadherin by E6)

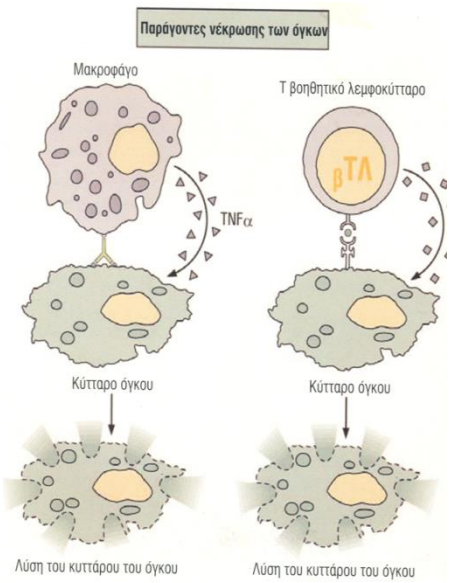


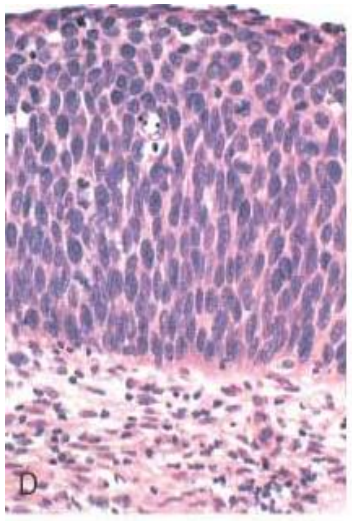


Influence on IFN expression by E6/E7 **Influence on IFN-dependent signal pathways by E6/E7**


MODEL OF CERVICAL CARCINOGENESIS
CLONAL SELECTION
PROMOTION OF TRANSFORMED CELLS
PAP SMEAR NORMAL
REG. 57%
REG. 43%
REG. 32%
REG. 32%
REG. 0%
Latent & Subclinical HPV
NORMAL
MILD DYSPLASIA
CIN I
MODERATE DYSPLASIA
CIN II
SEVERE DYSPLASIA
CIN III
CIS
BM
LSIL
HSIL
INVASIVE CANCER
Copyright K.S. 2000

Ανοσιακή απάντηση και καρκίνος





CIN III

- ✓ **Κατά την εξέλιξη του όγκου επιβιώνουν καρκινικά κύτταρα με χαμηλή αντιγονικότητα**
- ✓ **Καταστολή των αντιγόνων ιστοσυμβατότητας:**
  - ➢ **αντιγόνα τάξης I παρουσιάζουν μεταγραφική υποέκφραση**
  - ➢ **αντιγόνα τάξης II συνήθως απουσιάζουν**
- ✓ **Απουσία μορίων συν-ενεργοποιητών**
  - ➢ **ακόμα και αν εκφράζονται τα MHC-1 απουσιάζουν μόρια που δρουν συνεργιστικά για την ενεργοποίηση των Τ-κυττάρων**

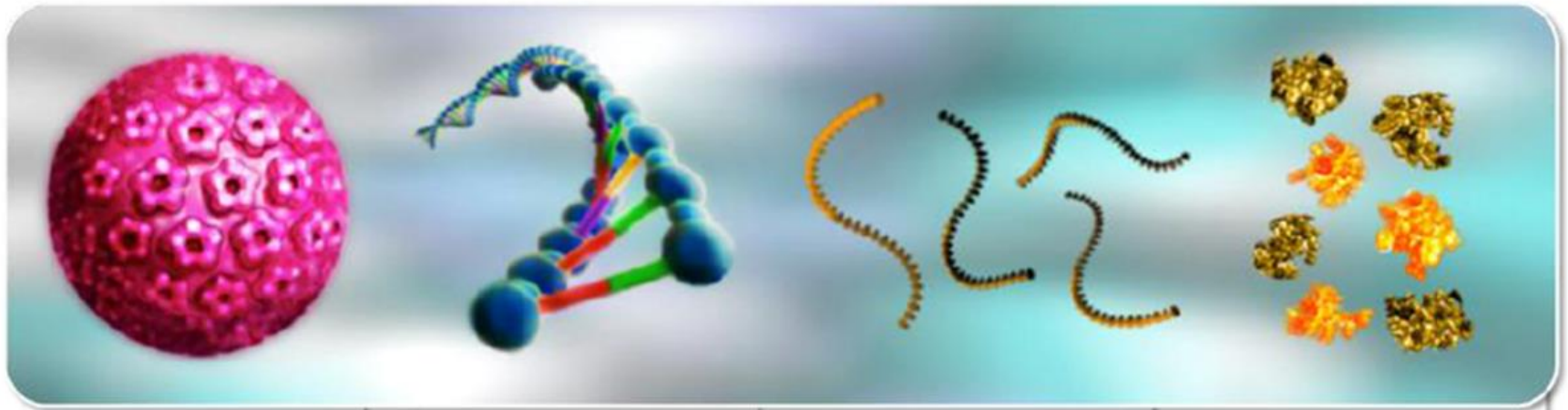
✓ Ανοσοκαταστολή

- ➢ **έκκριση παραγόντων που προκαλούν ανοσοκαταστολή (TGF-β, IL-10)**
- ➢ **ενεργοποίηση Τ-ανοσοκατασταλτικών κυττάρων**

✓ Καταστροφή των Τ-κυτταροτοξικών κυττάρων

- ➢ **έκκριση του FasL από στοιχεία του όγκου ο οποίος προσδένεται στον Fas των CTL και προκαλεί απόπτωση των τελευταίων**

HPV Molecular Biology



HPV viral particles

Viral DNA genome

E6/E7 mRNA expression by active virus

E6/E7 *oncoproteins* induce carcinogenesis

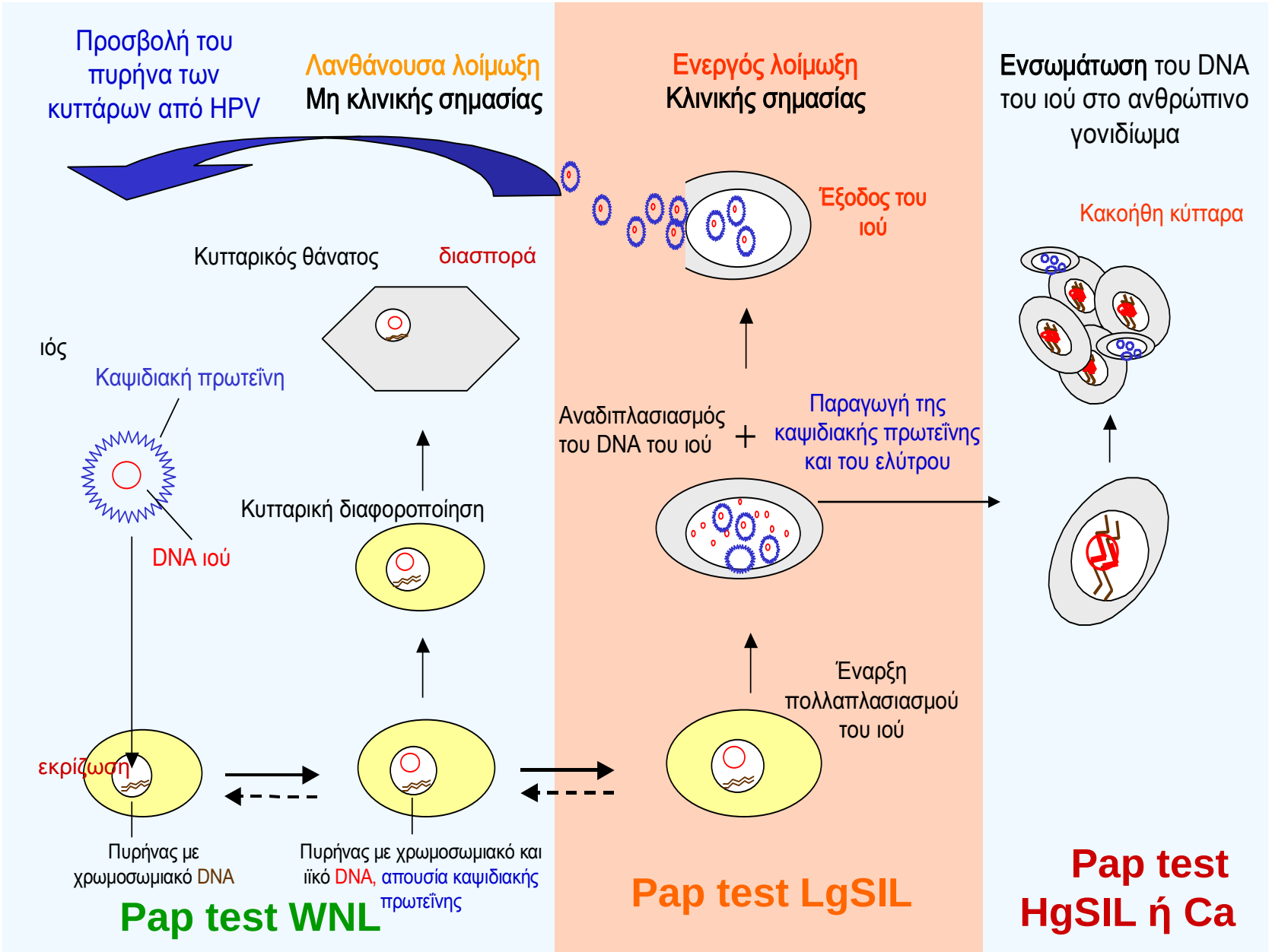
DNA indicates *presence* of HPV

Expression of E6/E7mRNA indicates *activity* of HPV

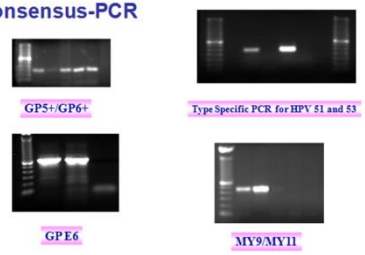
Doorbar. Clinical Science 2006. 110(5):525-41

Κύκλος λοίμωξης του HUMAN PAPILLOMAVIRUS (HPV)

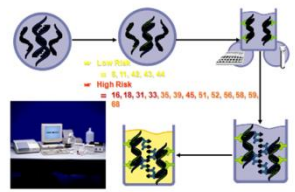
(απλοποιημένο μοντέλο)



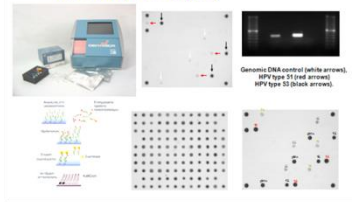
Consensus-PCR



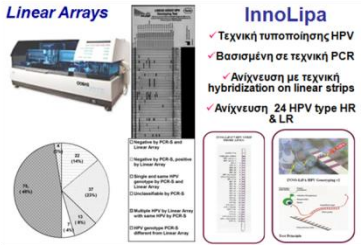
Hybrid Capture II



HPV Μικροσυστοιχίες



Linear Arrays



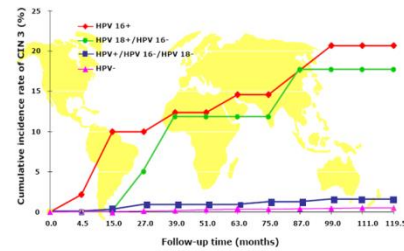
InnoLipa

- ✓Τεχνική τυποποίησης HPV
- ✓Βασισμένη σε τεχνική PCR
- ✓Ανίχνευση με τεχνική hybridization on linear strips
- ✓Ανίχνευση 24 HPV type HR & LR

Cumulative incidence of CIN 3+

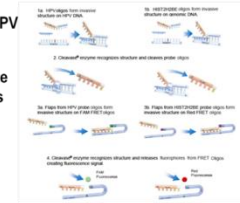
13,000 women over a 10 year period

(as a function of a single HPV test result at enrolment)



Cervista High Risk-Cervista 16/18

- ✓Invader Signal Amplification method Enzymatic cleavage of HPV targeted probes
- ✓Cleaved sequence is a substrate for a 2nd reaction that produces fluorescence
- ✓Solution based
- ✓No-typing



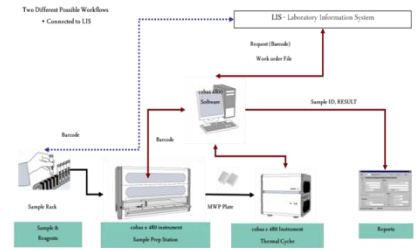
But:

Oligo 1: (A5,A6) 51, 56, 66

Oligo 2: (A7) 18, 39, 45, 59, 68

Oligo 3: (A9) 16, 31, 33, 35, 52, 58

System Workflow Design

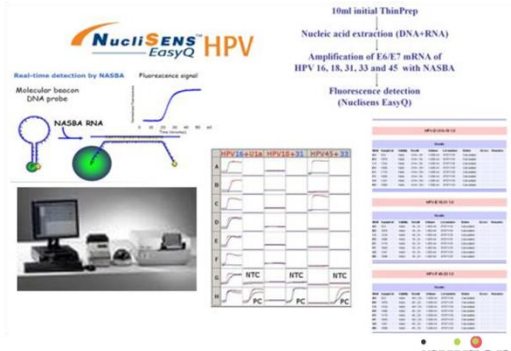


The only user intervention after the start of the run is the MWP transfer from cobas x to cobas z analyzer

Abbott Real Time HPV test

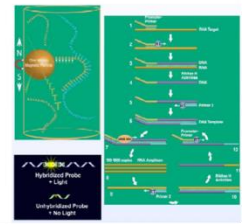
- ✓Τεχνική βασισμένη σε Real-Time PCR
- ✓Ανίχνευση 14 HR HPVs και τυποποίηση HPV16 HPV18
- ✓Απαιτεί λιγότερο χρόνο από τις τεχνικές PCR-hybridization

NucliSENS EasyQ HPV

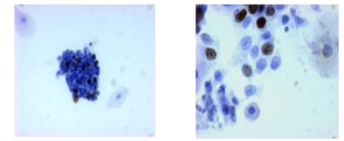


Aptima HPV

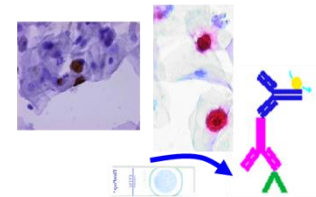
- ✓Solution based mRNA technique
- ✓Detection with fluorometry after DNA:RNA hybridization
- ✓Detects mRNA from 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)
- ✓Uses target capture, Transcription-Mediated Amplification, and Hybridisation Protection Assay technologies
- ✓Semi- of fully automated
- ✓No typing

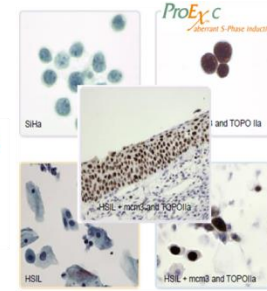


Topoisomerase IIα/MCM2



L1 HPV Test





Flow cytometric determination of E6/E7 mRNA of high risk HPV types

invirion

1ml of ThinPrep (max 10^6 cells)

↓

Fixation, permeabilization (90 min)

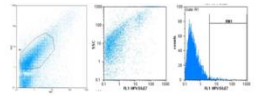
↓

Hybridization with probe coctail (30 min)

↓

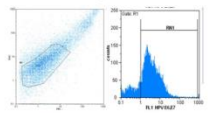
Strigent wash (15 min) → Count on flow cytometre (5 minutes)

Gating of ecto-cervical cells based on FSC/SSC parameters. Determination of fluorescent cells (Cut-off 1,5%)



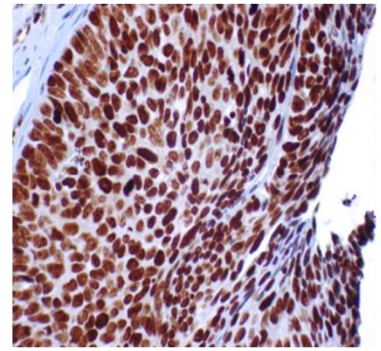
A WNL sample displaying under 2% positive cells (cut-off set at 5%). R1 region defines ecto-cervical cells.

Relatively fast technique Can detect E6/E7 mRNA of high risk HPV types

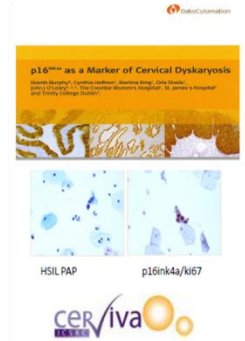


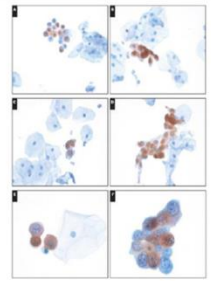
A HgSIL sample with 71.5% positive cells

Cannot discriminate which high risk



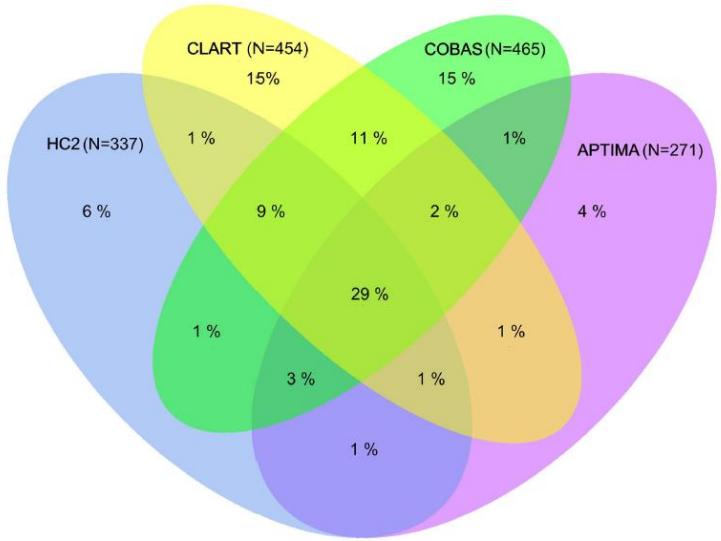
Novel kinetochore proteins in cervical pre-cancer





Schmidt et al., Am J Clin Pathol July 2010 vol. 134 1 12-21

Disagreement between Human Papillomavirus Assays: An Unexpected Challenge for the Choice of an Assay in Primary Cervical Screening



BMC Cancer

HPV Prevalence in the Dutch cervical cancer screening population (DuSC study): HPV testing using automated HC2, cobas and Aptima workflows

Figure 1. Primary samples, 30–65 years: Disagreement between Hybrid Capture 2, cobas, CLART, and APTIMA HPV assays. Proportions were calculated from all samples that tested positive on at least one assay.

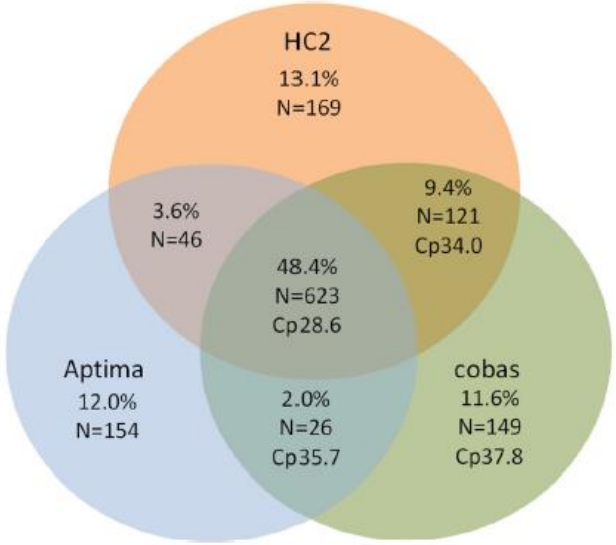


Fig. 4 Inter-assay agreement between HC2, cobas and Aptima. Each proportion was calculated based on the total number samples found hrHPV positive (n = 1,288) in at least one of the assays

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Comparative Evaluation of Three Commercial Systems for Detection of High-Risk Human Papillomavirus in Cervical and Vaginal ThinPrep PreservCyt Samples and Correlation with Biopsy Results

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Division of Clinical Microbiology[a] and Division of Anatomic Pathology,[b] Department of Laboratory Medicine and Pathology, Mayo Clinic and Mayo Clinic College of Medicine, Rochester, Minnesota, USA

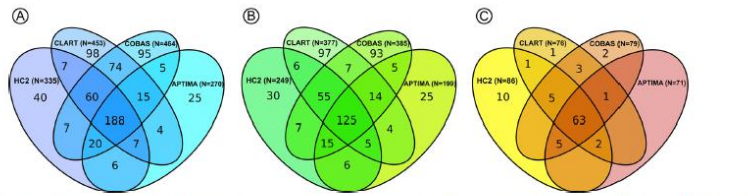
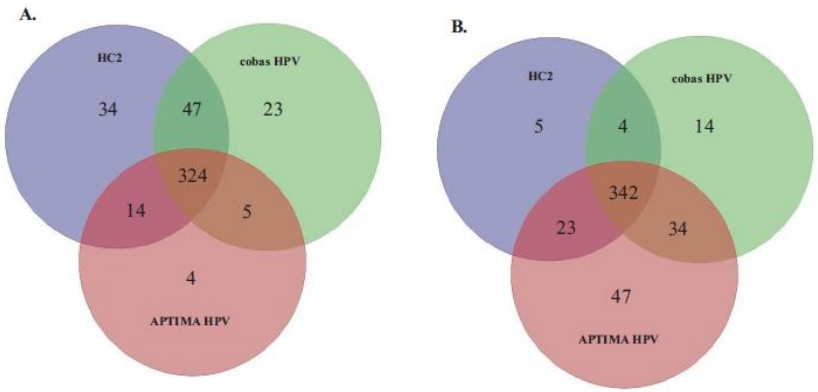


FIG 1 Distribution of test results at baseline in HPV-positive women with screening samples at age 30 to 65 years. (A) All screened women ($n = 651$). (B) Women with normal cytology ($n = 558$). (C) Women with abnormal cytology ($n = 93$).

Differential Detection of Human Papillomavirus Genotypes and Cervical Intraepithelial Neoplasia by Four Commercial Assays



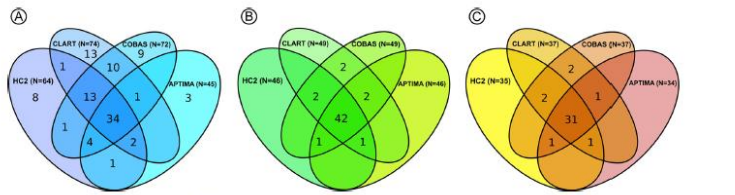


FIG 2 Distribution of histologically confirmed CIN lesions in HPV-positive women with screening samples at age 30 to 65 years, with follow-up from the baseline in June-August 2011 to December 2013. Linkage was performed through the national Patobank. (A) Women with ≤CIN1 ($n = 100$). (B) Women with ≥CIN2 ($n = 50$). (C) Women with ≥CIN3 ($n = 38$).

FULL PAPER

BJC

British Journal of Cancer (2013) 108, 908–913 | doi: 10.1038/bjc.2013.22

Keywords: biomarkers; cervix; HPV

Comparing the performance of six human papillomavirus tests in a screening population

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Background: Several new assays have been developed for high-risk HPV testing of cervical samples; we compare six HPV tests in a screening population.

Methods: Residual material from liquid-based PreservCyt samples was assayed. Four tests (Hybrid Capture 2, Cobas, Abbott and Becton–Dickinson (BD)) measured HPV DNA while two used RNA (APTIMA and NorChip).

Results: Positivity rates ranged from 13.4 to 16.3% for the DNA-based tests with a significantly lower positivity rate for the Abbott assay. The Gen-Probe APTIMA assay was positive in 10.3% of women, which was significantly lower than all the DNA tests; the NorChip PreTect HPV-Proofer test was much lower at 5.2%. 40 CIN2+ cases were identified, of which 19 were CIN3+. All CIN3+ cases were HPV positive by all tests except for one, which was negative by the Abbott assay and five which were negative by the NorChip test.

Conclusion: All HPV tests except NorChip showed high sensitivity for high-grade lesions positive by cytology, suggesting co-testing is unnecessary when using HPV tests. Positivity rates in cytology-negative specimens were similar for the DNA-based tests, but lower for the APTIMA test suggesting this maintains the high sensitivity of DNA tests, but with better specificity.

There is widespread interest in introducing HPV testing for primary screening and triage. Many studies have shown that HPV DNA testing has higher sensitivity but lower specificity than cytology (Cuzick *et al*, 2006, 2008a, Ronco *et al*, 2010). However, there are limited comparisons between the different HPV tests. We have previously carried out studies which have compared a number of adjunctive tests in women with abnormal smears who have been referred to colposcopy (Szarewski *et al*, 2008, Szarewski *et al*, 2012). These studies were focused primarily on identifying tests with good sensitivity, and the specificities reflect the typically lower values found in a referral setting. Although this approach does permit a comparison of relative specificity, it is desirable to also compare these tests in a screening setting. A definitive comparison of sensitivity in this setting would require studies of at least 20 000 women, but specificity can be accurately evaluated in a much smaller sample size. Here we compare four DNA-based HPV tests and two RNA-based HPV tests in a screening setting.

MATERIALS AND METHODS

Residual material was used from the liquid-based cytology PreservCyt samples from 6000 women who attended for a routine 3 or 5 yearly (depending on age) screening smear, and whose samples were sent to the cytology laboratory at St. Mary's Hospital, London. Unsatisfactory cytology samples were excluded; there were no other inclusion/exclusion criteria. Samples were linked to concurrent cytology results and any histology within 6 months of an abnormal smear, and this information was fully anonymised before being transferred for analysis.

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JCM

Journal of Clinical Microbiology

Comparison of Seven Tests for High-Grade Cervical Intraepithelial Neoplasia in Women with Abnormal Smears: the Predictors 2 Study

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High-risk human papillomavirus (HPV) DNA/RNA testing provides higher sensitivity but lower specificity than cytology for the identification of high-grade cervical intraepithelial neoplasia (CIN). Several new HPV tests are now available for this purpose, and a direct comparison of their properties is needed. Seven tests were evaluated with samples in liquid PreservCyt transport medium from 1,099 women referred for colposcopy: the Hybrid Capture 2 (Qiagen), Cobas (Roche), PreTect HPV-Proofer (NorChip), Aptima HPV (Gen-Probe), and Abbott RealTime assays, the BD HPV test, and CINtec p16^{INK4a} cytology (mtm laboratories) immunocytochemistry. Sensitivity, specificity, and positive predictive value (PPV) were based on the worst histology found on either the biopsy or the treatment specimen after central review. Three hundred fifty-nine women (32.7%) had CIN grade 2+ (CIN2+), with 224 (20.4%) having CIN3+. For detection of CIN2+, Hybrid Capture 2 had 96.3% sensitivity, 19.5% specificity, and 37.4% PPV. Cobas had 95.2% sensitivity, 24.0% specificity, and 37.6% PPV. The BD HPV test had 95.0% sensitivity, 24.2% specificity, and 37.8% PPV. Abbott RealTime had 93.3% sensitivity, 27.3% specificity, and 38.2% PPV. Aptima had 95.3% sensitivity, 28.8% specificity, and 39.3% PPV. PreTect HPV-Proofer had 74.1% sensitivity, 70.8% specificity, and 55.4% PPV. CINtec p16^{INK4a} cytology had 85.7% sensitivity, 54.7% specificity, and 49.1% PPV. Cytology of a specimen taken at colposcopy (mild dyskaryosis or worse) had 88.9% sensitivity, 58.1% specificity, and 50.7% PPV. Our study confirms that, in a referral setting, HPV testing by a number of different tests provides high sensitivity for high-grade disease. Further work is needed to confirm these findings in a routine screening setting.

High-risk (HR) human papillomavirus (HPV) is a necessary factor for the development of cervical cancer (31), but the presence of HR HPV DNA does not invariably lead to disease. We have shown that the detection of HR HPV DNA provides high sensitivity but has lower specificity than cytology for the identification of high-grade cervical lesions in a screening population in the United Kingdom (9), and this finding has been replicated in several other studies (1, 3, 8, 15–17, 21, 22, 26, 27). In addition, prospective studies have shown that HPV DNA-positive women who do not have disease initially are significantly more likely to develop high-grade squamous intraepithelial lesions (SILs) within 10 years than women with a negative HPV DNA test (4, 12, 14, 18). If testing for HR HPV DNA is to be used as a primary cervical screening test, refinements or additional tests are highly desirable to improve its specificity while retaining its very high sensitivity. Candidates include HPV typing, detection of HPV E6/E7 mRNA tests, and p16^{INK4a} cytology, which have shown higher specificity than HPV DNA testing (10, 19).

The introduction of a liquid-based medium for collection of cytological specimens has allowed other molecular techniques to be evaluated more easily as adjunctive or triage tests (2). We have previously compared a number of different molecular tests in a population referred for colposcopy because of abnormal cytology (7, 29). However, there are now a number of newer tests, which also require evaluation. A number of studies have compared two tests against each other (usually the comparator was the Hybrid Capture 2 [HC2] assay), but as far as we are aware, apart from our previous study, none have simultaneously compared such a wide range of tests using the same sample. The aim of this study was to compare directly the sensitivity and specificity of several tests for the detection of high-grade cervical intraepithelial neoplasia (CIN) using aliquots from the same sample from the same women in a population referred for colposcopy because of abnormal cytology. This population was chosen because the high disease rate allows comparison of the sensitivities of the different tests within a modest sample size. Use of a screening population would require a sample size at least 20 times larger in order to have similar power. All the tests were compared against the "gold standard" of centrally reviewed histopathology.

MATERIALS AND METHODS

The study population comprised 1,099 women who had been referred to the colposcopy clinics at the Hammersmith and St. Mary's Hospitals in London, United Kingdom, between September 2007 and October 2008 because of abnormal screening smears (Fig. 1). In England, women are referred for colposcopy if they have cytology showing mild dyskaryosis or worse or three smears showing borderline dyskaryosis. While not a screening population, the advantage was a broad range of outcomes and a

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Table 3. Summary of discordant results between different tests

	BD HPV	Roche Cobas	Qiagen Hybrid Capture 2	Abbott RealTime High Risk HPV	Gen-Probe APTIMA	NorChip PreTect HPV-Proofer
BD HPV	—	0.83	0.78	0.81	0.65	0.33
Roche Cobas	(145, 134)[a]	—	0.75	0.85	0.64	0.35
	1.1 (0.8, 1.4)					
Qiagen Hybrid Capture 2	(204, 141)	(225, 174)	—	0.78	0.68	0.35
	1.4 (1.2, 1.8)	1.3 (1.1, 1.6)				
Abbott RealTime High Risk HPV	(227, 57)	(194, 35)	(216, 108)	—	0.70	0.39
	4.0 (3.0, 5.4)	5.5 (3.9, 8.2)	2.0 (1.6, 2.5)			
Gen-Probe APTIMA	(421, 70)	(414, 77)	(353, 68)	(279, 97)	—	0.45
	6.0 (4.7, 7.9)	5.4 (4.2, 6.9)	5.2 (4.0, 6.8)	2.9 (2.3, 3.7)		
NorChip PreTect HPV-Proofer	(684, 61)	(670, 54)	(625, 63)	(532, 65)	(375, 82)	—
	11.2 (8.6, 14.8)	12.4 (9.4, 16.7)	9.9 (7.6, 13.1)	8.2 (6.3, 10.8)	4.6 (3.6, 5.9)	

Number in top half of Table represent kappa values. Numbers in bottom half of Table give discordant pairs (column positive/row negative vs column negative/row positive) and OR (95% CI).
[a]145 Tested positive for BD HPV and negative for Roche Cobas, and 134 tested negative for BD HPV and positive for Roche Cobas.

TABLE 3 Sensitivity, specificity, and PPV of different tests for detection of high-grade disease

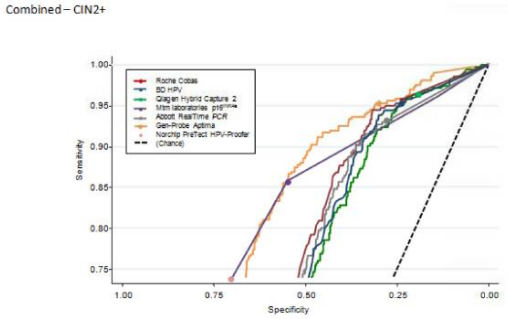
	All women			Women with referral less than or equal to single mild dyskaryosis		
Test and grade assessed	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)
Qiagen Hybrid Capture 2						
CIN3+	98.7 (96.1–99.7)[a]		24.0 (21.3–26.9)	100.0 (92.7–100.0)		9.2 (6.9–11.9)
CIN2+	96.3 (93.8–98.0)	19.5 (16.7–22.6)	37.4 (34.2–40.6)	93.0 (86.8–96.9)	19.9 (16.5–23.5)	20.0 (16.7–23.6)
CIN2	92.4 (86.5–96.3)			87.9 (77.5–94.6)		
Roche Cobas						
CIN3+	97.3 (94.2–99.0)		23.9 (21.1–26.8)	100.0 (92.7–100.0)		9.3 (7.0–12.2)
CIN2+	95.2 (92.5–97.2)	24.0 (20.9–27.2)	37.6 (34.5–40.9)	94.9 (89.2–98.1)	25.1 (21.6–29.0)	21.1 (17.7–24.9)
CIN2	91.9 (85.9–95.9)			91.2 (81.8–96.7)		
Abbott RealTime PCR						
CIN3+	97.3 (94.2–99.0)		24.7 (21.9–27.8)	100.0 (92.7–100.0)		9.8 (7.3–12.7)
CIN2+	93.3 (90.1–95.6)	27.3 (24.1–30.7)	38.2 (35.0–41.5)	92.3 (85.9–96.4)	28.9 (25.2–32.9)	21.6 (18.0–25.4)
CIN2	86.7 (79.7–91.9)			86.8 (76.4–93.8)		
BD HPV						
CIN3+	97.8 (94.8–99.3)		24.2 (21.5–27.2)	100.0 (92.7–100.0)		9.4 (7.0–12.2)
CIN2+	95.0 (92.2–97.0)	24.2 (21.2–27.5)	37.8 (34.6–41.0)	94.0 (88.1–97.6)	25.3 (21.7–29.2)	21.0 (17.6–24.8)
CIN2	90.4 (84.1–94.8)			89.7 (79.9–95.8)		
Gen-Probe Aptima						
CIN3+	97.8 (94.8–99.3)		25.1 (22.3–28.2)	100.0 (92.7–100.0)		9.8 (7.3–12.7)
CIN2+	95.3 (92.5–97.2)	28.8 (25.6–32.2)	39.3 (36.1–42.7)	92.3 (85.9–96.4)	29.1 (25.4–33.1)	21.6 (18.1–25.5)
CIN2	91.1 (85.0–95.3)			86.8 (76.4–93.8)		
mtm laboratories p16^{INK4a}						
CIN3+	90.2 (85.3–93.9)		32.2 (28.4–36.2)	83.7 (69.3–93.2)		12.5 (8.9–16.9)
CIN2+	85.7 (81.5–89.3)	54.7 (50.8–58.6)	49.1 (45.0–53.3)	76.2 (66.9–84.0)	57.2 (52.7–61.6)	27.8 (22.7–33.3)
CIN2	78.2 (69.9–85.1)			71.0 (58.1–81.8)		
NorChip PreTect HPV-Proofer						
CIN3+	80.3 (74.4–85.3)		37.7 (33.3–42.3)	80.9 (66.7–90.9)		16.6 (12.0–22.1)
CIN2+	74.1 (69.1–78.6)	70.8 (67.3–74.2)	55.4 (50.7–60.0)	73.6 (64.4–81.6)	72.1 (68.1–75.9)	35.4 (29.2–41.9)
CIN2	63.6 (54.6–71.9)			68.3 (55.3–79.4)		
Cytology (mild or worse)						
CIN3+	92.9 (88.7–95.9)		33.1 (29.4–36.9)			
CIN2+	88.9 (85.1–91.9)	58.1 (54.5–61.7)	50.7 (46.7–54.7)		NA[b]	
CIN2	82.2 (74.7–88.3)					

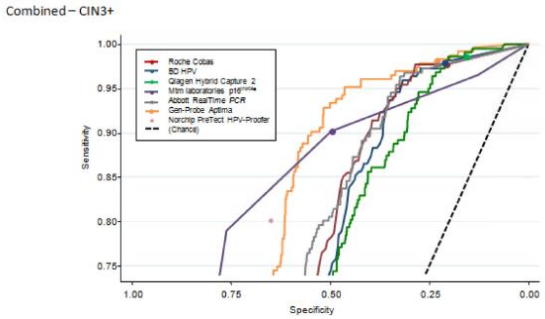
[a] Data in parentheses represent 95% confidence intervals.
[b] NA, not available.

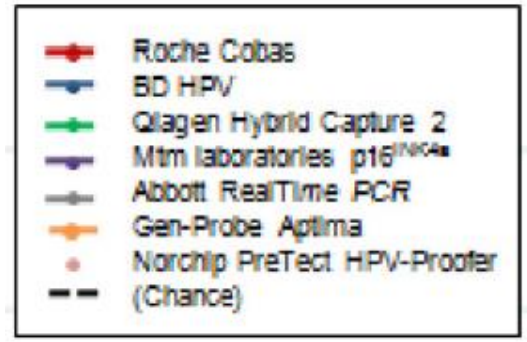
Table 4. Relative sensitivity, specificity and PPV of different tests for the detection of high-grade disease based on 19 CIN3+ cases and 40 CIN2+ cases

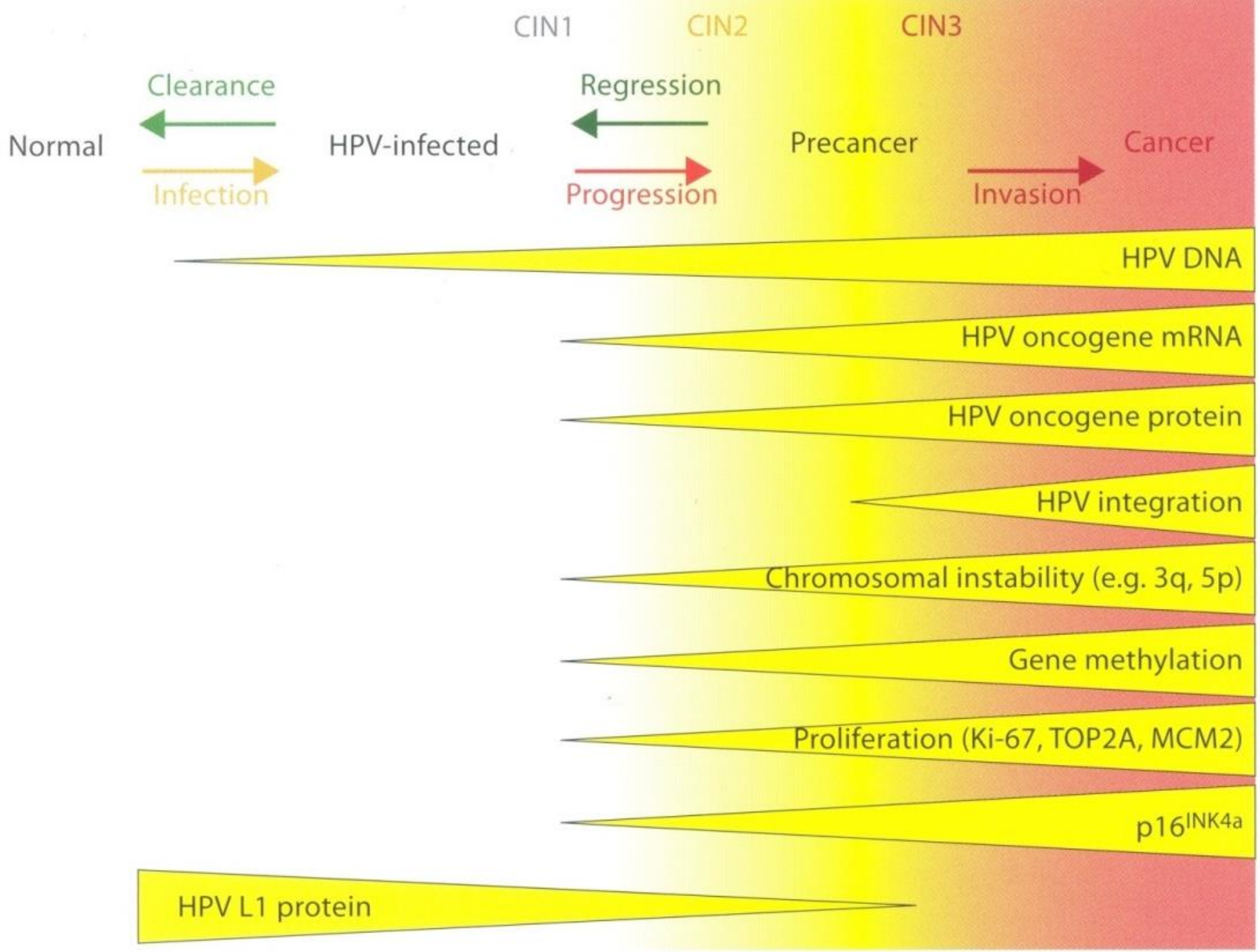
Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%,all) (95% CI)	PPV (%,only for those referred for colposcopy) (95% CI)
BD HPV				
CIN3+	100.0 (82.4–100.0)		2.0 (1.2–3.0)	16.5 (10.3–24.6)
CIN2+	97.5 (86.8–99.9)	84.3 (83.3–85.2)	4.0 (2.9–5.5)	33.9 (25.3–43.3)
Roche Cobas				
CIN3+	100.0 (82.4–100.0)		2.0 (1.2–3.1)	16.7 (10.3–24.8)
CIN2+	97.5 (86.8–99.9)	84.5 (83.6–85.4)	4.1 (2.9–5.5)	34.2 (25.6–43.7)
Qiagen Hybrid Capture 2				
CIN3+	100.0 (82.4–100.0)		2.1 (1.3–3.3)	16.0 (9.9–23.8)
CIN2+	97.5 (86.8–99.9)	85.4 (84.5–86.3)	4.3 (3.1–5.8)	32.8 (24.4–42.0)
Abbott RealTime High Risk HPV				
CIN3+	94.7 (74.0–99.9)		2.2 (1.3–3.5)	16.1 (9.8–24.2)
CIN2+	95.0 (83.1–99.4)	87.2 (86.3–88.0)	4.7 (3.4–6.5)	33.9 (25.3–43.5)
Gen-Probe APTIMA				
CIN3+	100.0 (82.4–100.0)		3.1 (1.9–4.7)	17.4 (10.8–25.9)
CIN2+	97.5 (86.8–99.9)	90.2 (89.5–91.0)	6.3 (4.5–8.5)	35.8 (26.8–45.5)
NorChip PreTect HPV-Proofer[a]				
CIN3+	68.8 (41.3–89.0)		3.7 (1.9–6.5)	20.0 (10.4–33.0)
CIN2+	71.4 (53.7–85.4)	95.2 (94.7–95.8)	8.4 (5.5–12.2)	45.5 (32.0–59.4)

Abbreviations: CI = confidence interval; HPV = human papillomavirus.
[a]Based on 16 cases of CIN3+ and 35 cases of CIN2+.

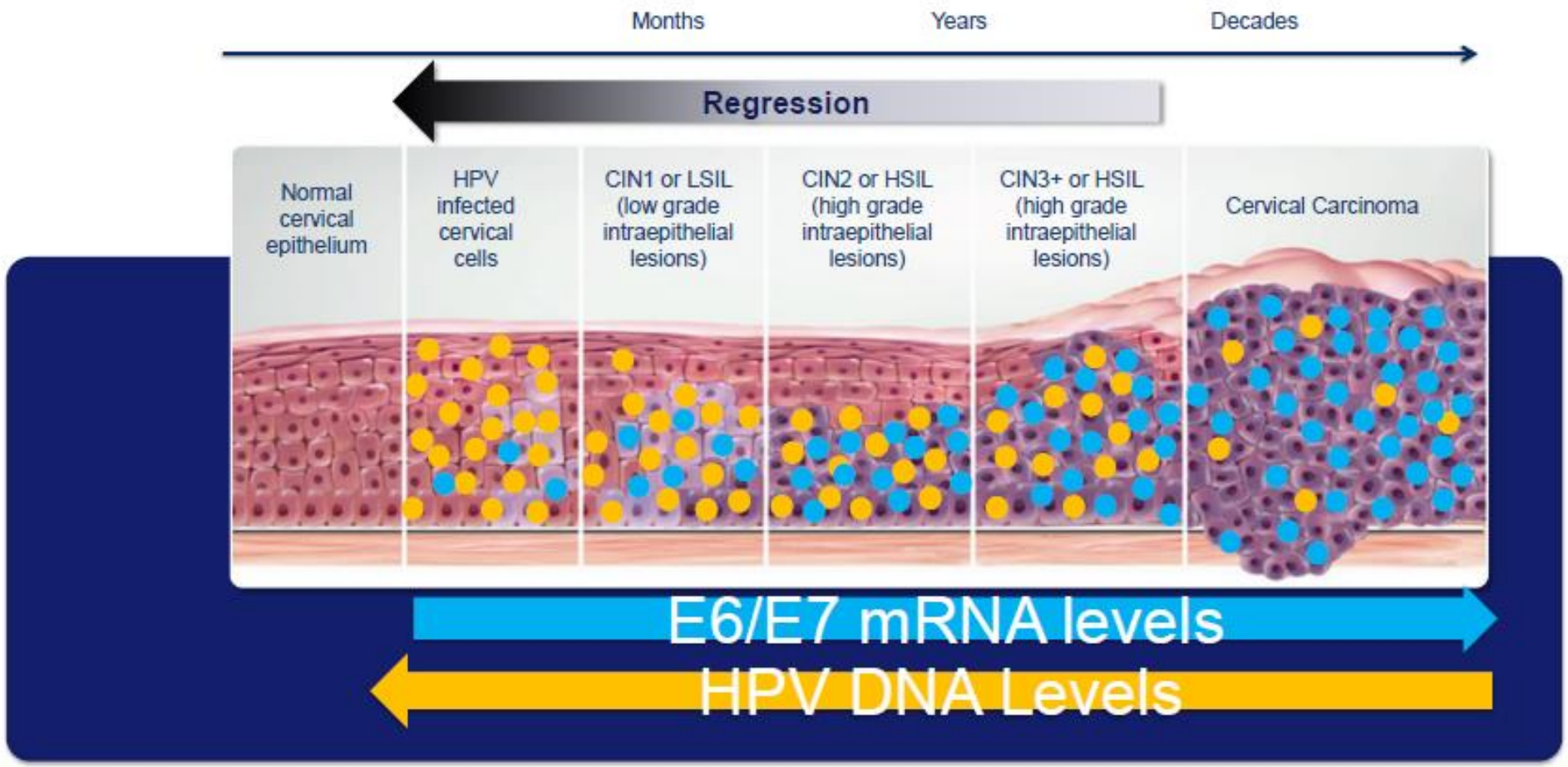







CIN1
CIN2
CIN3
Clearance
Regression
Normal
HPV-infected
Precancer
Cancer
Infection
Progression
Invasion
HPV DNA
HPV oncogene mRNA
HPV oncogene protein
HPV integration
Chromosomal instability (e.g. 3q, 5p)
Gene methylation
Proliferation (Ki-67, TOP2A, MCM2)
p16INK4a
HPV L1 protein

Cervical Disease Progression



Doorbar. Clinical Science 2006. 110(5):525-41

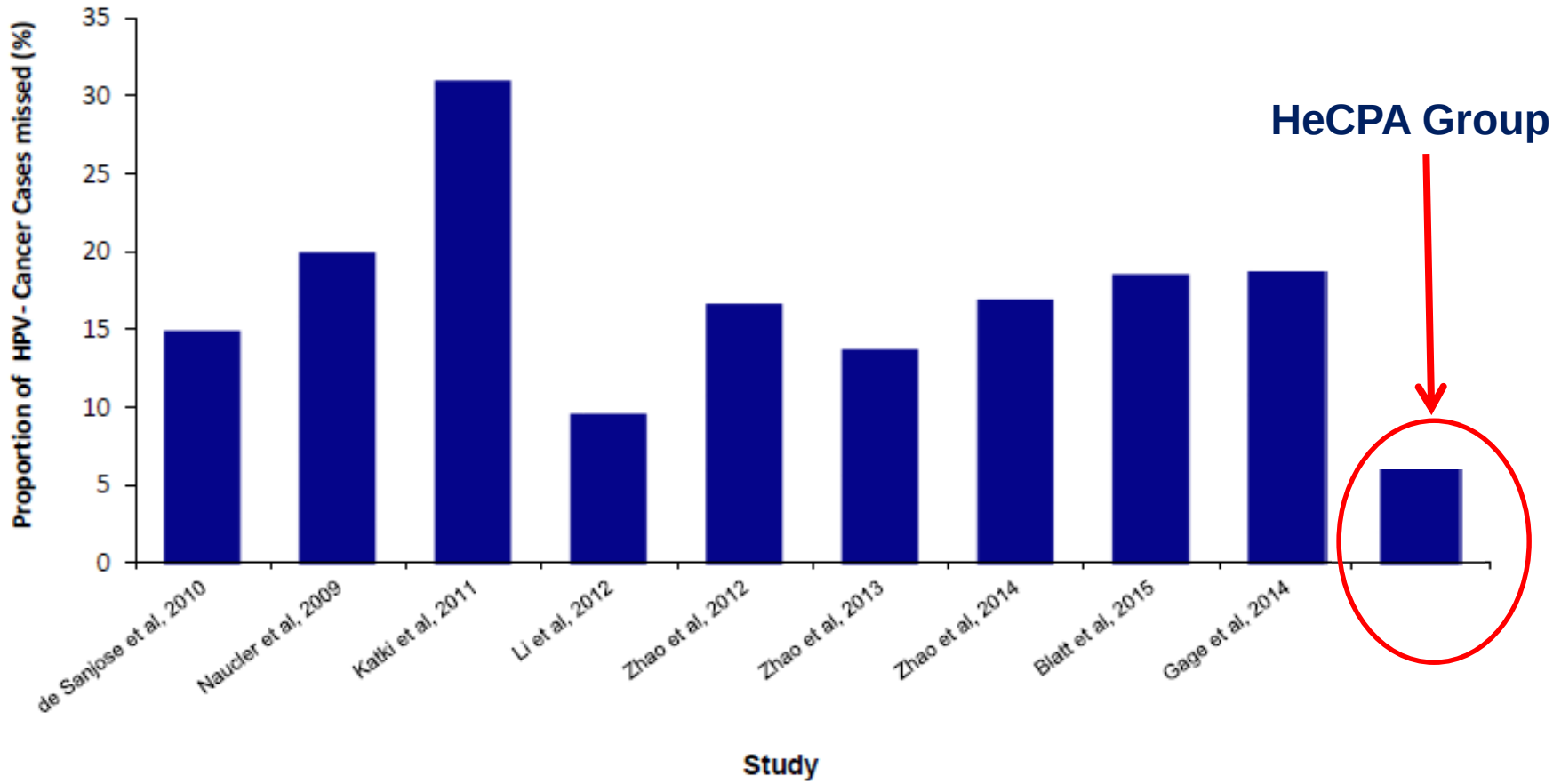
E6/E7 is a better HPV detection region

- E6/E7 regions are retained and the L1/E2 regions tend to be deleted as disease progresses
- Integration is an important step in progression to malignancy
  - leads to increased steady state mRNA encoding the viral oncogenes E6 and E7 as a consequence of increased stability
  - Deletions and Mutations in the L1 region raise concerns on PCR tests targeting this region
  - 'This is much less likely to happen for the E6 or E7 region, since any mutation could have functional implications, most likely deleterious to viral oncogenic activity, so that the ramifications of failure to detect are likely to be inconsequential.'
  - Conservation of E6/E7 DNA sequence

There is a risk of 15% of integrated HPV cancers being missed with a L1 HPV test

Morris Clin Chem Lab Med 2005;43(11):1171–1177; Tjalma, Depuydt. European Journal Gyneac Oncol. 2014 (2)

HPV Testing Alone Misses Cervical Cancer



1. De Sanjose. Lancet Oncol. 2010.11:1048-56. **2.** Naucler et al. JNCI. 2009.101:88-98. **3.** Katki HA, et al. Lancet Oncol. 2011;12(7):663-672. **4.** Li Z, et al. Arch Pathol Lab Med. 2012;136(12):1533-1540. **5.** Zhao Y, et al. J Med Virol. 2012;84(12):1920-1927. **6.** Zhao C, et al. Am J Clin Pathol. 2013;140(1):47-54. **7.** Zhao C, et al. Arch Pathol Lab Med. 2014. **8.** Blatt AJ, et al. Cancer Cytopathology 2015. **9.** Gage JC, et al. J Natl Cancer Inst. 2014;106(8).

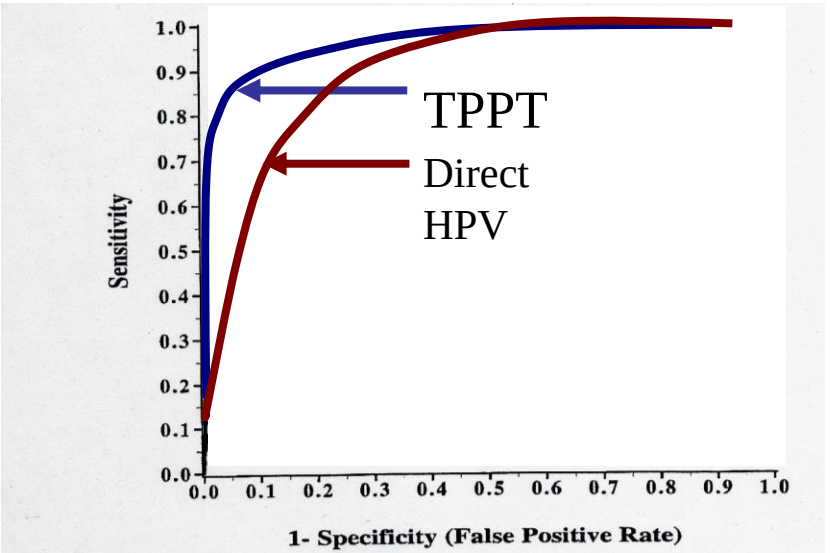
TABLE 1
Sensitivity and Specificity of the Screening Tests

	No. positive	Sensitivity for ≥CIN II	Specificity for ≥CIN II	Sensitivity for ≥CIN III	Sensitivity for cancer	Positive predictive value	Negative predictive value
HPV self-test	17%	83%	86%	81%	75%	21%	99.1%
(≥1.0 pg/ml)	340/1997[a]	71/86		35/43	9/12	71/340	1642/1657
Fluorescence	91%	94%	9%	93%	100%	5%	97%
spectroscopy	1759/1934[b]	81/86		40/43	12/12	81/1759	170/175
ThinPrep Pap	25%	94%	78%	98%	100%	16%	99.7%
(≥ASCUS)	506/1997[c]	81/86		42/43	12/12	81/506	1486/1491
ThinPrep Pap	10%	87%	94%	93%	100%	38%	99.4%
(≥LGSIL)	198/1997	75/86		40/43	12/12	75/198	1788/1799
ThinPrep Pap	5%	77%	98%	91%	100%	61%	99%
(≥HGSIL)	108/1997	66/86		39/43	12/12	66/108	1869/1889
HPV direct test	18%	95%	85%	98%	100%	23%	99.8%
(≥1.0 pg/ml)	364/1997[d]	82/86		42/43	12/12	82/364	1629/1633
Visual inspection	28%	71%	74%	79%	67%	11%	98%
(any abnormal)	552/1997	61/86		34/43	8/12	61/552	1420/1445
Colposcopy	26%	81%	77%	91%	100%	14%	99%
(any abnormal)	519/1997	70/86		39/43	12/12	70/519	1462/1478

[a] Seven insufficient material, 2 not reported.
[b] Sixty-three excluded due to no probes.
[c] Three unsatisfactory, 1 results not reported.
[d] Forty insufficient material, 17 not received/lost (using results obtained instead of tests administered, sensitivity of ≥CIN II = 98% and ≥CIN III = 100%).

TPPT=ThinPrep® Pap Test

Ferreccio et al. *Cancer Epidemiol Biomarkers Prev.* 2003;12:815-823.



Int J Gynecol Cancer. 2013 Mar;23(3):513-8. doi: 10.1097/IGC.0b013e318280f3bc.

Primary cervical cancer screening and triage using an mRNA human papillomavirus assay and visual inspection.

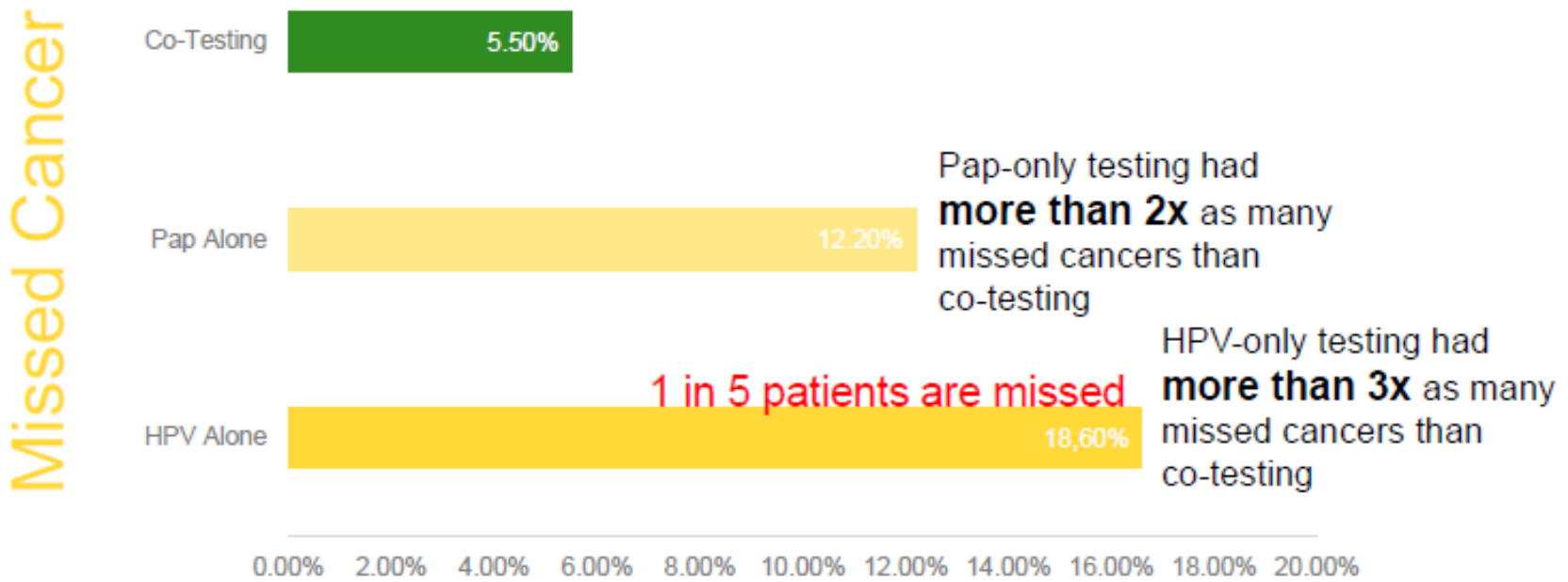
Nieves L[1], Enerson CL, Bellinson S, Brainard J, Chiesa-Vottero A, Nagore N, Booth C, Pérez AG, Chávez-Avilés MN, Bellinson J.

TABLE 1. Sensitivity and specificity of cervical cancer screening test for ≥CIN3

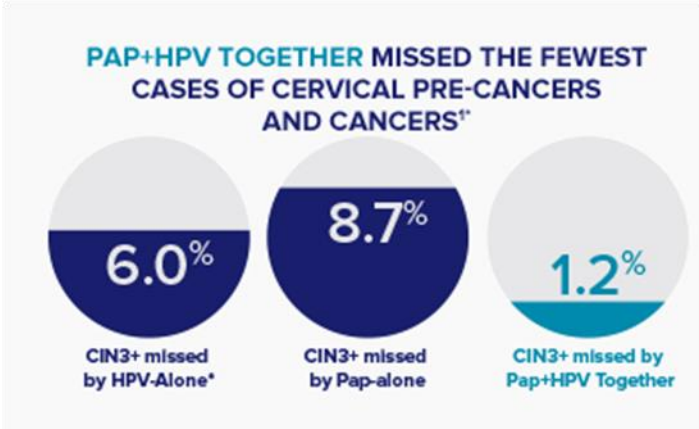
Screening Test	Sensitivity for CIN3 or Cancer, %	Specificity for CIN3 or Cancer, %	Positive Predictive Value, %
Physician-collected endocervical HR-HPV (HC2)	100 (79.4, 100)	92.2 (90.9, 93.4)	9.2 (5.3, 14.5)
Physician-collected endocervical HR-HPV (APTIMA)	100 (78.4, 100)	93.5 (92.3, 94.5)	10.7 (6.2, 16.9)
Self-collected vaginal HR-HPV (HC2)	62.5 (35.4, 84.8)	90.5 (89.1, 91.7)	4.9 (2.4, 8.9)
Self-collected vaginal HR-HPV (APTIMA)	62.5 (35.4, 84.8)	93.0 (91.8, 94.0)	6.5 (3.2, 11.7)
Cervical cytology ≥ASCUS	87.5 (61.7, 98.4)	94.1 (93.0, 95.1)	10.5 (5.9, 17.0)

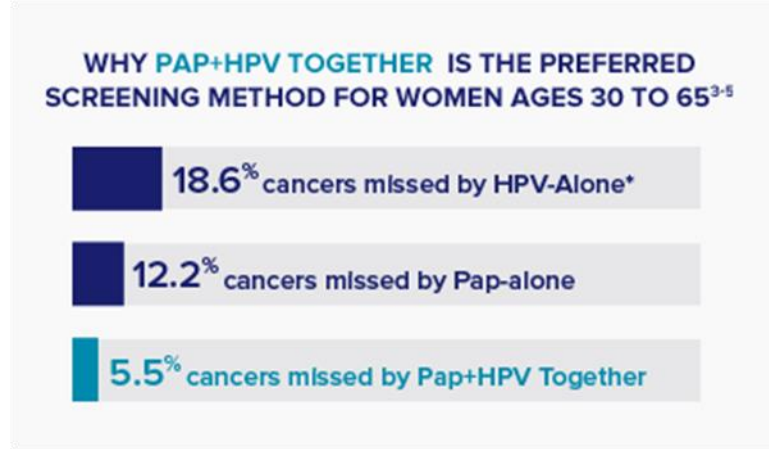
CONCLUSIONS: The specificity of the APTIMA assay along with high sensitivity is an advantage for primary screening. Follow-up evaluation will be important to determine the true impact of potential undertreatment in the screening algorithm. Self-sampling applications are explored.

In the largest US retrospective analysis of cervical cancer screening strategies involving 8.6M women: (published by Quest Diagnostics)



Co-Testing identified 70% of the cancers missed by HPV testing alone





The facts are clear: Screening with Pap+HPV Together provides the **best possible protection against cervical cancer for women ages 30 to 65**, and guidelines as well as data support this.[1, 3-5]

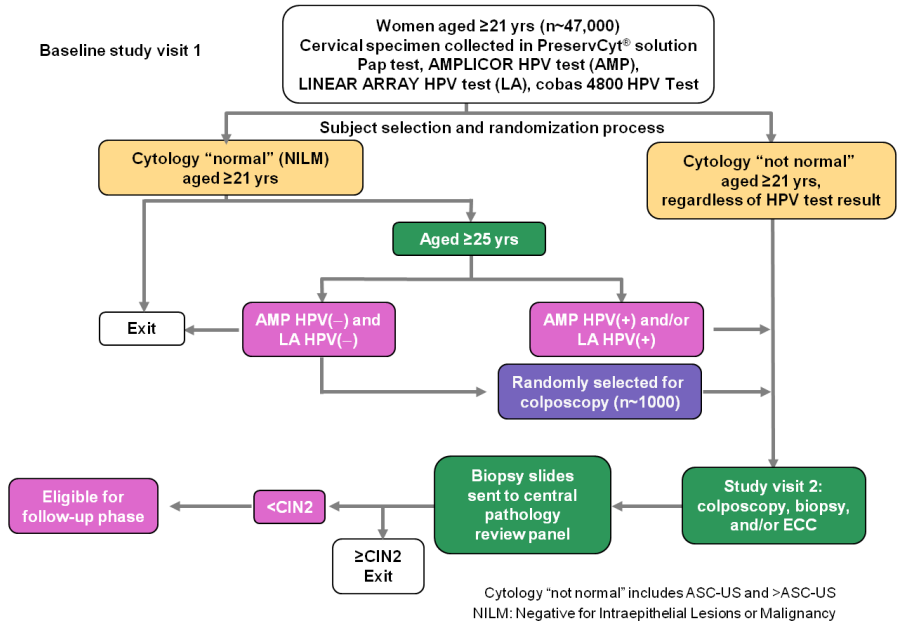
We can't afford to introduce more risk into women's lives with HPV-Alone* screening.

We've made a lot of progress in the fight against cervical cancer - we can't afford to let risk back into women's lives with HPV-Alone screening.

"...HPV-only testing would tragically miss many cervical cancers..."

- Dr. Marshall Austin

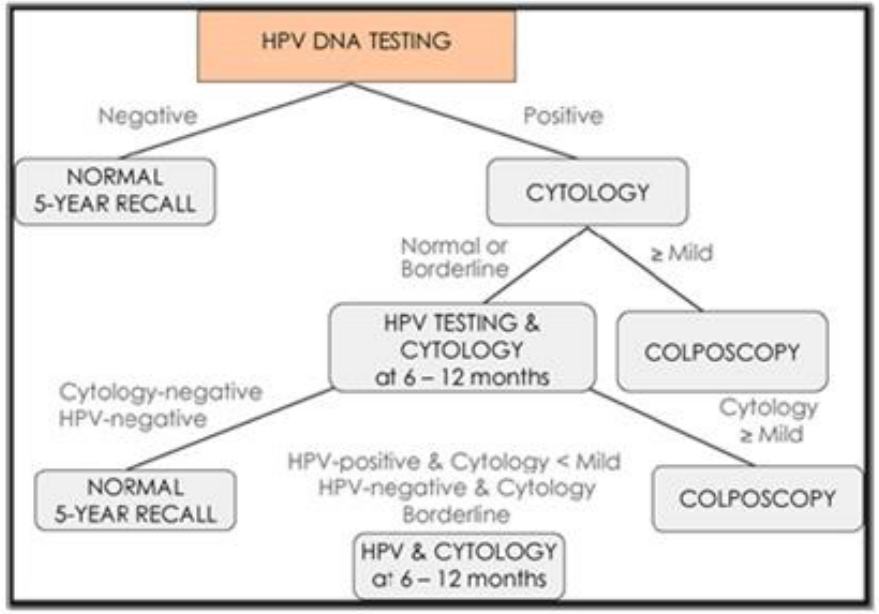
ATHENA study design



Australian Registry Data
Acta Cytologica 2011; 55: 307-312

Table 2. Percentage of negative HPV and cytology tests within 30 months preceding the histology

Subtype of high-grade histology	HPV n	HPV negative	Cytology negative
HSIL	1,920	13%	22%
SCC	26	8%	14%
HSIL + AIS	32	13%	9%
AIS	19	37%	28%
Endocervical adenocarcinoma	5	80%	40%



Australian Registry Data
Acta Cytologica 2011; 55: 307-312

Table 1. Percentage of negative HPV tests and the interval by which the HPV tests precede high-grade histology

	HPV tests, n	HPV negative
Concurrent	709	11%
<6 months	745	9%
6–12 months	203	14%
12–24 months	265	22%
24–30 months	80	29%
All	2,002	13%

Annals of Internal Medicine REVIEW

Genotyping for Human Papillomavirus Types 16 and 18 in Women With Minor Cervical Lesions

A Systematic Review and Meta-analysis

Marc Arbyn, MD, MSc, DrTMH; Lan Xu, MSc; Freija Verdoodt, PhD; Jack Cuzick, PhD; Anne Szarewski, MD, PhD†; Jerome L. Belinson, MD; Nicolas Wentzensen, MD, PhD; Julia C. Gage, PhD, MPH; and Michelle J. Khan, MD, MPH

Background: High-risk human papillomavirus (hrHPV) testing to triage women with minor cervical lesions generates many referrals.

Purpose: To evaluate the accuracy of genotyping for HPV types 16 and 18 and its utility as a second triage step after hrHPV testing in women with minor cervical lesions.

Data Sources: Searches of 4 bibliographic databases, without language restrictions, from 1 January 1999 to 1 February 2016.

Study Selection: Studies involving women with atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL) who were triaged with tests for hrHPV and HPV 16/18 to find cervical intraepithelial neoplasia (grade ≥2 [CIN2+] or grade ≥3 [CIN3+]).

Data Extraction: Independent study selection, extraction of data, and quality assessment by 2 reviewers.

Data Synthesis: Twenty-four moderate- to good-quality studies involving 8587 women with ASC-US and 5284 with LSIL were found. The pooled sensitivity of HPV 16/18 genotyping for CIN3+ was about 70% for women with either ASC-US or LSIL. The pooled specificity (with a threshold of grade <2 CIN) was 83% (95% CI, 80% to 86%) for women with ASC-US and 76% (CI, 74% to 79%) for those with LSIL. The average risk for CIN3+ was 17% and 19% in HPV 16/18–positive women with ASC-US and LSIL, respectively, and was 5% in hrHPV-positive but HPV 16/18–negative women with either ASC-US or LSIL.

Limitation: Methodological and technical heterogeneity among studies; insufficient data to assess accuracy of separate assays.

Conclusion: Testing for HPV 16/18 to triage women with minor abnormal cytology is poorly sensitive but may be useful as a second triage test after hrHPV testing, with direct referral if the woman is positive for HPV 16/18. Whether colposcopy or repeated testing is recommended for hrHPV-positive but HPV 16/18–negative women depends on local decision thresholds that can be derived from pretest-posttest probability plots.

Primary Funding Source: 7th Framework Programme of the European Commission.

Ann Intern Med. doi:10.7326/M15-2735 www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 15 November 2016.
† Deceased.

Several countries have switched to human papillomavirus (HPV)–based screening for cervical cancer, but cytologic examination of a Papanicolaou (Pap) smear remains the primary form of cervical cancer screening in many other countries. Direct referral for diagnostic work-up with colposcopy and biopsy is usually recommended for women with high-grade lesions. However, women with minor cytologic abnormalities, including atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL), have only a modestly increased risk for cervical cancer (1). In the past, repeating the Pap test (repeated cytology) was the recommended follow-up for women with ASC-US or LSIL. Given the strong etiologic link between high-risk HPV (hrHPV) infection and cervical cancer, hrHPV testing has been proposed as an alternative triage method for women with equivocal or mildly abnormal cytology.

Randomized trials and systematic reviews show that, compared with repeated cytology, hrHPV testing has higher sensitivity and similar specificity in identifying underlying or incipient cervical precancer in women with ASC-US (2–4). Accordingly, triage by hrHPV testing has become standard practice (5–8). Low-grade squamous intraepithelial lesions are associated with a risk for precancer similar to that among hrHPV-positive women with ASC-US (9). Because most women with LSIL test positive for hrHPV (10), triage by hrHPV testing is inefficient (11, 12). The widespread practice of referring all women with hrHPV infection and ASC-US or with LSIL to colposcopy carries a considerable burden and cost. Because HPV types 16 and 18 cause about 70% of cervical cancer cases (8), genotyping for these types has been proposed as an additional tool to allow more fine-tuned management.

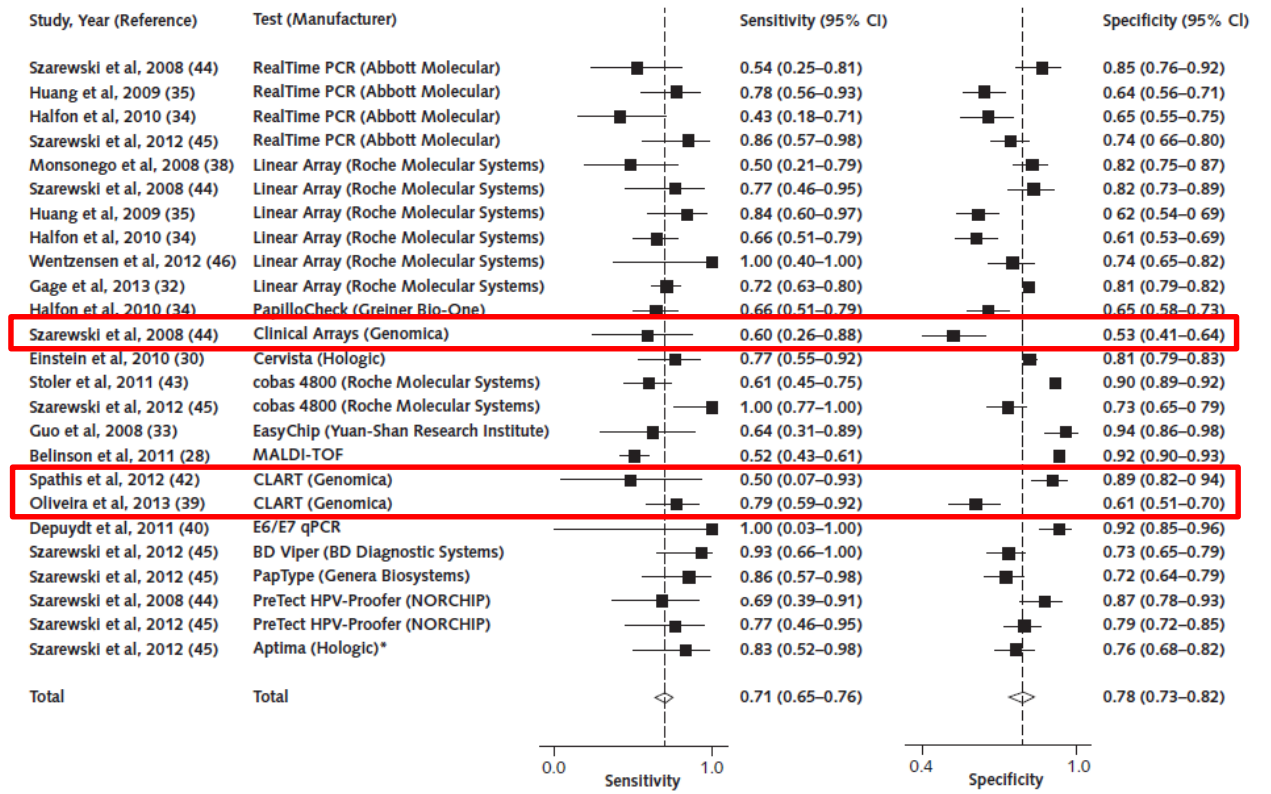
In this article, we present the results of a systematic review on the accuracy of genotyping for HPV types 16 and 18 to triage women with ASC-US or LSIL, including those who are hrHPV-positive. We also present a framework to assess the clinical utility of triage tests, based on the risk for cervical precancer before and after triage.

Methods

We developed a protocol (Supplement 1, available at www.annals.org), followed standard procedures for

See also:
Web-Only
Supplement

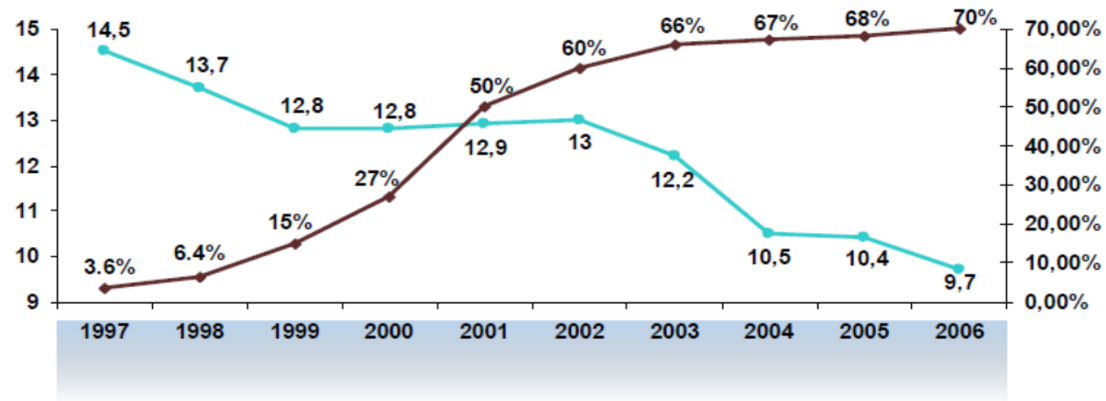
Figure 1. Meta-analysis of the sensitivity and specificity of genotyping for HPV 16/18 to detect CIN3+ in women with atypical squamous cells of undetermined significance.



CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; MALDI-TOF = matrix-assisted laser desorption/ionization time of flight; qPCR = quantitative polymerase chain reaction.
* Also included HPV 45 genotyping.

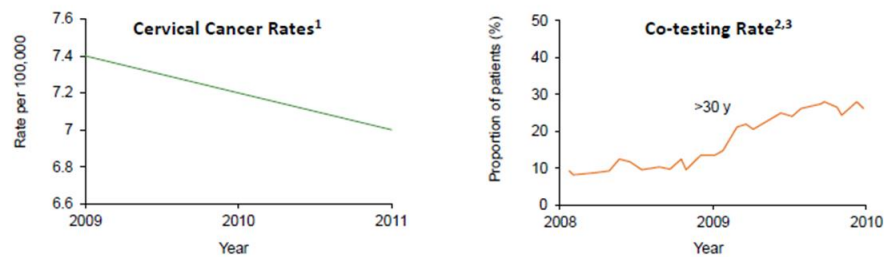
ThinPrep – Making an Impact

In 1996, Cytyc introduced the ThinPrep® Pap Test. Since then, the estimated number of cervical cancer cases in the U.S. decreased 33%.



Reference: American Cancer Society. Cancer Facts and Figures 1997-2007. Atlanta, GA: American Cancer Society: 1997-2007

Co-Testing Decreases Cervical Cancer Rates



- From 2009 to 2011 co-testing increased approximately 30% to nearly 40% in one laboratory that followed testing among 50,000 women[2,3]
- Cervical cancer rates among women ≥50 decreased approximately 3% per year from 2006-2010[4]
- Mortality from cervical cancer decreased approximately 1.2% per year from 2006-2010 in women ≥50[4]

As screening adoption Increases in the USA

1. Number of New Cases and Deaths per 100,000 people (all races, females), age-adjusted. http://seer.cancer.gov/statfacts/html/ld/cervix.html accessed 2014
2. Tatsas et al. *Am J Clin Path*. 2012; 138: 223-229.
3. Bekker et al. *Am J Clin Path*. 2013; 139: 259-262.
4. Cancer Facts and Figures, 2014. American Cancer Society. http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-04215

Value of Combining Cytology with HPV – Patient perspective

- Decrease Patient Stress:
  - UK researchers found that "HPV testing does not add significant psychological distress **when combined with cytology in routine primary cervical screening**".
  - This fits well into our own observation from a pilot project of HPV screening (Co-Testing) in Wolfsburg, Germany, with more than 20,000 participants. When we started in 2006 we offered a hotline for women with positive screening results. We shut down the line in 2008 because it was used just once.

7.8 %	• Preferred HPV only test.
41.4%	• Reported they would experience moderate to severe anxiety if screened by HPV test alone.

Medtech views.com, Prof. Ulrich Petry, 28 January 2015

Silver, M, et al. Patient Concerns About Human Papillomavirus Testing and 5-Year Intervals in Routine Cervical Cancer Screening. Obstet Gynecol 2015;125:317-29.

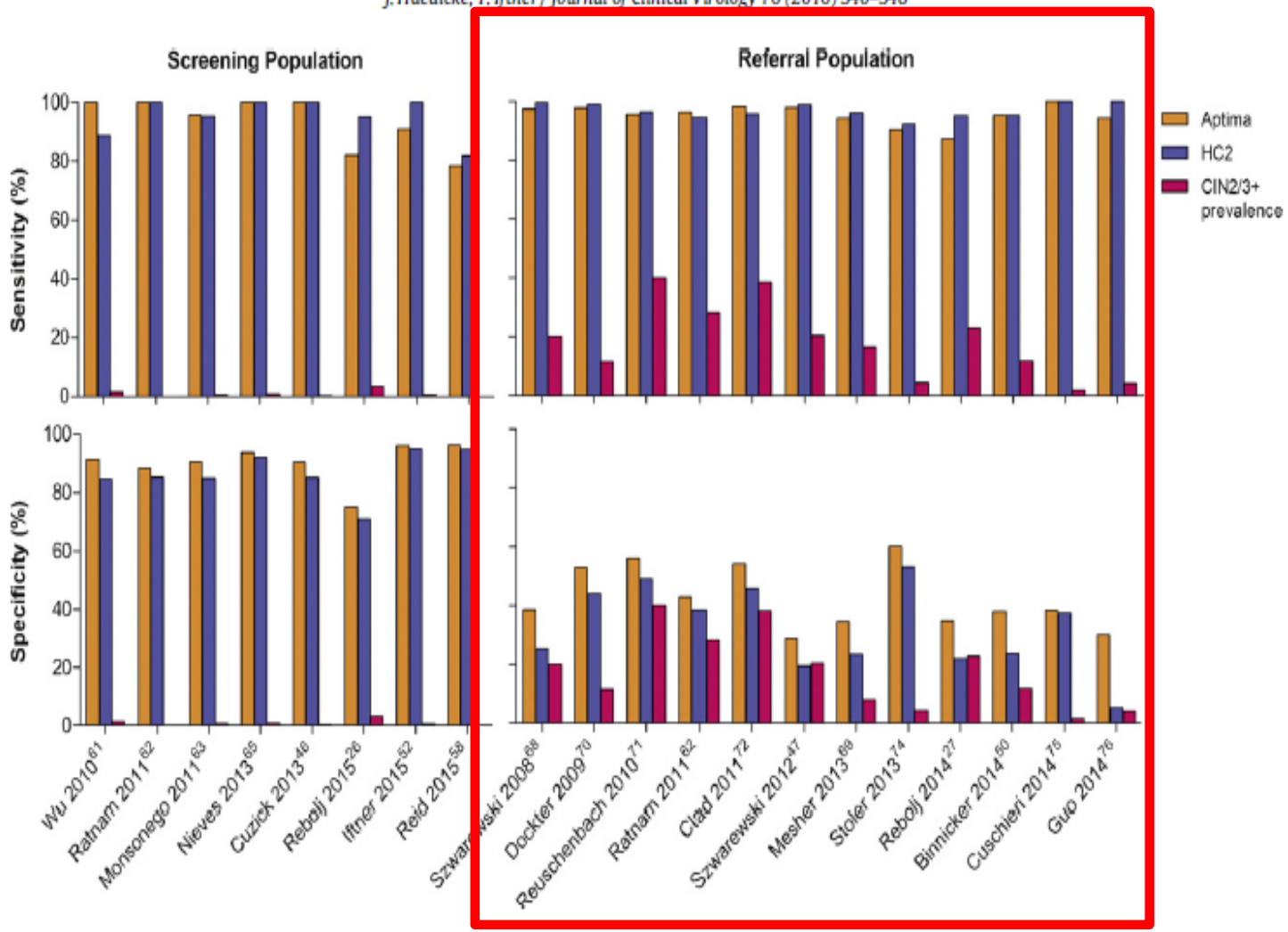
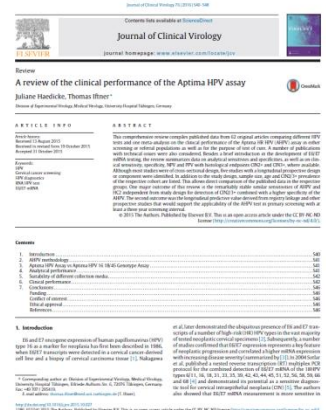


Fig. 1. Clinical sensitivities and specificities for CIN2/3+ detection of the AHPV (orange bars) and HC2 (purple bars) HPV tests from previously published studies on screening and referral populations. CIN2/3 prevalence of the respective study population is shown by magenta-colored bars.


Journal of Clinical Virology

Review

A review of the clinical performance of the Aptima HPV assay

Juliane Haedicke, Thomas Iftner *

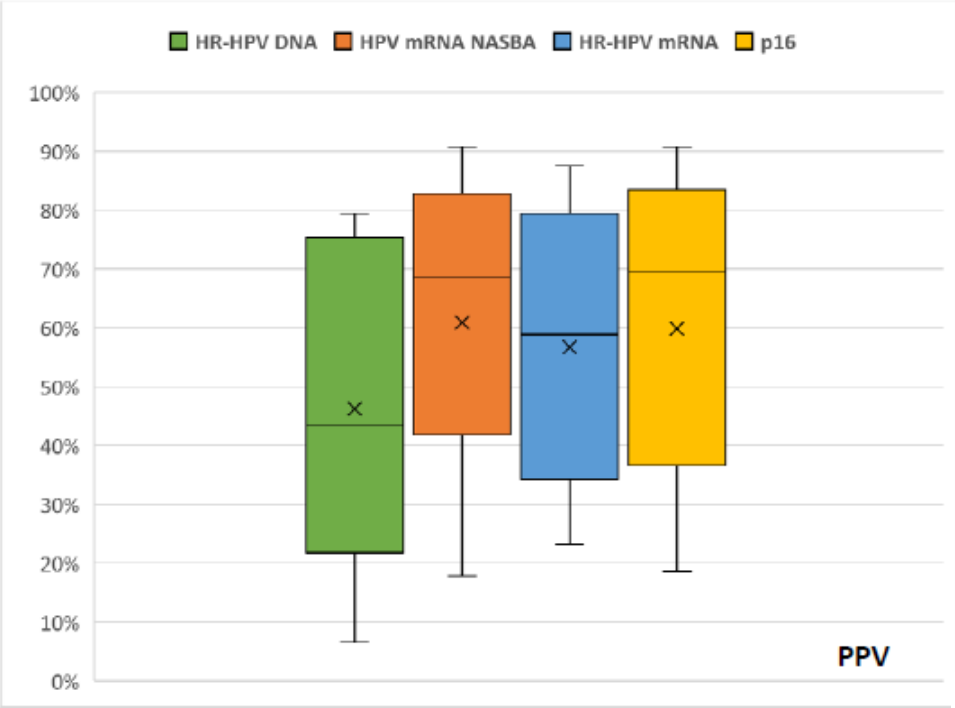
Contents

1. Introduction
2. APHV method map
3. Aptima HPV Assay vs Aptima HPV 16 18/45 Genotype Assay
4. Analytical performance
5. Suitability of different collection media
6. Clinical performance
7. Conclusions
8. Outlook
Conflict of interest
Ethical approval
References

1. Introduction

Histology endpoint CIN2+	Sensitivity	Specificity	PPV	NPV	Odds ratio	Recalls	Missed CIN2+
ASCUS+ cytology with clinical negative	97.0	67.4	37.5	99.1	65.7	509 (43.3%)	6 (3.0%)
ASCUS+ cytology		20.5		93.2	8.2		
ASCH+ cytology with clinical negative	72.1	96.4	80.2	94.5	69.4	177 (15.0%)	55 (27.9%)
ASCH+ cytology		91.3		86.9	26.9		
LSIL+ colposcopy	97.5	64.5	35.7	99.2	69.9	538 (45.8%)	5 (2.5%)
HSIL+ colposcopy	71.6	96.1	78.8	94.4	62.1	179 (15.2%)	56 (28.4%)
CLART2	92.4	51.9	27.9	97.1	13.1	651 (55.5%)	15 (7.6%)
CLART2 HR	89.8	57.4	29.8	96.6	11.9	593 (50.5%)	20 (10.2%)
CLART2 HPV16 or 18	55.8	87.1	46.6	90.7	8.5	236 (20.1%)	87 (44.2%)
IncellDx	85.8	81.6	48.6	96.6	26.8	348 (29.6%)	28 (14.2%)
NucliSens	71.1	88.0	56.8	93.2	17.9	227 (22.1%)	54 (28.8%)
$p16^{INK4A}$	58.4	94.8	68.9	92.0	25.5	161 (14.0%)	79 (41.6%)
ASCUS+ CLART+	89.8	79.3	46.7	97.5	33.9	379 (32.3%)	20 (10.2%)
ASCUS+ IncellDx+	83.8	90.8	64.7	96.5	50.7	255 (21.7%)	32 (16.2%)
ASCUS+ NucliSens HPV	68.4	93.2	68.4	93.2	29.6	190 (18.5%)	57 (30.4%)
ASCUS+ $p16^{INK4A}$	57.4	95.5	71.7	91.9	28.7	152 (13.2%)	81 (57.4%)
ASCH+ or ASCH- CLART+	97.5	50.7	28.5	99.0	39.5	673 (57.4%)	5 (2.5%)
ASCH+ or ASCH- IncellDx+	95.9	79.8	49.0	99.0	93.4	386 (32.9%)	8 (4.0%)
ASCH+ or ASCH- NucliSens+	86.6	89.5	64.8	96.8	55.3	250 (24.3%)	25 (13.3%)
ASCH+ or ASCH- $p16^{INK4A}$	82.1	92.5	68.4	96.3	56.5	228 (19.8%)	34 (17.9%)
ASCH+ or ASCUS/LSIL/CLART+	94.9	77.9	46.4	98.7	65.8	403 (34.3%)	10 (5.0%)
ASCH+ or ASCUS/LSIL/IncellDx +	93.9	88.9	63.1	98.6	123.9	293 (24.9%)	12 (6.1%)
ASCH+ or ASCUS/LSIL/ NucliSens+	85.0	90.3	66.3	96.4	53.1	240 (23.4%)	28 (14.9%)
ASCH+ or ASCUS/LSIL/ $p16^{INK4A}$	81.1	93.2	70.3	96.1	58.9	219 (19.0)	36 (18.9%)

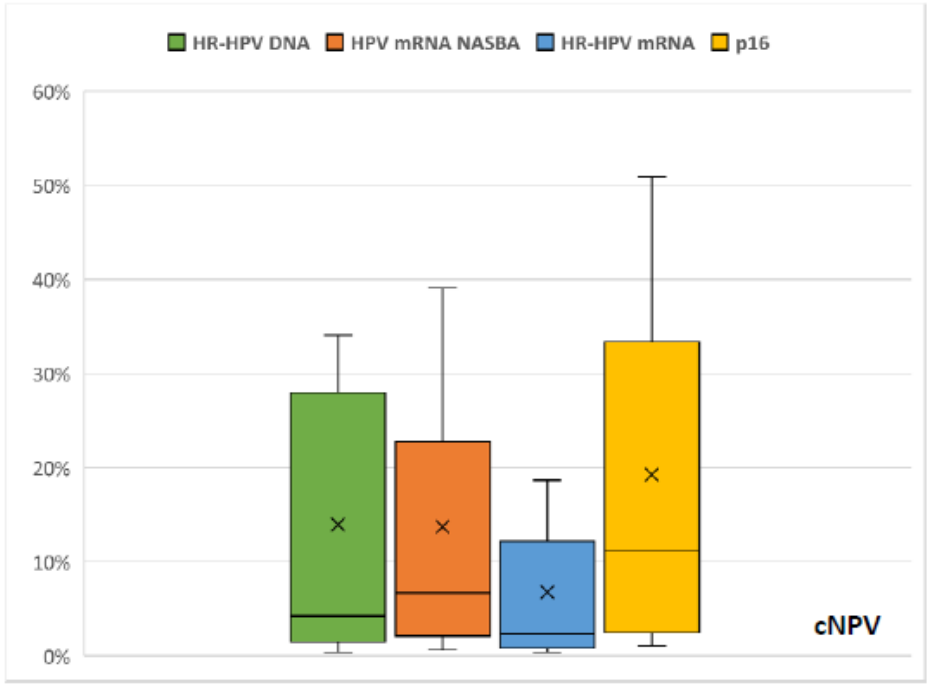
A. Spathis et.al. Plos one. 2012 Volume 7,Issue 11, e49205



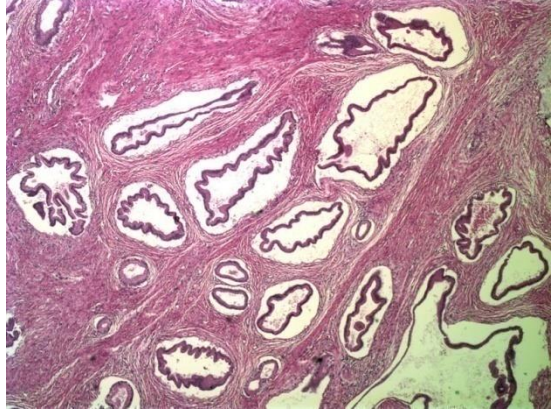
Γράφημα 9.1 Διακύμανση της PPV κάθε διαγνωστικού τεστ στην ανίχνευση CIN2+

Ανάλυση ευρωστίας

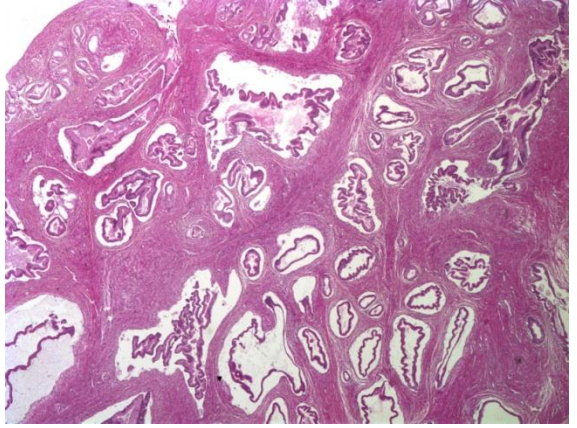
Αποτελέσματα Διδακτορικής Διατριβής Π. Μπούντρη

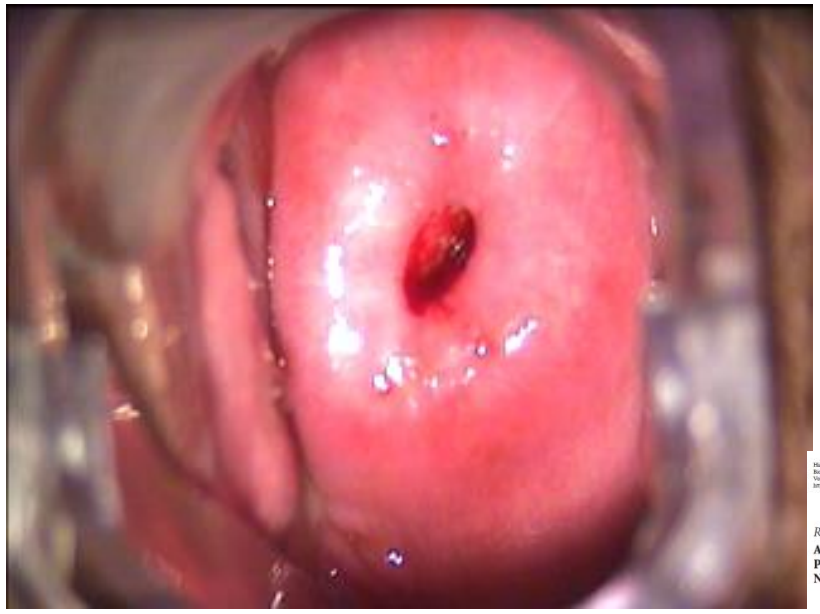


Γράφημα 9.2 Διακύμανση της cNPV κάθε διαγνωστικού τεστ στην ανίχνευση CIN2+



- **CLART® HPV : 45**
- **NASBA: 45**
- **HPV OncoTect™ : Positive**
- **p16: Negative**

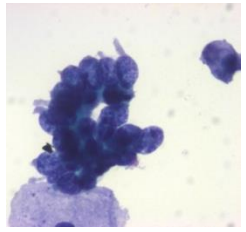


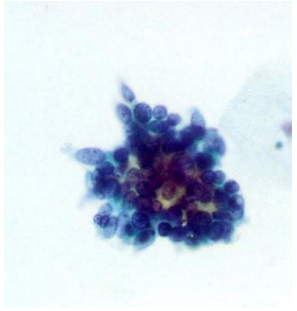


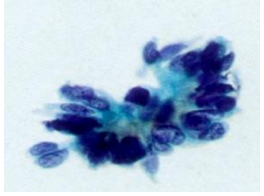
Pap Test	HPV DNA Type	NASBA Type	Flow	P16
AIS	45	45	Positive	Negative

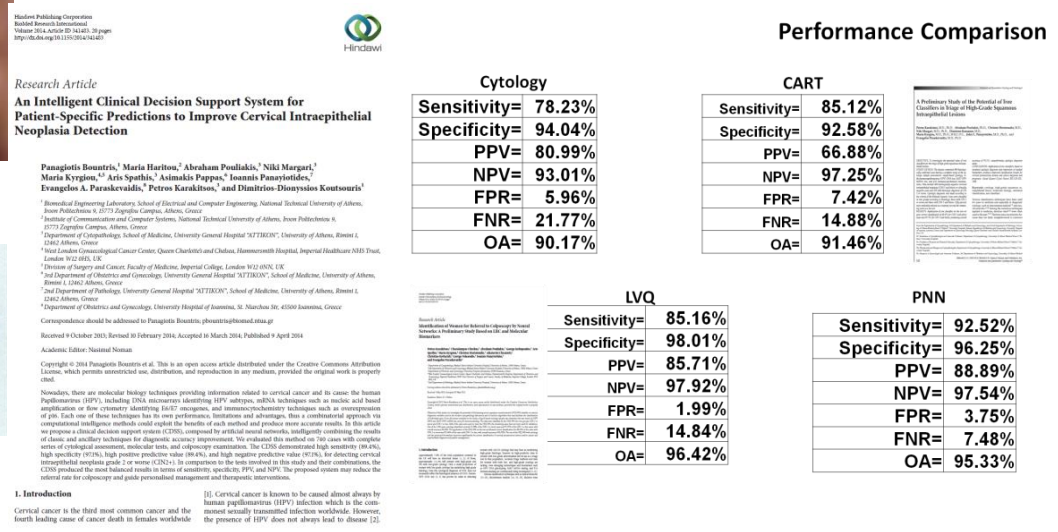
SCORING SYSTEM

Normal	CIN I	CIN II/III	Ca
1.1%	5.9%	8%	85%









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Hindawi

Research Article

An Intelligent Clinical Decision Support System for Patient-Specific Predictions to Improve Cervical Intraepithelial Neoplasia Detection

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Nowadays, there are molecular biology techniques providing information related to cervical cancer and its cause: the human Papillomavirus (HPV), including DNA microarrays identifying HPV subtypes, mRNA techniques such as nucleic acid based amplification or flow cytometry identifying E6/E7 oncogenes, and immunocytochemistry techniques such as overexpression of p16. Each one of these techniques has its own performance, limitations and advantages, thus a combinatorial approach via computational intelligence methods could exploit the benefits of each method and produce more accurate results. In this article we propose a clinical decision support system (CDSS), composed by artificial neural networks, intelligently combining the results of classic and ancillary techniques for diagnostic accuracy improvement. We evaluated this method on 740 cases with complete series of cytological assessment, molecular tests, and colposcopy examination. The CDSS demonstrated high sensitivity (89.4%), high specificity (97.1%), high positive predictive value (89.4%), and high negative predictive value (97.1%), for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+). In comparison to the tests involved in this study and their combinations, the CDSS produced the most balanced results in terms of sensitivity, specificity, PPV, and NPV. The proposed system may reduce the referral rate for colposcopy and guide personalised management and therapeutic interventions.

1. Introduction

Cervical cancer is the third most common cancer and the fourth leading cause of cancer death in females worldwide [1]. Cervical cancer is known to be caused almost always by human papillomavirus (HPV) infection which is the commonest sexually transmitted infection worldwide. However, the presence of HPV does not always lead to disease [2].

Performance Comparison

Cytology

Sensitivity=	78.23%
Specificity=	94.04%
PPV=	80.99%
NPV=	93.01%
FPR=	5.96%
FNR=	21.77%
OA=	90.17%

CART

Sensitivity=	85.12%
Specificity=	92.58%
PPV=	66.88%
NPV=	97.25%
FPR=	7.42%
FNR=	14.88%
OA=	91.46%

LVQ

Sensitivity=	85.16%
Specificity=	98.01%
PPV=	85.71%
NPV=	97.92%
FPR=	1.99%
FNR=	14.84%
OA=	96.42%

PNN

Sensitivity=	92.52%
Specificity=	96.25%
PPV=	88.89%
NPV=	97.54%
FPR=	3.75%
FNR=	7.48%
OA=	95.33%

A feasibility study of our lab
Selection of 343 (107 negative, 187 CIN1, 35 CIN2, 12 CIN3, 1 SCC, 1 AIS) samples with histology including 73 clinical negative samples (colposcopy and cytology negatives)

Co-testing with multiple methods:

- DNA typing (CLART2)
- mRNA typing (NucliSens)
- mRNA detection of 14 HR types (Aptima)
- p16 CINTec+

Method (CIN2)	Sensitivity	Specificity	PPV	NPV	Odds Ratio
CLART2	81.8%	49.1%	19.6%	94.7%	4.3
CLART2 14HR	77.8%	60.1%	23.3%	94.6%	5.2
NucliSens	60.0%	91.4%	60.0%	91.4%	16.0
Aptima	83.7%	87.4%	54.7%	96.7%	35.4
P16 CINTec+	52.4%	97.4%	68.8%	94.9%	41.3

CLINICAL-ECONOMIC MODELING ANALYSIS OF HUMAN PAPILLOMAVIRUS (HPV) CO-TESTING WITH GENOTYPING VERSUS PRIMARY HPV TESTING FOR CERVICAL CANCER SCREENING

Felix JC[1], **Lacey MJ**[2], Miller JD[2], Lenhart GM[2], Kulkarni R[2]

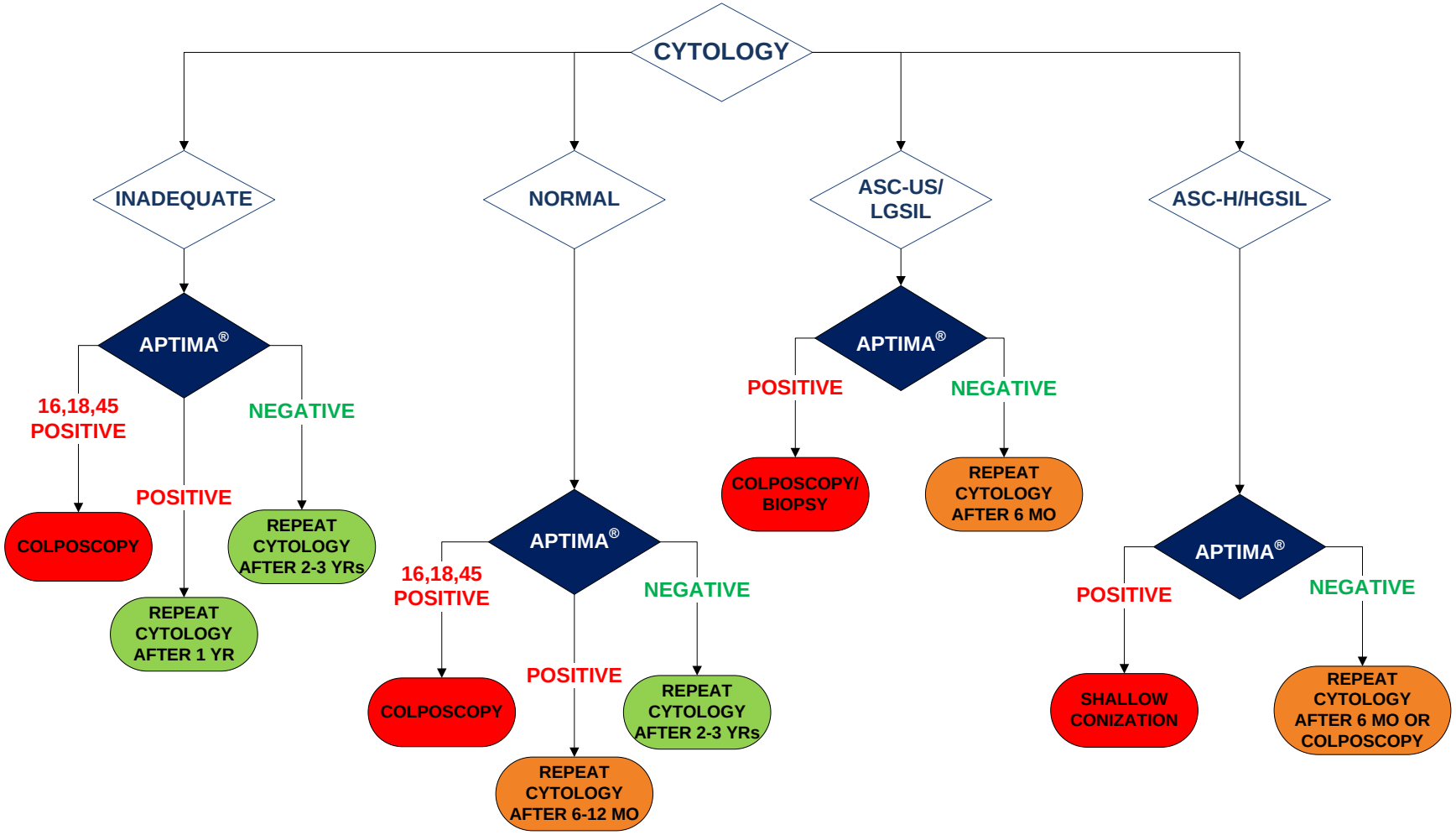
[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [2]Truven Health Analytics, Cambridge, MA, USA

"This study demonstrates that eliminating the Pap test as part of frontline screening would not reduce health care costs, despite what some in the medical community have argued," said lead author Juan Felix, MD, Chief of Cytopathology, Los Angeles County + University of Southern California Medical Center. "In fact, it's just the opposite. Co-testing, specifically with an mRNA-based HPV assay, would be more clinically effective and cost less money overall to the health care system than screening with a DNA-based HPV test alone."

The model predicted that compared to screening with HPV alone with a DNA-based test, screening with Pap+HPV Together using the ThinPrep Pap test and Aptima HPV assays could, over the next 40 years:

- ❑ Prevent nearly 150,000 cases of invasive cervical cancer.
- ❑ Save approximately $4 billion in health care costs, based on a $39 difference for each 30-year-old woman modeled in the study.

A new treatment algorithm based on a co-testing model using cytologic diagnosis and HPV APTIMA® HPV mRNA test results.



Οικονομική Αξιολόγηση Τεχνολογιών Υγείας (HTA)

- ✓ **Κλάδος που ασχολείται με την «συστηματική αξιολόγηση του οφέλους και του κόστους που προκύπτει από την σύγκριση διαφορετικών τεχνολογιών υγείας»**

- ✓ **Η εκτίμηση του οφέλους ως «αποτέλεσμα» της οικονομικής αξιολόγησης την κάνει να απευθύνεται όχι μόνο σε οικονομολόγους αλλά και σε κλινικούς επιστήμονες αλλά και σε διαμορφωτές πολιτικών σχετικών με την υγεία**

- ✓ **Η ανάλυση κόστους-αποτελεσματικότητας, είναι μια τυπική προσέγγιση του προβλήματος αξιολόγησης εναλλακτικών παρεμβάσεων μέσω του κόστους ευκαιρίας**

Η ανάλυση κόστους-αποτελεσματικότητας (CEA)

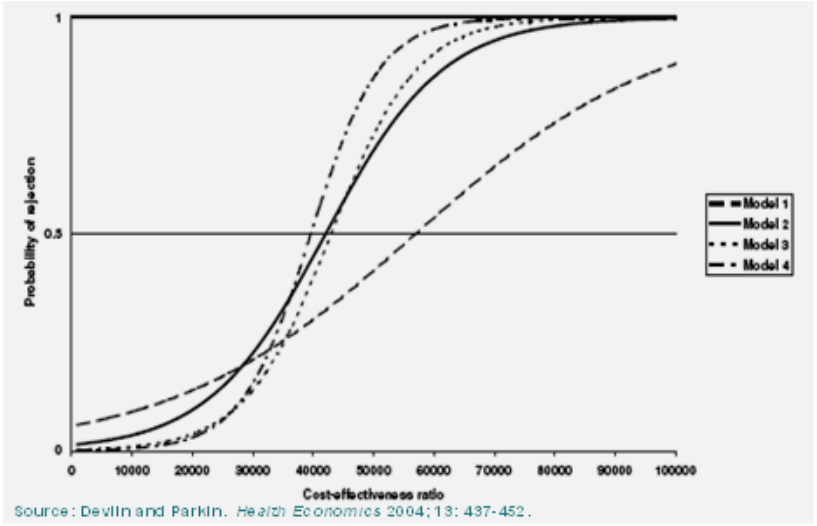
«Η αναλυτική τεχνική που αποσκοπεί στην συστηματική συγκριτική αξιολόγηση του συνολικού κόστους και οφέλους που προκύπτει από εναλλακτικές θεραπευτικές/διαγνωστικές παρεμβάσεις κατά την διαχείριση μιας νόσου»

Βασικοί στόχοι

- Ο προσδιορισμός της τιμής μιας τεχνολογίας,
- ο ορισμός του επίπεδου αποζημίωσης από τα ασφαλιστικά ταμεία
- η έκδοση κατευθυντήριων οδηγιών

Το μέτρο εκτίμησης της CEA

- **ICER= ΔC/ ΔE ή ICER= (CT - CS)/ (ET - ES)**
- **το αυξητικό (incremental) όφελος που προκύπτει από μια παρέμβαση και το αντίστοιχο κόστος έναντι της παρέμβασης που θεωρείται ως μέθοδος εκλογής (gold standard) και ο προσδιορισμός του λόγου της διαφοράς τους**
- **Στην πραγματικότητα τα ΔE, ΔC δεν είναι δύο απλά σημεία (τιμές), αλλά κατανομές με εκτιμώμενο μέσο και τυπική απόκλιση (όπως επίσης και το ICER).**



Δεδομένα κόστους

Συνδυασμός	Κόστος Εξέτασης	Κόστος Μεταφοράς	Συνολικό Κόστος
ASCUS+ cytology	17,22 €	40	57,00 €
ASCH+ cytology	17,22 €	40	51,21 €
Clart2	79,82 €	40	117,53 €
Clart2 HR	58,30 €	40	93,07 €
Clart2 16/18	58,30 €	40	95,17 €
IntellDx	74,29 €	40	117,33 €
ASCUS+ Clart+	97,04 €	40	136,32 €
ASCH+ or ASCH- Clart+	97,04 €	40	133,19 €
ASCH+ or ASCH- IntelDx+	91,51 €	40	133,66 €
ASCH+ or ASCUS/LSIL/Clart+	97,04 €	40	135,87 €
ASCH+ or ASCUS/LSIL/IntelDx+	91,51 €	40	136,53 €
p16	23,86 €	40	64,28 €
CDSS	270,10 €	40	315,70 €
NASBA	74,90 €	40	110,47 €

- **Το κόστος των εξετάσεων (συμπεριλαμβάνει το κόστος αγοράς των αντιδραστηρίων και το κόστος της εργατοώρας ανά εξέταση) και είναι σταθερό σύμφωνα με τις τιμές αποζημίωσης των κέντρων της μελέτης (τιμές παρατηρητηρίου)**
- **το κόστος μετάβασης της γυναίκας από και προς το κέντρο ελέγχου κάθε φορά που απαιτείται δειγματοληψία προσεγγίστηκε πιθανοθεωρητικά μέσω μίας κανονικής κατανομής με μέσο τα 40 ευρώ και τυπική απόκλιση 4 ευρώ**

Δεδομένα Αποτελεσματικότητας

Δείκτες αποτελεσματικότητας

- ✓ **η θετική προγνωστική αξία των τεστ (Positive Predictive Value-PPV- «πιθανότητα ένα άτομο με θετική εξέταση να νοσεί»-διαγνωστικό εργαλείο ταξιθέτησης/triage) αλλά και**

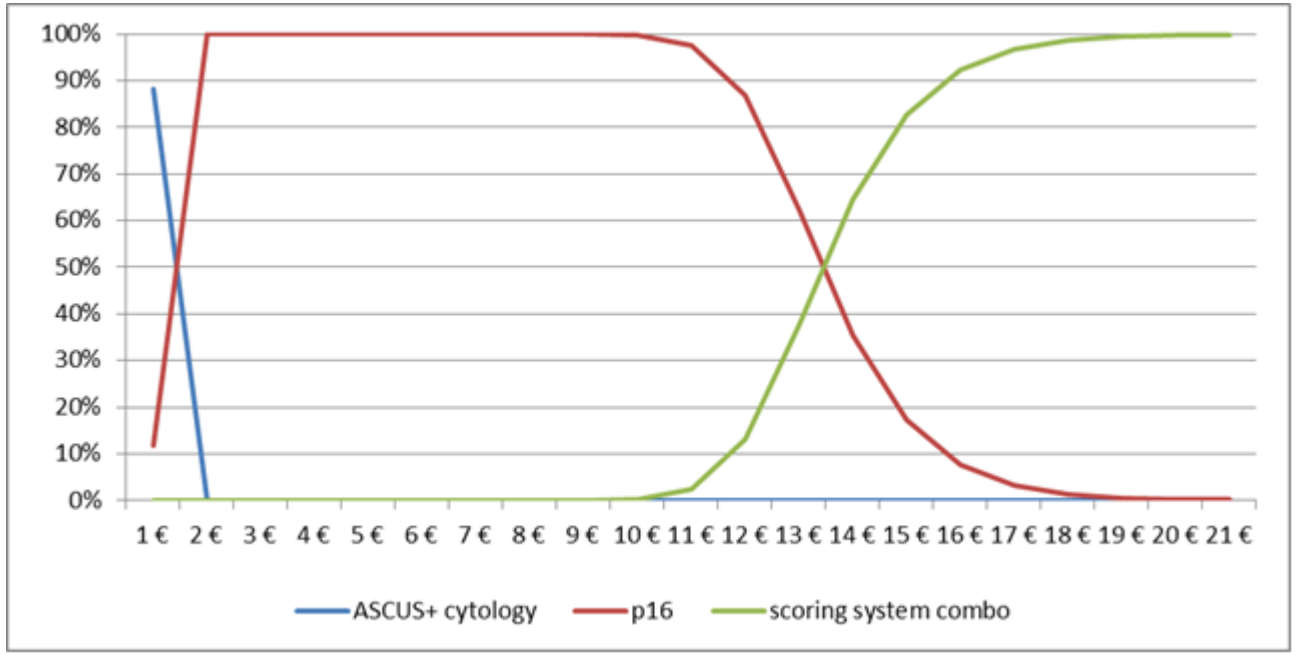
- ✓ **ο Youden's Index (έχει ενσωματώσει την ευαισθησία και την ειδικότητα ενός τεστ-μείωση της υποκειμενικότητας)**

Histology endpoint CIN2+	Sensitivity (TP)	Specificity (TN)	PPV	NPV	Odds ratio	Recalls (TP+FP)	Missed % of CIN2+ (FN)
ASCUS+ cytology	97.0 (191)	67.4 (658)	**37.5**	99.1	65.7	43.3 % (509)	3.0 % (6)
ASCUS+ cytology without clinical negative		20.5 (82)		93.2	8.2	85.2% (509)	
ASCH+ cytology	72.1 (142)	96.4 (941)	**80.2**	94.5	69.4	15.0% (177)	27.9% (55)
ASCH+ cytology without clinical negative		91.3 (365)		86.9	26.9	29.6% (177)	
LSIL+ colposcopy	97.5 (192)	64.5 (630)	**35.7**	99.2	69.9	45.8% (538)	2.5% (5)
HSIL+ colposcopy	71.6 (141)	96.1 (938)	**78.8**	94.4	62.1	15.2% (179)	28.4% (56)
CLART2	92.4 (182)	51.9 (507)	**27.9**	97.1	13.1	55.5% (651)	7.6% (15)
CLART2 HR	89.8 (177)	57.4 (560)	**29.8**	96.6	11.9	50.5% (593)	10.2% (20)
CLART2 HPV16 or 18	55.8 (110)	87.1 (850)	**46.6**	90.7	8.5	20.1% (236)	44.2% (87)
IncellDx	85.8 (169)	81.6 (797)	**48.6**	96.6	26.8	29.6% (348)	14.2% (28)
ASCUS+ CLART+	89.8 (177)	79.3 (774)	**46.7**	97.5	33.9	32.2% (379)	10.2% (20)
ASCUS+ IncellDx+	83.8 (165)	90.8 (886)	**64.7**	96.5	50.7	21.7% (255)	16.2% (32)
ASCH+ or ASCH- CLART+	97.5 (192)	50.7 (495)	**28.5**	99.0	39.5	57.4% (673)	2.5% (5)
ASCH+ or ASCH- IncellDx+	95.9 (189)	79.8 (779)	**49.0**	99.0	93.4	32.9% (386)	4.0% (8)
ASCH+ or ASCUS/LSIL/CLART+	94.9 (187)	77.9 (760)	**46.4**	98.7	65.8	34.3% (403)	5.0% (10)
ASCH+ or ASCUS/LSIL/IncellDx +	93.9 (185)	88.9 (868)	**63.1**	98.6	123.9	24.9% (293)	6.1% (12)

Ανάλυση με βάση την θετική προγνωστική αξία

Συνδυασμός	Κόστος			Θετική προγνωστική Αξία			Επικράτηση
Clart2	119,9 €	127,6 €	112,0 €	0,280	0,316	0,245	X
ASCH+ or ASCH- Clart+	137,1 €	144,8 €	129,4 €	0,285	0,320	0,253	X
Clart2 HR	98,2 €	105,8 €	90,5 €	0,299	0,337	0,263	X
ASCUS+ cytology	57,2 €	65,1 €	49,4 €	0,375	0,417	0,333	
ASCH+ cytology	57,2 €	64,8 €	49,7 €	0,375	0,418	0,335	
ASCH+ or ASCUS/LSIL/Clart+	137,1 €	145,0 €	129,4 €	0,464	0,512	0,416	X
Clart2 16/18	98,4 €	106,0 €	90,6 €	0,466	0,530	0,402	X
ASCUS+ Clart+	137,0 €	144,5 €	129,0 €	0,468	0,518	0,418	X
IntelIDx	114,3 €	122,0 €	106,4 €	0,485	0,538	0,432	X
ASCH+ or ASCH-IntelDx+	131,5 €	139,7 €	123,8 €	0,490	0,540	0,439	X
ASCH+ or ASCUS/LSIL/IntelDx+	131,6 €	139,4 €	123,7 €	0,632	0,686	0,576	X
NASBA	115,0 €	122,7 €	106,9 €	0,685	0,725	0,644	X
p16	63,9 €	71,6 €	56,1 €	0,696	0,735	0,656	
CDSS	310,2 €	318,4 €	302,2 €	0,894	0,917	0,870	

Καμπύλη Αποδοχής των Συγκρινόμενων Επιλογών

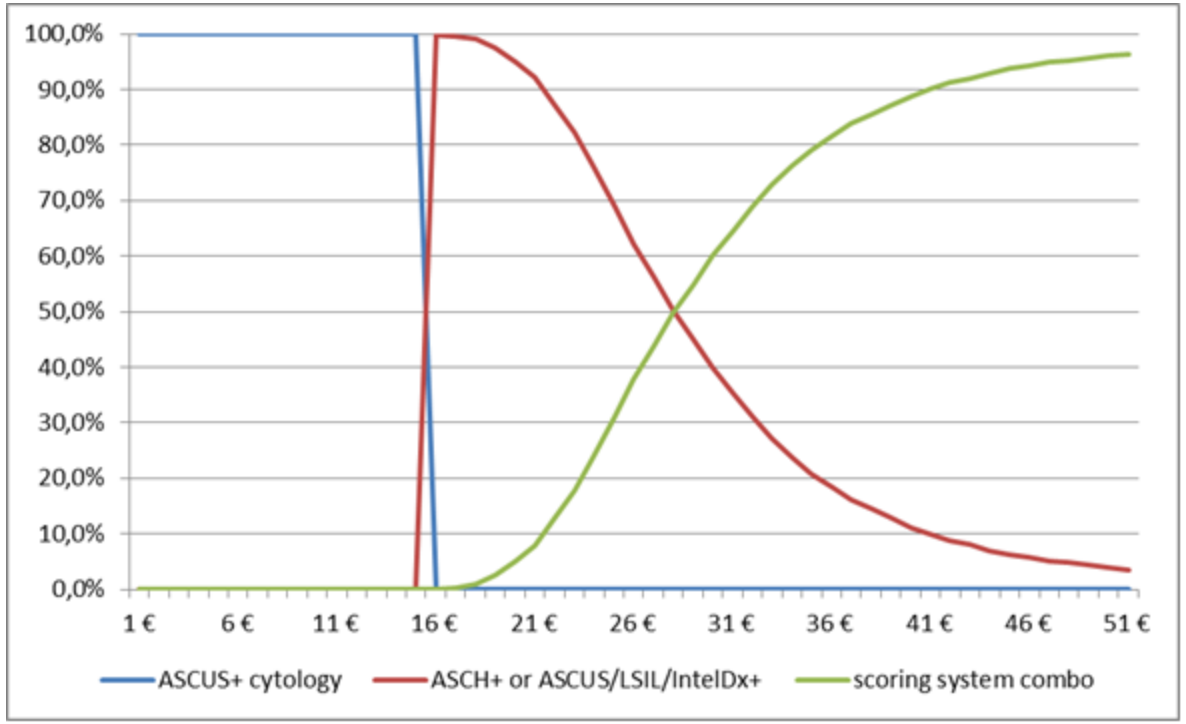


- ✓ **Όσο η οριακή διάθεση πληρωμής είναι λιγότερη του 1,5 (ανά μονάδα PPV) ευρώ η επιλογή τεστ pap αποτελεί τον πιο cost effective επιλογή.**
- ✓ **Όταν η οριακή διάθεση για πληρωμή με σκοπό τη βελτίωση κατά 1% του PPV βρίσκεται από 1 έως 11 ευρώ, τότε ο συνδυασμός P16 είναι cost-effective με πιθανότητα σχεδόν 100% ενώ όταν το όριο του λ εκτίνεται πέραν των 14 ευρώ τότε ο συνδυασμός CDSS είναι cost-effective επιλογή σε σχέση με τους συγκριτές του**

Ανάλυση με μέτρο αποτελεσματικότητας το Youden's Index

Συνδυασμός	Κόστος			Youden's Index			Επικράτηση
ASCH+ cytology	57,2 €	64,8 €	49,7 €	0,175	0,203	0,148	X
Clart2 16/18	98,4 €	106,0 €	90,6 €	0,429	0,464	0,394	X
Clart2	119,9 €	127,6 €	112,0 €	0,443	0,476	0,410	X
Clart2 HR	98,2 €	105,8 €	90,5 €	0,472	0,504	0,439	X
ASCH+ or ASCH-Clart+	137,1 €	144,8 €	129,4 €	0,482	0,512	0,453	X
ASCH+ or ASCH-IntelDx+	131,5 €	139,7 €	123,8 €	0,482	0,508	0,457	X
p16	63,9 €	71,6 €	56,1 €	0,513	0,549	0,476	X
ASCUS+ cytology	57,2 €	65,1 €	49,4 €	0,640	0,669	0,611	
NASBA	115,0 €	122,7 €	106,9 €	0,672	0,705	0,638	
IntellDx	114,3 €	122,0 €	106,4 €	0,674	0,705	0,646	
ASCUS+ Clart+	137,0 €	144,5 €	129,0 €	0,691	0,720	0,662	X
ASCH+ or ASCUS/LSIL/Clart+	137,1 €	145,0 €	129,4 €	0,757	0,783	0,730	X
ASCH+ or ASCUS/LSIL/IntelDx+	131,6 €	139,4 €	123,7 €	0,828	0,851	0,806	
scoring system combo	310,2 €	318,4 €	302,2 €	0,865	0,890	0,840	

Καμπύλη Αποδοχής των Επικρατούντων Επιλογών με βάση το δείκτη Youden

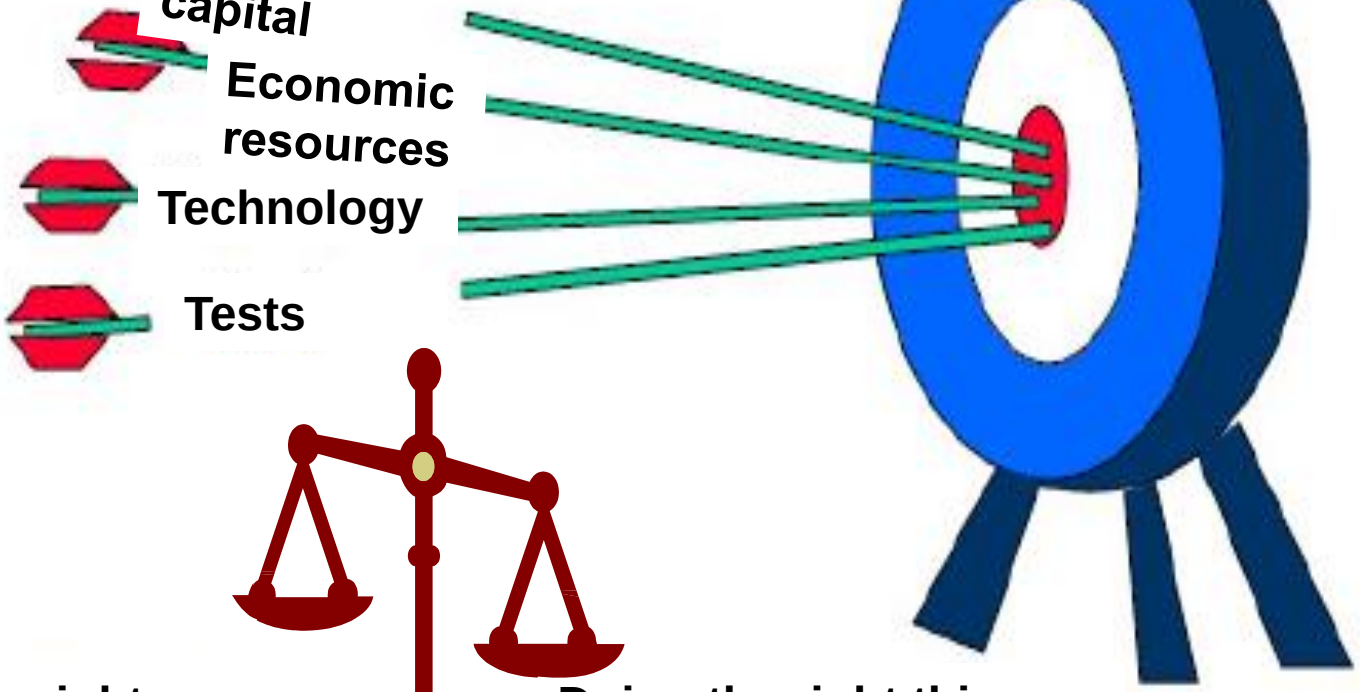


- ✓ **Το τεστ Παπανικολάου (όταν ως δείκτης αποτελεσματικότητας λαμβάνεται υπόψη ο Youden) αποτελεί με πιθανότητα σχεδόν 100% μία cost effective επιλογή για οριακή διάθεση πληρωμής έως και 16ευρώ**

- ✓ **Πέρα από το όριο των 27ευρώ ο συνδυασμός CDSS αποτελεί μια cost effective επιλογή**

Efficiency=
Optimal resources allocation in order to achieve goals

Efficacy=
Selection of appropriate goals and achievement of goals



Doing things right

Doing the right things

Cytology and Histology								
	Negative	HPV	CIN I	CIN II	CIN III	SCC	AdenoCa	Total
Inadequate	10	7	15	5	7	2	1	47
Negative	60	31	34	4	2	0	0	131
ASCUS	37	46	58	15	6	0	0	162
LGSIL	34	114	136	45	14	0	1	344
ASCH	5	4	2	2	3	1	0	17
HSIL	10	9	29	72	96	9	3	228
SCC	0	0	0	0	1	11	2	14
AdenoCa	0	0	0	0	0	1	7	8
Total	156	211	274	143	129	24	14	951

95.00%	ASCUS+ / CIN2+	LSIL+ / CIN2+	HSIL+ / CIN2+	ASCUS+ / CIN3+	LSIL+ / CIN3+	HSIL+ / CIN3+
PV	0.326	0.326	0.326	0.176	0.176	0.176
Sensitivity	93.2%	86.5%	65.2%	92.8%	89.2%	80.2%
Specificity	24.5%	46.5%	92.5%	21.2%	41.1%	84.7%
P PV	37.4%	43.9%	80.8%	20.1%	24.4%	52.0%
N PV	88.2%	87.6%	84.6%	93.3%	94.7%	94.7%
OA	46.9%	59.5%	83.6%	33.8%	49.5%	83.5%
PLR	1.235	1.616	8.702	1.177	1.514	5.242
NLR	0.277	0.291	0.377	0.339	0.262	0.233
Pretest prob	33%	33%	33%	18%	18%	18%
Posttest prob+	37%	44%	81%	20%	24%	52%
Pretest odds	0.484	0.484	0.484	0.213	0.213	0.213
Posttest odds+	0.597	0.781	4.208	0.251	0.323	1.117
Posttest odds-	0.134	0.141	0.182	0.072	0.056	0.050
Odds Ratio	4.464	5.544	23.107	3.470	5.769	22.469
Relative Risk	3.17	3.55	5.24	2.97	4.61	9.85

Colposcopy and Histology								
	Negative	HPV	CIN I	CIN II	CIN III	SCC	AdenoCa	Total
NSF	10	3	2	0	0	1	2	18
Negative	61	27	23	5	5	0	2	123
LGSIL	69	153	218	59	14	0	2	515
HSIL	16	27	31	79	108	4	1	266
SCC	0	0	0	0	1	18	1	20
AdenoCa	0	1	0	0	1	1	7	10
Total	156		274	143	129	24	15	952

95.00%	LSIL+ / CIN1+	LSIL+ / CIN2+	HSIL+ / CIN2+	LSIL+ / CIN3+	HSIL+ / CIN3+
PV	0.614	0.327	0.327	0.176	0.176
Sensitivity	93.16%	95.18%	71.06%	94.05%	84.52%
Specificity	45.51%	19.66%	88.30%	16.71%	80.36%
P PV	67.20%	36.50%	74.66%	19.48%	47.97%
N PV	50.35%	89.36%	86.28%	92.91%	96.04%
OA	64.71%	44.33%	82.67%	30.36%	81.09%
PLR	1.710	1.185	6.073	1.129	4.303
NLR	0.150	0.245	0.328	0.356	0.193
Pretest prob	61%	33%	33%	18%	18%
Posttest prob	67%	36%	75%	19%	48%
Pretest odds	1.594	0.485	0.485	0.214	0.214
Posttest odds+	2.725	0.575	2.947	0.242	0.922
Posttest odds-	0.239	0.119	0.159	0.076	0.041
Odds Ratio	11.381	4.828	18.531	3.170	22.343
Relative Risk	1.35	3.43	5.44	2.75	12.10

European & US CxCa Screening Guidelines

Country	Screening algorithms	Age Range	Interval	Organized	Comments
Germany	Cytology (CC) Cytology (2016) HPV (2016)	20-open end 20-60 30-60	1 1 5	N Y Y	„Option“ model with 6 years evaluation phase after April 2016, but not in guidelines yet
Italy	Cytology (CC & LBC) HPV (regional)	25-64 30-64	3 5	Y (regional) Y	Regional differences
France	Cytology (CC & LBC)	25-65	3	N	
UK	Cytology (LBC)	25-49 50-64	3 5	Y	Sentinel Screening Pilots
Spain	Cytology (CC & LBC) Cytology (interim) Co-Screen (interim) HPV	25-30 30-65 30-65 30-65	3 3 5 5	N	New guidelines (Sept 2014) recommend introduction of organized HPV primary screening
Netherlands	Cytology (LBC) HPV (2016)	30-60 30, 35, 40, 50, 60	5 5 & 10	Y	Tender process for assays and labs not yet finalized
Sweden	Cytology (LBC)	23-49 50-60	3 5	Y	New Guidelines will allow HPV primary Screening (2016)
Norway	Cytology (LBC)	25-69		Y	Regional Screening pilot
Denmark	Cytology (LBC)	23-49 50-60	3 5	Y	HPV DNA Test of Exit 55+
Finland	Cytology (CC)	30-60	5	Y	
USA	Cytology (CC & LBC) Co-Screening HPV (Roche cobas)	21-65 30-65 25-65	3 5 3	N	All algorithms exist in parallel, Co-screening is preferred, only guidance no guidelines for HPV primary screening yet

New recommendations for the use of HPV-tests in Denmark

The original report in Danish can be found on the homepage of the Danish National Board of Health:

http://www.sst.dk/publ/Publ2007/PLAN/Kraeft/Anbef_screen_livmoderhals.pdf

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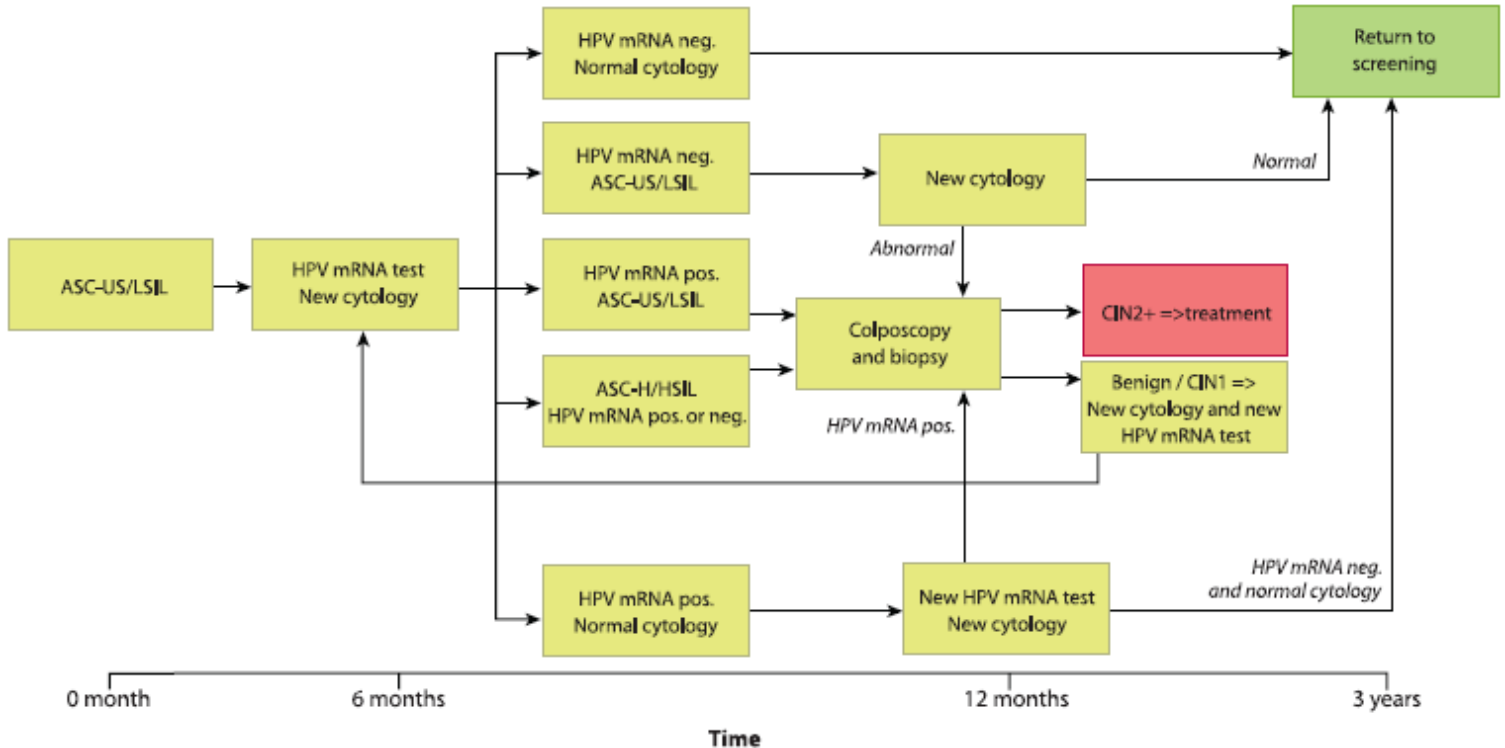
Table 11.1 Indications for HPV test 2006

Cell changes	Age	DNA	RNA
Atypical (unknown) cell changes (ASCUS)	Below 30 years of age	No	Yes
	Above 30 years of age	Yes	Yes
Low-grade cell changes (LSIL)	Below 30 years of age	No	Yes
	Above 30 years of age	No	Yes

GUIDELINES FOR HPV E6/E7 mRNA TESTING IN NORWAY



AHCPR / Duke

Base Case Results: Summary of Outcomes for TP vs. CP

	Q3 Year	Q2 Year	Q1 Year
% Reduction in Cancer	51%	57%	70%
% Reduction in Death	57%	61%	72%
% Reduction in Hysterectomies	44%	50%	66%
% Reduction in Radiation/Chemo	64%	74%	80%
Reduction in Cost/Patient	$ 132	$ 178	$ 298

*AHCPR model predicts **significantly improved outcomes** for ThinPrep relative to CP in **each of the 3 screening intervals** tested.*

THE ThinPrep® PAP TEST