

The 4th MEMAGO Annual Congress In Association with
the 1st Emirates Gynecological Oncology Conference

CYTOLOGY FOR HPV SCREENING “NOT YET” THE TWILIGHT OF AN ERA

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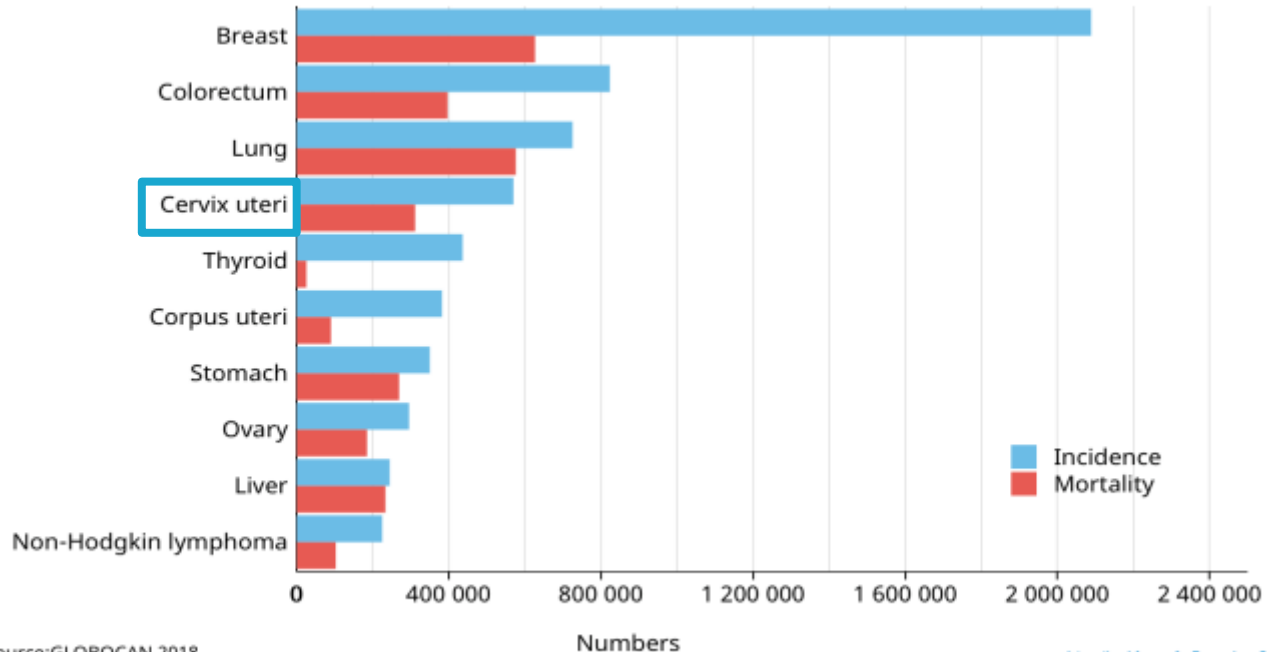
CERVICAL CANCER: THE GREAT PARADIGM SHIFT IN SCREENING

'Superstition is
the belief in the
causal nexus'

L. Wittgenstein

INCIDENCE AND MORTALITY

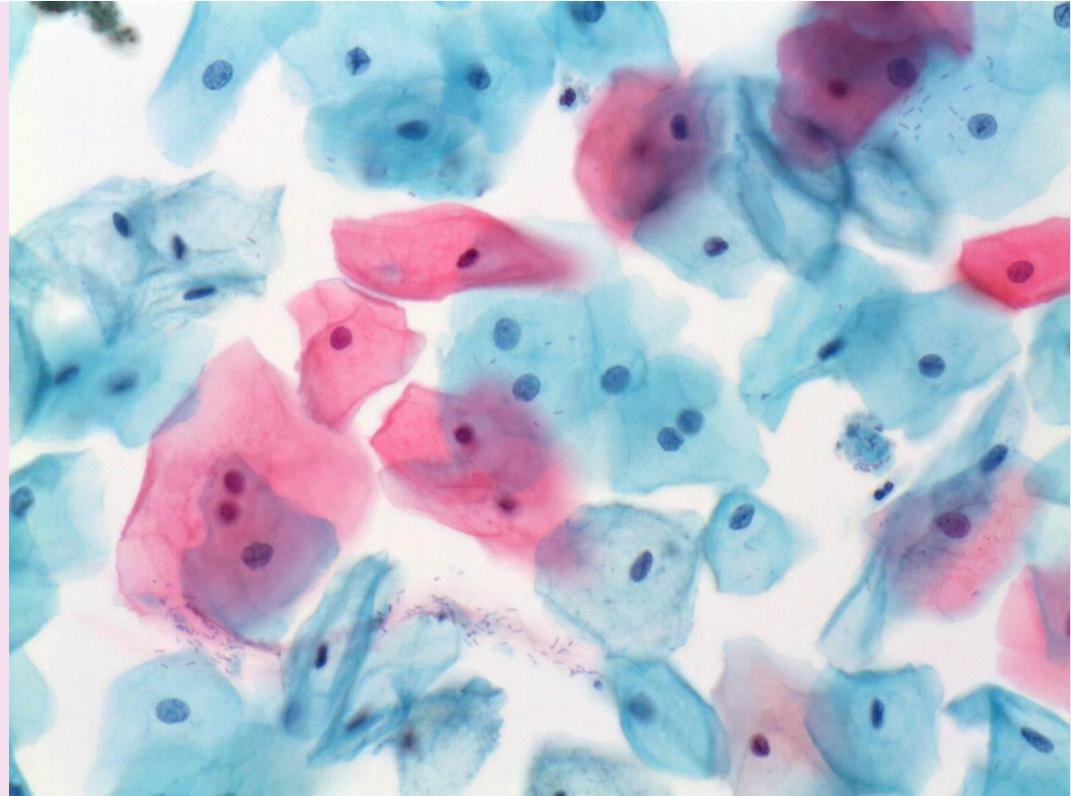
Estimated number of incident cases and deaths worldwide, females, all ages



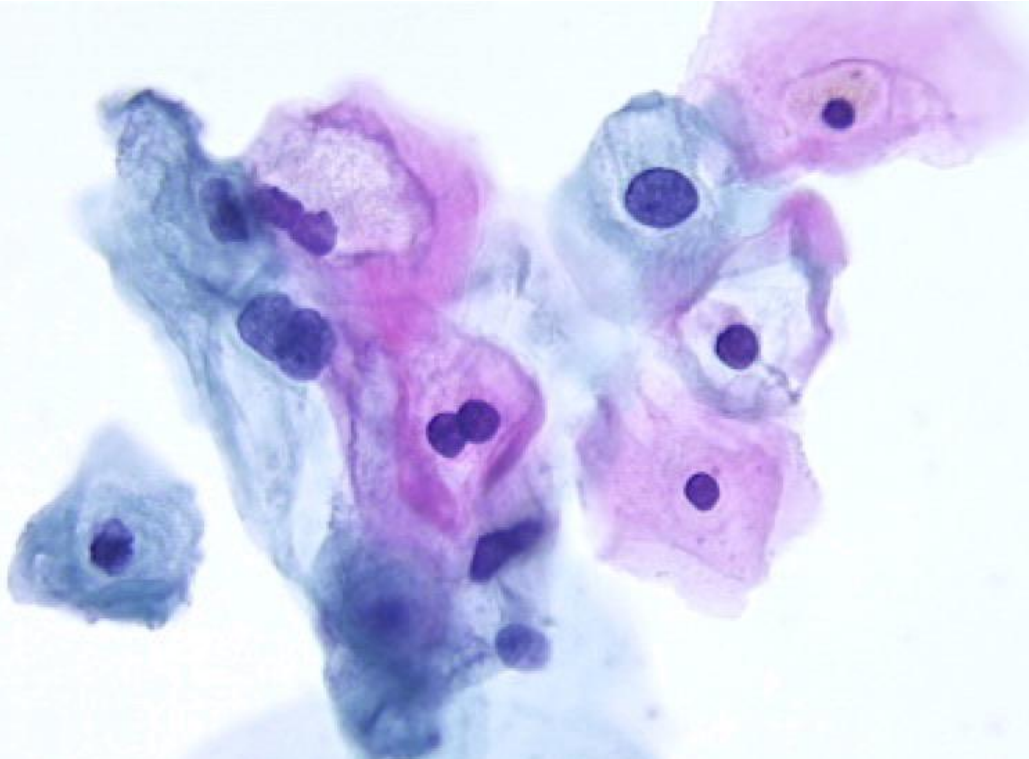
Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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CERVICAL CYTOLOGY

- Described by Papanicolaou in the 1940s
- Started being used in national screening programs in the late 1960s
- Has reduced the mortality of cervical cancer in countries where resources are available despite moderate sensitivity



THE PARADIGM SHIFT



- **1980s: High-risk HPV is a causative agent of cervical cancer**
- **1990s: Persistent infection with hrHPV is a necessary cause of nearly all cases of cervical cancer**
- **Screening could be done by testing for HPV**

HPV TESTING IS MORE SENSITIVE

ORIGINAL ARTICLE

Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer

Marie-Hélène Mayrand, M.D., Eliane Duarte-Franco, M.D., Isabel Rodrigues, M.D., Stephen D. Walter, Ph.D., James Hanley, Ph.D., Alex Ferenczy, M.D., Sam Ratnam, Ph.D., François Coutlée, M.D., and Eduardo L. Franco, Dr.P.H. for the Canadian Cervical Cancer Screening Trial Study Group*

- **10,154 women**
- **Sensitivity of HPV testing for cervical intraepithelial neoplasia of grade 2 or 3 was 94.6% whereas the sensitivity of Pap testing was 55.4%.**
- **The specificity was 94.1% for HPV testing and 96.8% for Pap testing.**

HPV TESTING IS MORE SENSITIVE

BJC
British Journal of Cancer

Clinical Study | [Open Access](#) | Published: 20 November 2012

Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial – the HPV FOCAL Study

G S Ogilvie , M Krajden, D J van Niekerk, R E Martin, T G Ehlen, K Ceballos, L W Smith, L Kan, D A Cook, S Peacock, G C E Stuart, E L Franco & A J Coldman

- **6154** women in the control arm and **12 494** in the HPV arm
- **Women randomised to the HPV arms had increased CIN2+ detection compared with women randomised to the cytology arm**

HPV TESTING IS MORE SENSITIVE

THE LANCET

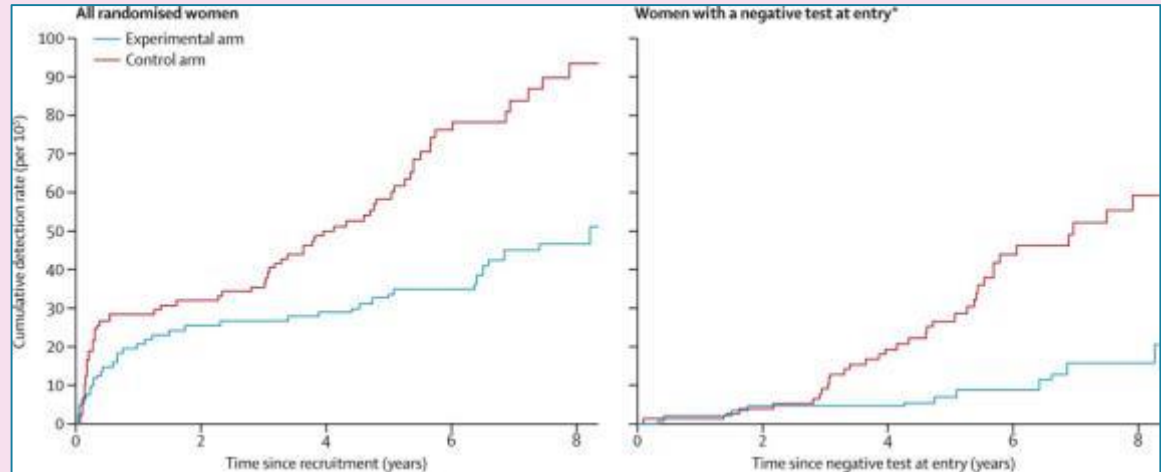
Volume 383, Issue 9916, 8–14 February 2014, Pages 524–532

THE LANCET

Articles

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Dr Guglielmo Ronco MD^{a, B, C}, Prof Joakim Dillner MD^c, K Miriam Elfström MPH^c, Sara Tunesi PhD^d, Prof Peter J F Snijders PhD^d, Marc Arbyn MD^e, Prof Henry Kitchener MD^f, Nereo Segnan MD^{a, b}, Clare Gilham MSc^g, Paolo Giorgi-Rossi PhD^h, Johannes Berkhof PhD^d, Prof Julian Peto DSc^h, Prof Chris J L M Meijer MD^d, the International HPV screening working group[†]



HPV screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology.

HPV TESTING IS MORE SENSITIVE



Does cervical cancer screening using primary cervical HPV testing compared with liquid-based cytology result in a lower likelihood of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) at 48 months?

CONCLUSION HPV-based screening resulted in a significantly lower likelihood of CIN3+ than cytology at 48 months, but further research is needed to understand long-term clinical outcomes as well as cost-effectiveness.

POPULATION



19 009 Women

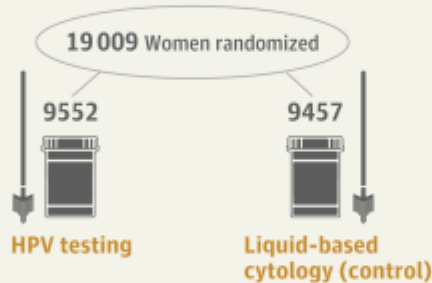
Women aged 25 to 65 years
with no history of CIN2+
Mean age: 45 years

LOCATIONS

224
Collaborating
clinicians in Canada



INTERVENTION



PRIMARY OUTCOME

Cumulative incidence of CIN3+
48 months following randomization

FINDINGS

Incidence of CIN3+ at 48 months

HPV testing	Liquid-based cytology
2.3/1000 women (95% CI, 1.5 to 3.5)	5.5/1000 women (95% CI, 4.2 to 7.2)

Absolute between-group difference:

-3.22/1000 women
(95% CI, -5.12 to -1.48)

© AMA

The use of primary HPV testing compared with cytology testing resulted in a significantly lower likelihood of CIN3+ at 48 months


WHY IS HPV TESTING CONQUERING THE LAND OF SCREENING?



The Bayeux Tapestry:
William, Duke of Normandy conquers Britain

- **HPV infection is an upstream event in the carcinogenesis; a negative HPV test provides greater and longer reassurance against cervical cancer**
- **Better sensitivity**
- **Better cost-effectiveness (longer screening intervals)**
- **Not subjective, can be automated and centralized**

HPV TESTING HAS BECOME THE MAINSTAY OF THE GUIDELINES



**U.S. Preventive Services
TASK FORCE**

Cervical Cancer: Screening
Release Date: August 2018

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Women aged 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting).	A
	See the <i>Clinical Considerations</i> section for the relative benefits and harms of alternative screening strategies for women 21 years or older.	
Women older than 65 years	The USPSTF recommends against screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.	D
	See the <i>Clinical Considerations</i> section for discussion of adequate prior screening and risk factors that support screening after age 65 years.	
Women younger than 21 years	The USPSTF recommends against screening for cervical cancer in women younger than 21 years.	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (ie, cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

Women aged 21 to 65 years

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HPV TESTING HAS BECOME THE MAINSTAY OF THE GUIDELINES

Journal of Global Oncology[®]

An American Society of Clinical Oncology Journal

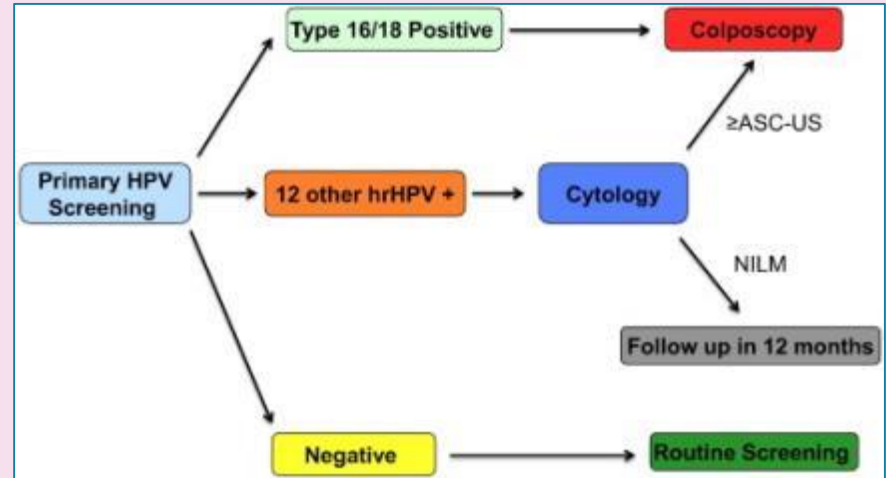
SPECIAL ARTICLES

Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline

[Jose Jeronimo](#), [Philip E. Castle](#), [Sarah Temin](#), [Lynette Denny](#), [Vandana Gupta](#), [Jane J. Kim](#), [Silvana Luciani](#), [Daniel Murokora](#), [Twalib Ngoma](#), [Youlin Qiao](#), [Michael Quinn](#), [Rengaswamy Sankaranarayanan](#), [Peter Sasieni](#), [Kathleen M. Schmeler](#), and [Surendra S. Shastri](#)

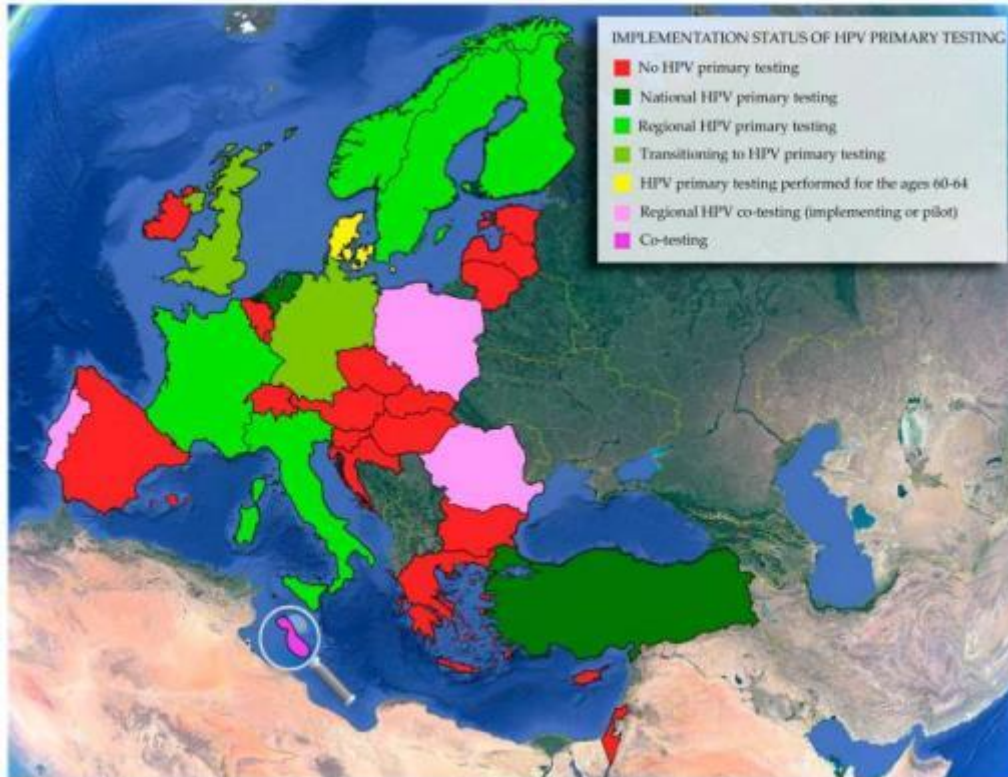
- Human papillomavirus (HPV) DNA testing is recommended in all resource settings for primary screening.
- This guideline does not recommend the use of cytology in primary screening, but only as one alternative of reflex testing.

HPV TESTING HAS BECOME THE MAINSTAY OF THE GUIDELINES



- Primary hrHPV screening offers better reassurance of low cancer risk compared to cytology-only screening and can be considered as an alternative to both cytology alone and cotesting.
- The use of HPV 16/18 genotyping and reflex cytology achieves a reasonable balance of disease detection with the number of screening tests and colposcopies required to achieve that detection.

WHAT IS BEING DONE?



The landscape in Europe (2018) shows a progressive transition to the adoption of HPV primary testing in national screening programs

Chrysostomou, Andreas C et al. "Cervical Cancer Screening Programs in Europe: The Transition Towards HPV Vaccination and Population-Based HPV Testing."

Viruses vol. 10,12 729. 19 Dec 2018

CYTOLOGY: WHERE DO WE GO FROM HERE?

'One should
die proudly
when it is no
longer
possible to
live proudly'
F. Nietzsche

HPV TESTING IS LESS SPECIFIC



Cochrane Database of Systematic Reviews

Cytology versus HPV testing for cervical cancer screening in the general population (Review)

Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPL, Mustafa RA, Schünemann H, Paraskevaidis E, Arbyn M

- A negative HPV test is more reassuring than a negative cytological test
- Whilst HPV tests are less likely to miss cases of CIN 2+ and CIN 3+, these tests do lead to more unnecessary referrals.

HPV TESTING IS LESS SPECIFIC

- False-positive rates are higher for both primary hrHPV screening and cotesting.
- Rates of colposcopy referral are higher, indicating a greater relative burden with hrHPV screening and potential differences in downstream consequences of treatment compared with screening cytology.

Melnikow et al. *Other supporting document for cervical cancer: screening.*
JAMA. 2018;320(7):687-705

- Unnecessary colposcopies can cause increased costs to the healthcare system


HPV TESTING IS LESS SPECIFIC

What are the downstream consequences of higher colposcopy and treatment rate?

- Harms of treatment of the cervix to remove precancerous cells include pain, bleeding, and harms related to fertility and subsequent pregnancy outcomes.
- Limited evidence suggests that, compared with abnormal cytology results, hrHPV test positivity may be associated with greater short-term psychological harm.

Melnikow et al. *Other supporting document for cervical cancer: screening.*
JAMA. 2018;320(7):687-705

HPV TESTING IS NOT APPROPRIATE IN YOUNGER WOMEN

 U.S. Preventive Services
TASK FORCE

Cervical Cancer: Screening
Release Date: August 2018

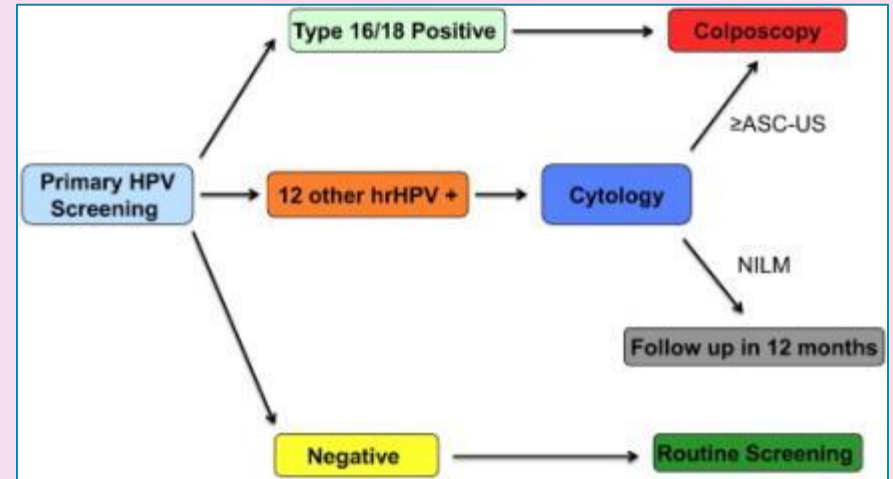
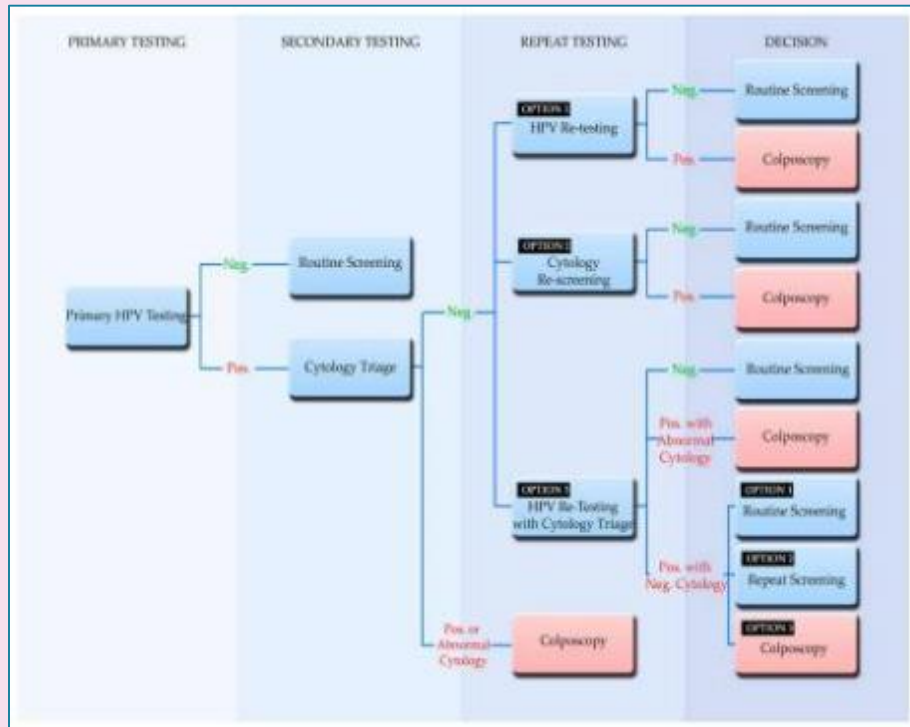
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CYTOLOGY IS STILL NEEDED FOR REFLEX TESTING AND FOR COTESTING



Chrysostomou, Andreas C et al. "Cervical Cancer Screening Programs in Europe: The Transition Towards HPV Vaccination and Population-Based HPV Testing." *Viruses* vol. 10,12 729. (2018)

**VACCINATION:
THE YET TO BE REVEALED
DEMISE OF CYTOLOGY?**

'Et tu, Brute?'

Julius Caesar

VACCINATION HAS LOWERED THE PREVALENCE OF CERVICAL LESIONS

- **Current vaccines do not offer protection against all hrHPV types; screening will continue to be recommended.**
- **Vaccination has substantially reduced the prevalence of cervical lesions and this is becoming even more apparent as the first cohort of the vaccination era is coming of age.**
- **This decreased prevalence inevitably decreases the PPV of any screening test, since PPV is a function of prevalence.**

Tota et al. Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. Prev Med. 2017 May;98:5-14.

WHY WILL CYTOLOGY'S PPV DECREASE MORE THAN HPV TESTING?

- The reduced prevalence of abnormalities on cytology slides will lead to cytopathologist's fatigue and impact the sensitivity of the test, further decreasing the PPV.
- The prevalence of low-grade lesions, inflammation and reactive atypias won't be decreasing thus reducing the signal-to-noise ratio. Cytopathologists could therefore make more mistakes.
- The context of reflex testing for triaging hrHPV positive cases, the prevalence will be artificially high and this problem won't be of any relevance.

Tota et al. Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. Prev Med. 2017 May;98:5-14.

THE CASE OF THE ARAB WORLD

وبالتالي في الطب
يجب علينا أن
نعرف أسباب
المرض والصحة.
ابن سينا

CAN HPV TESTING BE USED ON SELF-TESTING SAMPLES?

- When used with hrHPV assays based on polymerase chain reaction, testing on self samples was similarly accurate as on clinician samples.

Arbyn et al. *BMJ*. 2018 Dec 5;363:k4823

- HPV testing done with a clinically validated PCR-based assay had similar accuracy on self-collected and clinician-collected samples in terms of the detection of CIN2+ or CIN3+ lesions. These findings suggest that HPV self-sampling could be used as a primary screening method in routine screening.

Polman et al. *Lancet Oncol*. 2019 Feb;20(2):229-238

SELF-TESTING IS ADVANTAGEOUS FOR THE ARAB WORLD

- Khan and Woolhead (BMC Women's Health, 2015) have undergone an ethnography showing that in the UAE, women's fear, pain and embarrassment, along with cultural influences, deterred them from undergoing screening.
- The availability of self-testing samples kits, would possibly constitute a effective step to overcome arab women's cultural impediments to screening.

EPILOGUE: THE CYTOPATHOLOGIST'S WORRIES

'The greatest
geniuses
sometimes
accomplish
more when
they work less'

L. Da Vinci

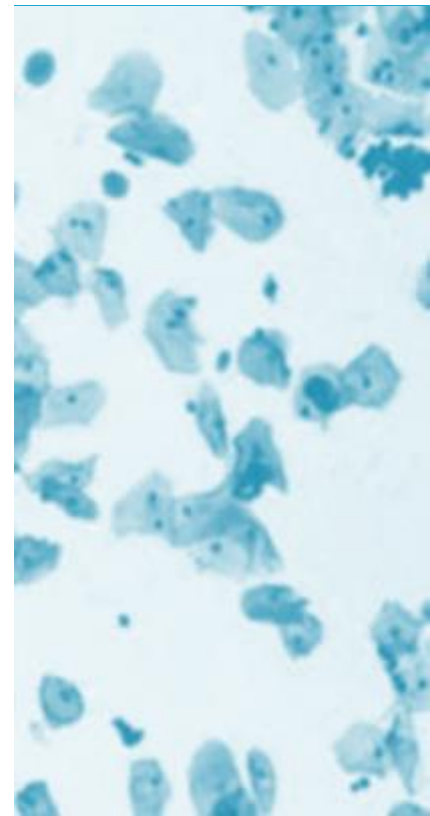
THE CYTOPATHOLOGIST'S WORRIES

- **There is concern about loss of income by professions that rely on continued use of Pap cytology**
- **It is a real concern, but cytology for triaging HPV + women will continue as a more prestigious, diagnostic activity for a little < 10% of today's current volume.**
- **Diversification of cytopathology labs into molecular techniques will alleviate the concern.**
- **Reduction in cytology workload will be beneficial; delays in reporting Pap test results are a major concern in some settings.**
- **Not a scientifically valid concern.**

Tota et al. Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. Prev Med. 2017 May;98:5-14.

TAKE HOME MESSAGES:

- A paradigm shift from morphology to causality has occurred in cervical cancer screening.
- HPV testing is more sensitive than cytology at detecting pre-cancerous lesions
- HPV testing has replaced cytology as the mainstay of current screening guidelines and is being progressively introduced into national programs.
- Cytology still has a role for reflex testing and for screening younger women.
- Cytology's PPV is expected to decrease in the vaccination era.



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Pathology Resident