Consortium for Infectious Disease Control

A neutral, third party platform supporting infectious disease projects,
providing continuing medical education, coordinating initiatives, and undertaking research

Winnipeg, Manitoba, Canada
October 31, 2019

HPV-based Cervical Screening:
Why is NOW the time?

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Clinical Lead for the CPAC HPV-Cervix OncoSim model

Moderator: Dr. Marc Steben, MD

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Family Physician, Family Medicine Group 1851
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Director, Canadian Network on HPV Prevention

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and with assistance by BD Diagnostics

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Webinar Objectives

- List some of the key findings from comparative studies of different HPV tests in prospective cohorts and cross-sections;
- Identify the important clinical performance issues that inform implementation decisions;
- Outline the Health System Outcomes and Cost Effectiveness with Primary HPV screening;
- Discuss the future possibilities of HPV testing

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Moderator

Dr. Marc Steben, MD

- Chair, Canadian HPV Prevention Network
- Family Physician, Family Medicine Group 1851
- Board Member, International Papillomavirus Society

- Montreal, Quebec, Canada

Presenter

Dr. Catherine Popadiuk, MD, FRCP(C), MBA

- Associate Professor, Gynecologic Oncology, Memorial University
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"HPV-based cervical cancer screening: Why is NOW the time?"

Presented by Dr. Catherine Popadiuk, MD, FRCS, MBA

Disclosure

- None to declare

Objectives

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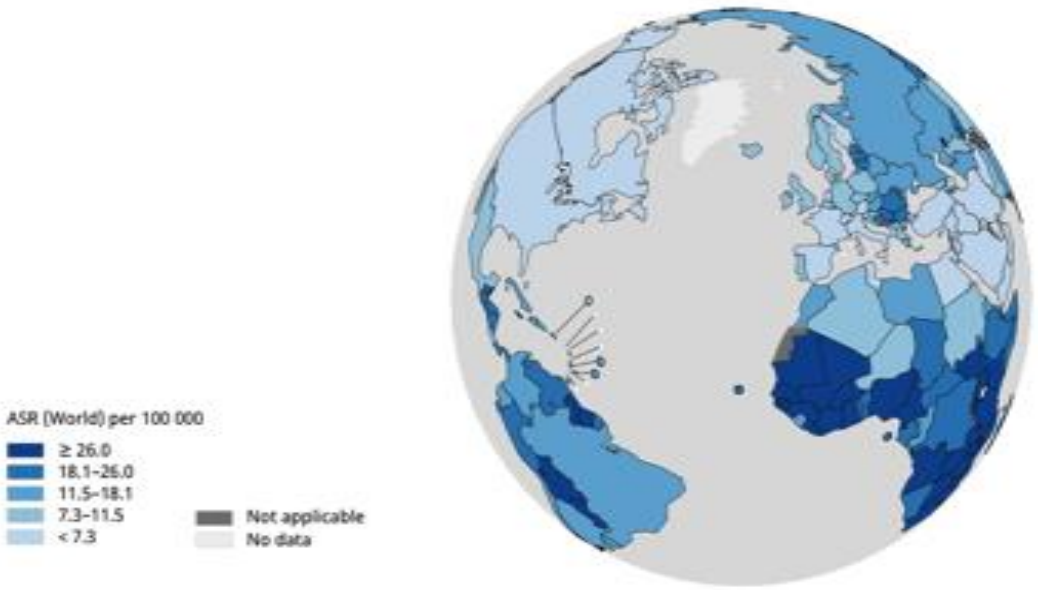
- Discuss the future possibilities of HPV testing

BACKGROUND: CERVICAL CANCER AND SCREENING TESTS

Cervical Cancer

- Estimated 570,000 new cases/ year world wide (2018)
- 90% of new cases occur in developing countries
  - 270 000 deaths/year
- In Canada during year 2016, there were 1500 new cases and 400 deaths

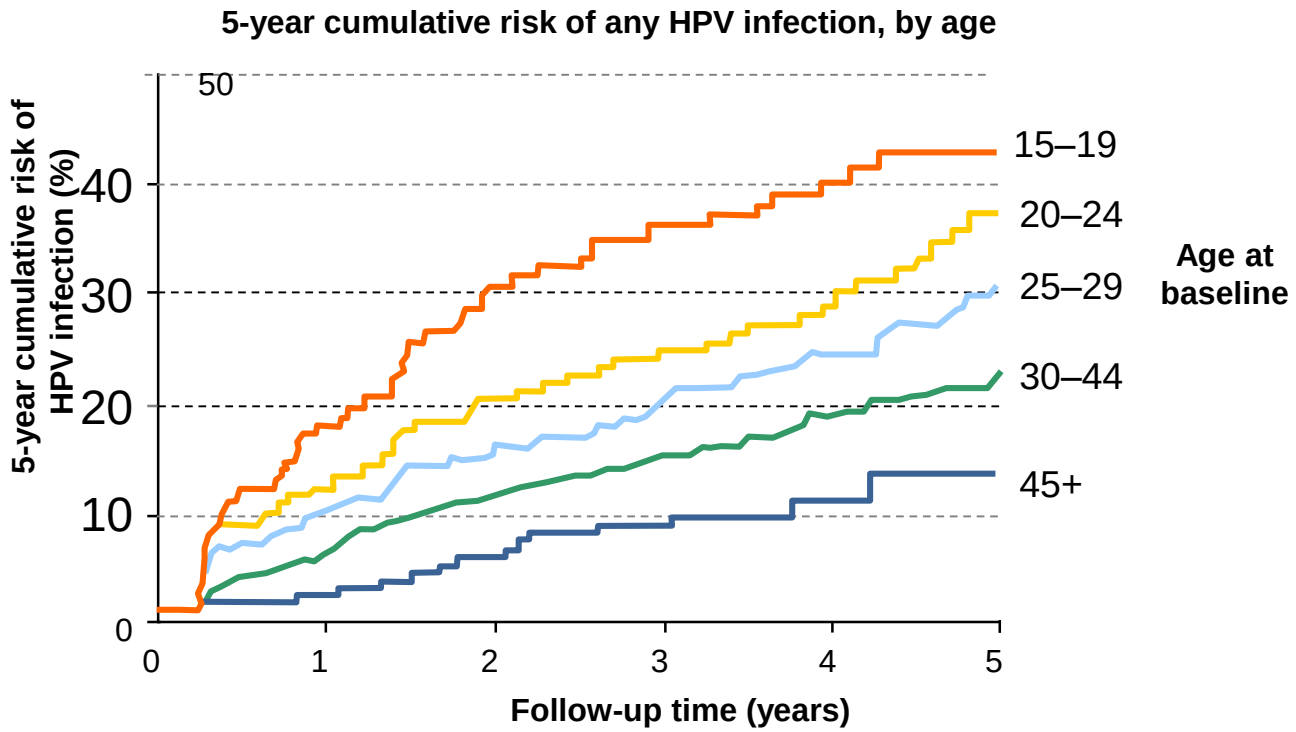
Estimated age-standardized incidence rates (World) in 2018, cervix uteri, females, all ages



https://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/

80% of (Unvaccinated) women will acquire an HPV infection throughout their lives

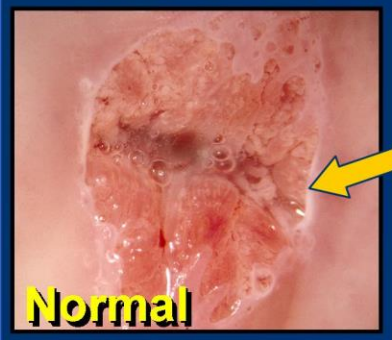
- 65 to 85% risk of transmission after one encounter
- 60% of women testing positive have had only had one male partner

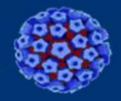


Approximately 75% of these infections will be oncogenic HPV

Munoz N, et al. J Infect Dis 2004; 190:2077–2087.

Natural History of Oncogenic HPV Infections in Squamous Disease

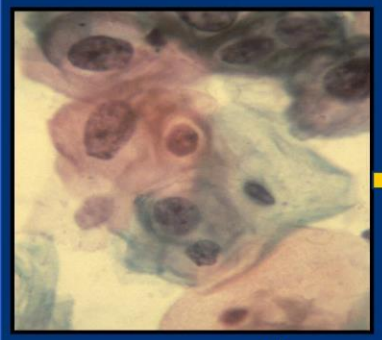




HPV Virion

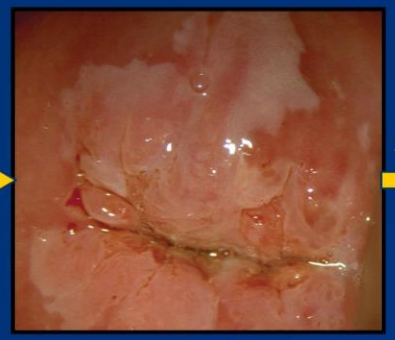
Persistence and Progression

HPV- infected cells



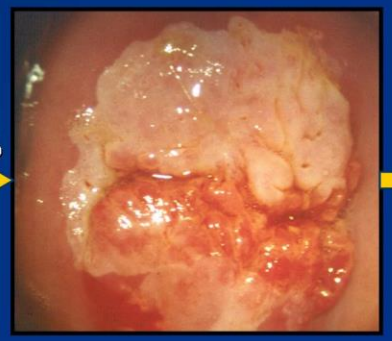
20%

CIN 1



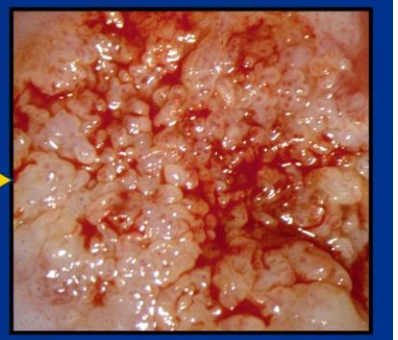
5-10%

CIN 2-3



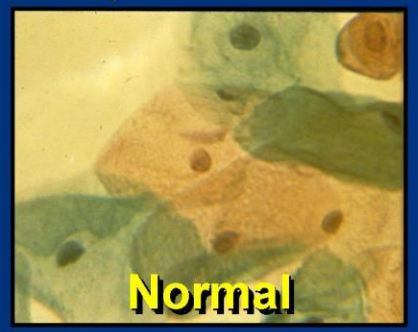
30%

SCC

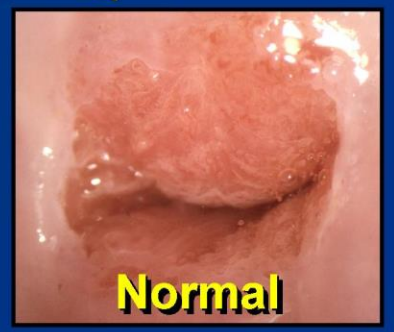


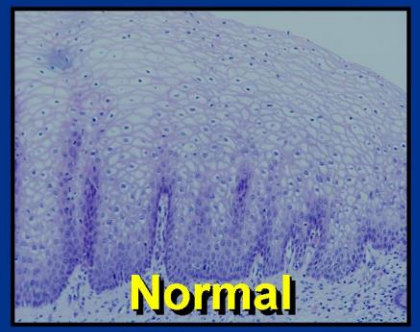
Cancerous lesions do not regress

80%



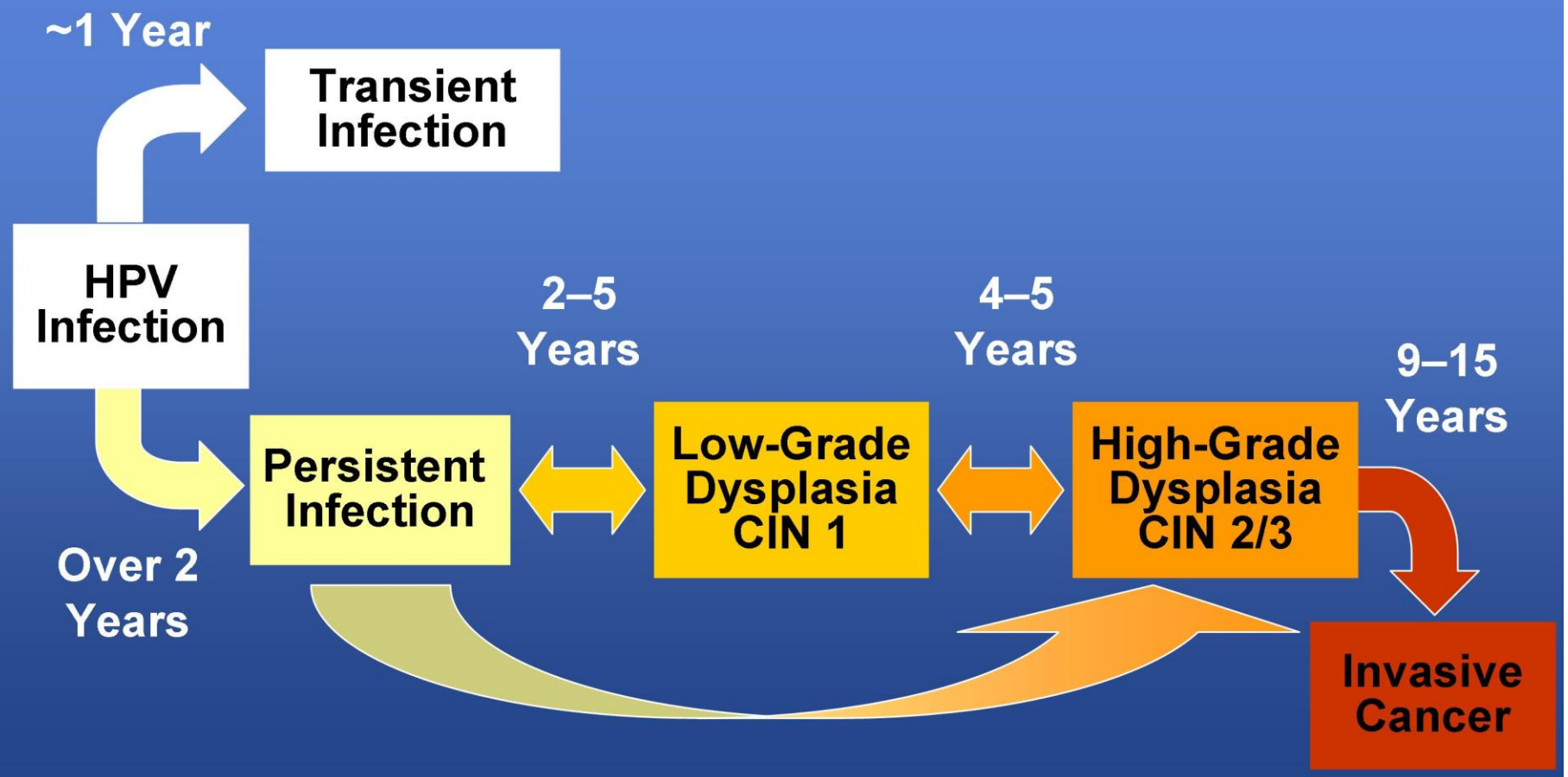
Most





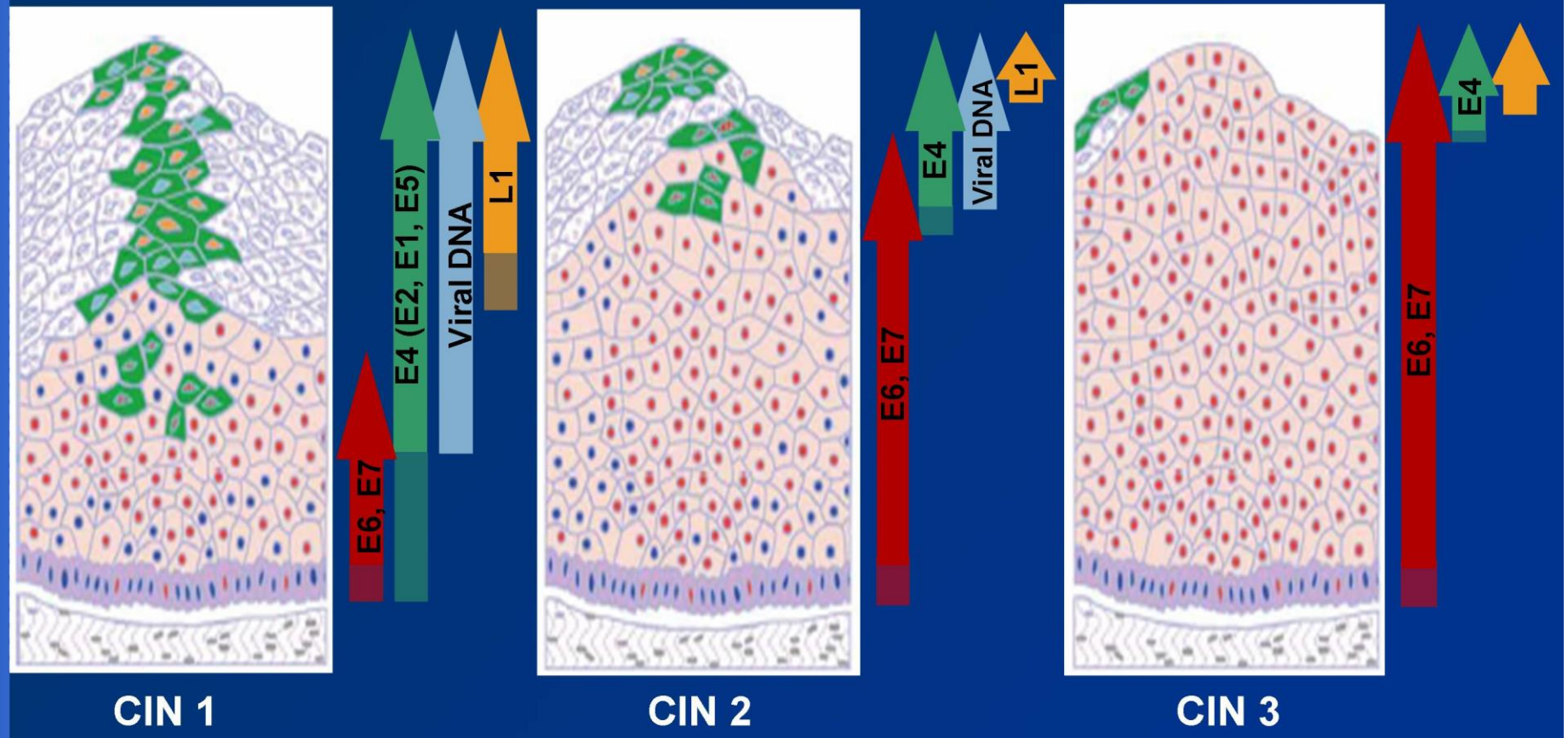
Regression and Clearance

Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer[1]



1. Reprinted from Pagliusi SR, Aguado MT., *Vaccine*, 2004;23:569–578, Copyright © 2004, with permission from Elsevier.

HPV Life Cycle and Progression to Cancer[1]



1. Adapted from Doorbar J. *J Clin Virol*. 2005;32(suppl):S7–S15. Reprinted with permission from Elsevier Inc.

Cervical Cytology

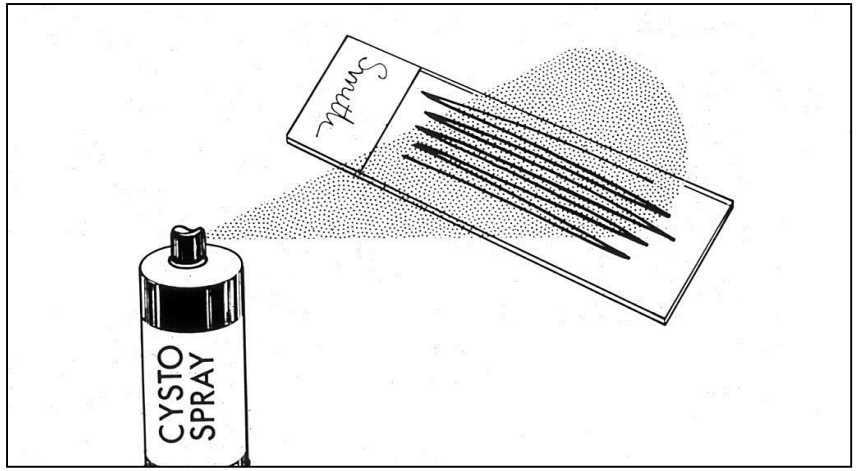
- Dr. George Papanicolaou
- In 1923 he determined that exfoliated cells obtained from epithelial surfaces

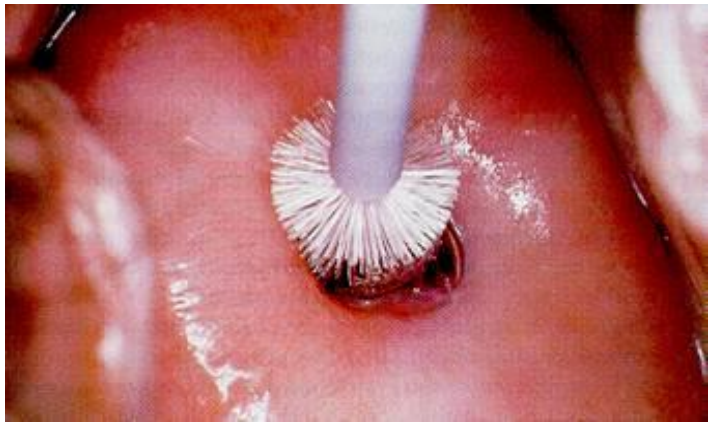
  accurately reflect deeper

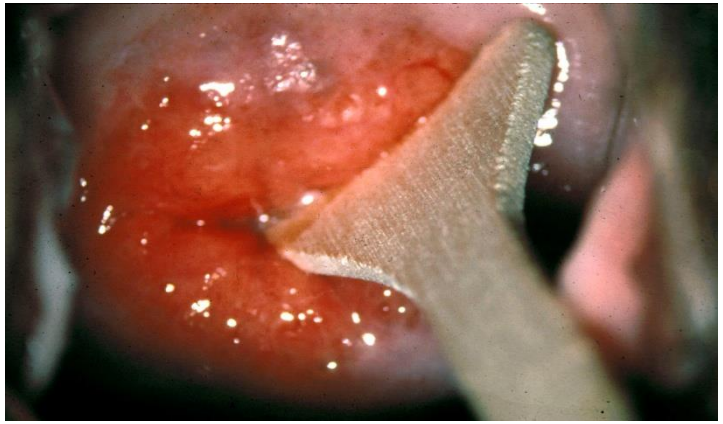
  processes

Conventional Cytology

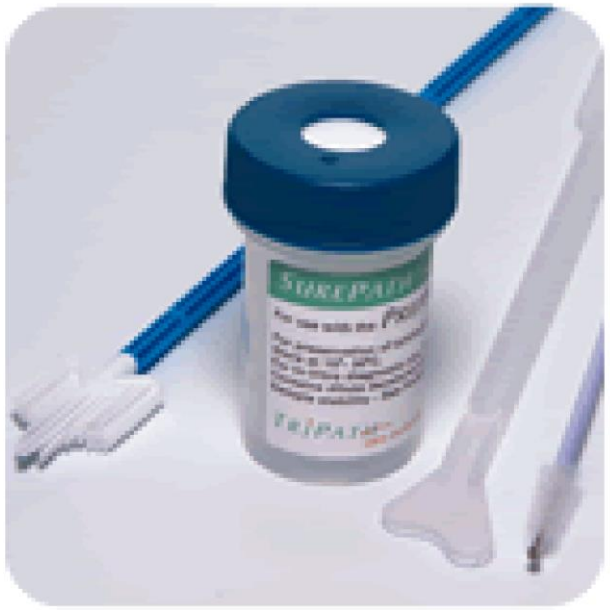
- **Ayre's Spatula**
- **Cytobrush**
- **Cytospray fixative (air dry in BC)**







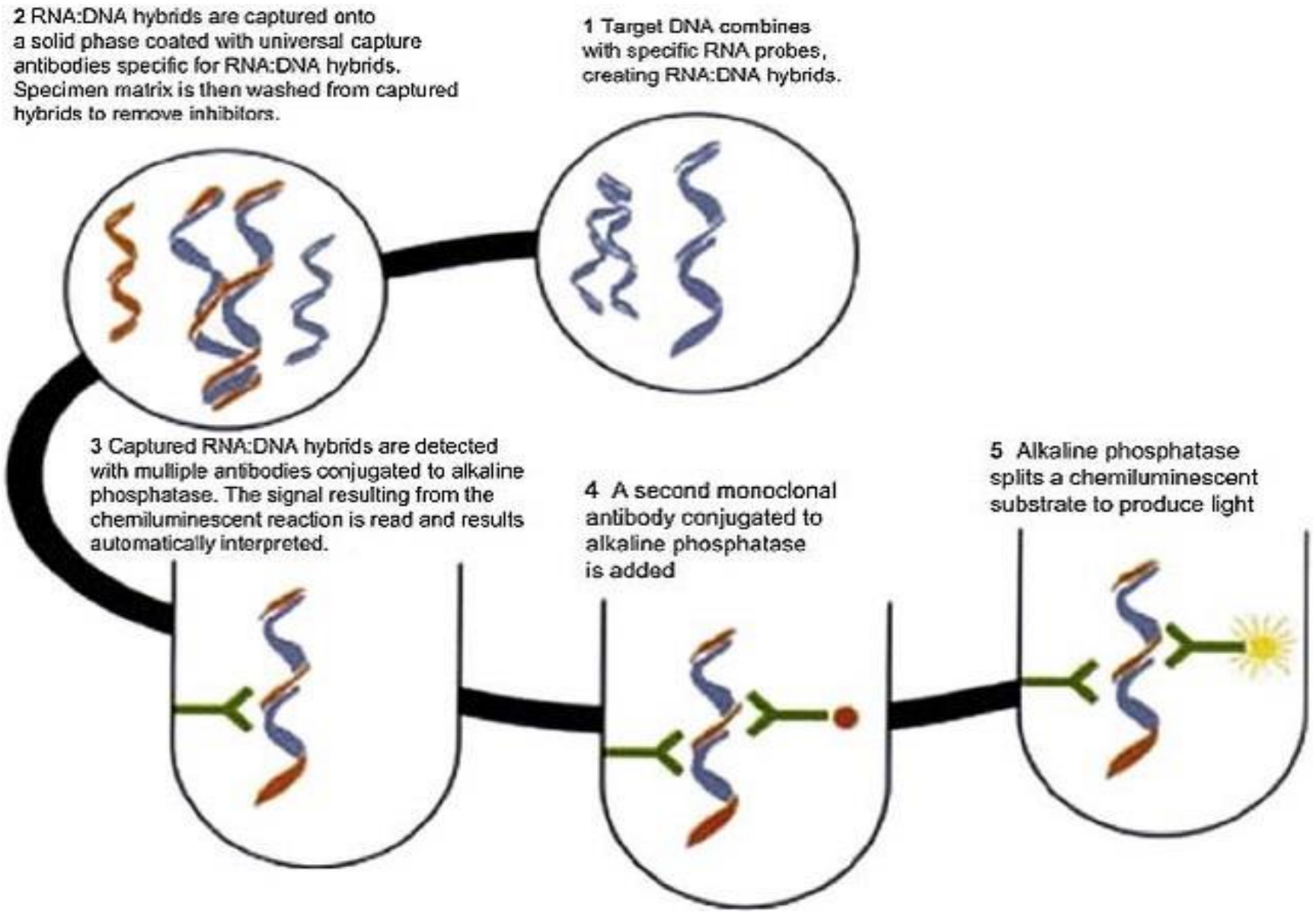
Liquid Based Cytology



Human Papillomaviruses (HPV) and Test Characteristics

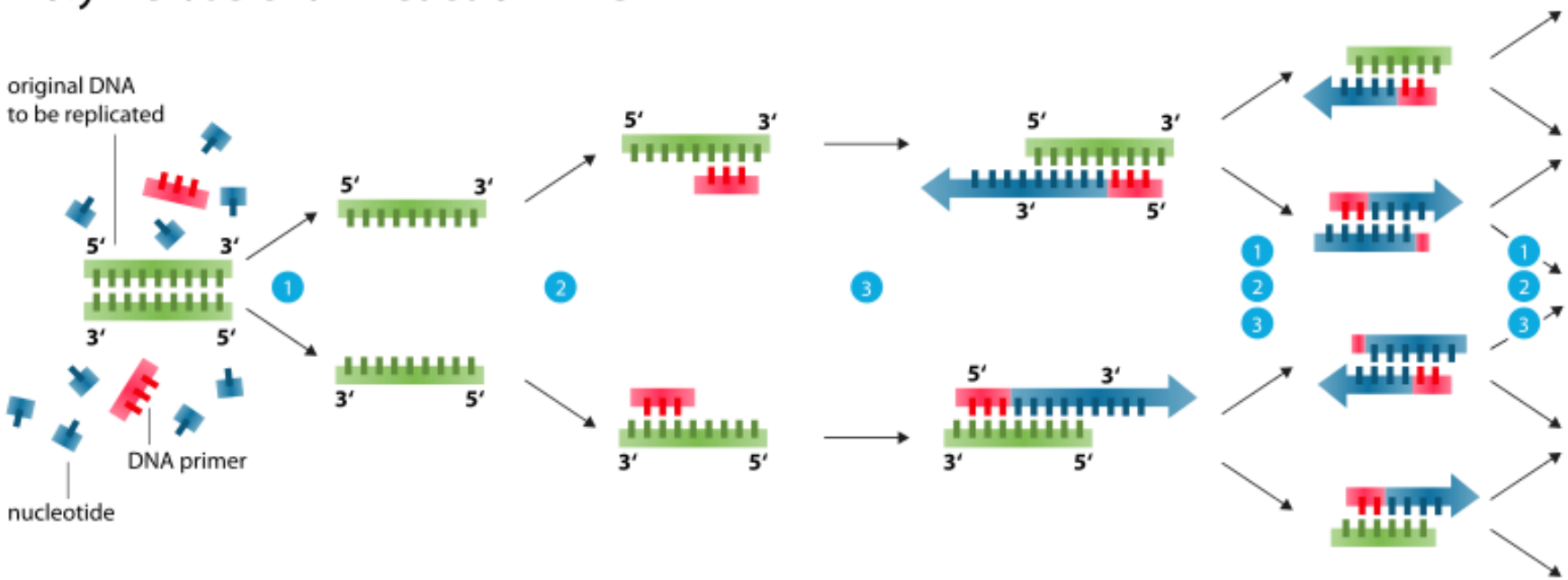
- The HPV family includes at least 170 high and low risk types
- HPV types 16 and 18 are the most common cause of cervical cancer.
- Abbott, Roche, Aptima (Hologic), BD, Qiagen, Cephid all have Health Canada approved HPV tests.
- There are four major FDA-approved HPV assays currently on the market:
  - (1) Digene Hybrid Capture 2 (Qiagen),
  - (2) Cervista HPV HR (Hologic),
  - (3) Aptima HPV (Hologic)
  - (4) Cobas HPV (Roche)

- Digene HC2 is considered the gold standard for comparison and is based on Signal Amplification.
- Other assays include genotyping for HPV types 16 and 18, either as reflex tests or integral to the screening assay.
- 170 commercial assays available worldwide
- The tests on the market are based on unique molecular principles, each with advantages and limitations.
- “For clarity, the test kit name is connected to the manufacturer. It’s always good to use the manufacturer’s name because sometimes the same kits are marketed and licensed under different trade names.” (Sam Ratnam)



Bluth MJ and Bluth MH (2013). Molecular pathology techniques. Clin Lab Med. 33(4):753-772.

Polymerase chain reaction - PCR



1. **Denaturation** at 94-96°C
2. **Annealing** at ~68°C
3. **Elongation** at ca. 72 °C

KEY FINDINGS FROM COMPARATIVE STUDIES OF DIFFERENT HPV TESTS IN PROSPECTIVE COHORTS AND CROSS-SECTIONAL CHARACTERISTICS OF STUDY POPULATIONS

Gynecologic Oncology 136 (2015) 189–197

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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

Thomas C. Wright [a,*], Mark H. Stoler [b], Catherine M. Behrens [c], Abha Sharma [c], Guili Zhang [c], Teresa L. Wright [d]

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[b] Department of Pathology, University of Virginia, Charlottesville, VA, USA
[c] Roche Molecular Systems, Pleasanton, CA, USA
[d] Genentech, South San Francisco, CA, USA

HIGHLIGHTS

- A negative HPV results at baseline predicts one-half the risk of CIN3+ over 3 years than a negative cytology result.
- HPV primary screening with triage using 16/18 genotyping and cytology increases sensitivity to detect CIN3+ 28% over cytology.
- Cytology failed to detect approximately 50% of CIN3+ in women 25–29 years.

ATHENA – results

- The results support the use of HPV primary screening
  - triage of HPV-positive women using a combination of genotyping for HPV 16/18 and reflex cytology beginning at age 25 years
- Screening with HPV is significantly more sensitive for the detection of CIN3+ than either cytology or the hybrid strategy

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

*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

www.thelancet.com **Published online November 3, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62218-7**

	Swedescreen (NCT00479375)	POBASCAM (ISRCTN20781131)	ARTISTIC (ISRCTN25417821)	NTCC (ISRCTN81678807)
Target age at recruitment (years)	32–38	29–61	20–64	25–60
Randomisation ratio (experimental *vs* control)	1:1	1:1	3:1	1:1
Primary test in the experimental arm	HPV (GP5+/GP6+ PCR) and conventional cytology	HPV (GP5+/GP6+ PCR) and conventional cytology	HPV (hybrid capture 2) and liquid-based cytology	Phase 1: HPV (hybrid capture 2) and liquid-based cytology Phase 2: stand-alone HPV (hybrid capture 2)
Primary test in the control arm	Conventional cytology	Conventional cytology	Liquid-based cytology	Conventional cytology
Tests in secondary and later screening rounds	In both arms: conventional cytology	At round 2 in both arms: HPV (GP5+/GP6+ PCR) and conventional cytology At round ≥3 in both arms: conventional cytology	At round 2 in both arms: corresponding with primary test At round ≥3 in both arms: cytology	In both arms: conventional cytology
Management of HPV-positive women	Cytological triage*	Cytological triage*	Cytological triage*	Colposcopy (in phase 2 and in women ≥35 years old in phase 1) Cytological triage* (in women aged 25–34 years in phase 1)
Screening interval for women with negative result (years)	3	5	3	3

*If cytology was negative, HPV-positive women were invited for repeat HPV testing, then colposcopy if infection persisted. If cytology was positive, women were referred immediately for colposcopy. This approach was denoted cytological triage.

***Table 1*: Main features of the four randomised controlled trials**

Interpretation

Our extended follow-up of the four randomised controlled trials with data for two screening rounds enabled large-scale estimation of the effect of HPV screening on invasive cervical carcinoma in women who have regular screening. HPV-based screening prevented more invasive cervical cancers than did cytology. Different screening protocols used in the four studies did not affect efficacy of HPV testing. Increased protection against invasive cervical cancer was noted in women aged 30–35 years, and HPV screening every 5 years was most protective against invasive cancers of the cervix, compared with cytology done every 3 years. We recommend implementation of HPV-based cervical screening with triage from age 30 years at intervals of at least 5 years.

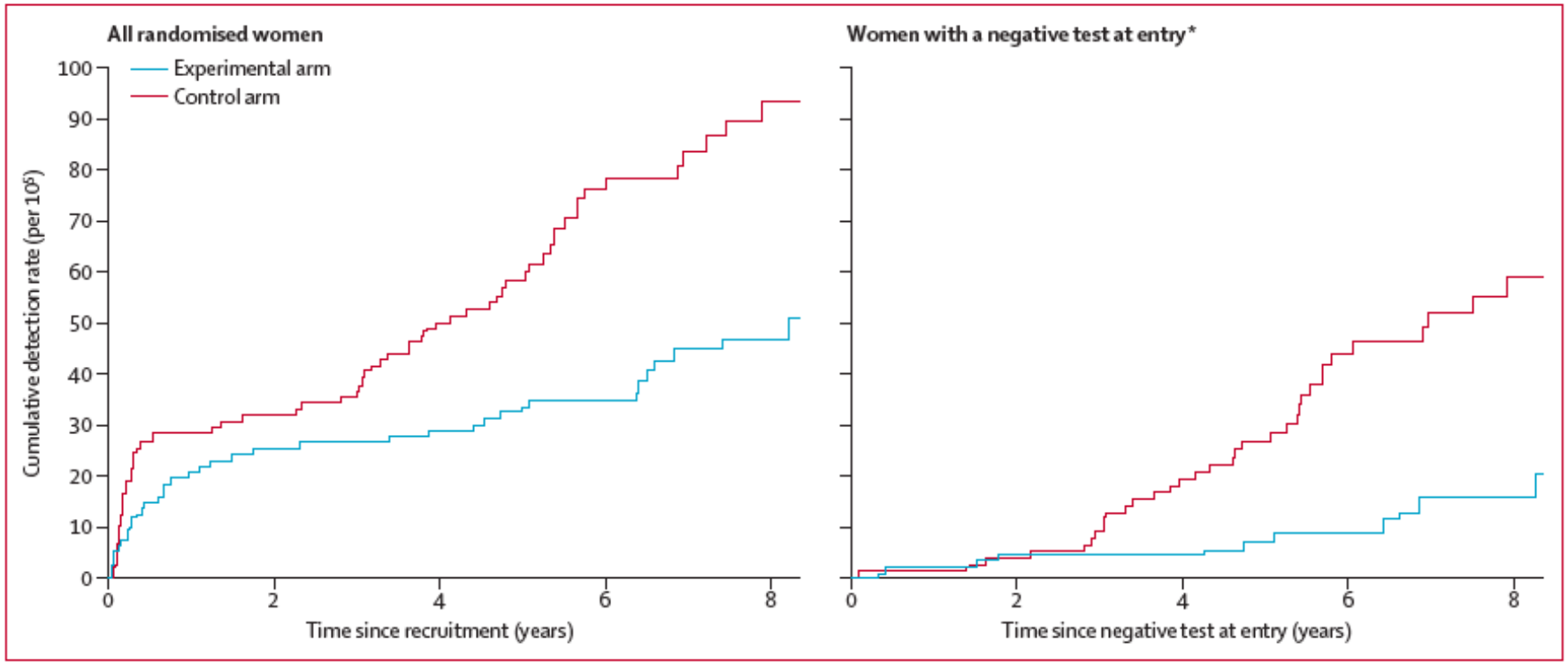


Figure 2: **Cumulative detection of invasive cervical carcinoma**
*Observations are censored 2·5 years after CIN2 or CIN3 detection, if any.

Research

JAMA | Original Investigation

Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months

The HPV FOCAL Randomized Clinical Trial

JAMA. 2018

FOCAL: Conclusion

- By 48 months:
  - For the women screened for cervical cancer with HPV testing without cytology: significantly fewer high grade cases
    - Versus
  - Women screened with cytology alone at baseline

- Women – HPV negative at baseline were significantly less likely to have CIN3+ and CIN2+ at 48 months compared with women who were cytology negative at baseline

- These results have demonstrated that primary HPV testing detects cervical neoplasia earlier and more accurately than cytology.

Journal of Clinical Virology 108 (2018) 32–37

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Comparative performance of human papillomavirus messenger RNA versus DNA screening tests at baseline and 48 months in the HPV FOCAL trial

Darrel A. Cook[a,b], Laurie W. Smith[b], Jennifer H. Law[c], Wendy Mei[c], Lovedeep Gondara[b], Dirk J. van Niekerk[b,c,d], Kathy M. Ceballos[b,c,d], Dan Jang[e], Max Chernesky[e], Eduardo L. Franco[f], Gina S. Ogilvie[a,b,d], Andrew J. Coldman[b,d], Mel Krajden[a,c,d,*]

[a] BC Centre for Disease Control, Vancouver, BC, Canada
[b] BC Cancer Agency, Vancouver, BC, Canada
[c] Lower Mainland Pathology & Laboratory Medicine, Provincial Health Services Authority, Vancouver, BC, Canada
[d] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[e] McMaster University/St. Joseph's Healthcare, Hamilton, ON, Canada
[f] Division of Cancer Epidemiology, McGill University, Montreal, QC, Canada

Conclusion: There was no significant difference in CIN2+ detection for AHPV vs. HC2 at baseline or at 48 months. Baseline AHPV – and HC2- women had similar CIN2+ rates at 48 months, demonstrating safety of a four year screening interval for AHPV – women.

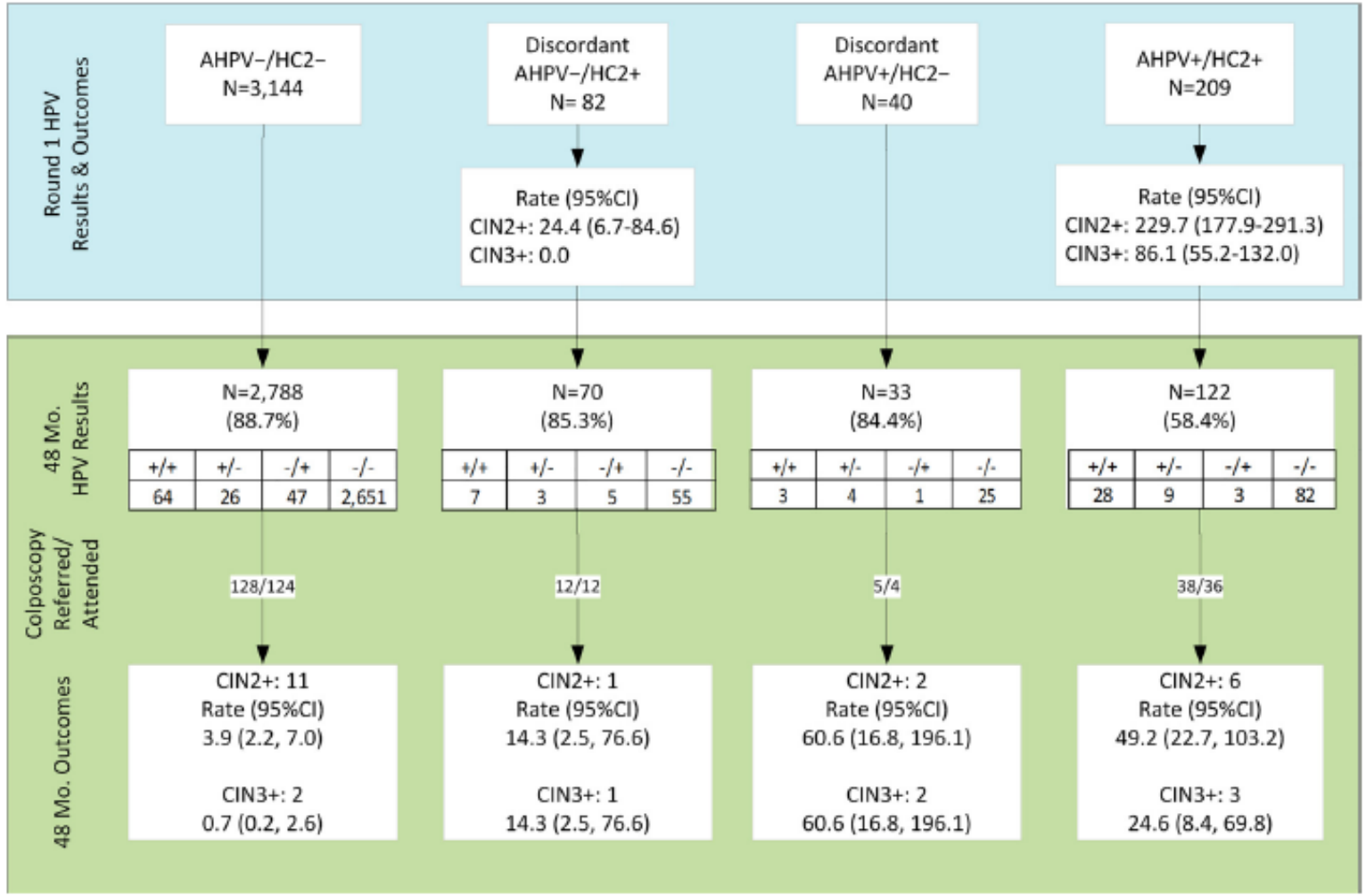


Fig. 2. AHPV and HC2 Results and Outcomes at HPV FOCAL Round 1 and 48 Months.
Abbreviations: AHPV: Aptima HPV assay; HC2: hybrid capture 2 HPV test; CIN: cervical intraepithelial neoplasia.
Note: The tables within the 48 mo. exit HPV results boxes (+/+, +/−, −/+, −/−) represent AHPV/HC2 result combinations. Women with CIN2 + detected at round 1 are not included in the 48 mo. denominators. CIN rates are expressed as the number of cases per 1000 for each result category.

Longitudinal Clinical Performance of the RNA-Based Aptima Human Papillomavirus (AHPV) Assay in Comparison to the DNA-Based Hybrid Capture 2 HPV Test in Two Consecutive Screening Rounds with a 6-Year Interval in Germany

Thomas Iftner,[a] Klaus-Joachim Neis,[b] Alejandra Castanon,[c,d] Rebecca Landy,[c] Barbara Holz,[a] Astrid Woll-Herrmann,[b] Angelika Iftner,[a] Annette Staebler,[e] Diethelm Wallwiener,[f] Claus Hann von Weyhern,[e] Felix Neis,[f] Juliane Haedicke-Jarboui,[a] Peter Martus,[g] Sara Brucker,[f] Melanie Henes,[f] Peter Sasieni[c,d]

January 2019 Volume 57 Issue 1 e01177-18 Journal of Clinical Microbiology

German AHPV Screening Trial (GAST)

- N=10,040 women recruited and tested with LBC, HC2 and AHPV
- 411 women tested positive for at least one test
- 3295 Triple Negative test women were rescreened after 6 years
- The data show the longitudinal performance of the AHPV test over 6 years is comparable to the performance of the HC2 test and that the absolute risk of CIN3+ over six years following a negative AHPV result in a screening population is low.

TABLE 3 Second-round LBC and HPV test results among women who were triple negative at baseline

HPV test result during follow-up (HC2/AHPV)	LBC results (no.)				Total no.	No. with CIN2+
	Negative	Inadequate	Low-grade (Pap III)	High-grade (Pap IIID)		
Both missing	71	4	0	0	75	0
Missing HC2 result	1	0	0	0	1	0
Missing AHPV result	4	0	0	0	4	0
−/−	3,057	18	5	12	3,092	0
−/+	13	0	0	0	13	0
+/−	48	0	1	1	50	1
+/+	44	0	3	13	60	8
Total	3,238	22	9	26	3,295	9

TABLE 5 Six-year cumulative incidence, risk per 1,000 women screened, and negative predictive value among those testing negative at baseline

Characteristic	Cumulative incidence (% [95% CI])		Risk per 1,000 women screened (95% CI)		Negative predictive value (% [95% CI])[a]	
CIN2 or worse						
AHPV negative	0.62	0.24–1.59	6.2	2.4–15.9	99.38	98.41–99.76
HC2 negative	0.47	0.27–0.81	4.7	2.7–8.1	99.53	99.19–99.73
LBC negative	1.66	0.72–3.83	16.6	7.2–38.3	98.34	96.17–99.28
CIN3 or worse						
AHPV negative	0.31	0.17–0.57	3.1	1.7–5.7	99.69	99.43–99.83
HC2 negative	0.22	0.10–0.49	2.2	1.0–4.9	99.78	99.51–99.90
LBC negative	0.93	0.29–3.02	9.3	2.9–30.2	99.07	96.98–99.71

[a]Note the NPV is estimated excluding the risk among those attending the second round of screening.

Longitudinal Performance of the AHPV Test

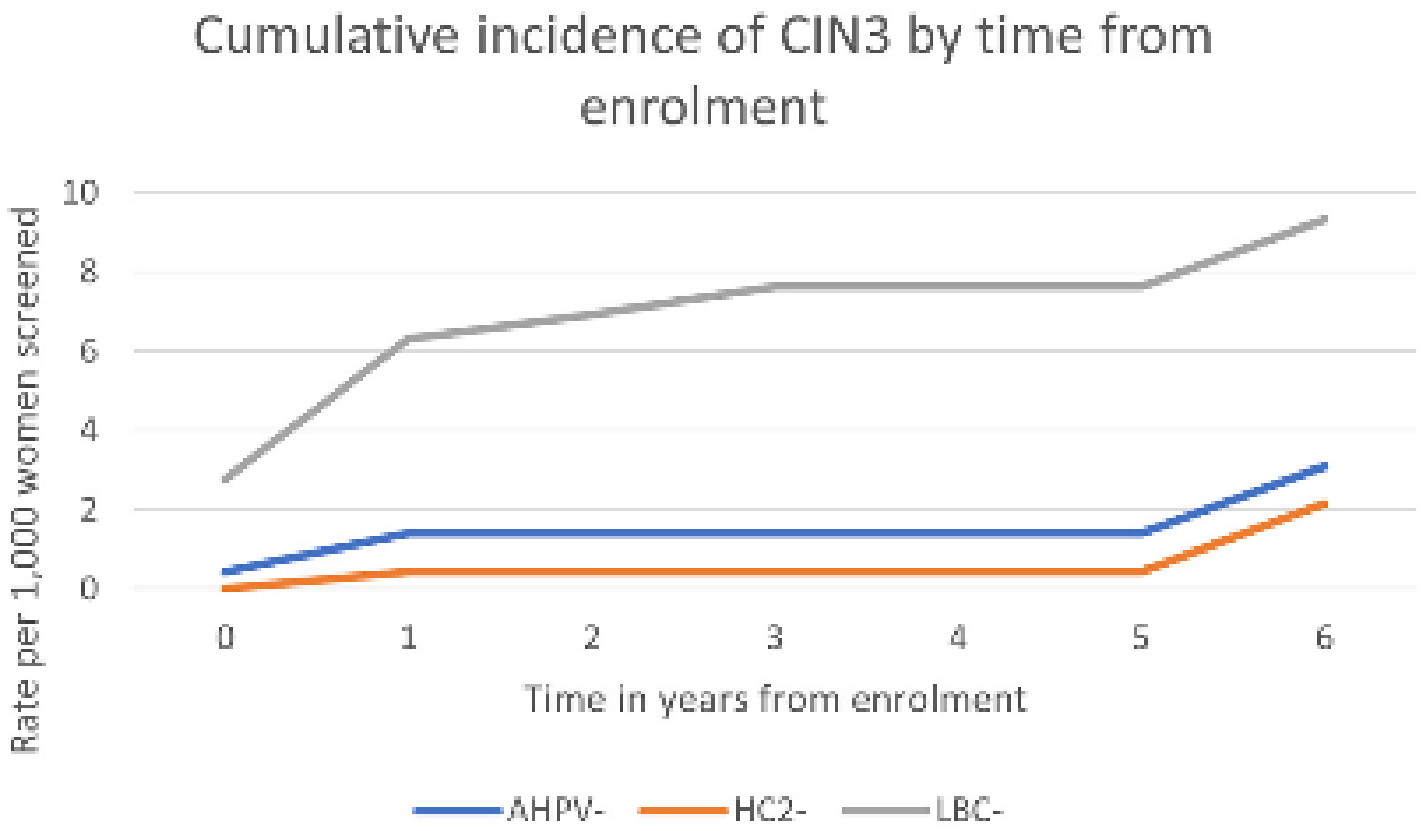


FIG 3 Rate of CIN3+ per 1,000 women screened following a negative baseline test result. Follow-up visits should have been annual up to 5 years for those with a positive test result at baseline and at 6 years for those with triple negative baseline test results.

IMPORTANT CLINICAL PERFORMANCE ISSUES THAT INFORM IMPLEMENTATION DECISIONS

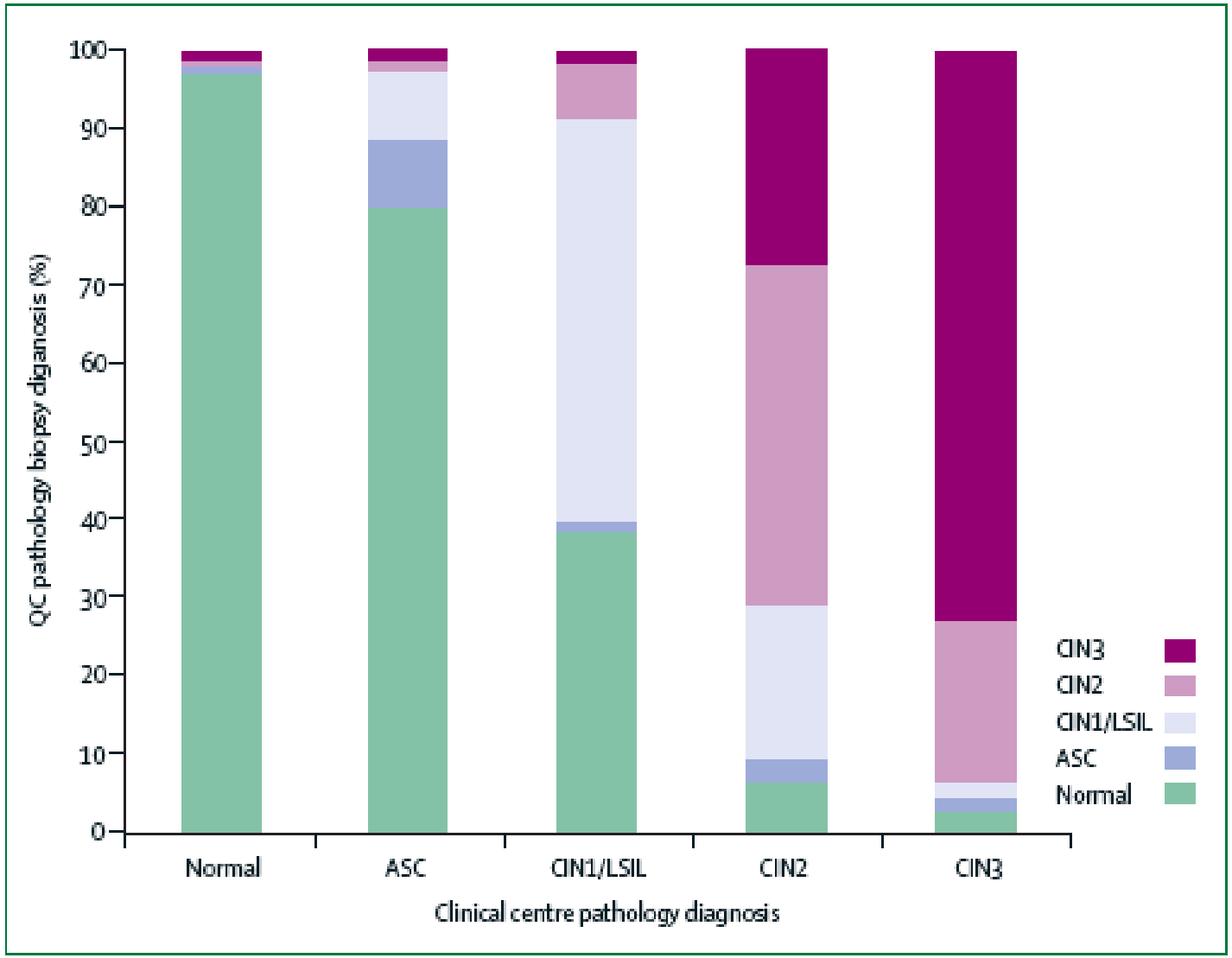


Figure 7: A comparison of community pathology biopsy diagnoses to quality control pathology review diagnoses

www.thelancet.com Vol 370 September 8, 2007 Schiffman

CADTH Health Technology Assessment/ Optimal Use – Devices
HPV Testing for Primary Cervical Cancer Screening

Table 8: Comparative Sensitivity and Specificity – HPV Tests versus Cytology for the Detection of CIN2+

Test	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Number of Studies
Cochrane[38]			
HC2 (1pg/mL) [all ages]	92.6 (89.6 to 95.3)	89.3 (87 to 91.2)	25
HC2 (1pg/mL) [>30 years]	93.9 (89.3 to 96.6)	91.3 (88.9 to 93.2)	2
Conventional cytology (ASCUS+)	65.9 (54.9 to 75.3)	96.3 (94.7 to 97.4)	16
LBC (ASCUS+)	75.5 (66.6 to 82.7)	91.9 (90.1 to 90.5)	15
Conventional cytology (LSIL+)	62.8 (46.8 to 76.5)	97.7 (96.1 to 98.7)	9
LBC (LSIL+)	70.3 (59.7 to 79.1)	96.2 (94.6 to 97.4)	10
Aptima	92.7 (31.7 to 99.7)	93.3 (47.3 to 99.5)	3
Cobas	NP	NP	2
PCR (13+ hr types)	NP	NP	6

Table 9: Comparative Sensitivity and Specificity – HPV Tests versus Cytology for the Detection of CIN3+

Test	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Number of Studies
Cochrane[38]			
HC2 (1pg/mL)	96.5 (94 to 97.9)	89.2 (86.7 to 91.3)	15
Conventional cytology (ASCUS+)	70.3 (57.9 to 80.3)	96.7 (94.6 to 98.0)	9
LBC (ASCUS+)	76.0 (64.7 to 84.5)	91.2 (90.1 to 90.5)	13
Conventional cytology (LSIL+)	74.4 (67.8 to 80.1)	96.9 (94.9 to 98.1)	5
LBC (LSIL+)	71.9 (61.2 to 76)	96.1 (93.5 to 97.6)	5
Aptima	96 (72.9 to 99.5)	92.8 (86.2 to 96.3)	4
Cobas	NP	NP	2
PCR (13+ hr types)	NP	NP	4
PCR (10-11 hr types)	NP	NP	1
HIQA[b]			
HC2 (1pg/mL)	98.2 (96.7 to 99.1)	87.6 (78.7 to 93.2)	20
Conventional cytology	71.9 (53.6 to 85.7)	96.3 (92.1 to 98.2)	9
LBC	85.0 (53.2 to 96.9)	92.6 (75.5 to 98.2)	6
Combined	78.0 (63.5 to 88.4)	95.1 (91.6 to 97.3)	15

ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia ; HC2 = Hybrid Capture 2; HIQA = Health Information and Quality Authority; LSIL = low-grade squamous intraepithelial lesion; mL = milliliter; PCR = polymerase chain reaction; pg = picograms

Table 47: Sensitivity and Specificity of Cytology and HPV Tests (Adjusted for Verification Bias)

Systematic Reviews

Test	CIN2+					CIN3+				
	Sensitivity (%)		Specificity (%)		Number of studies	Sensitivity (%)		Specificity (%)		Number of studies
	Range	Pooled (95% CI)	Range	Pooled (95% CI)		Range	Pooled (95% CI)	Range	Pooled (95% CI)	
Cochrane (2017)[38]										
CC or LBC (ASCUS+)	34 to 94	72.2 (57.5 to 83.3)	77 to 99	93.6 (88.9 to 96.4)	8	NR	NR	NR	NR	0
HC2 (1 pg/mL)[a]	67 to 97	89.0 (81.1 to 93.9)	64 to 95	88.6 (84.2 to 91.9)	12	NR	NR	NR	NR	0

Primary Studies Published after Cochrane[38]

Study (year) (n)	CIN2+		CIN3+	
	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
LBC (ASCUS+)				
Iftner (2015)[68] (n = 9,451)	39.5 (29.4 to 49.5)	98.4 (98.1 to 98.7)	49.8 (34.7 to 64.9)	NR
Wright (2015)[68] (n = 40,901)	40.6 (36.1 to 45.1)	97.3 (97.1 to 97.5)	47.8 (41.6 to 54.1)	97.1 (96.9 to 97.2)
HC2 (1 pg/mL)				
Iftner (2015)[68] (n = 9,451)	93.2 (87.1 to 99.2)	94.9 (94.1 to 95.7)	100 (91.8 to 100)	NR
Aptima				
Iftner (2015)[68] (n = 9,451)	87.8 (80.2 to 95.5)	96.1 (95.5 to 96.7)	90.9 (81.1 to 100)	NR
Cobas				
Wright (2015)[68] (n = 40,901)	69.1 (63.7 to 74.4)	94.0 (93.8 to 94.3)	76.1 (70.3 to 81.8)	93.5 (93.3 to 93.8)

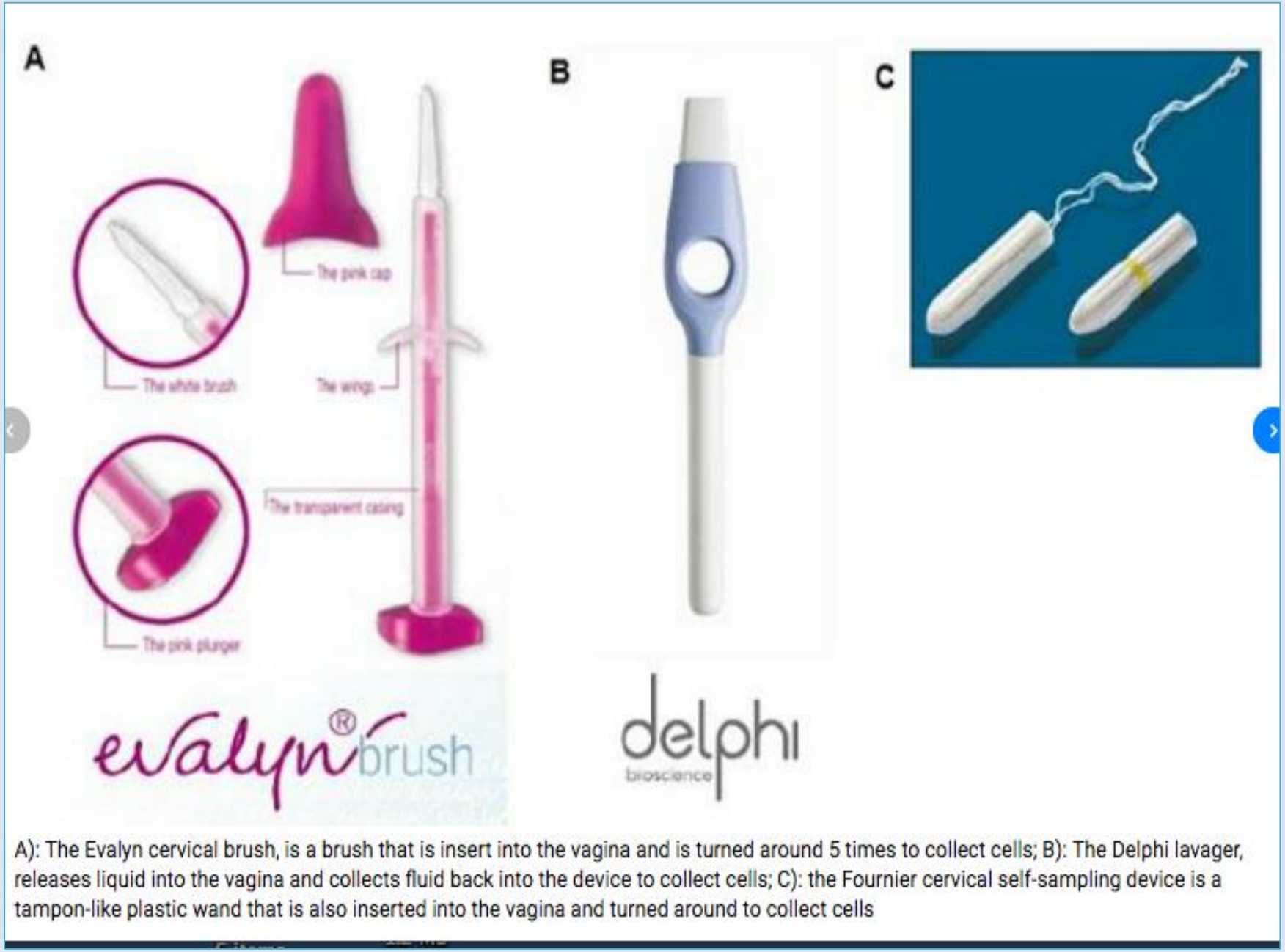
ASCUS = atypical squamous cells of undetermined significance; CC = conventional cytology; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; LBC = liquid-based cytology; NR = not reported

[a] The pooled sensitivity and specificity of HC2 are 87.8% (95% CI 79.8% to 92.9%) and 88.8% (95% CI 84.3% to 92.1%) respectively if the statistics from Sankaranarayanan 2004a in the Cochrane review was corrected and the diagnostic test accuracy was pooled based on a bivariate random-effects model from the *mada* package within R environment.

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

HPV Self-Sampling for Primary Cervical Cancer Screening: A Review of Diagnostic Test Accuracy and Clinical Evidence

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 19, 2018
Report Length:	31 Pages



A): The Evalyn cervical brush, is a brush that is insert into the vagina and is turned around 5 times to collect cells; B): The Delphi lavager, releases liquid into the vagina and collects fluid back into the device to collect cells; C): the Fournier cervical self-sampling device is a tampon-like plastic wand that is also inserted into the vagina and turned around to collect cells

HerSwab

Conclusions and Implications for Decision or Policy Making

- Self-sampled HPV tests were similarly sensitive and specific to clinician-sampled HPV tests if certain types of HPV tests were used, such as Cobas (tested in one primary study[22]),GP5+/6+PCR, and SPF10 PCR (both meta-analyzed in the SR by Arbyn et al.[16]).
- The most widely examined test, HC2, was less sensitive and less specific with self-sampled specimens.[16]

Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses

Marc Arbyn,[1] Sara B Smith,[2] Sarah Temin,[3] Farhana Sultana,[4,5] Philip Castle,[2,6] on behalf of the Collaboration on Self-Sampling and HPV Testing

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tests performed on self samples are less sensitive and less specific than tests performed on clinician samples when using a high-risk human papillomavirus (hrHPV) assay based on signal amplification

Response rates for hrHPV testing are higher for self sampling kits than for conventional invitations

WHAT THIS STUDY ADDS

Tests performed on self samples are similarly sensitive and slightly less specific than tests performed on clinician samples when using a hrHPV assay based on polymerase chain reaction

Response rates for hrHPV testing continue to be higher for self sampling kits than for conventional invitations

the bmj | *BMJ* 2018;363:k4823 | doi: 10.1136/bmj.k4823

Table 1 | Pooled relative sensitivity and specificity of high-risk human papillomavirus (hrHPV) assays based on signal amplification (SA) and polymerase chain reaction (PCR) on self samples versus clinician samples

			Ratio (95% CI)			
Assay	Outcome	No of studies	Sensitivity	Specificity	Test positivity	PPV
SA	CIN2+	23	0.85 (0.80 to 0.89)*	0.96 (0.93 to 0.98)*	1.14 (1.05 to 1.24)	0.71 (0.62 to 0.82)
	CIN3+	9	0.86 (0.76 to 0.98)*	0.97 (0.95 to 0.99)*		0.65 (0.57 to 0.78)
PCR	CIN2+	17	0.99 (0.97 to 1.02)	0.98 (0.97 to 0.99)*	1.00 (0.94 to 1.06)	0.97 (0.90 to 1.04)
	CIN3+	8	0.99 (0.96 to 1.02)	0.98 (0.97 to 0.99)*		0.90 (0.78 to 1.05)

PPV=positive predictive value; CIN2+=cervical intraepithelial neoplasia of grade 2 or worse; CIN3+=cervical intraepithelial neoplasia of grade 3 or worse.
*Statistically significantly different from unity.

THE HEALTH SYSTEM OUTCOMES AND COST EFFECTIVENESS WITH PRIMARY HPV SCREENING

Table 6: HPV DNA Testing in Canada

	Capacity in which HPV DNA testing is being used	Current status of implementation of HPV testing for primary screening
NU[†]	N/A	No current plans
NWT[†]	Triage in women	No current plans
YK	No organized screening program available	
BC	Post treatment	Under consideration
AB	Triage in women Reflex HPV test for ASCUS at age 30 and LSIL at age 50	No current plans
SK	Pilot trial (for gynecologist to use only when requested, not a pilot for primary screening)	No current plans
MB	Pilot trials/research Follow-up for research Personal requests Triage in women – under consideration	No current plans, continue to advocate for HPV testing for primary screening
ON	Triage in women (HPV DNA testing is not yet funded, but current recommendations include option to triage ASCUC with HPV testing) Frequent ad hoc use on a patient pay basis and available in some hospital-based colposcopy units for exit testing	Actively planning implementation in screening and colposcopy
QC[†]	Triage in women ≥ 30 with ASCUC	Reviewing the possibility of using HPV as a primary screening method.
NB	Triage in women ≥ 30 with ASCUC or women ≥ 50 with LSIL	No current plans
NS	Colposcopy clinic	No current plans
PEI	Triage in women > 30 with ASCUS and no previous abnormal Pap Follow-up on negative cytology and positive HPV	No current plans
NL	Pilot trials/research Triage in women > 30 with ASCUS	No current plans

† No organized screening program. Responses refer to opportunistic cervical cancer screening.

Using the Cancer Risk Management Model to evaluate the health and economic impacts of cytology compared with human papillomavirus DNA testing for primary cervical cancer screening in Canada

C. Popadiuk MD,* C.L. Gauvreau PhD,† M. Bhavsar MPH,† C. Nadeau PhD,‡ K. Asakawa PhD,‡ W.M. Flanagan BM,‡ M.C. Wolfson PhD,§ A.J. Coldman PhD,† S. Memon MBBS MPH,† N. Fitzgerald MA,† J. Lacombe MSc,† and A.B. Miller MD||

Curr Oncol. 2016 Feb;23(S1):S56-S63

HPV/Cervical Cancer Model: Conceptual Framework

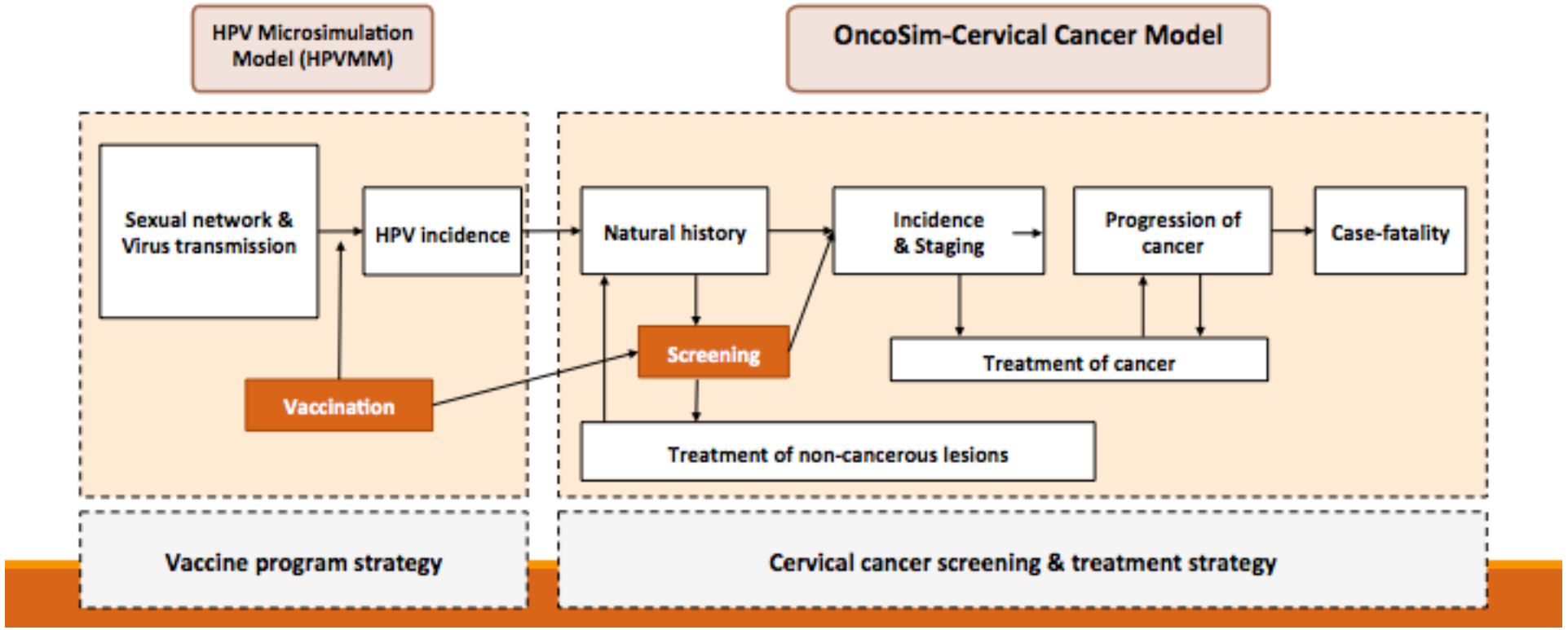


TABLE III Health and resource utilization outcomes[a] projected for 2046 using the Cancer Risk Management Model

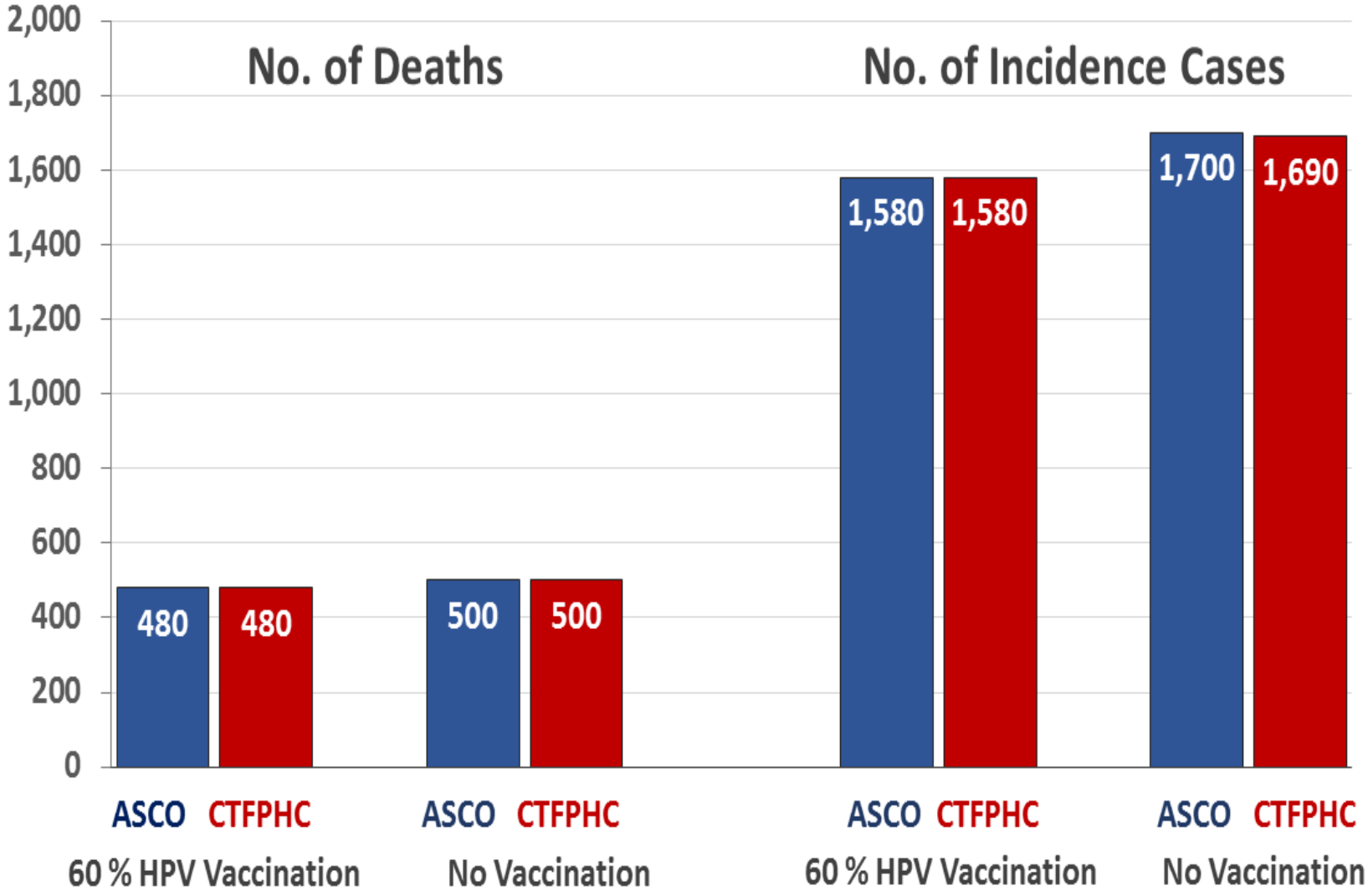
Scenario	Difference compared with reference scenario [*n* (%)]			
	Incident	Deaths	Colposcopies	Screens
Cytology (25×3)	Reference[b]			
Cytology (21×3)	–10 (1)	–10 (1)	15,000 (10)	163,000 (6)
HPV (30×3)	–180 (12)	–70 (14)	–56,000 (37)	–194,000 (7)
HPV (30×5)	1 (0)	–10 (1)	–82,000 (55)	–1,195,000 (43)
HPV (30×7.5)	180 (13)	50 (10)	–96,000 (64)	–1,619,000 (58)
HPV (30×10)	330 (23)	100 (20)	–110,000 (74)	–1,819,000 (65)
ABS (21×3; 30×3)	–210 (14)	–80 (16)	–19,000 (13)	217,000 (8)
ABS (21×3; 30×5)	–20 (2)	–10 (3)	–45,000 (30)	–771,000 (28)
ABS (21×3; 30×7.5)	140 (10)	30 (6)	–59,000 (39)	–1,196,000 (43)
ABS (21×3; 30×10)	290 (20)	80 (17)	–72,000 (48)	–1,388,000 (50)
ABS (25×3; 30×3)	–200 (14)	–80 (15)	–35,000 (23)	52,000 (2)
ABS (25×3; 30×5)	–20 (1)	–10 (2)	–61,000 (41)	–927,000 (33)
ABS (25×3; 30×7.5)	160 (11)	40 (7)	–74,000 (49)	–1,343,000 (50)
ABS (25×3; 30×10)	300 (21)	100 (17)	–87,000 (58)	–1,542,000 (55)

[a] All figures in table are rounded.
[b] Incident cases, 1400; deaths, 500; colposcopies, 50,000; screens, 2,801,000.
HPV = human papillomavirus; ABS = age-based sequential screening.

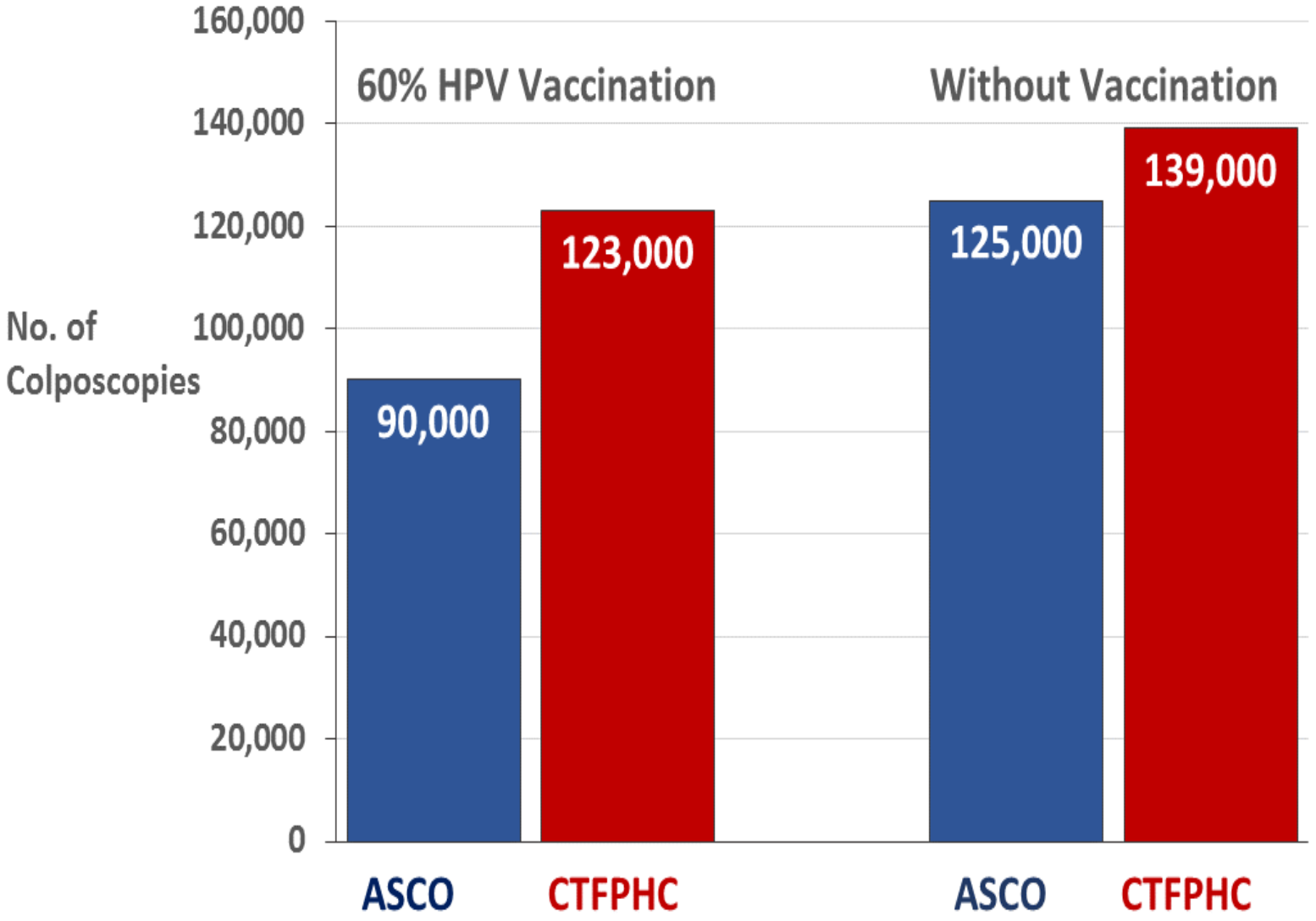
Scenario Assumptions

	SQ	ASCO-Max	CTFPHC
Screening Method	Cytology	HPV DNA Testing	Cytology
Age range	21 to 69	25 to 65	25 to 69
Frequency	Every 3 years	Every 5 years	Every 3 years
Recruitment period	2017 onward		
Screening participation	90%		
Rescreen rate	80%		
	Costs (2008 Canadian dollars)		
Colposcopy	$955.71		
Cytology screen	$59.49	n/a	$59.49
HPV DNA test	n/a	$87.79	n/a
	Vaccination Program		
Age	12		
Sex	Female		
Deployment Year	2007		
Vaccine Type ($cost)	Quadrivalent ($500 per 3-dose schedule)		
Vaccination Coverage	60%		
Proportion Protected	100%		
Degree of Protection	100% efficacy, no waning		

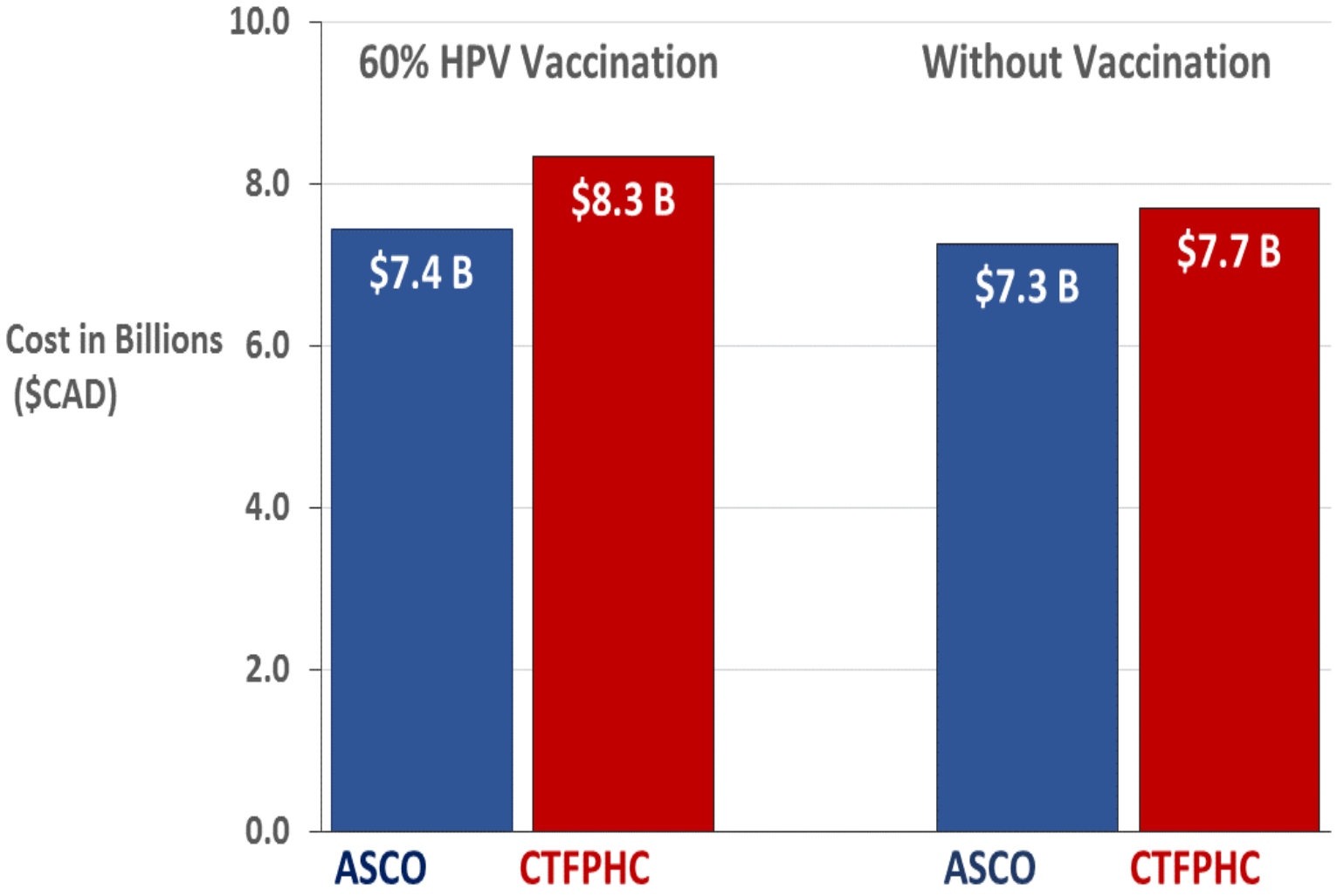
Average Annual Deaths and Incidence 2016-2036



Average Annual Colposcopies 2016-2036



Total Cost 2016-2036 in Billions $CAD
(vaccination, screening, all treatment)



Study Conclusions:

- Over the next 20 years, cervical cancer incidence and mortality are projected to be similar under either CTFPHC cytology based or ASCO HPV based guidelines. BUT colposcopy usage and total costs would be greater under CTFPHC guidelines for both vaccinated and non-vaccinated settings.
- In the vaccinated setting these differences are more pronounced, suggesting health service resource utilization advantages for 5-yearly HPV testing in the Canadian context.

Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries.

Int J Cancer. 2016 Dec 15;139(12):2771-2780. doi: 10.1002/ijc.30392. Simms KT[1,2], Smith MA[1,2,3], Lew JB[1,2], Kitchener HC[4], Castle PE[5,6], Canfell K[7,8,9].

Table 1. Lifetime number of screening tests for each setting. The lifetime number of tests is shown for cytology-based programs, and for new screening recommendations which use HPV testing (or based on preliminary analyses for countries yet to formulate recommendations under HPV screening).

If screened according to recommendations	Lifetime number of screening tests given cytology-based screening*	Lifetime number of screening tests given HPV-based screening*
Australia	26 [NCSP: 2-yearly ages 18–69 years][41]	10 [From 2017: 5-yearly HPV ages 25–74 years][42]
England	12 [NHS CSP: 3-yearly ages 25–49 years; 5-yearly ages 50–64 years][43]	7-8 [Preliminary analysis assuming longer intervals, HPV ages 25–64 years][18]
NZ	18** [NSU: 3-yearly cytology ages 20–69 years][44]	9 [From 2018: 5-yearly HPV ages 25–74 years][45]
USA	14–15 [ASCCP 2012: 3-yearly cytology ages 21–64 years][8]	10 [ASCCP 2012: 3-yearly cytology ages 21–29 years; 5-yearly cotesting ages 30–64 years][8]

*The estimated lifetime number of tests in each country is based on the assumption that women will attend cervical screening in line with country-specific recommendations for screening start-age, interval and screening end-age. We do not take into account additional tests women may experience due to abnormal results.
**The first two tests in women who have initiated cervical screening are recommended to be one year apart.

Int. J. Cancer: **139**, 2771–2780 (2016)

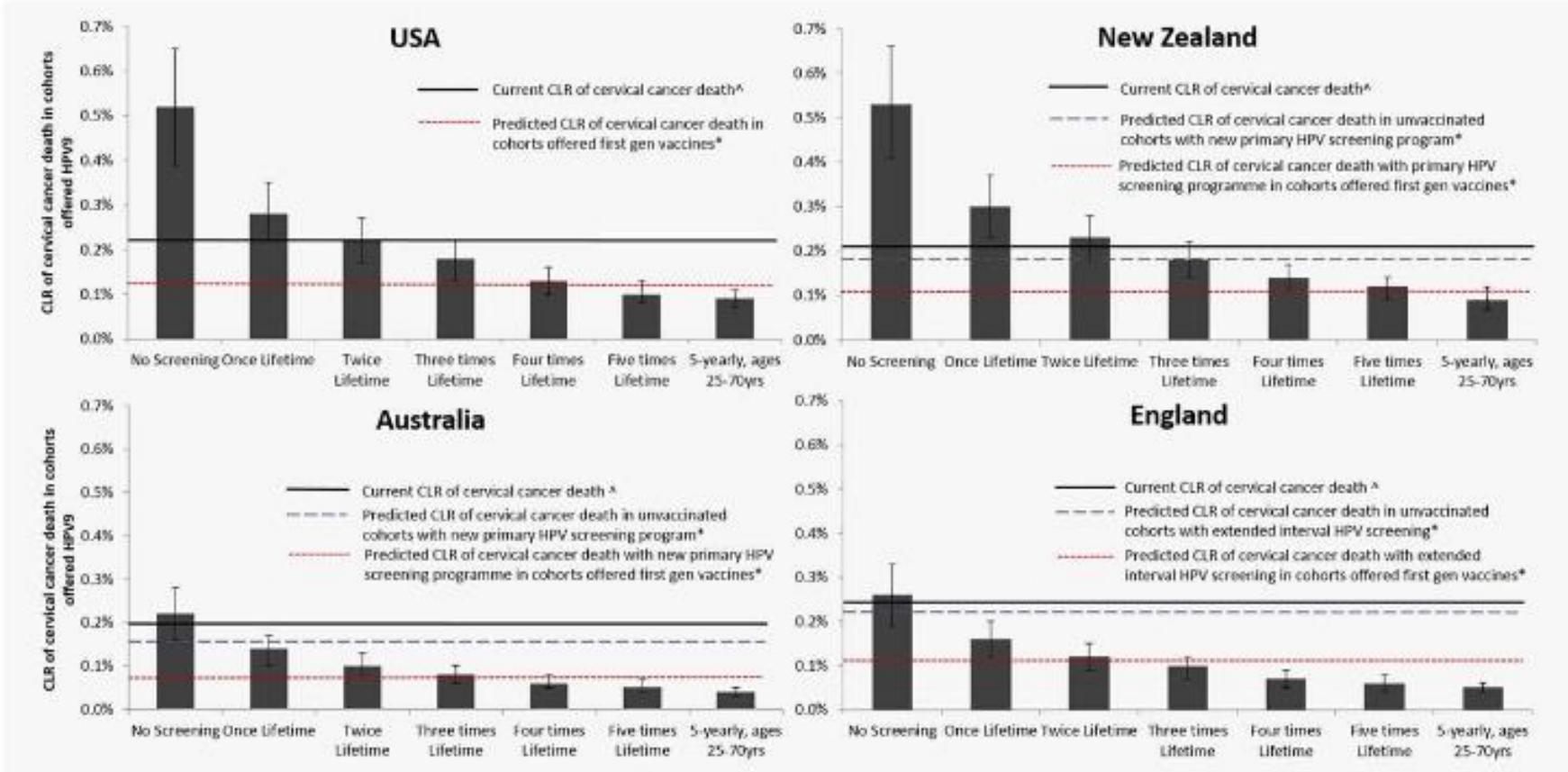


Figure 2. Predicted CLR of cervical cancer death in cohorts offered the nonavalent vaccine for the various screening strategies in each country, benchmarked to the current risks in unvaccinated women and predictions for cohorts offered first-generation quadrivalent vaccines in the four countries (HPV2/4 benchmark assumes that current levels of vaccine uptake and screening practices are retained). ^National cancer registries informed the rates for USA,[26] New Zealand,[25] Australia[27] and England.[28] * Estimates based on model predictions for England,[18] Australia[5] and New Zealand.[29] For the USA, we assumed ~40% reduction of HPV4-included types based on vaccine uptake and that HPV4-included types are responsible for 78% of cervical cancers, resulting in a decrease in CLR incidence of 30%.

Table 3. Summary of the optimal screening strategy in each country according to the various benchmarks

	Benchmark 1 Equivalence to current CLR of cervical cancer death in unvaccinated cohorts + current screening	Benchmark 2 Equivalence to predicted CLR of cervical cancer death in HPV2/4 cohorts + current screening	Benchmark 3 Most cost-effective approach
USA	2× lifetime	4–5× lifetime	4× lifetime
New Zealand	2–3× lifetime (benchmarked to both current cytology screening and new HPV screening program)	5× lifetime or 5-yearly screening (benchmarked to new HPV screening program)	5× lifetime
Australia	1× lifetime (benchmarked to new HPV screening program; no screening if benchmarked to current screening program)	3–4× lifetime (benchmarked to new HPV screening program)	2× lifetime (4× lifetime cost-effective at WTP>$60,000/LYS)
England	No screening (benchmarked to both current cytology screening and new HPV screening program)	2–3× lifetime (benchmarked to new HPV screening program)	4× lifetime

THE FUTURE POSSIBILITIES OF HPV TESTING

Elimination of Cervical Cancer, 2018

The Secretary General of the WHO, Tedros Gebreysus:

"I made a commitment to support the global elimination of cervical cancer. We have the tools to turn that commitment into a reality...we also have the political commitment."

Acceleration of Cervical Cancer Elimination
Targets for the Future

1. Promote the rapid transition and implementation to Primary HPV testing for cervical cancer screening
2. Continue to advance the importance of HPV vaccination as a concerted effort for all young boys and girls eligible through the school based programme, catch up, and men and women eligible as adults.
3. Create culturally appropriate strategies to reach the under-screened and unvaccinated eligible populations such as some Aboriginal communities, immigrant and refugee groups, socially disadvantaged groups regarding the import of HPV elimination and each individual's role in achieving this goal.

Short Term Goals for HPV Testing

- Universal adoption for ASCUS Triage
- Universal use for test of cure in colposcopy and for patient discharge guidance to return to community care
- Implementation of primary HPV testing in Canada
- WHO Elimination of Cervical Cancer by 2030: 90% Vaccinated, 70% Screened with HPV (90% in Canada) and 90% receiving Treatment

Finally! Important Considerations for HPV Testing

- Public Education and Clear Communication: HPV is not H-Pylori!
- Keep Algorithms for HPV testing Very Simple for Health Care Providers and Participants
- Health Systems Impact – Labs, colposcopy…
- Change management requires effort and time.

Recommendations for changes to cervical screening in 2017

National Cervical Screening Program Renewal **Updated April 2015**

The Medical Services Advisory Committee (MSAC) has recommended significant changes to the National Cervical Screening Program. The new screening recommendations are now planned to come into effect in May 2017. GynaePath is committed to keeping you informed about these changes and how they will impact you and your patients.

Why have changes been recommended?

As a result of the successful, school-based HPV vaccination program, fully vaccinated women will develop less cervical disease.

With the cervical screening population now composed of both vaccinated and un-vaccinated women, the Government has undertaken a large review of available technologies and used economic modelling to determine the most advantageous screening program for all Australian women.

What are the proposed changes?

The new screening program recommends the following changes:

- HPV testing to replace conventional Pap testing as the Medicare funded screening test
- Screening to commence at age 25 and cease at age 74
- The screening interval using HPV testing to change to 5 years

A flowchart showing the proposed screening pathway is shown overleaf.

When would the changes come into play?

The new program is now scheduled to commence in May 2017 to allow sufficient time to implement changes across all components of the screening program.

What does this mean for you?

Between now and the launch of any new program, it's 'business as usual' in terms of screening women for cervical cancer. This means that two-yearly conventional Pap tests

What does this mean for your patients?

Patient reaction to the proposed changes will vary, depending on how well informed your patients are, and how comfortable they are with the current screening program. As with anything new, there is likely to be some resistance to change, especially since the education program about the need for two-yearly Pap tests has been so effective.

The Australian Government will conduct education programs for both you and your patients as part of the implementation strategy for the Renewal.

During the interim period, patients need to know what Medicare covers and what attracts a private fee. They need to be reassured that the conventional Pap test is a proven, reliable testing method. Patients also need to understand that the new five-yearly testing frequency will only apply when HPV becomes the primary screening test. Until then, Pap tests will still need to be performed every two years.

National cancer screening register delayed by poor planning: auditor-general

By political reporter Matthew Doran

Posted 29 Jun 2017, 5:22am

A series of stumbles in creating a national cancer screening service have led to a seven-month delay and a multi-million-dollar blow-out in costs, according to the auditor-general.

The National Cancer Screening Register (NCRS) was originally announced in the 2015-16 federal budget, at a cost of $148.4 million.

The aim was to draw together current bowel and cervical cancer screening databases, and give doctors and patients better reminders on when they are due for check-ups.

In May 2016, the Health Department signed a $200 million contract with Telstra to develop and run the NCSR over five years.

But auditor-general Grant Hehir has found the tender process was flawed because of poor planning, a failure by some health officials to declare conflicts of interest, and concerns Telstra has not met key security requirements.

Mr Hehir also argued the project has suffered because of "ambitious timeframes".

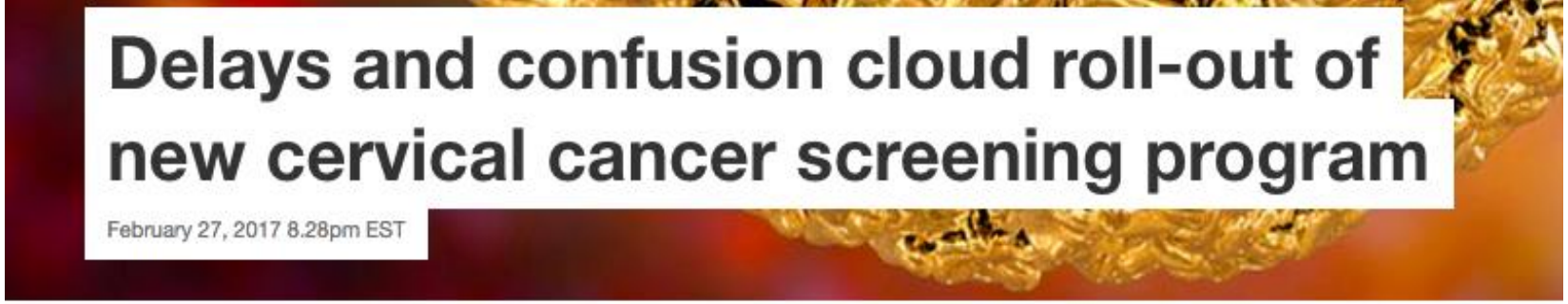
"On February 23, 2017, health released a public statement confirming that, due to the complexity of assimilating and migrating data from eight state and

PHOTO: The new system would bring together current registers for bowel and cervical cancer screenings. (bowelcanceraustralia.org)

MAP: Australia

Key points:

- Register was intended to draw together current bowel, cervical cancer screening databases
- $200 million contract awarded to Telstra in 2016
- Auditor-general's report found poor planning, failures to declare conflicts of interest among the reasons for delays and cost blow-outs



Delays and confusion cloud roll-out of new cervical cancer screening program

February 27, 2017 8.28pm EST

Women are confused about how the new test for human papillomavirus (HPV), pictured here, will help them prevent cervical cancer. Let's fix that. from w

Australia's new national cervical cancer screening program has had a bad week.

The government announced it would delay the May 1 roll-out of its new program until Dec 1, 2017. And a petition opposing the new program swept social media.

But it's not all bad news. The delay gives the Standing Committee on Screening, which is responsible for implementing the new program, the chance to engage with the public and communicate why the changes are being made and what they mean.

If the online petition is anything to go by, this is badly needed to counter the widespread misunderstanding of the new cervical screening program and the role of human papillomavirus (HPV) in causing cervical cancer.

Online petition shows women want to know more

The past week saw 70,000 people (so far) sign an online petition opposing the changes to the cervical screening program.

The letter accompanying the petition, since removed, unfortunately misrepresented the effectiveness of screening women under the age of 25, the role of HPV as the cause of cervical cancer and the rationale behind the new screening program.

The petition struck a chord and quickly gathered steam.

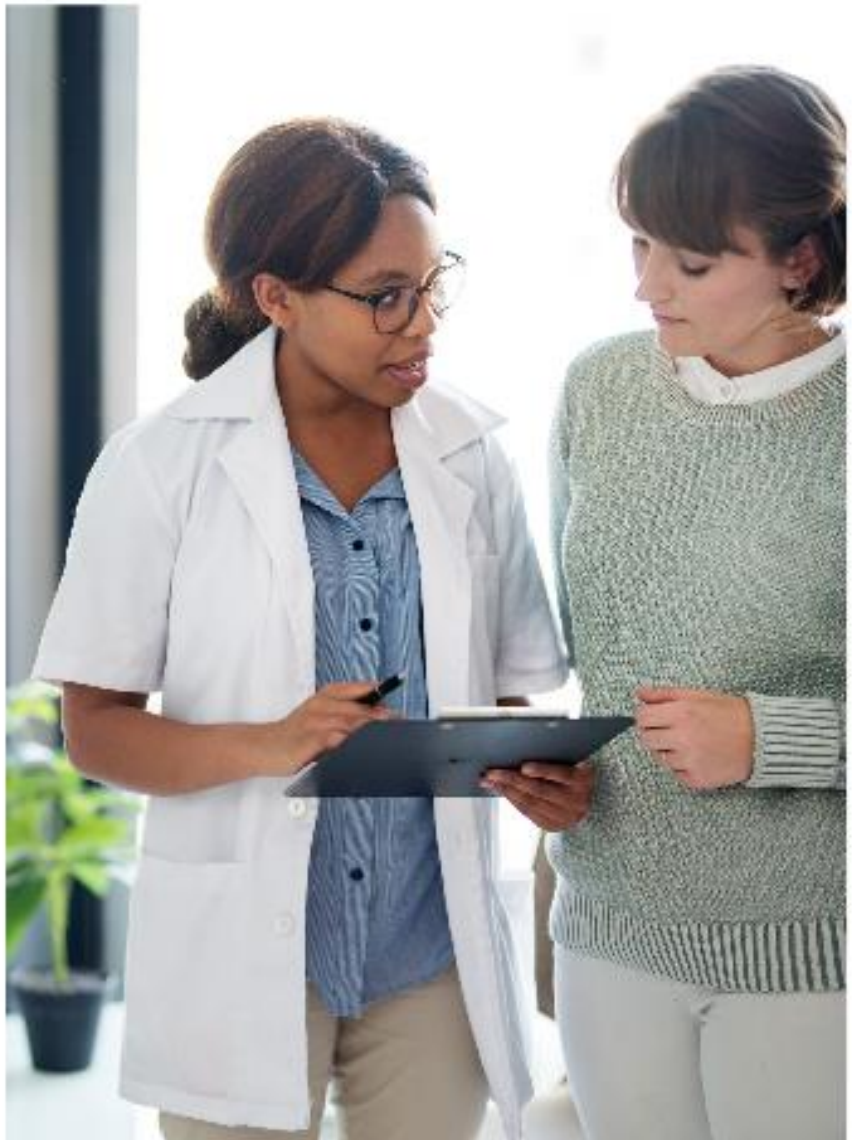
In an interview, the person behind the petition said she was motivated by "concern and worry", because "[she] didn't know about it and no one seemed to know about it", and because "[she'd] love someone to be able to get down on our level and explain the testing".

Responses to her petition indicated widespread concern about safety of the new starting age and the wider screening interval. In addition, women perceived the renewed program as a cutback – that less screening is being driven by cost-savings rather than the availability of a better test.

HPV Testing for Primary Cervical Cancer Screening

Key Messages

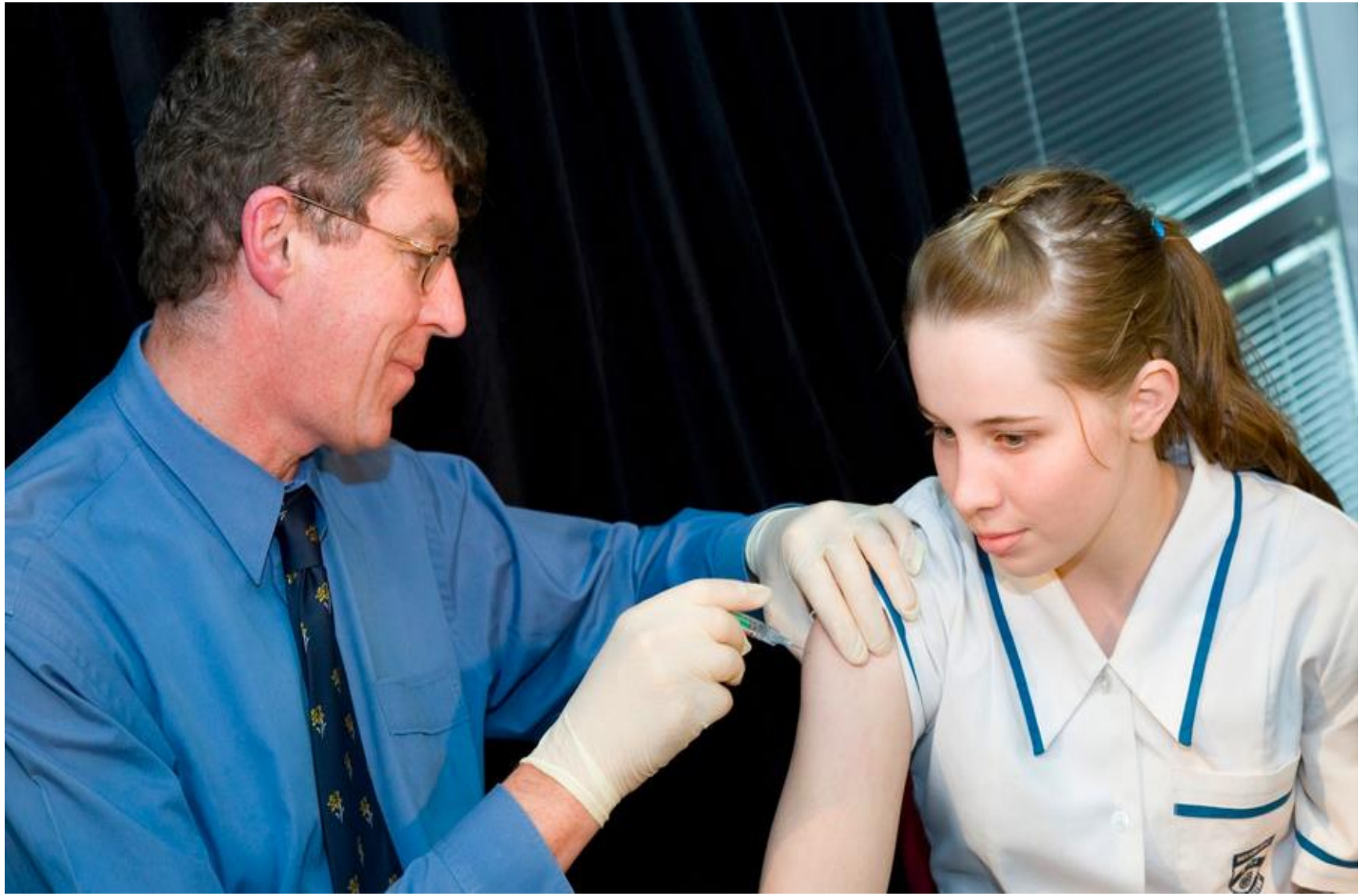
- Human papillomavirus (HPV) is the major risk factor for the development of cervical cancer; HPV testing directly detects the presence of the virus.
- The CADTH review found that HPV tests are better at detecting cancer precursors than cytology but less effective at identifying those who may not have cancer despite having HPV. Screening with HPV tests is also associated with increased referral to colposcopy compared with cytology.
- The CADTH review found that switching the primary test from cytology to HPV testing and decreasing the screening frequency decreased costs, with limited harms.
- Screening involves balancing the benefits of disease detection with the harms and burdens of screening participation, including false positives and overdiagnosis.
- A switch to HPV testing would be a large operational and cultural shift for clinicians, patients, and laboratories. Successful implementation would require appropriate planning, funding, and coordination.



"HPV-based cervical cancer screening: NOW is the time!"

- The WHO Objectives are 10 years away!!!!
- We cannot let technical operational obstacles circumvent our efforts
- Canada was a world leader for cervical cancer screening through the rapid implementation of pap testing.
- We are well positioned to achieve the WHO goals

Ian Frazer, HPV (Vaccine) Pioneer



Ian Frazer, HPV (Vaccine) Pioneer

HPV vaccine: a gift for all?

♀♂
- Oropharyngeal
- Anal

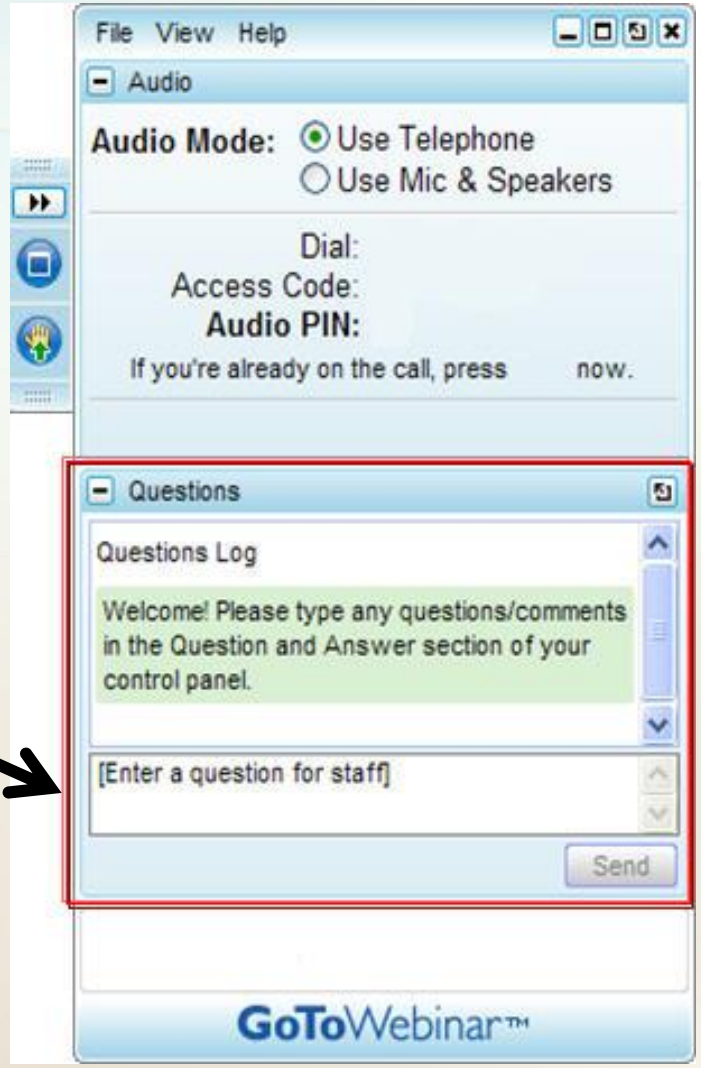
♂
- Penile

♀
- Cervical
- Vulvar
- Vaginal

Thank You for Your Attention

Question & Answer Period

Submit your text question using the Questions pane



HPV-based Cervical Screening::

Why is NOW the time?

- **Evaluation:** https://www.surveymonkey.com/r/J7N9PBQ
- **Slide Set, Video recording, HPV documents at: www.CIDCgroup.org**
- Join the **Canadian HPV Prevention Network** at: **www.CIDCgroup.org**

(it's free! Fill out the 'Contact' form)

Next CIDC Webinar: Tuesday, November 12, 2019

Topic: Accelerating Cervical Cancer Elimination

Thank you for participating!

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