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
June 26, 2019

HPV Testing in the Canadian Context

Pros, Cons and Implementation Challenges

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Moderator: Dr. Marc Steben, MD

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Family Physician, Family Medicine Group 1851

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Executive Director, Consortium for Infectious Disease Control

This educational program is made possible with support from **Hologic Canada ULC**
and with assistance by BD Diagnostics and Immunize Canada

www.CIDCgroup.org

Relevant documents available on www.CIDCgroup.org

Counselling Patients About HPV Test Results

Transmission, Screening / Testing & Vaccination

Canada's Role in Accelerating Global Elimination of Cervical Cancer

Webinar Objectives

1) Understand the benefits and limitations of HPV testing as a cervical cancer screening tool
2) Compare the performance characteristics of different HPV tests
3) Outline the lessons learned from the British Columbia randomized FOCAL Trial to assess primary HPV testing as part of organized screening program
4) Outline the array of HPV implementation challenges including the impact of HPV vaccination.

Housekeeping

How to participate:

- You can hear the audio for today's webinar via your computer by selecting "Use Mic & Speakers"
- Or, to join by phone, select "Use Telephone" in your Audio window. Info for dial in then will be displayed
- Submit your text question using the Questions pane & click 'Send' button
- Questions will be answered at the end of the presentation

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- Questions will be answered following the presentation

Note: A recording of the presentation will be made available at www.CIDCgroup.org

Slides and Video Recording

The webinar **Slides and Recording** will be archived at:
https://www.CIDCgroup.org

Evaluation Survey:
https://www.surveymonkey.com/r/986M582

Completion of survey is requested – all registered participants will receive an email with this link

Moderator

Dr. Marc Steben, MD

- Chair, Canadian HPV Prevention Network
- Family Physician, Family Medicine Group 1851

- Montreal, Quebec, Canada

Presenter

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Disclosures

Grants/contracts to my institution from Roche and Hologic

Objectives

1) Understand the benefits and limitations of HPV screening to detect cervical cancer
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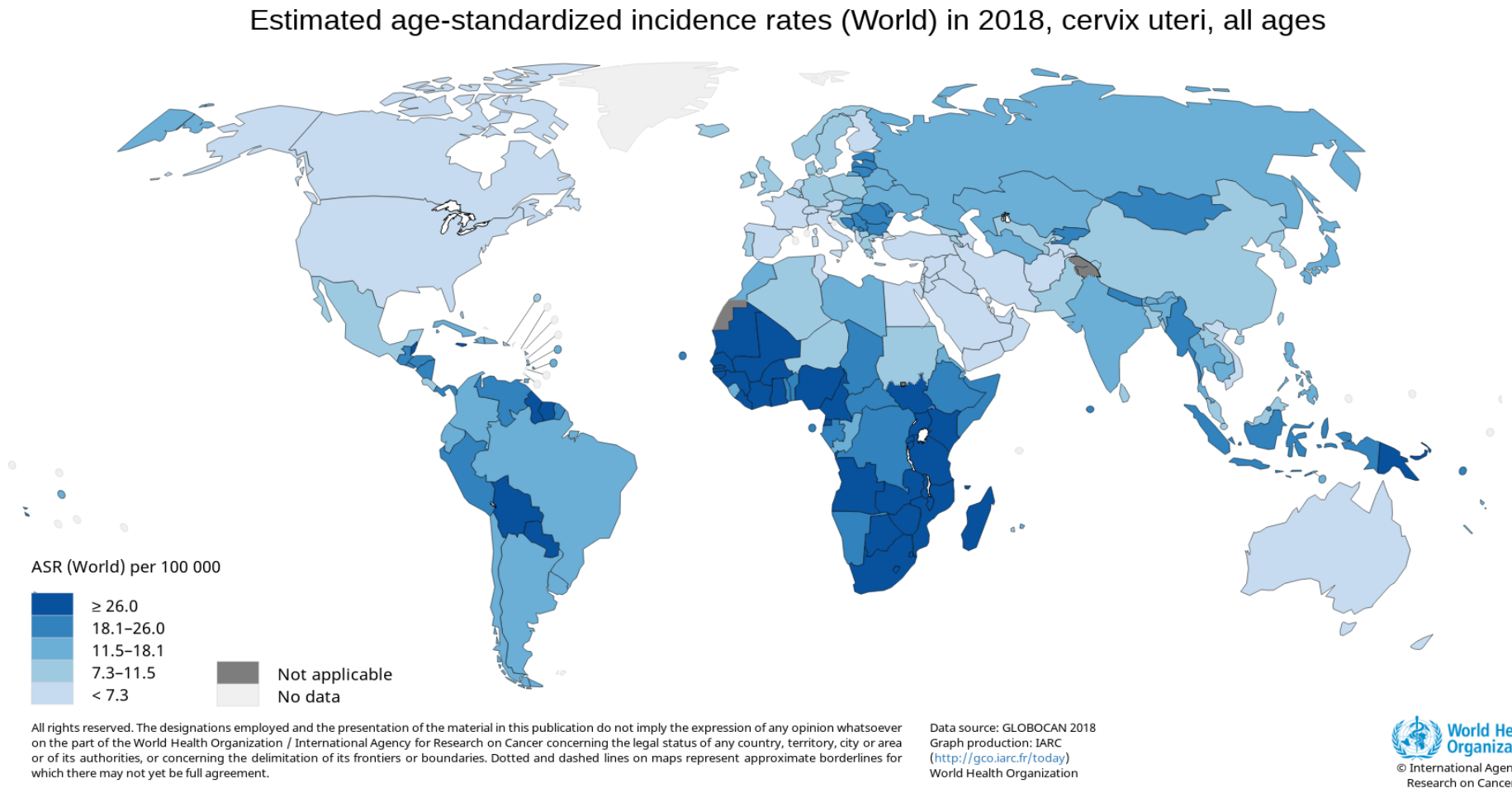
Global Cervical Cancer

(an avoidable disease associated with gross inequities)



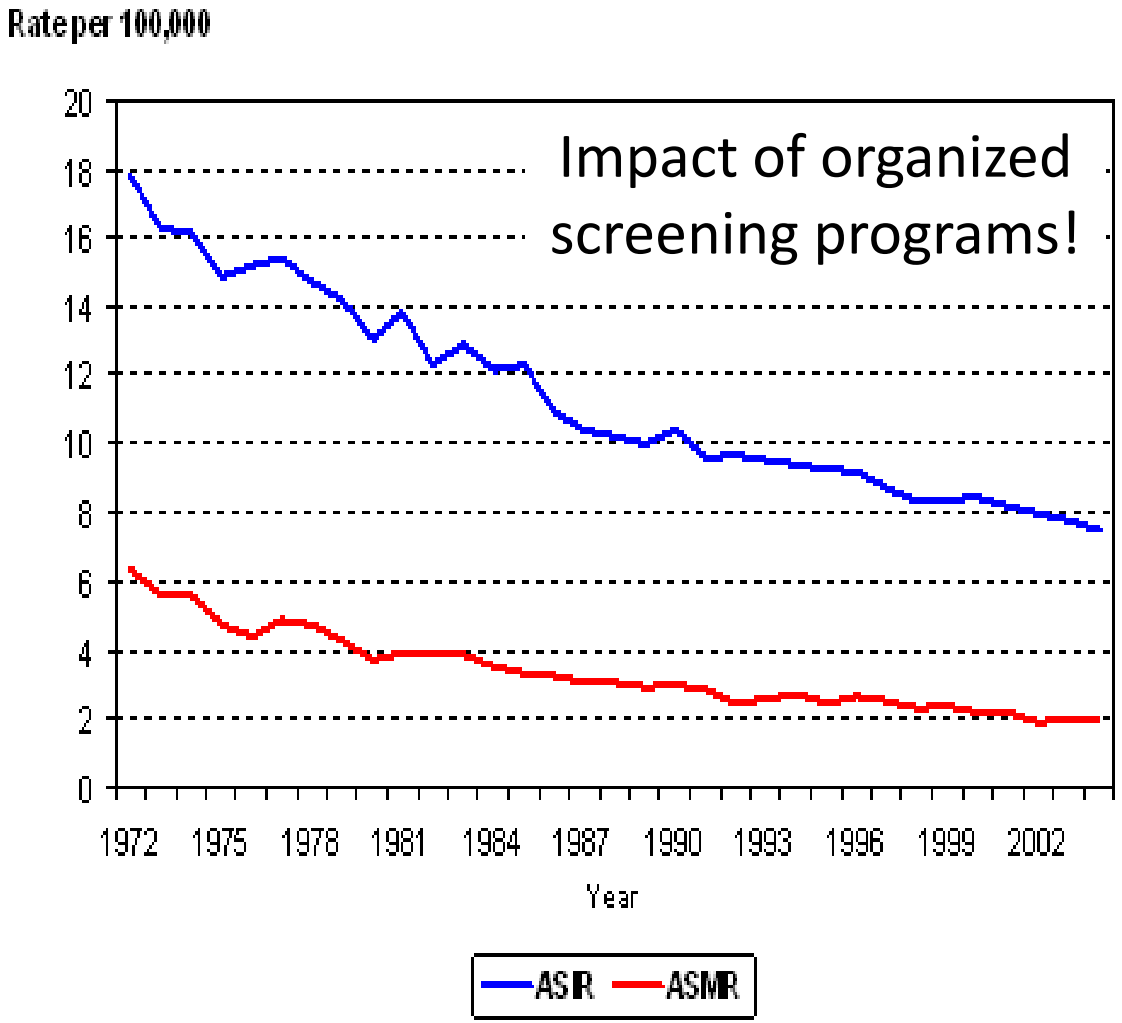
Globally in 2012: ~530,000 cases of cervical cancer diagnosed - rate 14/100,000

~85% in less developed regions

~44 M women projected to be dx in next 50 years

Simms et al.
thelancet.com/oncology
2019

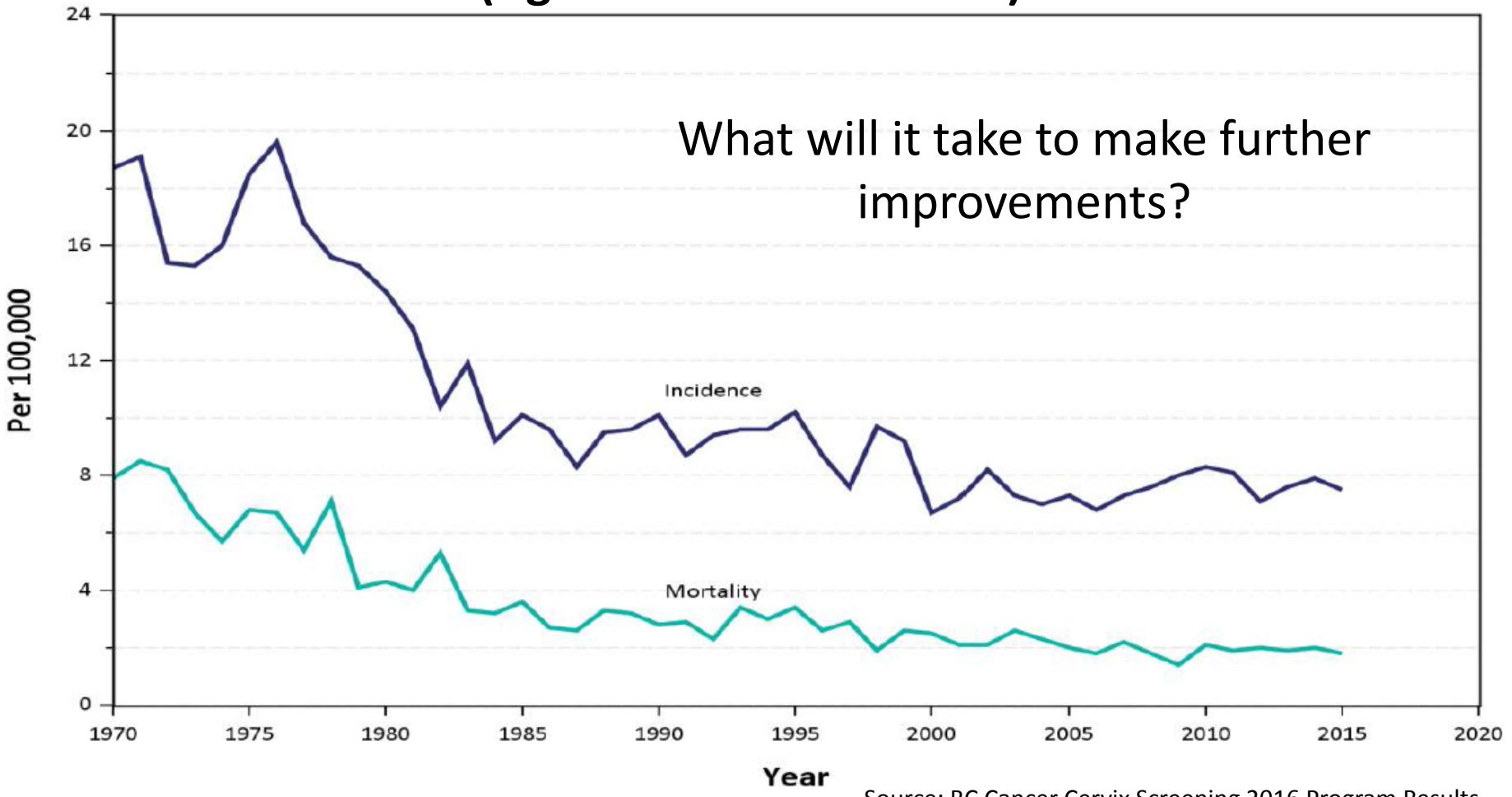
Age standardized incidence and mortality rates women cervical cancer, Canada, 1972-2004



Canada 2017:
~1,550 women were dx with cervical cancer &
~400 died

Invasive Cervical Cancer in BC

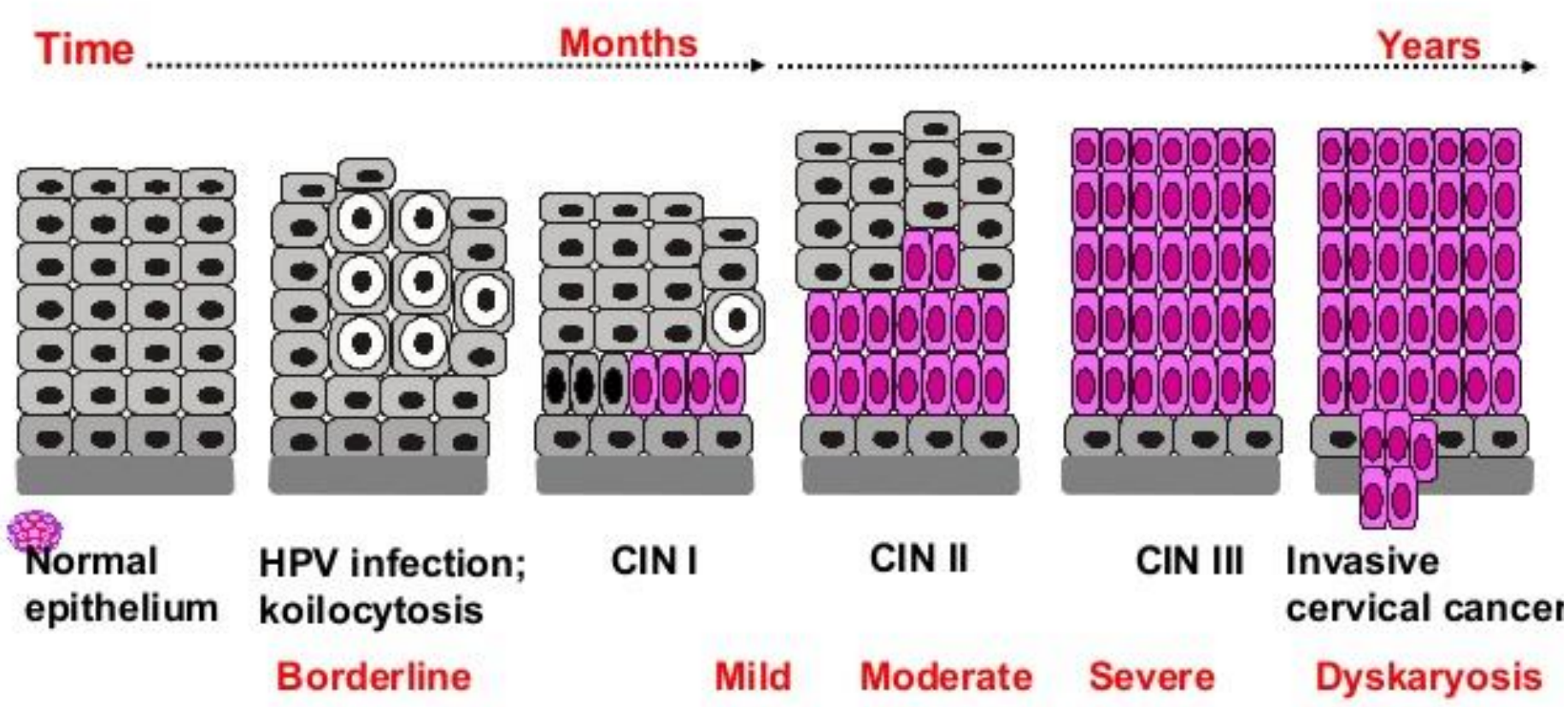
(Age Standardized Rates)



Source: BC Cancer Cervix Screening 2016 Program Results

- BC 2015: 179 invasive cervical cancers dx (~70% squamous)
- 65% of squamous and 39% of adenocarcinomas had no screening hx or were last screened >5 yrs ago

DISEASE PROGRESSION

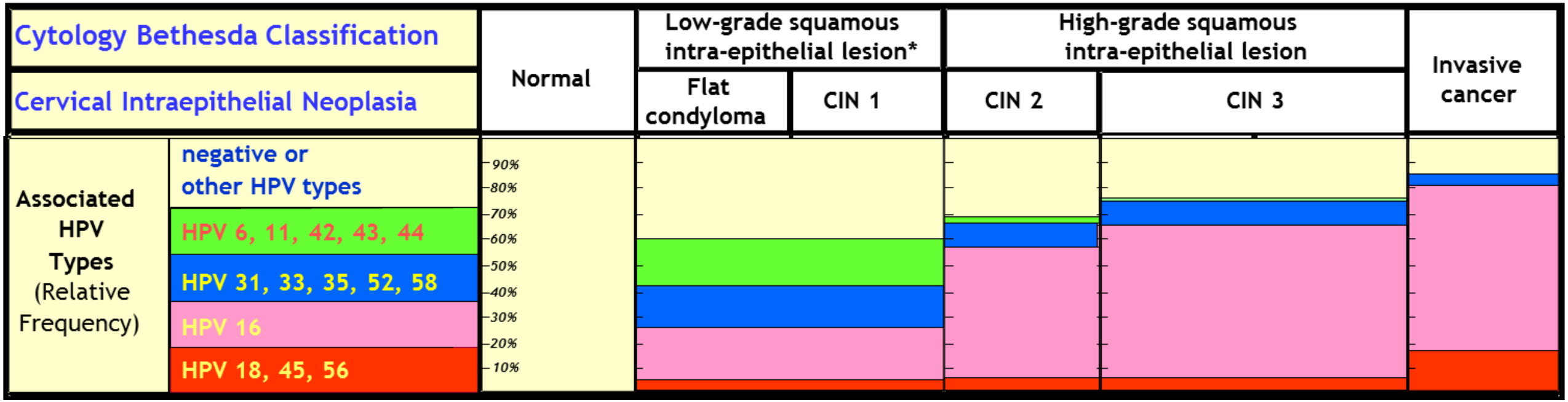


CIN I 57% CIN II 43% CIN III 32%
Approx. likelihood of regression

LifeCare center

Moscicki et al. Obstet Gynecol 2010; Motamedi et al. BMC Infectious Disease 2015

Cervical Evolution from Condyloma to Cancer



Modified from Bonnez W. Papillomavirus. In: Richman RD et al eds. Clinical Virology. 2nd ed. Washington, DC: American Society for Microbiology; 2002:557-596.

Screening Assays

- Prioritize sensitivity → reduce the risk of missing an important diagnosis
- Prioritize specificity → reduce the risk of false positives
  - whether for Dx or for management → risk of harm is too high
- To maximize screening benefits:
  - organized programs strive to provide the right test, for the right person, at the right time
  - Opportunistic screening → make do

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Analytical vs Clinical Sens & Spec

Pap → analytical & clinical sens/spec are aligned → detects the host tissue response, not the inciting agent i.e., HPV infection

Single Pap has a sens of ~55% to 60% (range 30% to 87%) to detect CIN2/CIN2+

- Sens approaches ~85% to 90% because of multiple tests over time!
- Spec for CIN2/CIN2+ is 60% to 95%
- Negative predictive value is low because Paps are insensitive → dependent on repeat testing, but the positive predictive value is high!

CIN2/CIN2+ is a clinically actionable endpoint → usually treated by excision or ablation

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Analytical vs Clinical Sens & Spec

HPV tests → analytical sens to detect HPV is ~95% & analytical spec is >99%

- Most infections "resolve" within 6 m to 2 yrs
- What really matters is the clinical sens and spec for CIN2/CIN2+

A single high-risk HPV screen has a **clinical sens** of ~95% for CIN2/CIN2+

- **Clinical spec is poor (<20%) because > 99% of infections resolve/or don't cause high grade disease (positive predictive value ~10% or lower)** (Szarewski et al. JCM 2012)
  - Age, duration of infection, genotypic oncogencity, host and other factors

Benefits of HPV screening:

- Higher sens enables earlier CIN2/CIN2+ detection
- Substantially higher negative predictive value i.e., if the HPV test is negative the CIN2/CIN2+ risk over 5 to 10 yrs is very low → extend screening intervals!

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Cervical Screening Perspective

A multipronged approach is required!

- Increase vaccine uptake
- **Improve screening uptake**
- Improve treatment
    - Chrysostomou et al. Viruses 2018 → EU cervical screening program perspective focused on HPV vaccination & population-based HPV testing

Screening:

1. Continue with Paps → unlikely to bend the curve further
2. **Primary HPV screening → potential to ↑ reach/access → self-collection!**
3. Combine HPV screening with Pap testing → "co-testing"
    - Combination improves analytical sens and clinical spec but at a much higher cost

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Lessons from the FOCAL Trial

- BC has a highly centralized cervical cancer screening program based on conventional Pap smears
  - ~460,000 women screened in 2014
  - Database/registry dates back to 1960
  - Current guidelines include tri-annual screening for women aged 25-65
  - Screening coverage **~70%** of those eligible (hysterectomy corrected)

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HPV FOCAL Trial

Human Papillomavirus (HPV) Testing FOr CerviCAL Cancer Screening

Enrollment 2008 to 2012
F/U until 2016

Ogilvie et al. 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

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FOCAL Trial Objectives

Establish the efficacy of:

Primary high-risk HPV screening (Intervention Arm)

liquid based cytology (LBC) triage of HPV positive women

vs.

Primary cytology (LBC) screening (Control Arm)

HPV triage of ASCUS (atypical squamous cells of unknown significance)

Outcome measures: CIN2+ and CIN3+ rates at 48 mo.

Determine a safe screening interval for HPV negative women

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FOCAL Trial Methods

- Population: women 25-65 yr. from Vancouver and Victoria, BC
- Cervical samples in ThinPrep® for both cytology and HPV screening (hybrid capture 2 high-risk HPV test)
- Women and providers were blinded to trial arm assignment at enrollment
- Cytology and HPV screening at one centralized laboratory
- Standardized colposcopy procedures with biopsy
- Centralized histopathology review, blinded to HPV & cytology results

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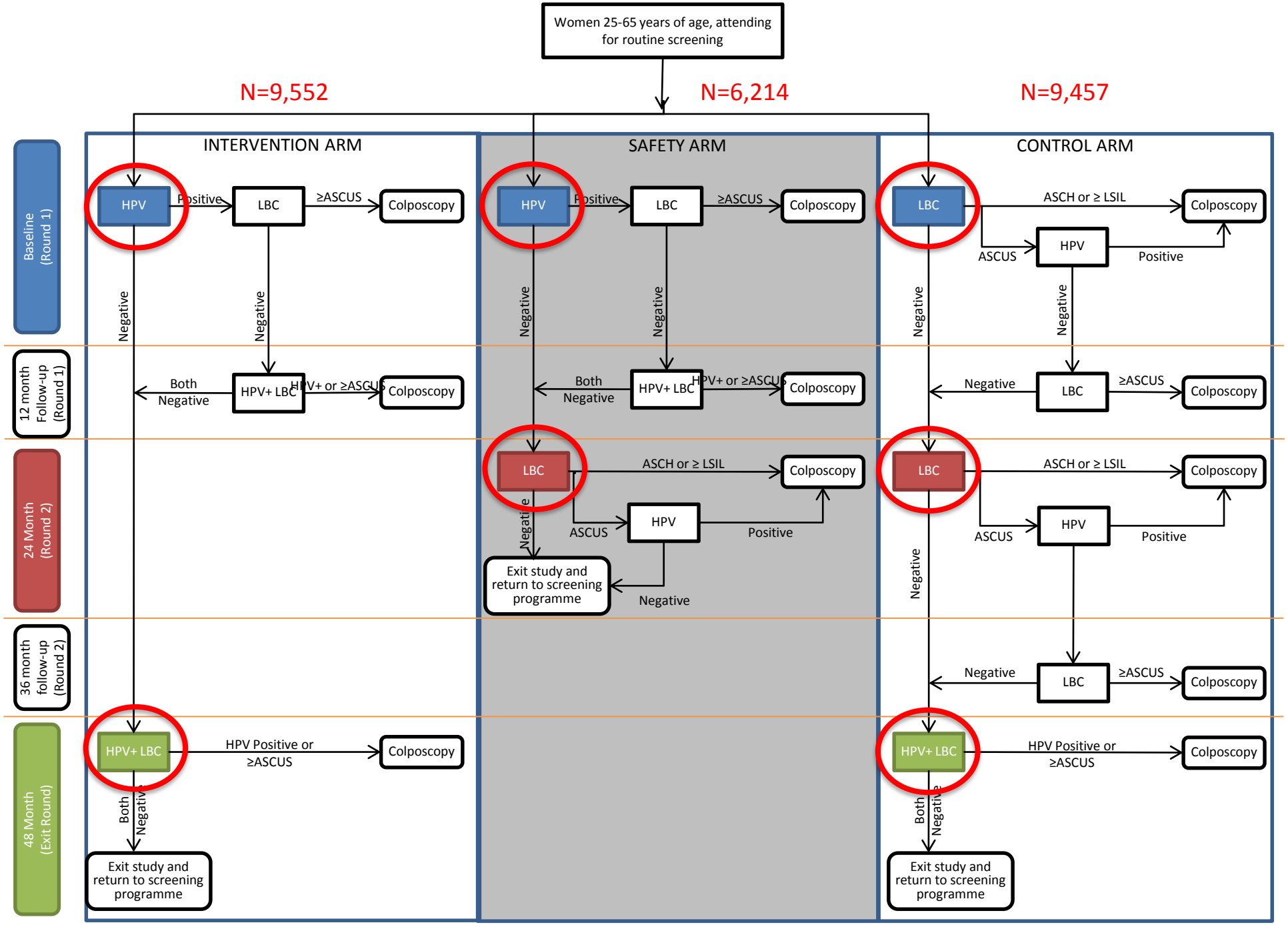
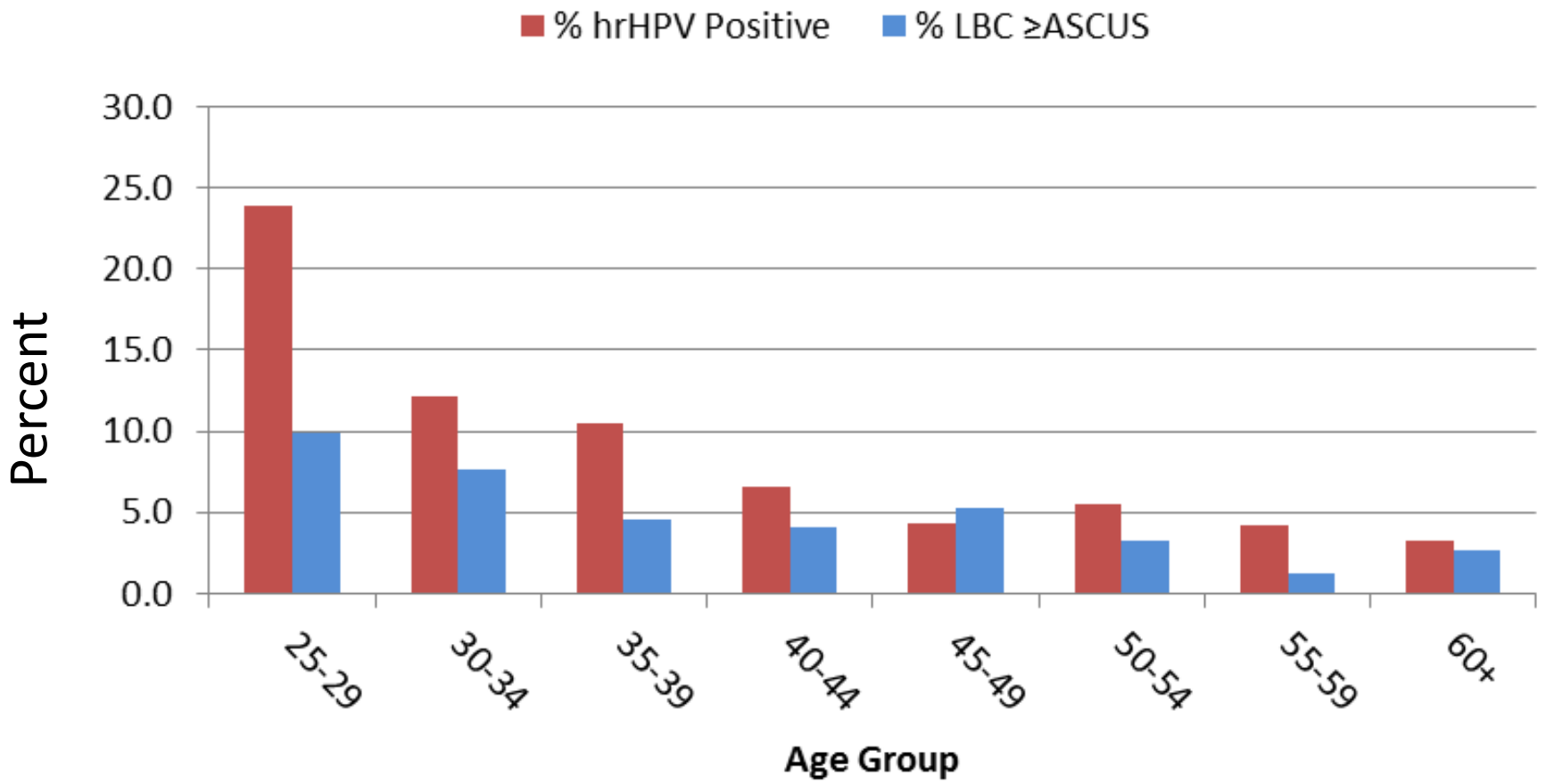

Women 25-65 years of age, attending for routine screening
N=9,552
N=6,214
N=9,457
INTERVENTION ARM
SAFETY ARM
CONTROL ARM
Baseline (Round 1)
12 month Follow-up (Round 1)
24 Month (Round 2)
36 month follow-up (Round 2)
48 Month (Exit Round)
HPV
Positive
LBC
≥ASCUS
Colposcopy
Negative
Both Negative
HPV+ LBC
HPV+ or ≥ASCUS
ASCH or ≥ LSIL
ASCUS
HPV Positive or ≥ASCUS
Exit study and return to screening programme

HPV and Cytology Rates by Age Group
(HPV FOCAL Trial Baseline Screen)

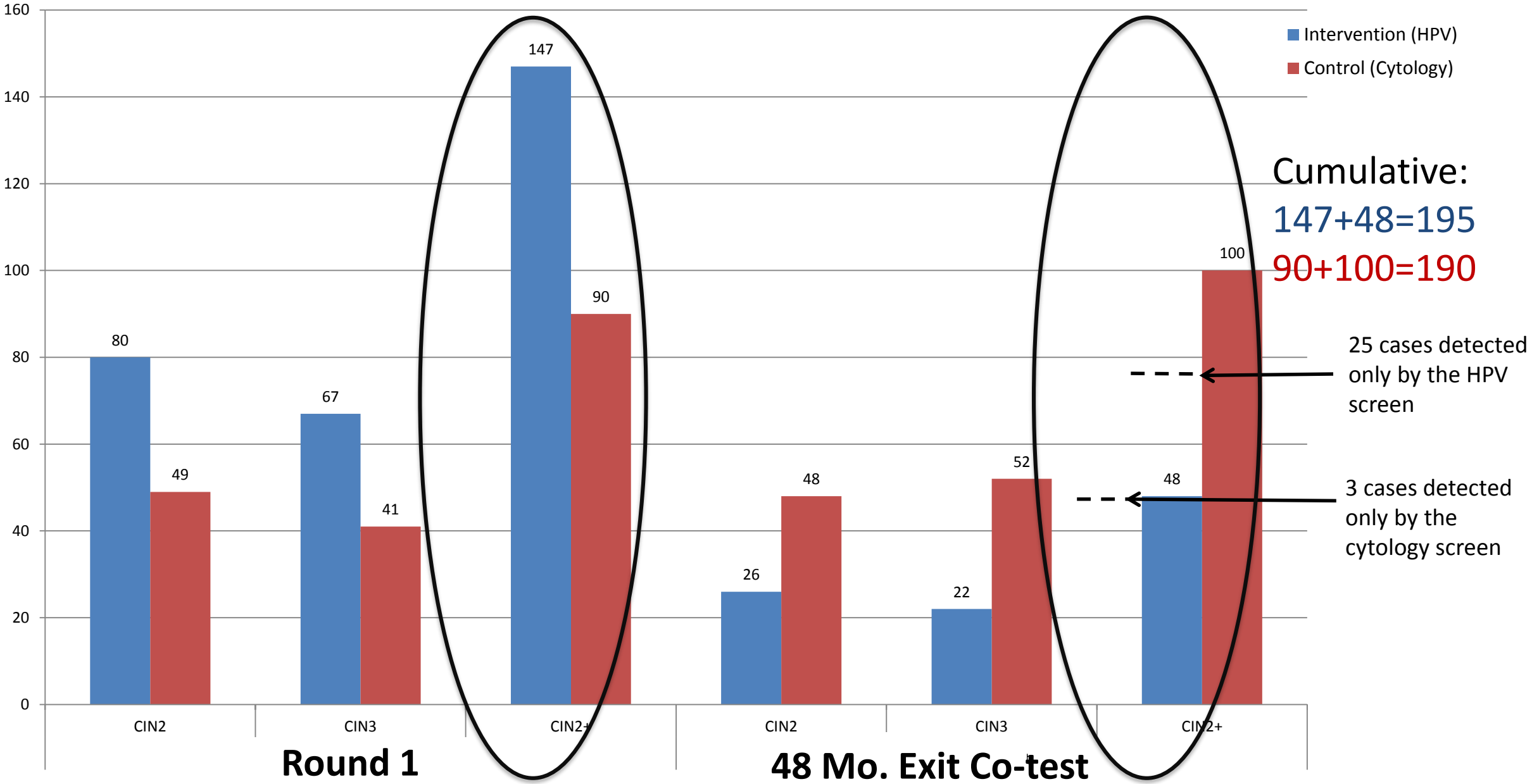


N screened: HPV - 4,131; LBC - 2,019

Overall positivity: HPV - 7.6%; LBC ≥ASCUS - 4.5%

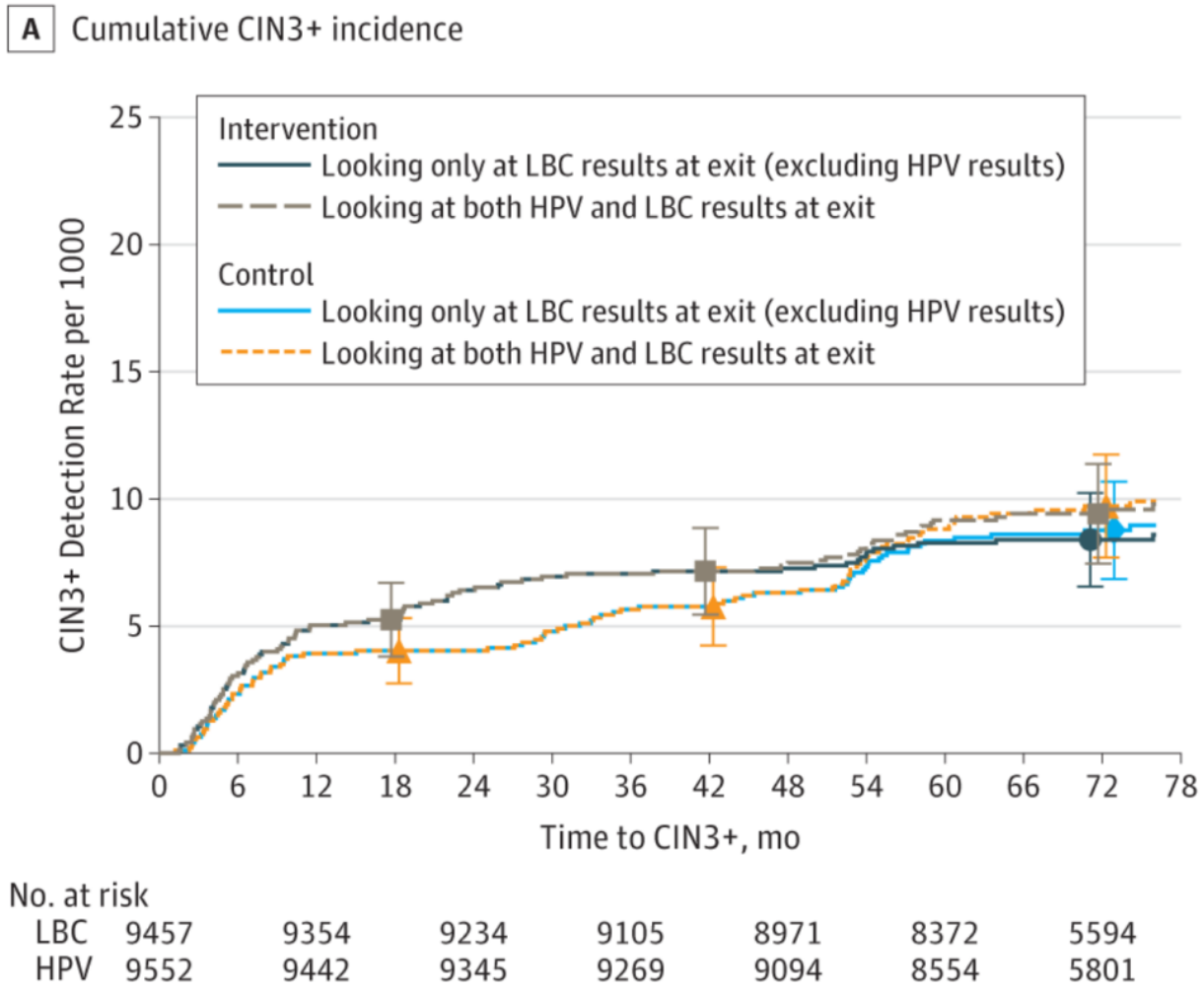
Ogilvie et al. BMC Cancer 2010

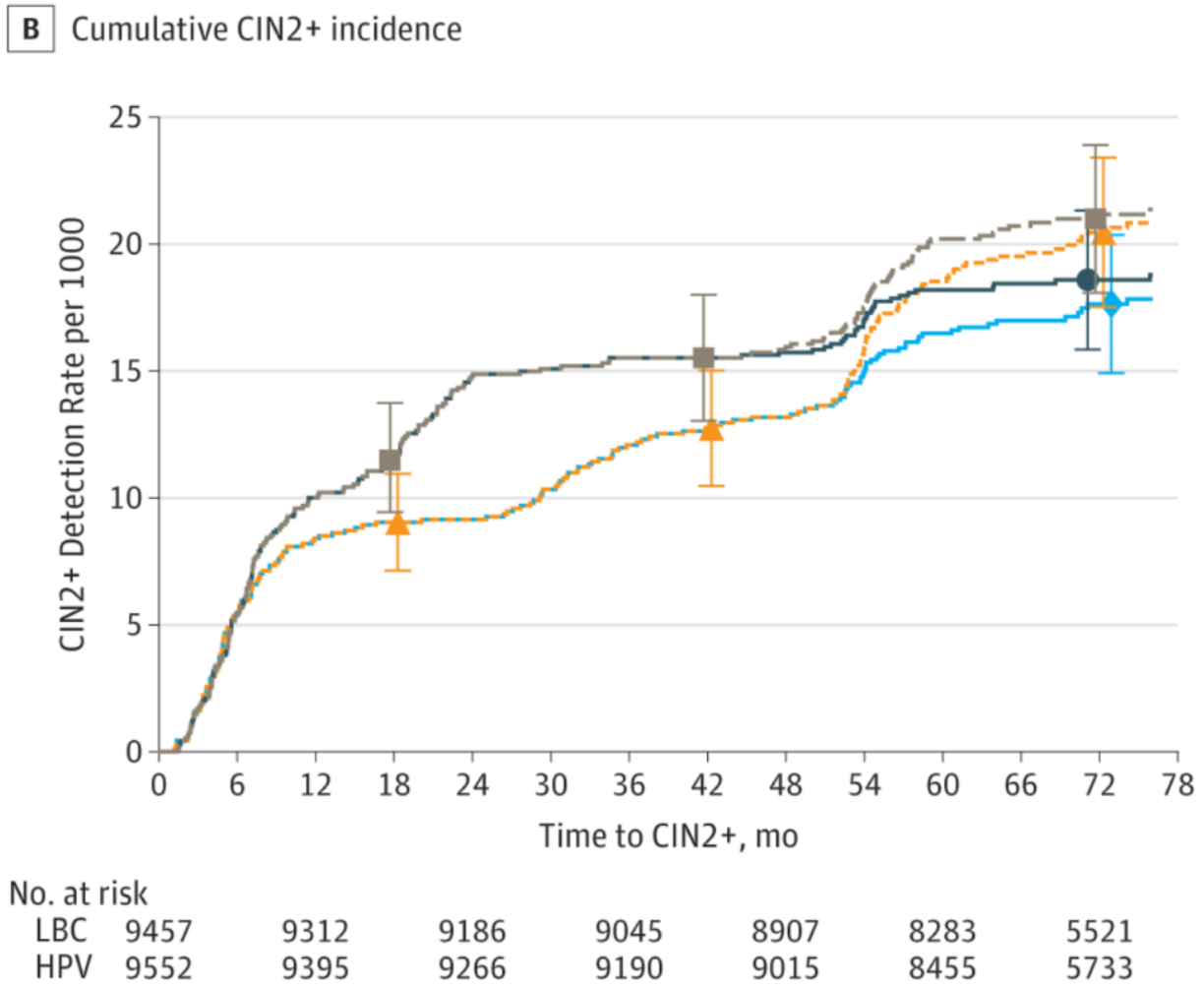
Trial Detected High-Grade CIN



Cumulative CIN3+ & CIN2+ Incidence

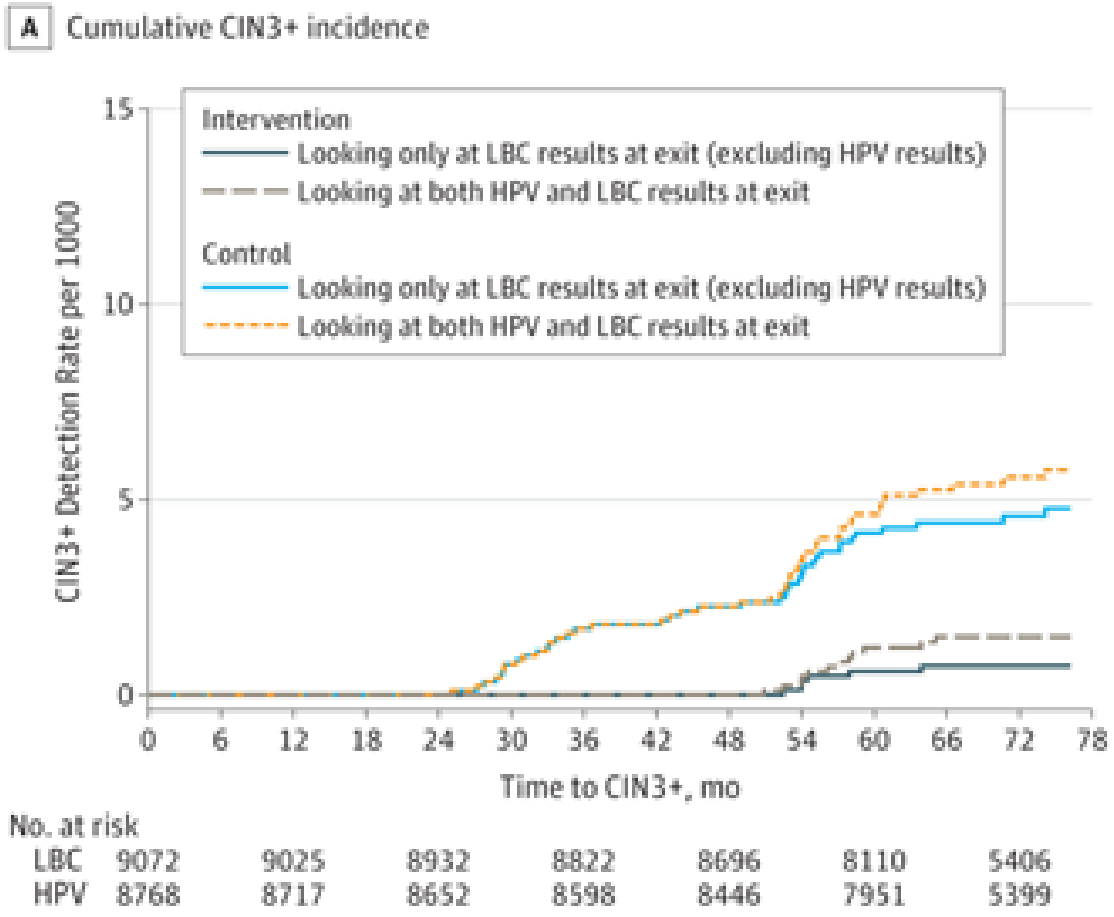
(All Participants Attending 48-Month Exit)

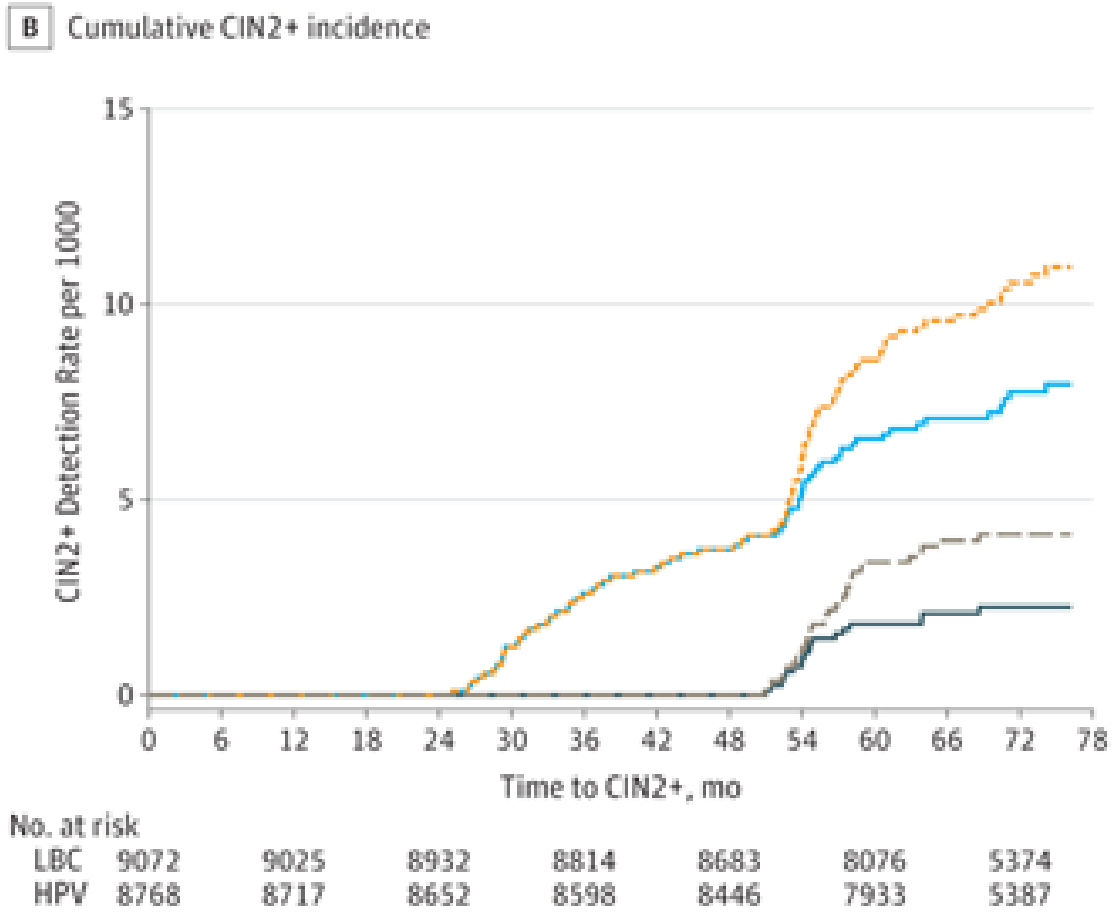




Cumulative CIN3+ & CIN2+ Incidence

(Baseline Negative Participants Attending 48-Month Exit)






MAGIC

FOCAL Trial Colposcopy Referral Rates
(Per 1,000 Women Screened)

Age	Round 1		48 Mo. Exit		Cumulative	
	Intervention	Control	Intervention	Control	Intervention	Control
25-29	181.6 (156.8-209.3)	82.1 (65.3-102.8)	101.7 (82.9-124.2)	141.3 (119.2-166.7)		
30+	45.2 (41.0-49.8)	25.9 (22.7-29.5)	44.2 (40.1-48.7)	63.6 (58.7-69.0)		
All	57.0 (52.5-61.9)	30.8 (27.5-34.5)	49.2 (45.0-53.7)	70.5 (65.5-75.8)	106.2 (100.2-112.5)	101.5 (95.6-107.8)

FOCAL Trial Summary

- Primary HPV screening detected CIN2+ earlier
- A negative baseline HPV result had a higher negative predictive value for CIN2+ at 48 mo. than a negative baseline cytology result
- Colposcopy referral rates were initially higher for HPV-based screening
  - Primarily at the baseline screen for women <30 yr.
  - After the 48 month screening round the cumulative number of colpo exams was similar for both arms

FOCAL Team & Acknowledgements

- Trial funded by the Canadian Institutes of Health Research
- Women who agreed to participate in the trial
- FOCAL Study Centre and laboratory staff at the BCCDC and BC Cancer Agency

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Study Centre Administration

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Statistical Analysis

Lovedeep Gondara

www.bccancer.bc.ca/hpvfocal

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How do the HPV tests compare?

- All are ~95% sens for CIN2+ (Szarewski et al. JCM 2012)
- Qiagen (Digene) lowest spec, cross reacts with some non HR-HPV
- Roche cobas types 16, 18 & detects 12 other HR types
  - spec slightly better than Digene (Roche ≈ equivalent to Abbott Real Time)
- Hologic Aptima (mRNA) types 16, 18/45 and detects 11 other HR types
  - has slightly better spec for high-grade lesions likely because the targeted viral E6 and E7 oncoproteins are necessary for malignant conversion (Yim and Park, Cancer Res Treat 2005)

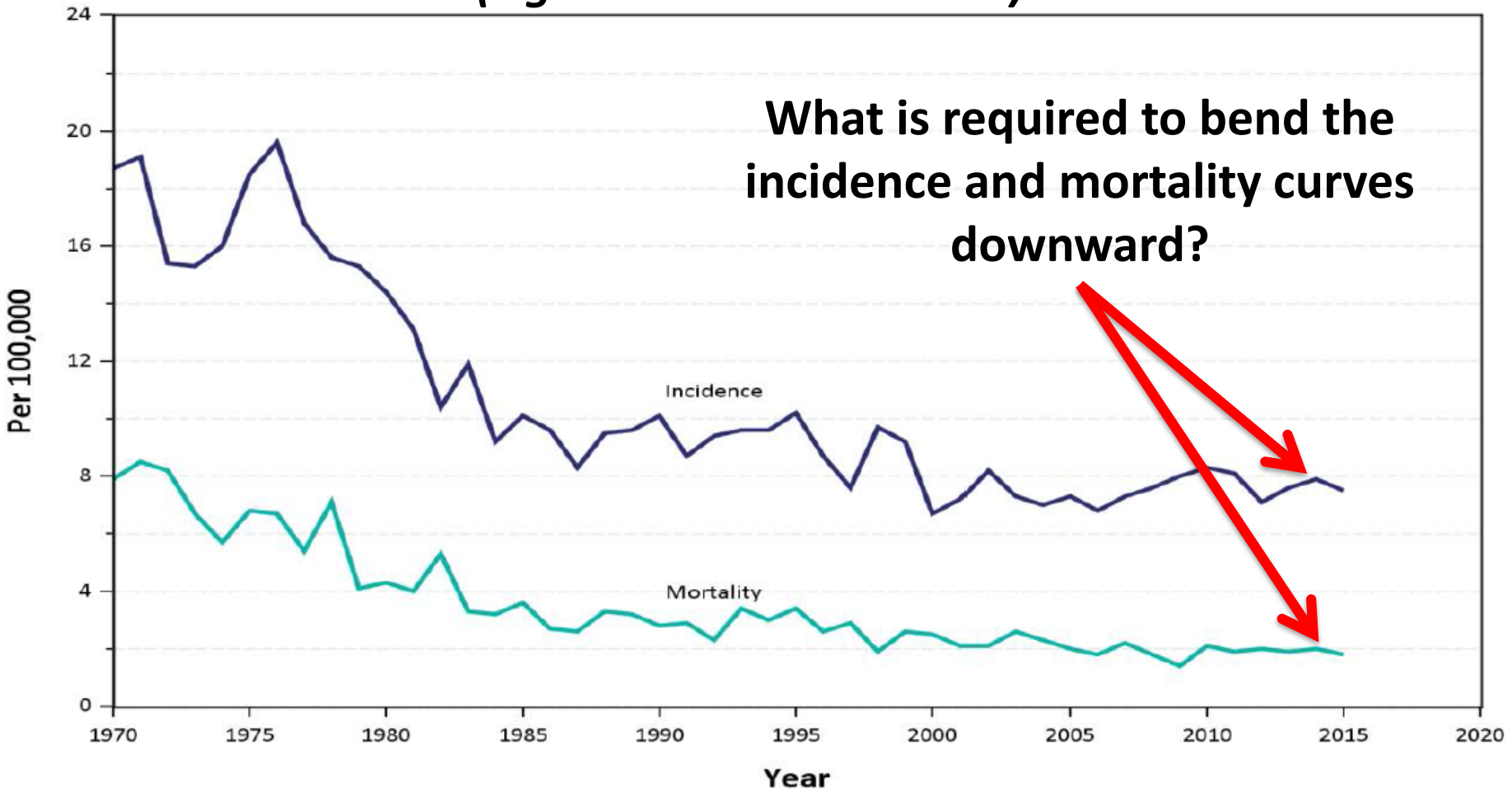
Cook et al. Roche cobas® 4800 versus Digene Hybrid Capture® 2 HPV, BMC Cancer. 2015
Cook et al. Aptima HPV Assay versus Hybrid Capture® 2 HPV test, J Clin Virol. 2017
Cook et al. Aptima HPV Assay versus Hybrid Capture® 2 HPV test at baseline and 48 months, J Clin Virol. 2018

- Why should Canada transition to primary HPV screening?

- What needs to be in place to optimize outcomes?

Invasive Cervical Cancer in BC

(Age Standardized Rates)



Source: BC Cancer Cervix Screening 2016 Program Results

Who is being missed?

- Invasive cervical cancers in BC in 2015 (n=179; ~70% squamous)
- **65% of squamous and 39% of adeno had no screening history or were last screened >5 yr ago**

Screening Uptake in Canada 2017

Canadian Partnership Against Cancer (CPAC) – personal communication

- 71.4% to 85.1% of women aged 25-69 reporting at least one Pap test in the past three years
- Uptake was about 12% lower in those most socially and materially deprived

Increase Screening Uptake

- The incremental yield of primary HPV screening in the FOCAL Trial was small
  - Enabled earlier CIN2/CIN2+ detection
  - Extended screening intervals for those HPV negative
  - Improves adenocarcinoma detection
- Gap: Improving screening reach & access
  - **Benefit of HPV screening is that it enables self-collection**

Self-Collection

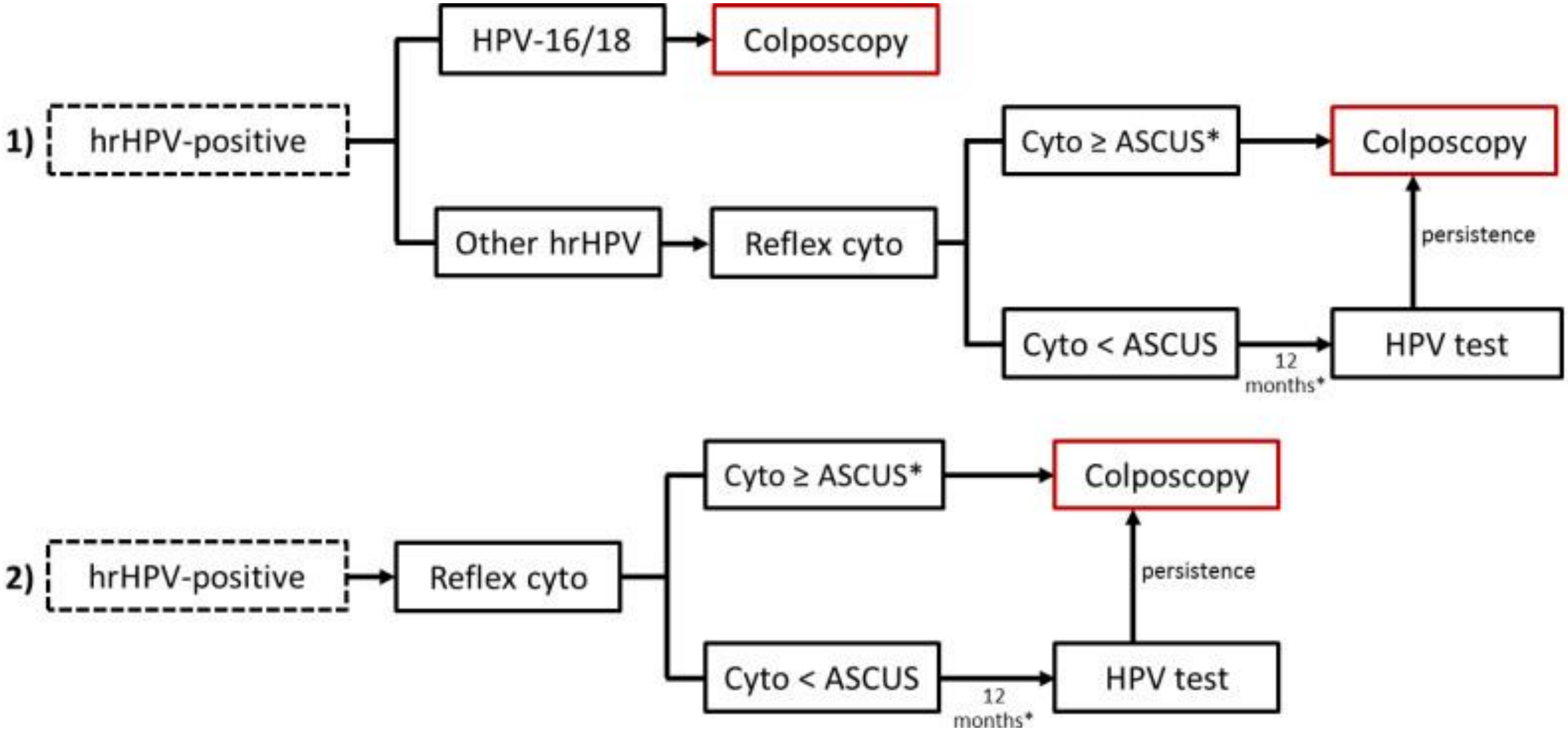
- Arbyn et al. BMJ 2018
  - Meta-analysis of self- vs. clinician collection
  - Using PCR-based HPV assays, self-collection was as accurate as clinician samples
  - Offering self-collection kits is generally more effective than sending clinic-based screening invitations
  - Response rates highly variable among settings, but screening uptake increased by up to four times (Kitchener et al. J Med Screen 2018; Racey et al. J Womens Health 2016; Arrossi et al. Lancet Glob Health, 2015)
- Self-collection is only possible if HPV screening is used!
  - Self-collection won't work for cytology or cytology triage
  - Triage: HPV genotyping; methylation; etc.
- BC pilot of self-collection for HPV screening (CervixCheck.ca) in underserved South Asian and First Nations populations

Triage

For HPV screening you still need a triage process

- Cytology ± P16/Ki67 immunostaining
- Cytology + genotyping
- Genotyping alone
- Methylation?
  - May be suitable for triage of self-collected samples

Potential Triage/Management Algorithm for HPV Screening



Kim et al. USPSTF Evidence Synthesis 2018

Improving reach and access

Registry to remind physicians and/or women to be tested

- Scottish Cervical Call Recall System (SCCRS)
  - http://www.healthscotland.scot/publications/cervical-screening-toolkit
- Longer screening interval creates benefits and risks

Rolling out self-collection

- Cervixcheck.ca – online self-testing

Special programs to support vulnerable populations – Indigenous, immigrants, etc.

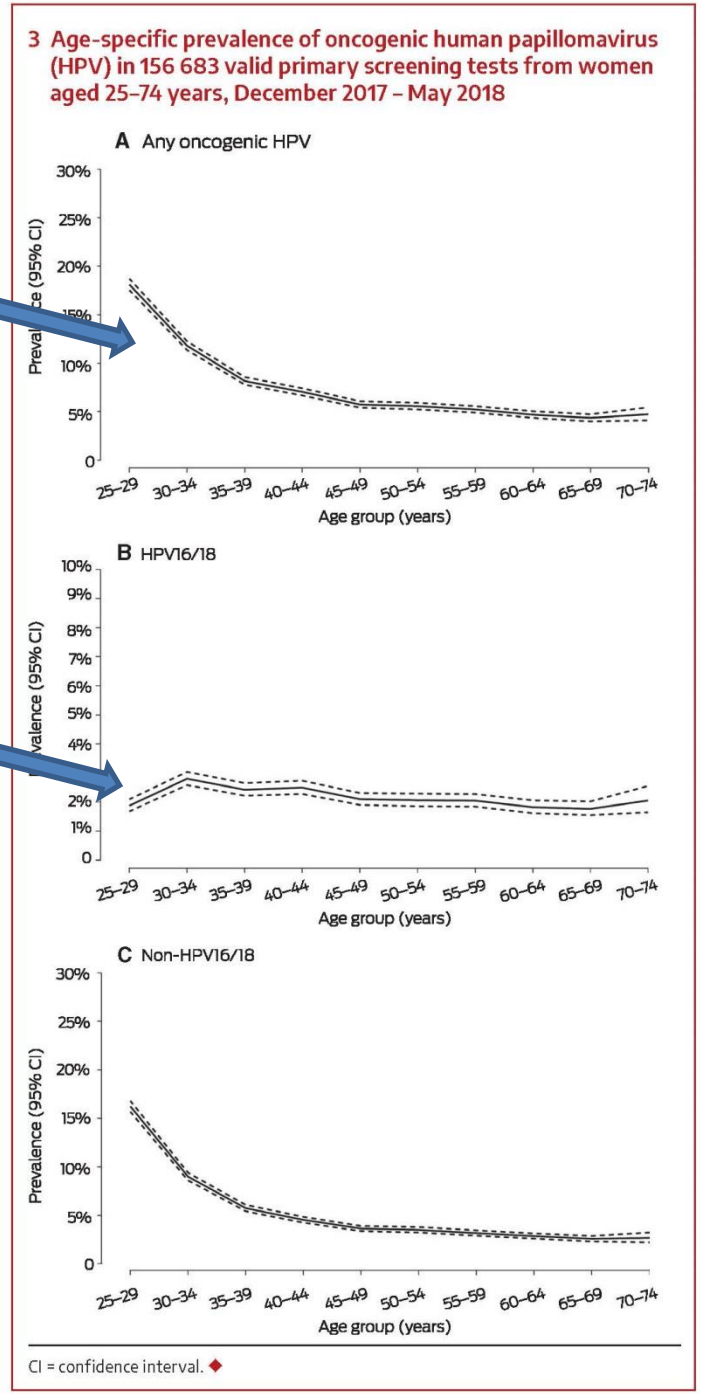
Other considerations

As the vaccinated cohort reaches screening age the 4 valent (~70% of cervical cancers) and 9 valent vaccine (~90%) will profoundly impact screening programs

- Cytology will have limited value and the value/frequency of HPV testing will need to be reassessed

Business cases – “hump” cost for the HPV technology shift followed by lifetime cost savings

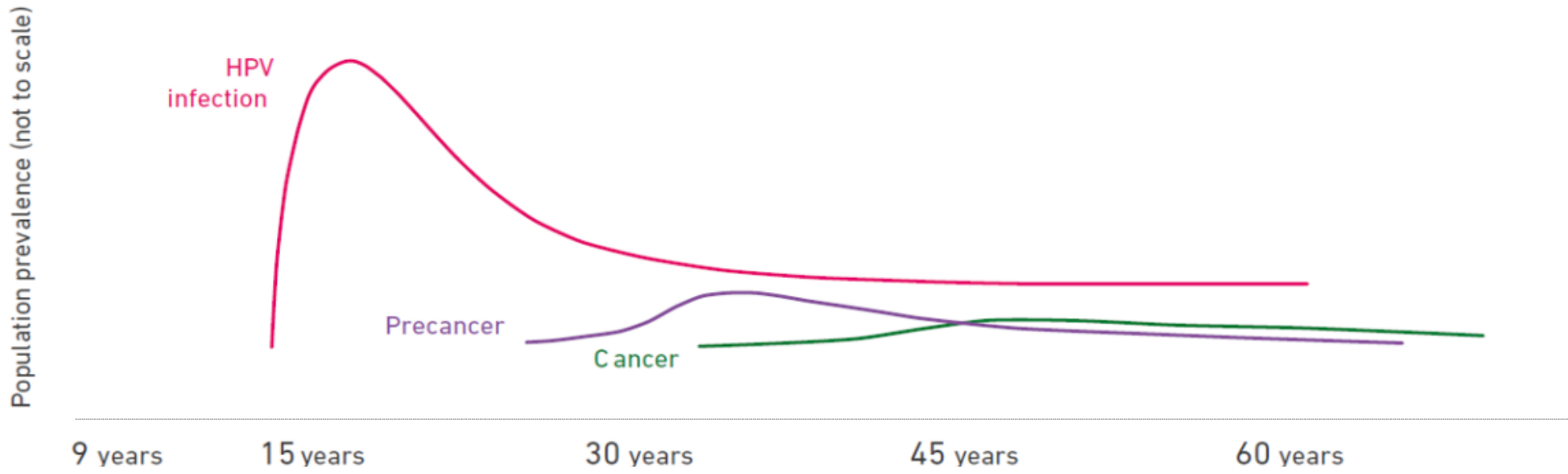
- Cytology staff are aging and needing retaining
- **Put resources in improved screening uptake!**



Machalek et al. (Medical J Australia 2019)

- Reported on the first 6 months after implementing primary HPV screening
- 157,700 for primary screening
- 5 year cycle of screening for those HPV negative

WHO Life-Course Approach to Cervical Cancer Control



Primary Prevention	Secondary Prevention	Tertiary Prevention
Girls 9-14 years • HPV vaccination Girls and boys, as appropriate •Health information and warnings about tobacco use •Sexuality education tailored to age & culture •Condom promotion/provision for those engaged in sexual activity •Male circumcision	Women > 30 years of age “Screen and treat” – single visit approach • Point-of-care rapid HPV testing for high risk HPV types • Followed by immediate treatment • On site treatment	All women as needed Treatment of invasive cancer at any age and palliative care •Ablative surgery •Radiotherapy •Chemotherapy •Palliative Care

Conclusions

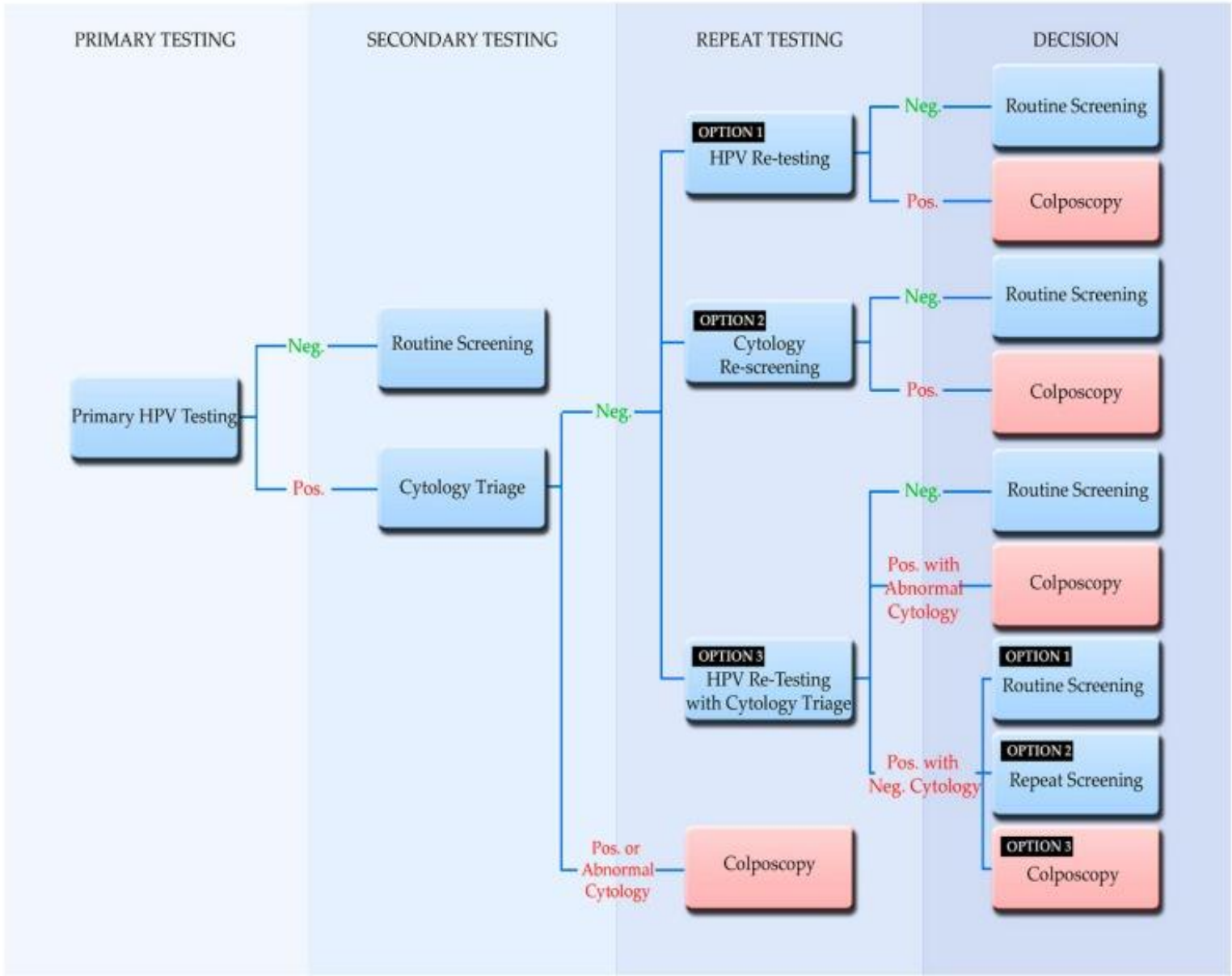
- HPV screening detects CIN2/CIN2+ earlier and if negative enables extended screening intervals in the 5 yr range
  - Enables self-collection which is likely to increase screening uptake
  - Implementation will require efforts to directly engage with women to ensure effective screening uptake
- It is time to retire the Pap test as a screening tool and use it as a triage tool

References

- Zhang and Batur. Human papillomavirus in 2019: An update on cervical cancer prevention and screening guidelines. Cleve Clin J Med. 2019
- Chrysostomou et al. Cervical Cancer Screening Programs in Europe: The Transition Towards HPV Vaccination and Population-Based HPV Testing. Viruses 2018
- Simms et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. Lancet Oncol. 2019

Thank you for your attention!

Potential Management Algorithm for HPV Screening



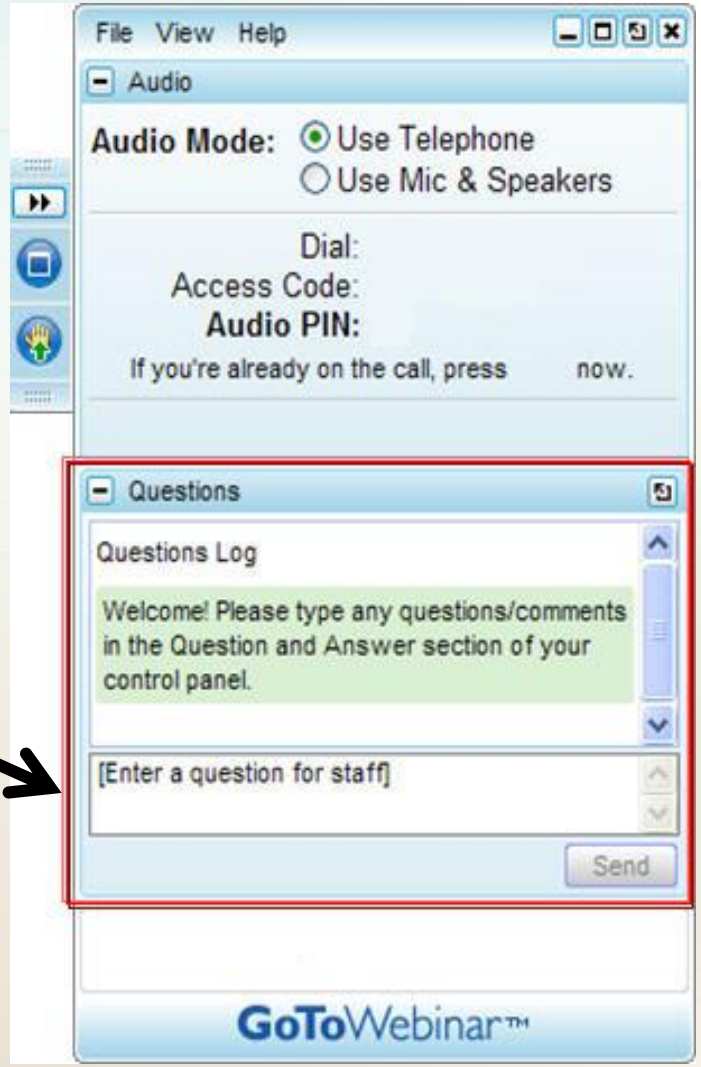
Chrysotomou et al. Viruses 2018

HPV Screening Assay Characteristics

	Hybrid Capture® 2 High-Risk HPV DNA Test	Aptima® HPV Assay	cobas® 4800 HPV Test
Nucleic acid target	hrHPV DNA	hrHPV E6/E7 mRNA	hrHPV L1 DNA
HPV genotypes detected	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	Same as HC2 plus HPV 66	Same as HC2 plus HPV 66
Specific genotyping	None	HPV 16 & 18/45 (reflex test)	HPV 16, 18 & a pool of 12 other hrHPV types
Internal control for specimen cellularity	No; reject samples without visible cell pellet at prep. stage	No; an internal control is added to monitor test process	Yes; β-globin
Methodology	Signal amplification	Nucleic acid amplification (TMA)	Nucleic acid amplification (real-time PCR)

Question & Answer Period

Submit your text question using the Questions pane



HPV Testing in the Canadian Context:

Pros, Cons, and Implementation Challenges

- **Evaluation: https://www.surveymonkey.com/r/986M582**
- **Slide Set, Video recording, HPV documents at: www.CIDCgroup.org**
  - "**Counselling Patients about HPV Test Results**", and
  - "**Canada's Role in Accelerating Global Elimination of Cervical Cancer**"
- Join the **Canadian HPV Prevention Network** at: **www.CIDCgroup.org**

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

Next CIDC Webinar: in September

Thank you for participating!

More Info: George Wurtak, Executive Director, CIDC
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This educational program is made possible with support from **Hologic Canada ULC** and with assistance by BD Diagnostics and Immunize Canada