Fall Provincial Colposcopy Community of Practice (CoP)

Webinar 2

NOVEMBER 26, 2020, 5:30 – 7:00 P.M.

Recommended browser for Microsoft Teams: Google Chrome

Ontario Health
Cancer Care Ontario

With Thanks

Housekeeping items

- Please **mute** yourself when you are not speaking
- Please turn off your webcam to minimize connection issues
- Please use the **chat box** to ask questions or share comments and avoid using the "**raise hand**" option
- During the case studies, please click on the link for the Microsoft Forms poll in the **chat box**

Open the task bar by hovering near the middle of the screen

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Microsoft Forms live polling

- Please click on the link for the Microsoft Forms poll provided in the chat-box

https://forms.office.com/Pages/ResponsePage.aspx?id=XGz5Tj_Ya0akeIFqW7SvYrd7mlkRUk5LvzzNVf2OYC1UQkVPTzZFTlRZV05JT0JWVkJFVVRONDExQi4u

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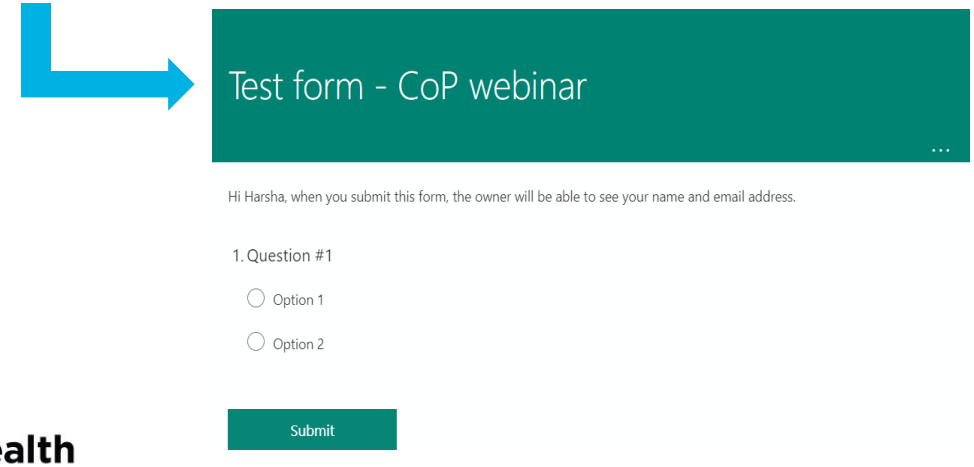
- Select your response from the provided options



Accreditation

- Today's session is a Royal College of Physicians and Surgeons Accredited Group Learning Activity
- To receive a letter of accreditation for 1.5 credit hours, you must:
  - **Participate in today's event**
  - **Be registered as a member of the CoP**
  - **Complete and submit the post-webinar evaluation survey**

Planning Committee

Thank you to our CoP Planning Committee:

Dr. Paul Gurland

Dr. Keiyan Sy

Dr. Laura White

Welcome to the Colposcopy Community of Practice (CoP) fall webinar

Please note that this session will be recorded and will be available on the Colposcopy CoP Resources Hub in the coming weeks

Agenda: November 26

Item	Presenter	Time
Welcome and Introductions	Dr. Joan Murphy	5:30-5:35 pm
Ontario Cervical Screening Program (OCSP) update: Human papillomavirus (HPV) testing implementation	Dr. Joan Murphy	5:35-5:40 pm
Impact of COVID-19 on cervical screening and colposcopy	Dr. Joan Murphy and Dr. Rachel Kupets	5:40-6:00 pm
Colposcopy quality reporting in Ontario and highlights from 2020 newsletter	Dr. Rachel Kupets	6:00-6:15 pm
Questions from the field	Dr. Joan Murphy	6:15-6:25 pm
Case study and review of adenocarcinoma in-situ in Ontario (AIS)	Dr. Brenna Swift and Dr. Rachel Kupets	6:25-6:55 pm
Concluding remarks	Dr. Joan Murphy	6:55-7:00 pm

Learning Objectives

Following this meeting, participants will better understand:

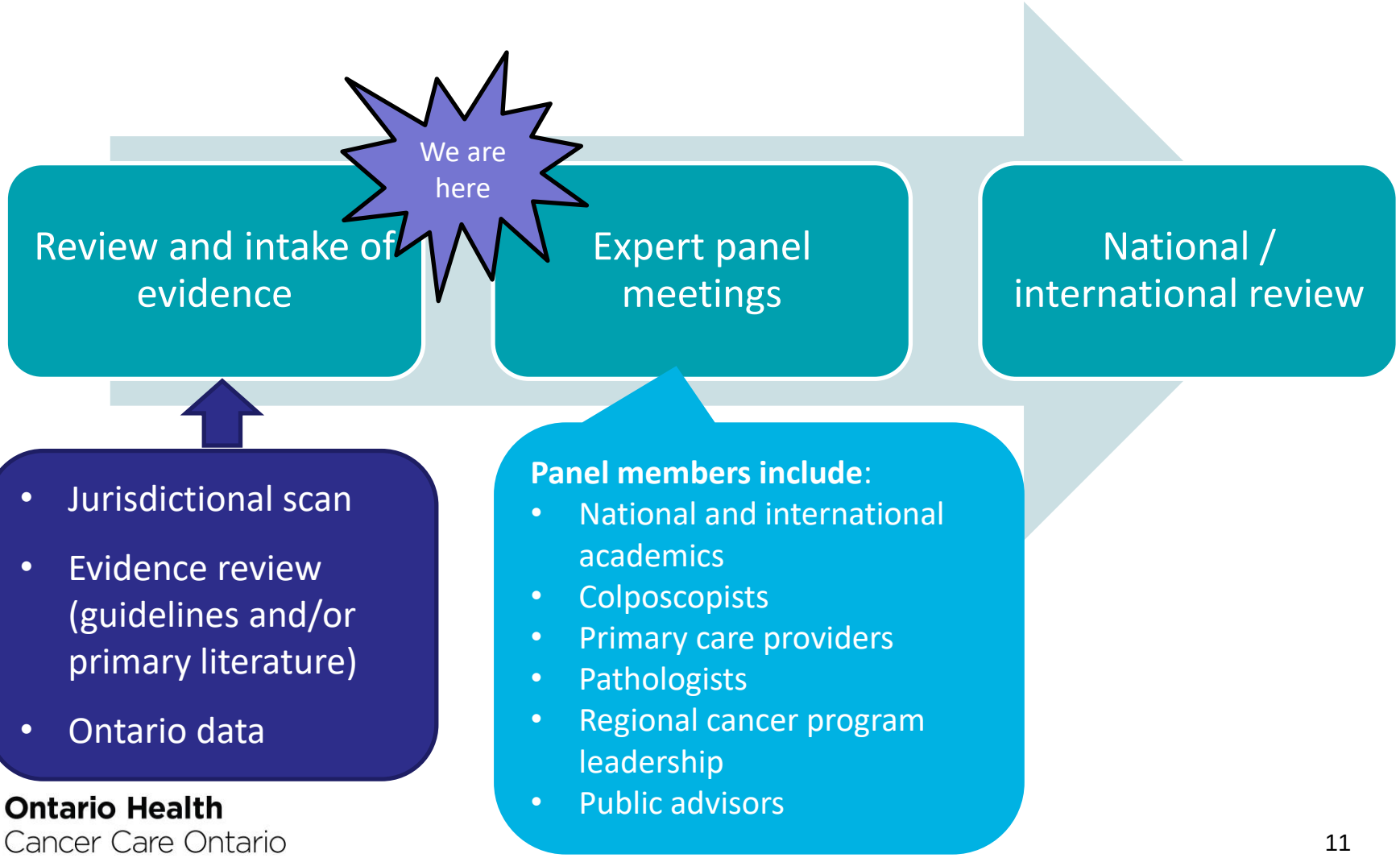
- Considerations for cervical screening and colposcopy care amidst the COVID-19 pandemic
- Risk assessment of patients with AIS cytology results and implications for colposcopy
- Appropriate use of HPV testing within the current screening setting

Ontario Cervical Screening Program (OCSP) update: Human papillomavirus (HPV) testing implementation

Ongoing work

- Procurements of Laboratory Services and HPV Test System
- Working with the Ministry of Health to develop a proposal to update Schedule of Benefits to support the implementation of HPV testing
- Finalizing OCSP's recommendations for cervical screening and colposcopy care

Approach to updating OCSP screening and colposcopy recommendations



Webinar: Australia's implementation of HPV testing

- On October 8, Ontario Health's (Cancer Care Ontario's) HPV Consultant, Dr. Marion Saville, gave a webinar on the experience implementing HPV testing for cervical screening in Australia, including lessons learned
- The webinar was recorded and is available on the Community of Practice resource hub

Impact of COVID-19 on cervical screening and colposcopy

Reminder: COVID-19 colposcopy tip sheet

- The Ontario Cervical Screening Program developed a COVID-19 tip sheet
- The tip sheet contains a priority classification framework for prioritization of colposcopy services during COVID-19

Prioritization of colposcopy services during the pandemic based on risk

- Prioritization framework uses risk-based thresholds
- Ontario data and evidence from the literature were used to establish the thresholds
- Each priority level corresponds to a person's immediate risk of cervical intraepithelial neoplasia 3+ (CIN3+) and is based on recent cervical screening history (i.e., cytology and/or HPV)

Priorities B1 and B2

Priority	Risk-based threshold	Referral cytology	HPV status
A Patients who are deemed critical and require colposcopy because their situation is unstable, is causing unbearable suffering and/or is immediately life threatening	N/A (no cervical screening abnormalities meet the criteria for priority A)		
B1 Non-critical patients who require services or treatment for conditions that may cause an early negative impact on quality of life or functional status – colposcopy will alter management or outcome	**Immediate risk of CIN3+ is >15%** (any high-risk cytology result)	AIS	Regardless of HPV status
		HSIL+	
		AGC	
		ASC-H	
B2 Non-critical patients who require services or treatments with conditions for which a delay of several weeks will not likely alter quality of life or prognosis	**Immediate risk of CIN3+ is 7% to 15%** Single (HPV 16/18 positive) or consecutive (HPV status unknown) low-risk cytology results	ASCUS	HPV 16/18 positive
		LSIL	
		LSIL x2	HPV status unknown
		LSIL x3	
		LSIL, ASCUS x2	
		LSIL, ASCUS	
		ASCUS, LSIL	
		ASCUS x2	
		ASCUS x3	

Priority C

Priority	Risk-based threshold	Referral cytology	HPV status
C These patients should not be referred to colposcopy. Referrals received by colposcopists for these patients should be declined to facilitate repeat screening in primary care with cytology within approximately twelve months*	**Immediate risk of CIN3+ is < 7%**	ASCUS	HPV status unknown or HPV positive for non 16/18
		LSIL	

Acronyms: adenocarcinoma in-situ (AIS), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells; cannot exclude high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cells (AGC), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASCUS), cervical intraepithelial neoplasia (CIN) and human papillomavirus (HPV)

COVID-19 tip sheet for primary care providers (PCPs)

- In June 2020, Ontario Health (Cancer Care Ontario) released a tip sheet to support PCPs as they resume cancer screening

First time low-grade result

- People with a first time LSIL or ASCUS can be rescreened with cytology within approximately 12 months

Age of initiation

- Primary care providers are encouraged to initiate cervical screening at **age 25**
  - Based on evidence that there is limited benefit in cervical screening for younger people
  - This guidance is aligned with other organized cervical screening programs in Canada such as British Columbia, Alberta, and Nova Scotia

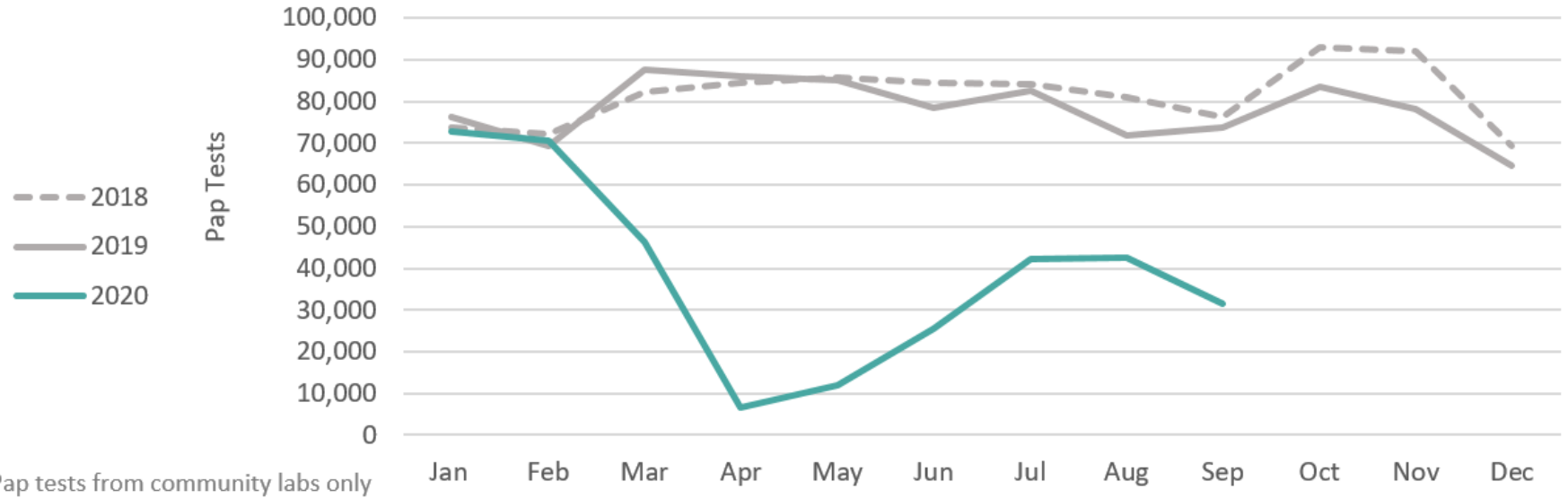
Cancer Screening COVID-19 Monitoring and Planning Tool

- Ontario Health (Cancer Care Ontario)'s cancer screening team developed regional monitoring and planning tools for each cancer screening program
- The purpose of the tools is to support regions as they resume cancer screening services during the pandemic
- The OCSP tool allows Regional Cancer Programs (RCPs) to monitor monthly volumes of completed **Cytology tests, colposcopies and cervical treatments**

Cytology Volume, Ontario, 2018-2020

Pap Tests Volumes by Month[1]

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2018	73,620	71,997	82,345	84,509	85,791	84,485	84,065	81,076	76,219	93,061	92,106	69,213
2019	76,108	69,407	87,516	86,135	84,912	78,501	82,397	71,807	73,591	83,366	78,120	64,642
2020	72,815	70,706	46,219	6,628	12,091	25,469	42,076	42,398	31,510			
% Change 2020 vs 2019	-4%	2%	-47%	-92%	-86%	-68%	-49%	-41%	-57%			



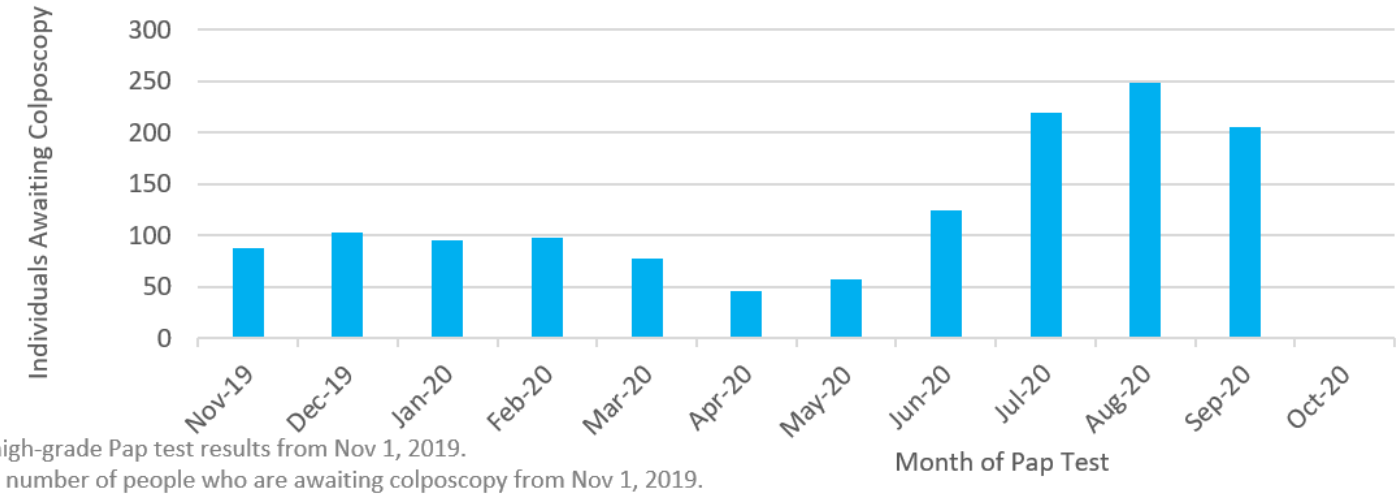
[1]Pap tests from community labs only

Note: data in the last month is likely incomplete due to the data lag

Individuals with High-grade Pap Test Results Requiring Colposcopy

Number of Individuals Awaiting Colposcopy[2]

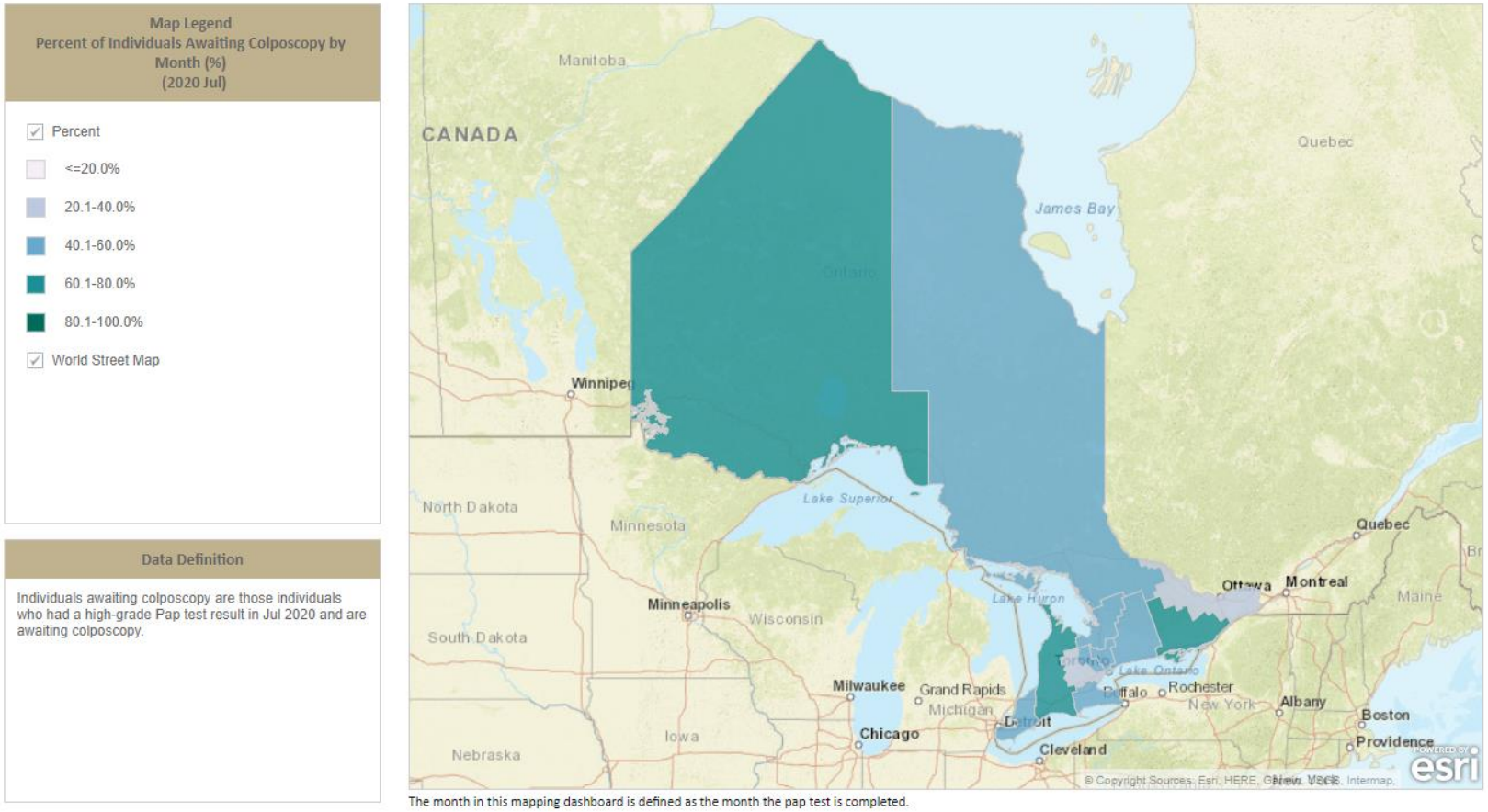
	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Total[3]
Individuals who had a high-grade Pap test result	653	549	574	512	325	117	180	308	435	314	218		**4,185**
Had colposcopy	**565**	**446**	**478**	**414**	**247**	**71**	**122**	**184**	**216**	**65**	**12**		**2,820**
Had colposcopy & treatment	279	245	239	198	111	30	37	62	29	5	1		**1,236**
Awaiting colposcopy	**88**	**103**	**96**	**98**	**78**	**46**	**58**	**124**	**219**	**249**	**206**		**1,365**



[2] Individuals with high-grade Pap test results from Nov 1, 2019.
[3] Total: cumulative number of people who are awaiting colposcopy from Nov 1, 2019.

Note: colposcopy data in recent months may be incomplete due to lags in OHIP data submission

Individuals with High-grade Pap Test Results Requiring Colposcopy by LHIN



The month in this mapping dashboard is defined as the month the pap test is completed.

- Map component shows the percent of individuals with high-grade Pap test result that are awaiting colposcopy by residential LHIN

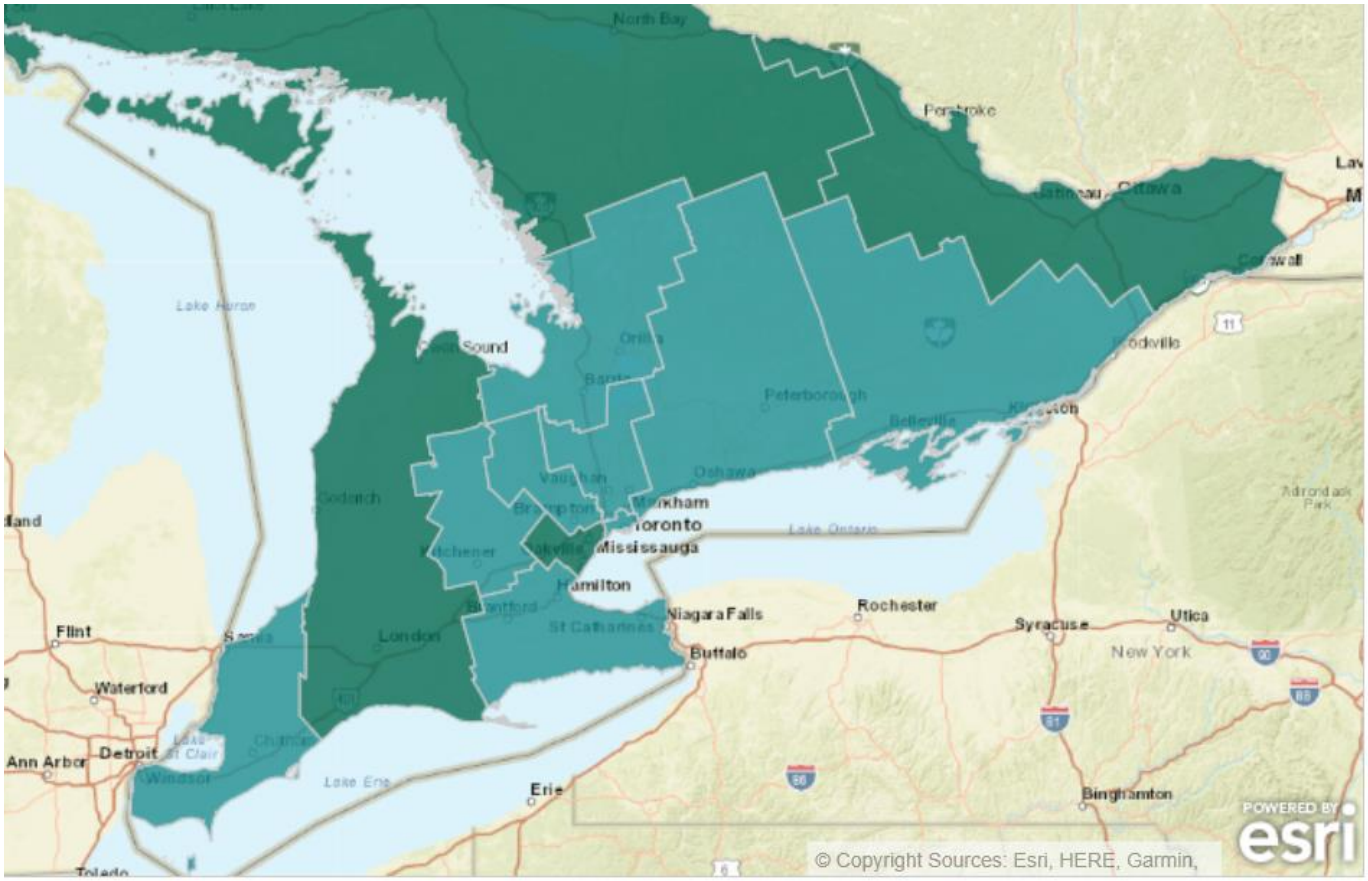
Individuals with High-grade Pap Test Results Requiring Colposcopy by LHIN

Map Legend
Percent of Individuals Awaiting Colposcopy by Month (%) (2020 Jul)

- ☑ Percent
- <=20.0%
- 20.1-40.0%
- 40.1-60.0%
- 60.1-80.0%
- 80.1-100.0%
- ☑ World Street Map

Data Definition

Individuals awaiting colposcopy are those individuals who had a high-grade Pap test result in Jul 2020 and are awaiting colposcopy.

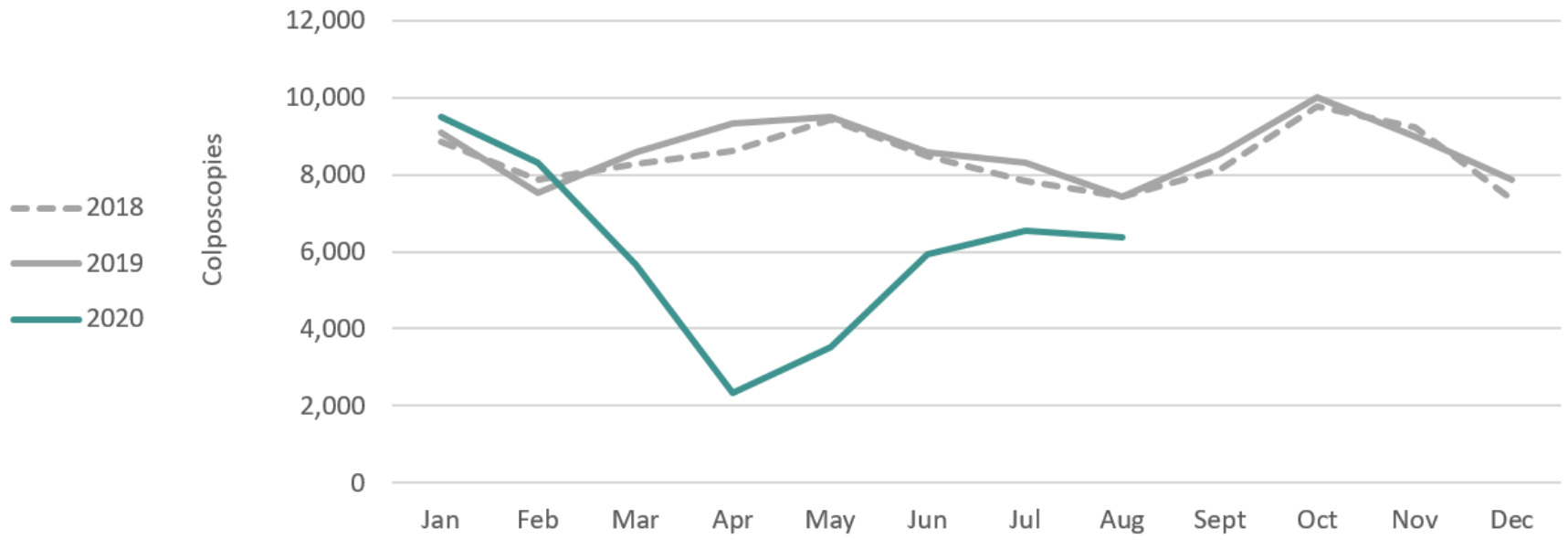


- Map component shows the percent of individuals with high-grade Pap test result that are awaiting colposcopy by residential LHIN

Colposcopy Volume, Ontario, 2018-2020

Colposcopy Volumes by Month and Year

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
2018	8,862	7,863	8,278	8,596	9,416	8,468	7,840	7,440	8,125	9,761	9,207	7,361
2019	9,090	7,541	8,563	9,325	9,505	8,563	8,306	7,422	8,541	10,006	8,990	7,860
2020	9,489	8,297	5,670	2,324	3,525	5,936	6,539	6,362				
% Change 2020 vs 2019	4%	10%	-34%	-75%	-63%	-31%	-21%	-14%				

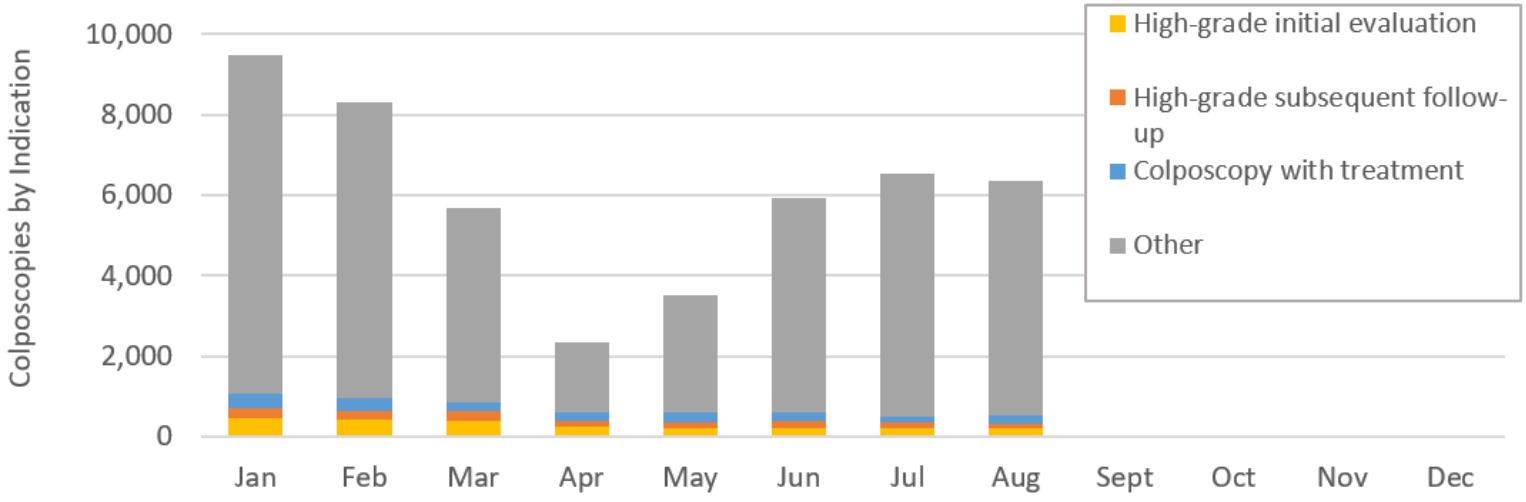


Note: colposcopy data in recent months may be incomplete due to lags in OHIP data submission

Colposcopy Volume by Indication

Colposcopy Volumes by Month and Type, 2020

Indication	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
High-grade initial evaluation	468	425	396	252	206	207	193	199				
High-grade subsequent follow-up	248	220	227	149	161	169	146	100				
Colposcopy with treatment	342	299	224	211	249	211	165	214				
Other	8,431	7,353	4,823	1,712	2,909	5,349	6,035	5,849				
All indications	**9,489**	**8,297**	**5,670**	**2,324**	**3,525**	**5,936**	**6,539**	**6,362**				
% High-grade follow-up (initial and subsequent)	**8%**	**8%**	**11%**	**17%**	**10%**	**6%**	**5%**	**5%**				



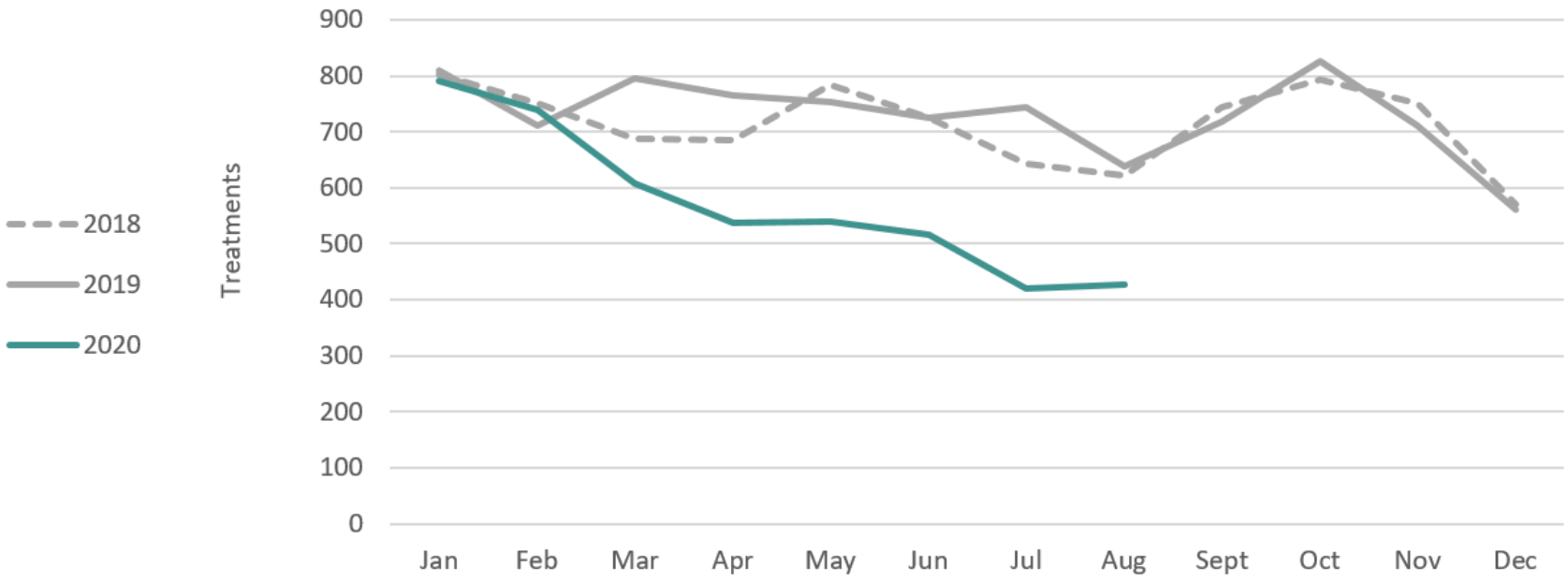
Note: colposcopy data in recent months may be incomplete due to lags in OHIP data submission

Ontario Health
Cancer Care Ontario

Treatment Volume, Ontario, 2018-2020

Treatment Volumes by Month and Year

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
2018	803	751	687	686	784	726	642	621	743	794	751	570
2019	809	710	795	765	753	725	743	638	719	826	712	560
2020	791	739	607	538	540	517	420	428				
% Change 2020 vs 2019	-2%	4%	-24%	-30%	-28%	-29%	-43%	-33%				

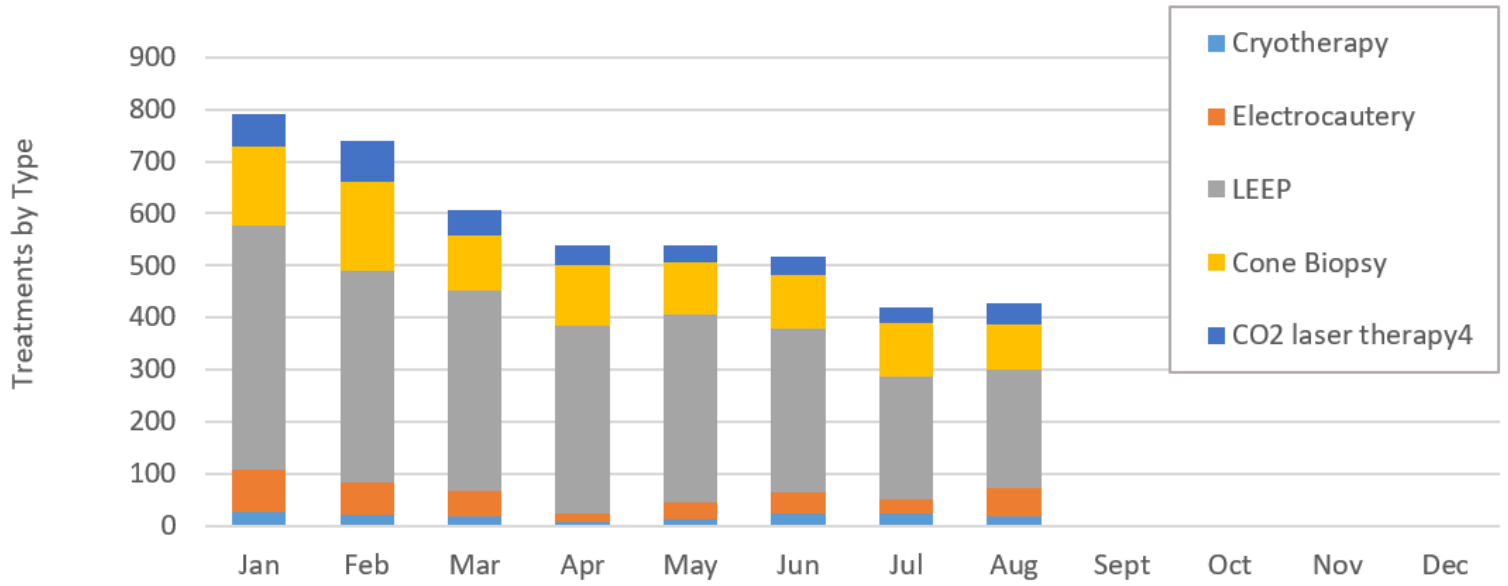


Note: data in recent months may be incomplete due to lags in OHIP data

Treatment Volume by Type

Treatment Volumes by Month and Type, 2020

Type	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Cryotherapy	25	20	19	7	11	24	24	18				
Electrocautery	83	63	48	15	34	39	27	55				
LEEP	469	406	386	363	360	315	236	228				
Cone Biopsy	151	173	104	115	102	104	103	85				
CO2 laser therapy[4]	63	77	50	38	33	35	30	42				
Total	**791**	**739**	**607**	**538**	**540**	**517**	**420**	**428**				



[4] CO2 laser therapy includes cryoconization or electroconization with or without curettage for premalignant lesion (dysplasia or carcinoma in-situ), out-patient procedure

Ontario Health
Cancer Care Ontario

Note: data in recent months may be incomplete due to lags in OHIP data

2020 newsletter

2020 Newsletter

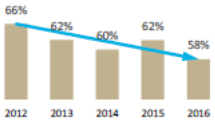
Cervical Screening and Colposcopy Services in Ontario:
Screening and Diagnosis for the Prevention of Cervical Cancer in 2019

Cervical Screening in Ontario

Participation

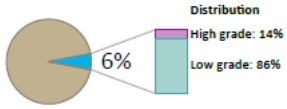
From 2015 to 2019, the cervical screening participation rate remained stable at around 60% (the OCSP target is 85%).

Retention



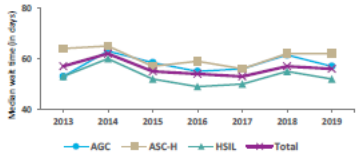
The screening retention rate decreased from 66% in 2012 to 58% in 2016.

Abnormal screening results

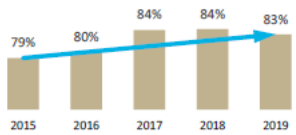


In 2019, out of 931,767 cytology tests with known results, 6% were abnormal: 14% of these abnormal results were high grade and 86% were low grade.

Access to Diagnostic Care: Wait Time



From 2013 to 2019, the median wait time from high-grade cytology test result to colposcopy remained consistent at around 56 days.



The proportion of participants with a high-grade cytology test result who were seen in colposcopy within 6 months increased from 79% in 2015 to 83% in 2019.

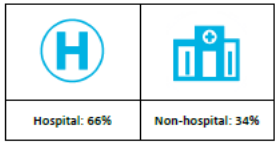
Colposcopy Services

Colposcopy visits

103,703

The number of colposcopy visits remained stable from 2015 to 2019.

Colposcopy location



Number of physicians who performed colposcopy

Acronyms and abbreviations:
AGC: atypical glandular cells
ASC-H: atypical squamous cells, cannot exclude HSIL
HSIL: high-grade squamous intraepithelial lesion

Notes:
All the above indicators are focused on Ontario participants ages 21 to 69. Most indicators are for 2019. Indicators that are not for 2019 are noted. For more information about cervical screening and colposcopy, please visit our website at cancercareontario.ca/en/types-of-cancer/cervical/screening

Ontario Health Cancer Care Ontario

Cervical Screening and Colposcopy Services in Ontario:
Screening and Diagnosis for the Prevention of Cervical Cancer in 2019

Screening Effectiveness

Positive predictive value (pre-cancer or invasive cancer)

1 in 16

In 2018, 5.9% of participants with an abnormal cytology test result were diagnosed with pre-cancer and 0.3% were diagnosed with invasive cervical cancer. This data was consistent from 2014 to 2018.

Detection rate

3.0 / 1,000

In 2018, the cytology test detection rate for CIN 3+ was 2.9/1,000 for pre-cancer and 0.1/1,000 for invasive cervical cancer. This data was consistent from 2014 to 2018.

Colposcopy Care: Adherence to OCSP Recommendations

First time ASCUS cytology test result

6%

of participants who had their first ASCUS cytology test result were seen for colposcopy in 2019. These were unnecessary referrals to colposcopy.

More information: The OCSP recommends that participants with a first ASCUS get a repeat screening test in 6 months before referral to colposcopy is considered. During the COVID-19 pandemic, OCSP recommends repeat testing at 12 months after a first ASCUS. Providers can also offer HPV testing (not covered by OHIP) to people with ASCUS age 30 and older[1,2].

Lost to follow-up post-treatment

In 2018, approximately 1 in 7 participants (16%) did not receive follow-up care within 12 months of being treated for cervical dysplasia. This is an important area for improvement because all participants should receive follow-up colposcopy post-treatment.

Treatments

4,248

In 2019, 4,248 participants were treated for HSIL – a decrease from the 4,650 who were treated in 2018.

Exit from colposcopy

From 2011 to 2015, the percentage of participants discharged from colposcopy post-treatment after having 3 consecutive normal cytology results remained stable, ranging from 77% and 80%.

Tip: According to OCSP's recommendations, after 3 consecutive normal cytology results in colposcopy, most patients can be discharged to primary care for screening every 3 years[1].

Acronyms and abbreviations:
ASCUS: atypical squamous cells of undetermined significance
HSIL: high-grade squamous intraepithelial lesion
CIN 3+: cervical intraepithelial neoplasia grade 3 or higher

References:
1. Cancer Care Ontario. Clinical Guidance: Recommended Best Practices for Delivery of Colposcopy Services in Ontario [Internet]. Toronto: CCO; 2016 [cited 2019 Sept 13]. Available from cancercareontario.ca/en/guidelines-advice/types-of-cancer/43336
2. Murphy J, Kennedy E, Dunn E, Fung Kee Fung M, Gzik D, McLachlin CM, Shier M, and Paszat L. Cervical Screening. Toronto (ON): Cancer Care Ontario; 5 Oct 2011 [cited 2017 Oct 4]. Program in Evidence-based Care Evidence-based Series No.: 15-9. Available from cancercareontario.ca/en/guidelines-advice/types-of-cancer/2156

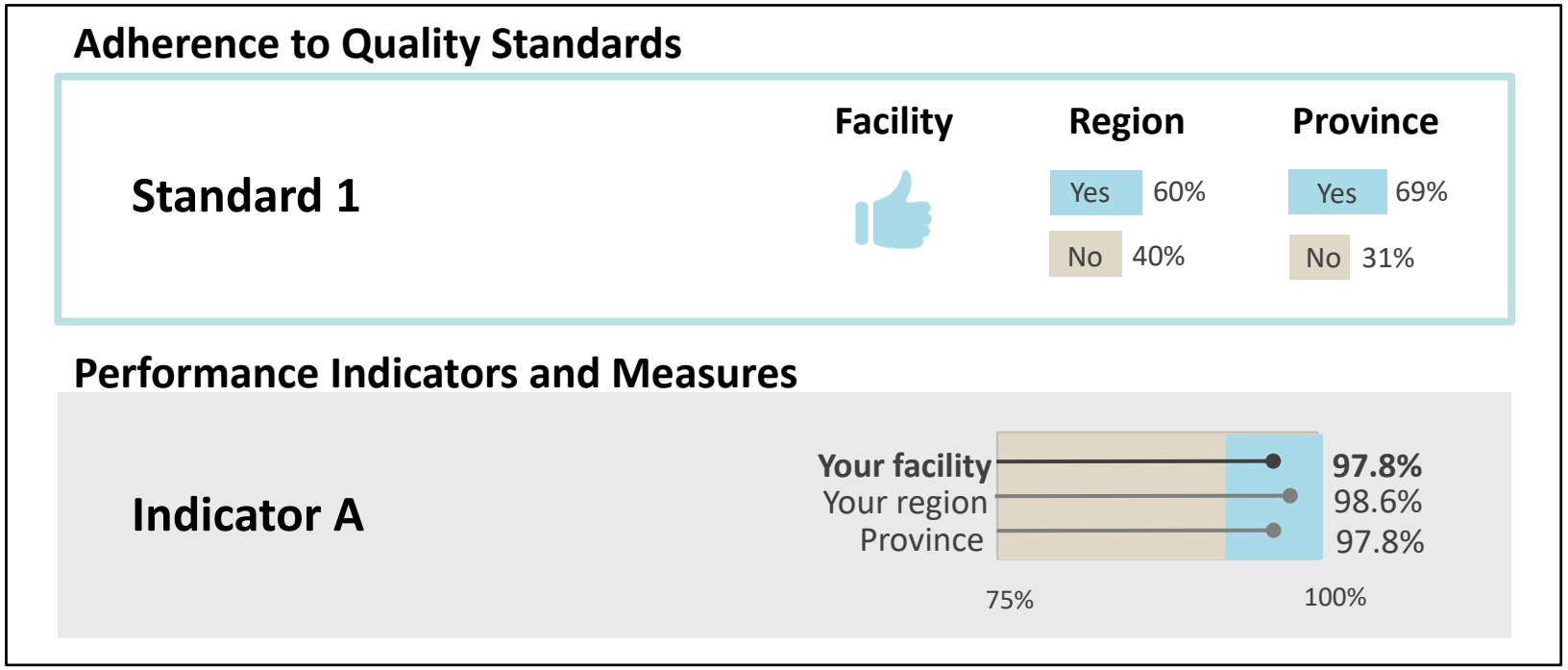
Notes:
All the above indicators are focused on Ontario participants ages 21 to 69. Most indicators are for 2019. Indicators that are not for 2019 are noted. For more information about cervical screening colposcopy, please visit our website at cancercareontario.ca/en/types-of-cancer/cervical/screening

Ontario Health Cancer Care Ontario

Future annual quality reporting

What can you expect from Ontario Health's quality reports?

- Reports that provide an overview of quality measured by select standards and indicators at varying levels (e.g., provincial, regional, facility and physician)



Dissemination of quality reports in Cancer Screening

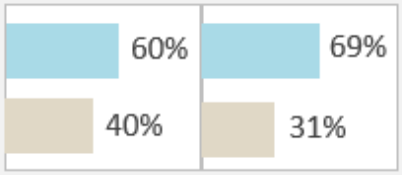
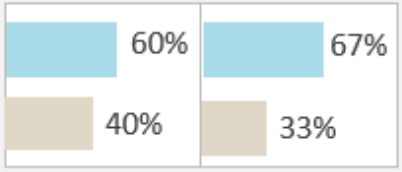
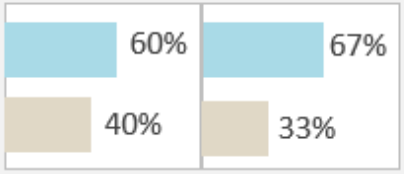
	Colonoscopy	Mammography	Cervical Screening & Colposcopy
Provincial	✓	✓	Planned for 2021
Regional	✓	✓	Planned for 2021
Facility (hospitals and non-hospital clinics)	✓ (n=156)	✓ (n=242)	Planned for 2021
Physician	✓ (n=941)	✓ (n=538)	Planned for fiscal year 2022/23

Sample: Colonoscopy quality facility report

Colonoscopy Quality Facility Report (Release Year 2020)

Facility: [NAME] Region: [NAME]

Standards

	Your facility	Region	Province
Standard 1. Facilities must adopt electronic and standardized reporting.			
Standard 2. Facilities must have equipment to record digital photographic evidence of relevant landmarks and lesions.			
Standard 3. Personnel involved in reprocessing must participate in a formalized training program beyond that provided by the manufacturers.			

Sample: Colonoscopy quality facility report

Colonoscopy Quality Facility Report (Release Year 2020)

Facility: [NAME] Region: [NAME]

Volumes and demographics, 2019

Total colonoscopy volume

1,000

Your region: 10,000
Province: 100,000

of region

Number of endoscopists

Your region: 41
Province: 987

Number of hospitals

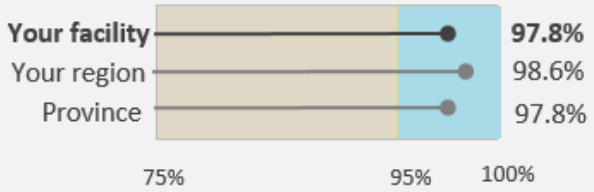
Your region: 14
Province: 100

Number of out-of-hospital premises

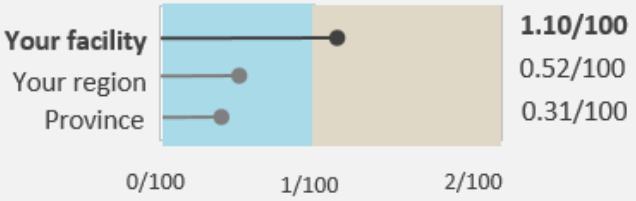
Your region: 20
Province: 60

Performance indicators

Outpatient cecal intubation, 2019
(Target > 95%)

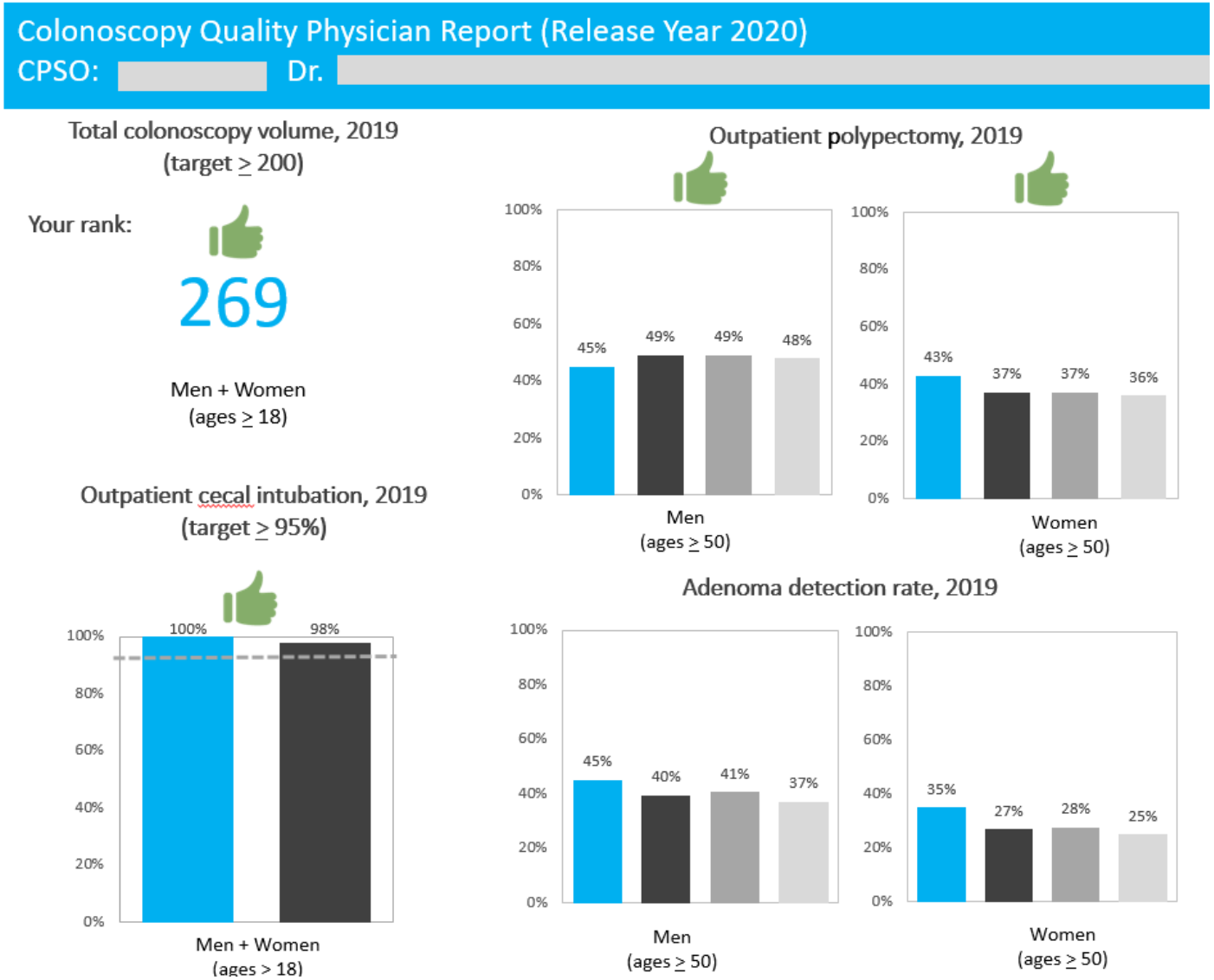


Post-polypectomy bleeding, 2019
(Target < 1/100)



Colonoscopy colorectal cancer detection rate, 2018

Sample: Colonoscopy quality physician report



What can you expect from us next?

- Fall 2020/Winter 2021: Engagement with facilities that provide colposcopy services (hospital and non-hospital)
  - Identify facility contacts who will receive reports and provide QI leadership
  - Communicate reporting plans and objectives
- Winter 2021: Dissemination of a facility survey to collect information on facilities' adherence to quality standards
- Spring 2021: Quality reporting update at the CoP webinar

Questions from the field

Questions from the field

- How can patients currently access HPV testing for screening?

Questions from the field

- HPV testing is currently available in Ontario:
  - For screening, on a patient-pay basis; or
  - In colposcopy, provided without charge in some hospital-based colposcopy units or is available on a patient-pay basis

Questions from the field

- Should I offer HPV testing for screening to patients who are ages 25-30?

Questions from the field

- OCSP currently recommends HPV testing as an optional triage test for people **≥ 30 years old** with cytology ASCUS
  - LSIL or ASCUS with HPV positive → colposcopy
  - LSIL or ASCUS with HPV negative → routine screening with cytology in 3 years
- We currently do not have recommendations for the use of HPV testing for people < 30 years old

Future state screening recommendations will recommend initiating *screening* at age 25 with HPV testing

Case study and review of adenocarcinoma in-situ (AIS) in Ontario

Case study

- A 37 year old patient is seen by her family doctor for an unrelated visit, and the doctor notices she is not up to date on cervical screening. Past screening history is normal. A cytology test is done and returns showing AIS cytology. The doctor should:

  A. Refer the patient to colposcopy for next available appointment

  B. Refer the patient to colposcopy as soon as possible

  C. Repeat the cytology test in 12 weeks

  D. Repeat the cytology test in 6 weeks

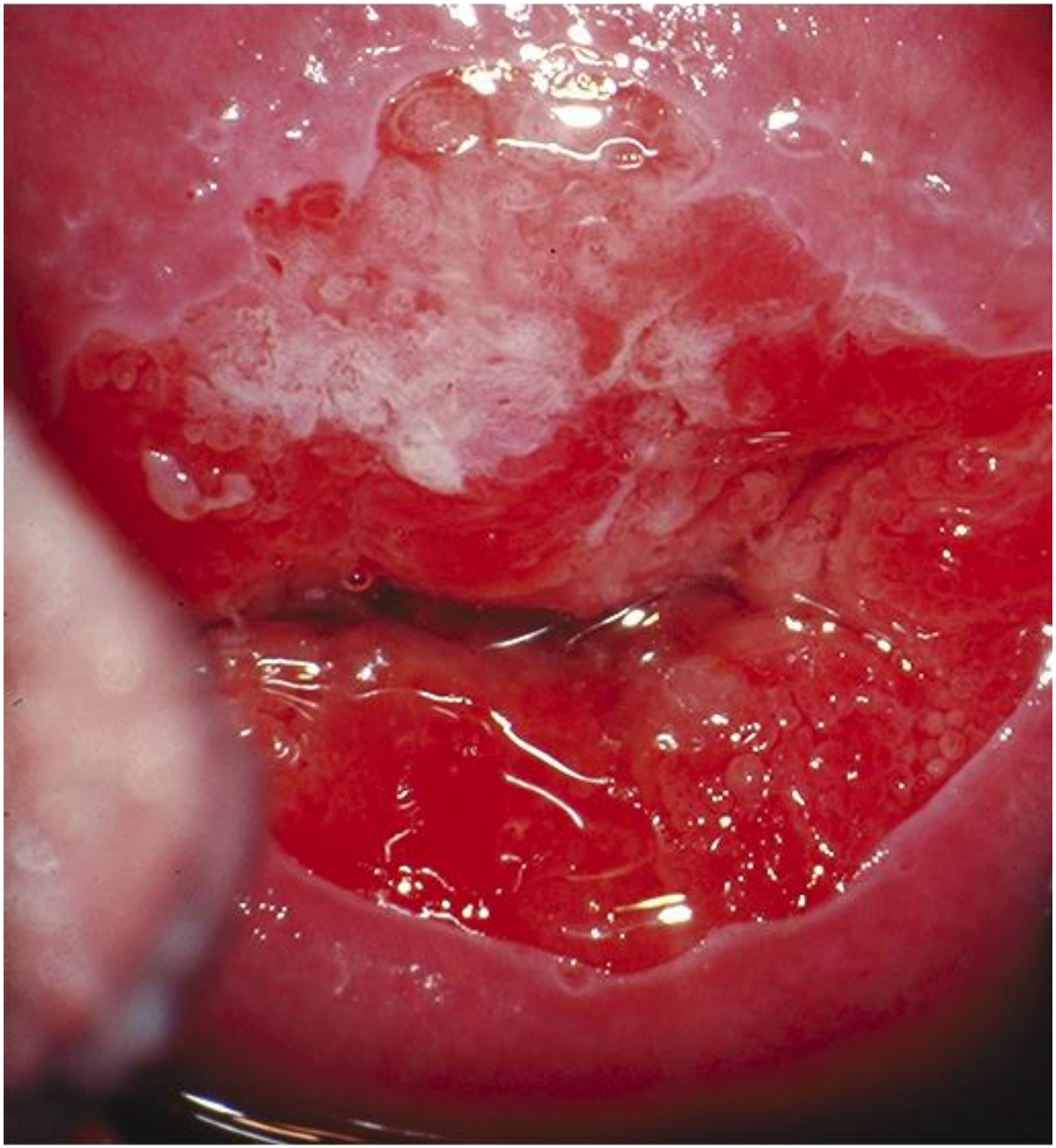
Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #1: Scenario A – fertility is desired

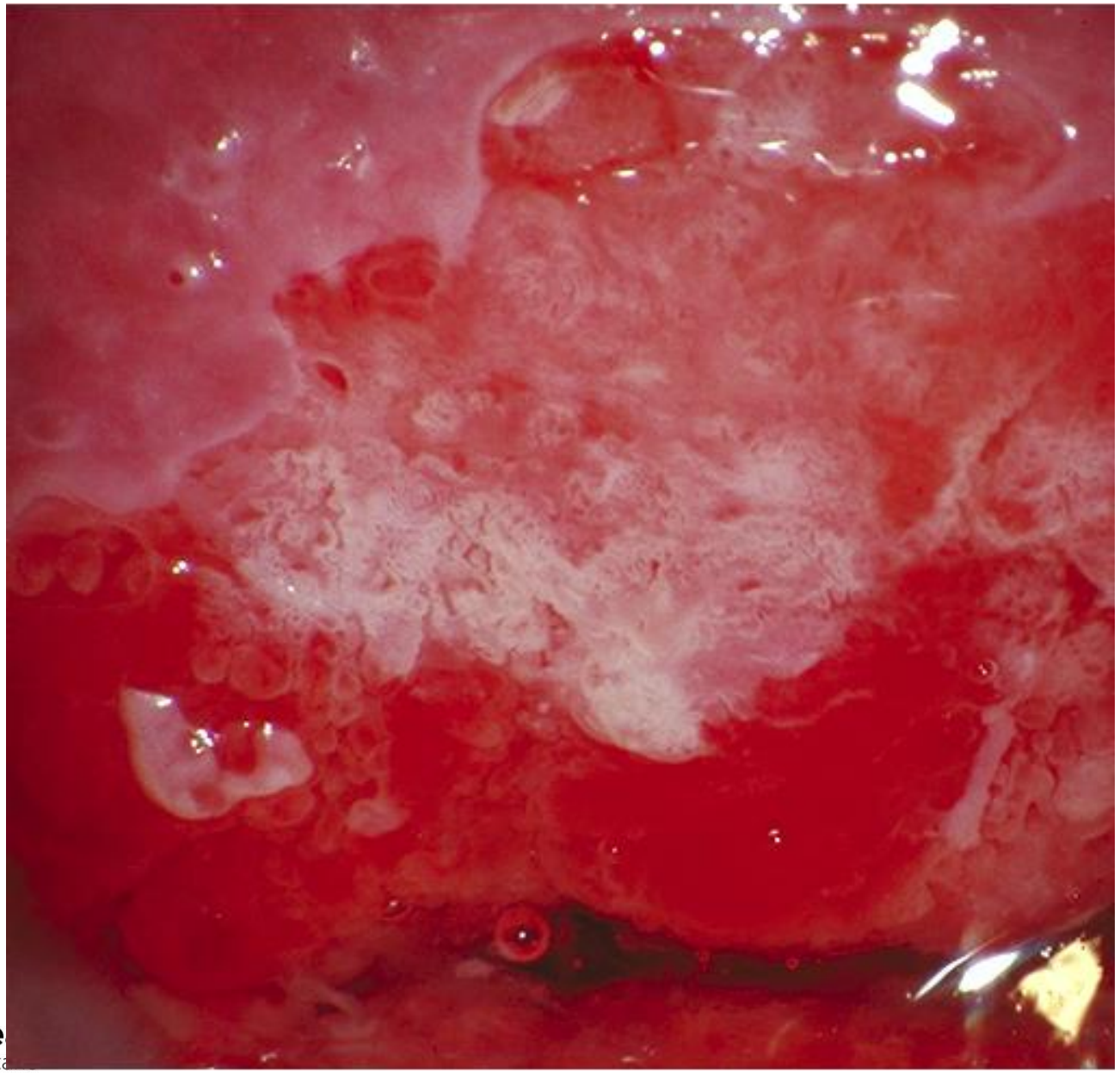
- The patient is seen in colposcopy within **2** weeks. The initial colposcopy findings are adequate and positive.

Visit #1: Images of cervix

Visit #1: Images of cervix



Visit #1: Images of cervix

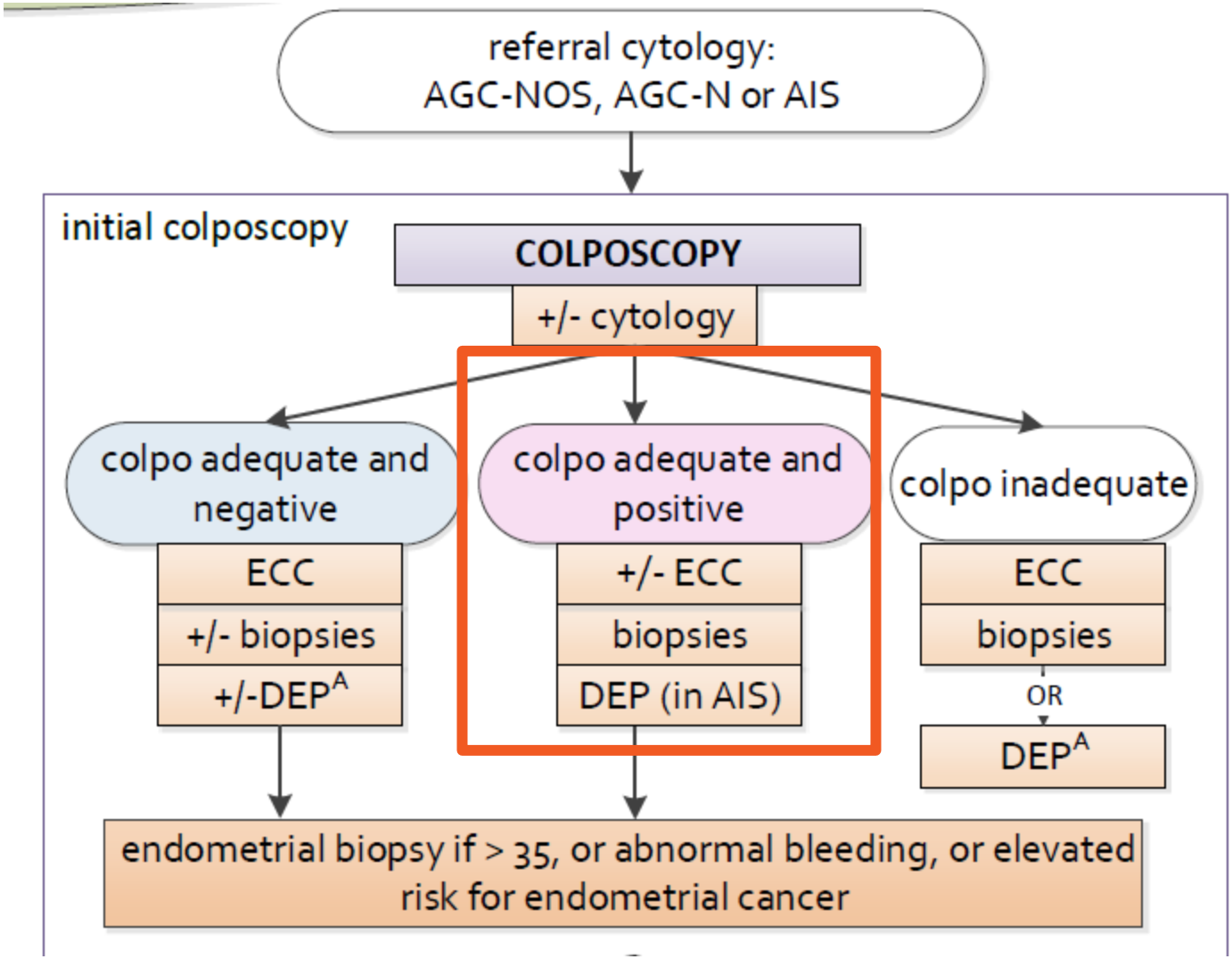


Visit #1: Scenario A – fertility is desired

- The patient is seen in colposcopy within **2** weeks. The initial colposcopy findings are adequate and positive.
- Based on these findings, you recommend:
  A. Repeat cytology and HPV testing
  B. Endo-cervical curettage (ECC)
  C. Loop electrosurgical excisional procedure (LEEP)
  D. Biopsy of lesion +/- endo-cervical sampling

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #1: Scenario A



Visit #2: Scenario A – fertility is desired

A biopsy is performed. Results are:

- Histologically confirmed AIS on biopsy

What is the recommended follow-up for this patient?

A. Repeat colposcopy in 3 months
B. Perform LEEP and post-LEEP ECC
C. Perform cold-knife conization (CKC)
D. Perform cryotherapy
E. B or C

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #3: Scenario A – fertility is desired

A LEEP and post-LEEP ECC are performed. Results are:

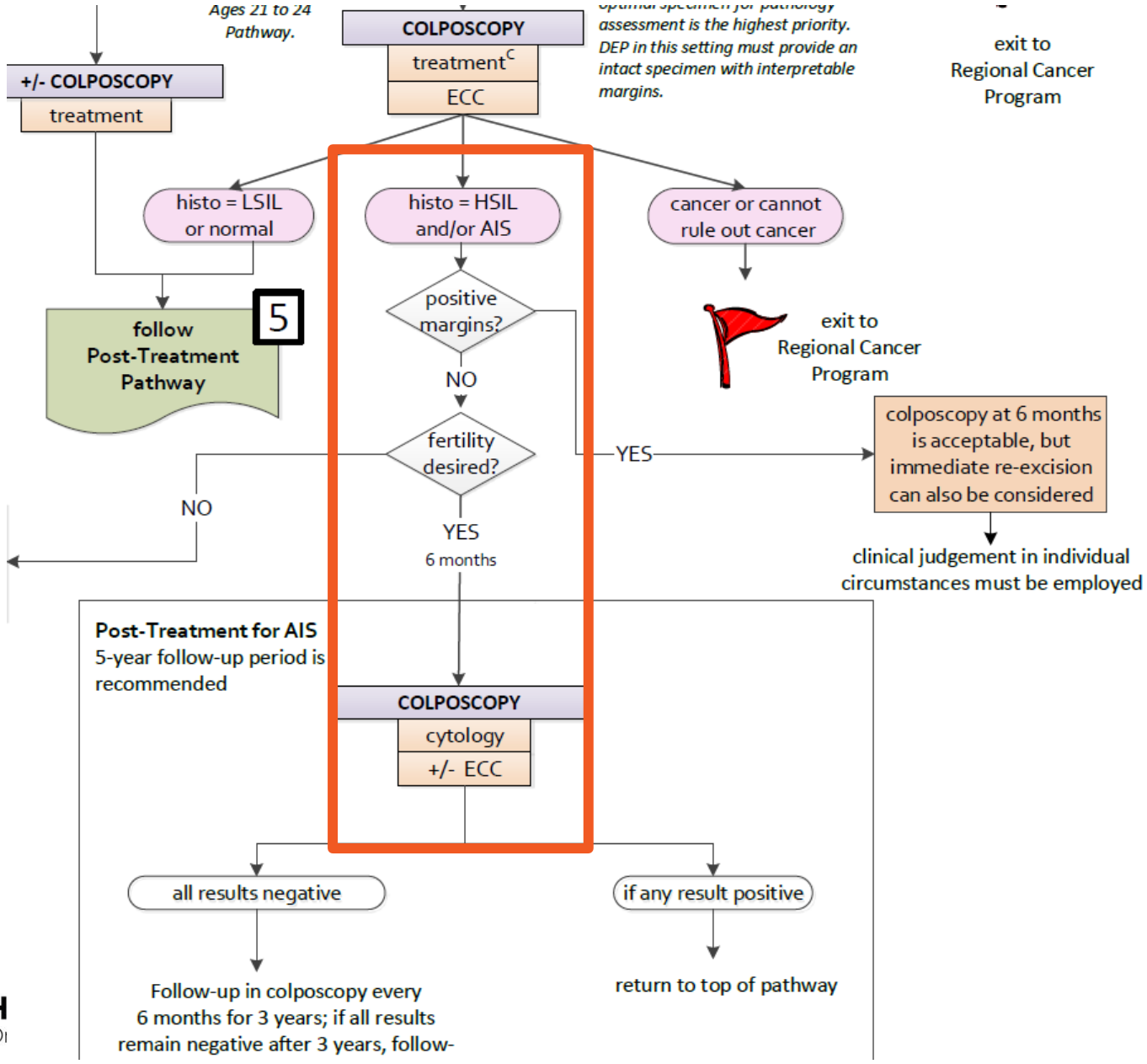
- Histology shows AIS with negative margins on LEEP
- ECC is negative

What is the next follow-up step?

A. Repeat colposcopy in 6 months
B. Repeat LEEP
C. Repeat colposcopy in 3 months
D. Perform cytology and HPV exit test
E. Perform hysterectomy

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #3: Scenario A



Guidelines from other jurisdictions

Society of Gynecologic Oncology (2020)[1]:

- HPV and cytology co-test and endo-cervical sampling every 6 months for 3 years, then annually until hysterectomy
- If co-testing and sampling test consistently negative for 5 years, extending surveillance interval to every 3 years indefinitely is acceptable

Clinical Practice Committee of Italian Society of Colposcopy and Cervical Pathology (2019)[2]:

- Colposcopy with cytology and HPV testing every 6 months for 2 years and subsequently every 12 months for 3 years
- Annual cytology indefinitely after 5 years

1. Teoh D, Musa F, Salani R, Huh W, Jimenez E. Diagnosis and management of adenocarcinoma in situ: a society of gynecologic oncology evidence-based review and recommendations. Obstetrics and Gynecology. 2020 Apr;135(4):869
2. Ciavattini A, Giannella L, Carpini GD, Tsiroglou D, Sopracordevole F, Chiossi G, Di Giuseppe J, of Colposcopy IS. Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV). European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019 Sep 1;240:273-7.

Visit #1: Scenario B – fertility not desired

- The patient is seen in colposcopy within **2** weeks after an AIS screening cytology result. The initial colposcopy findings are adequate and positive. A biopsy is performed, and you see:
  - Histology that shows AIS

What is the next follow-up step?

A. Perform hysterectomy
B. Repeat colposcopy in 3 months
C. Perform LEEP within a reasonable timeframe
D. Perform cytology and HPV exit test

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #2: Scenario B – fertility not desired

A LEEP and post-LEEP ECC are performed. Results are:

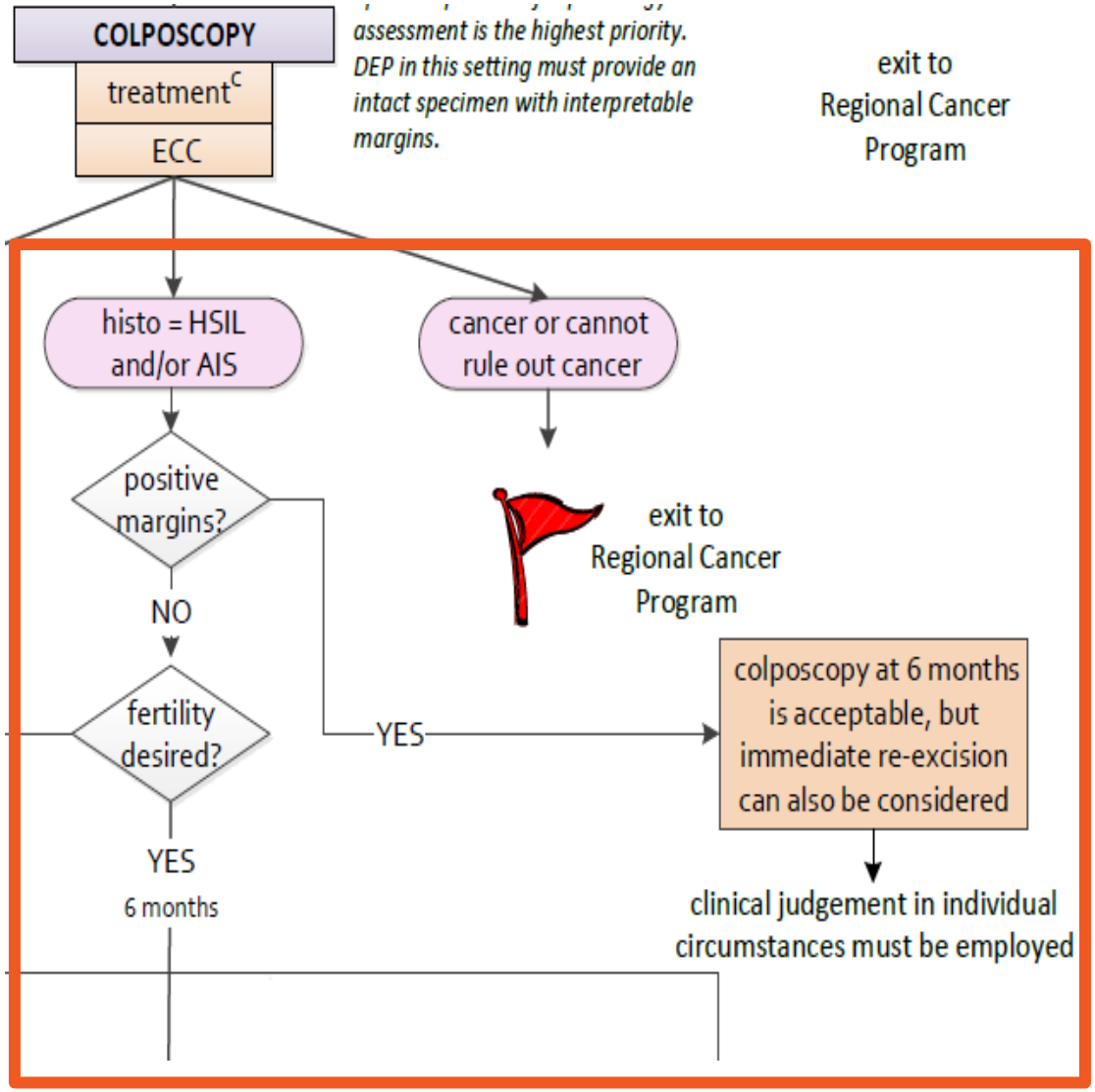
- Histology shows AIS with positive margins on LEEP
- ECC is negative

What is the next follow-up step?

A. Perform hysterectomy
B. Repeat colposcopy in 3 months
C. Repeat LEEP within a reasonable timeframe
D. Perform cytology and HPV exit test

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Visit #3: Scenario B



Visit #3: Scenario B – fertility not desired

A hysterectomy is performed. Final pathology shows:

- Invasive carcinoma (5 mm)

What is the next follow-up step?

A. Repeat colposcopy in 3 months
B. Repeat colposcopy in 6 weeks
C. Refer to gynecology oncology centre (GOC)

Please submit your answer by clicking on the Microsoft Form poll link in the chat box

Risk of Recurrence after Treatment for CIN3 and AIS of the Cervix

ORIGINAL RESEARCH ARTICLE: CERVIX AND HPV

Risk of Recurrence After Treatment for Cervical Intraepithelial Neoplasia 3 and Adenocarcinoma In Situ of the Cervix: Recurrence of CIN 3 and AIS of Cervix

Brenna E. Swift, MD, MASc,[1] Li Wang, MD, MSc,[2] Nathaniel Jembere, HBSc, MPH,[2] and Rachel Kupets, MD, MSc[1,2,3]

Brenna Swift
Gynecologic Oncology Fellow
University of Toronto

Swift BE, Wang L, Jembere N, Kupets R. Risk of recurrence after treatment for cervical intraepithelial neoplasia 3 and adenocarcinoma in situ of the cervix: recurrence of CIN 3 and AIS of cervix. Journal of lower genital tract disease. 2020 Jul 1;24(3):252-8.

Learning Objectives

At the end of this session, participants will:

1. Understand the risk of recurrence of CIN3 and AIS in Ontario women
2. Assess factors associated with a higher risk of recurrence
3. Discuss strategies to identify women requiring increased surveillance compared with women who can resume routine screening

Introduction: Exit Testing from Colposcopy

- Higher risk of invasive cancer (2.6 to 5-fold) in women previously treated for pre-cancerous lesions compared to general population
  - Increased risk persists despite 3 negative Pap smears after treatment
- Current strategies for exit testing from colposcopy:
  - Cytology alone: highest risk of recurrent HSIL at 5 years
    - 4.2–5.8% after 1 negative test and 2.9% after 2–3 negative tests
  - HPV testing alone: 0.9%–4.4% risk of recurrent HSIL at 5 years
  - Co-testing with HPV and cytology: lowest recurrence rate of cervical dysplasia at 5 years after treatment
    - 0.5%–3% after 1 negative co-test and 1%–1.5% after 2 negative co-tests.

(Melnikow *et al.*, 2009; Katki *et al.*, 2013; Kocken *et al.*, 2011; Soutter *et al.*, 2006; Coldman *et al.*, 2003; Gosvig *et al.*, 2015)

Study Objectives

- Evaluate 5-year recurrence risk of CIN3+ or AIS+ in a large population cohort of Ontario women previously treated for CIN3 or AIS
- Identify women requiring increased surveillance compared with women who can resume routine screening

Methods

- Study design: Population-based retrospective cohort study of Ontario women with CIN3 or AIS

- Exclusion criteria:
  - Women under 21
  - Treatment for cervical abnormalities in preceding 5 years
  - Previous hysterectomy or cancer

- Outcome: Recurrent cervical dysplasia or cancer after local treatment with LEEP, laser or cone for CIN3 or AIS

- Data sources: OHIP, Cytobase, Ontario Cancer Registry, Registered Persons Database, Canadian Institute for Health Information Database

Results

TABLE 1. Patient Characteristics Comparing Recurrence Rate of CIN 3 and AIS for Patients Previously Treated for CIN 3 or AIS of the Cervix

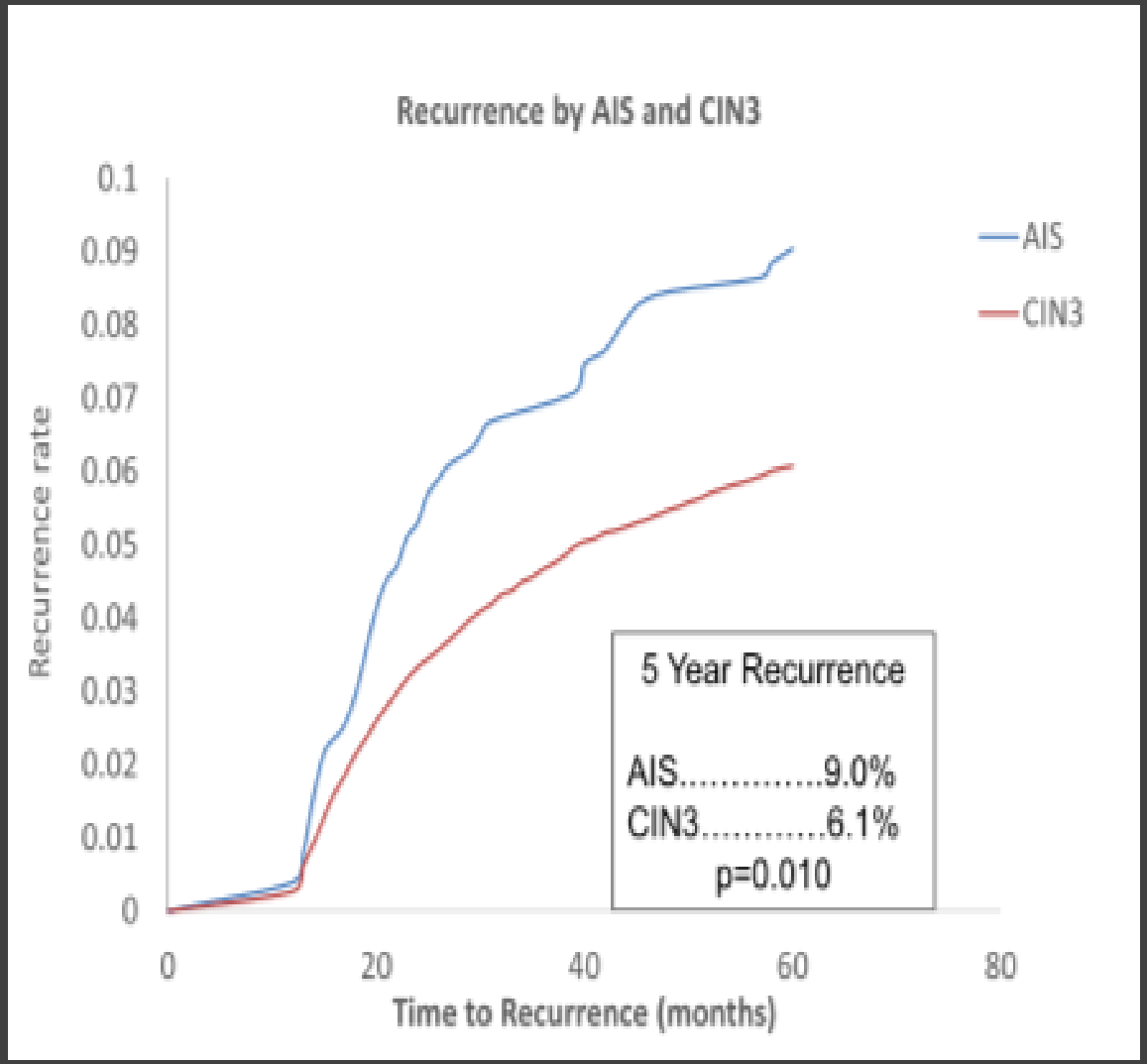
		AIS recurrence				CIN 3 recurrence			
		No, *n*	Yes, *n*	No (%)	Yes, %	No, *n*	Yes, *n*	No, %	Yes, %
Total	15177	463	46	90.96	9.04	13777	891	93.93	6.07
Age group									
	Total	No, *n*	Yes, *n*	No, %	Yes, %	No, *n*	Yes, *n*	No, %	Yes, %
<45	13290	386	42	90.19	9.81	12174	688	94.65	5.35
45+	1887	77	4	95.06	4.94	1603	203	88.76	11.24
First Pap result after treatment									
AGC	53	6	0	100	0	35	12	74.47	25.53
ASC-H	97	0	0	0	0	61	36	62.89	37.11
ASCUS	663	15	3	83.33	16.67	583	62	90.39	9.61
Adeno in situ	1	1	0	100	0	0	0	0	0
HSIL	196	0	1	0	100	99	96	50.77	49.23
LSIL	484	5	0	100	0	402	77	83.92	16.08
Normal	8724	257	24	91.46	8.54	8202	241	97.15	2.85
Other abnormalities	5	0	0	0	0	5	0		
Squamous cell carcinoma	2	0	0	0	0	1	1	50	50
Unknown (OHIP Pap)	4952	179	18	90.86	9.14	4389	366	92.3	7.7

Results

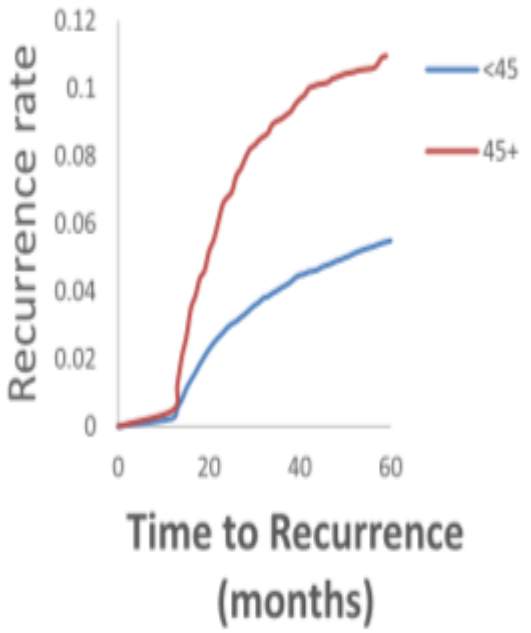
TABLE 1. Patient Characteristics Comparing Recurrence Rate of CIN 3 and AIS for Patients Previously Treated for CIN 3 or AIS of the Cervix

		AIS recurrence				CIN 3 recurrence			
		No, *n*	Yes, *n*	No (%)	Yes, %	No, *n*	Yes, *n*	No, %	Yes, %
Treatment used with diagnosis									
Cone	4373	328	30	91.62	8.38	3793	222	94.47	5.53
LEEP	9217	129	16	88.97	11.03	8521	551	93.93	6.07
Laser	1587	6	0	100	0	1463	118	92.54	7.46
Physician workload, no. procedures per year per surgeon									
<40	9016	284	28	8.97	8.97	8217	487	94.4	5.6
40+	6161	179	18	9.14	9.14	5560	404	93.23	6.77

Results


Recurrence by AIS and CIN3
Recurrence rate
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
20
40
60
80
Time to Recurrence (months)
AIS
CIN3
5 Year Recurrence
AIS.....9.0%
CIN3.....6.1%
p=0.010

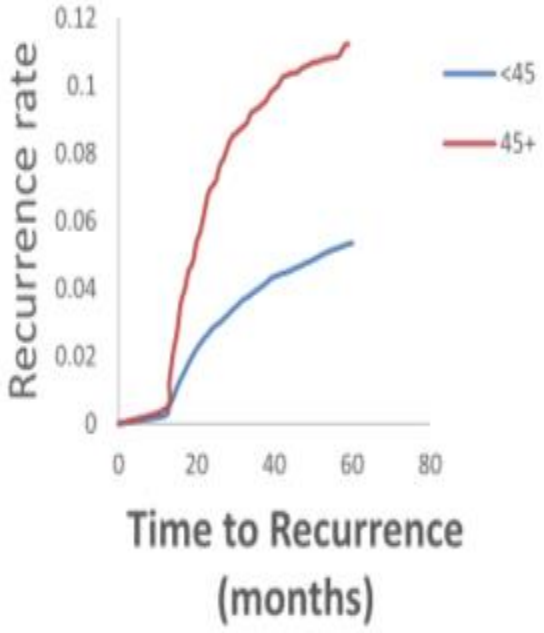
A



5 Year Recurrence

<45.....5.6%
45+.....11.2%
p=0.0001

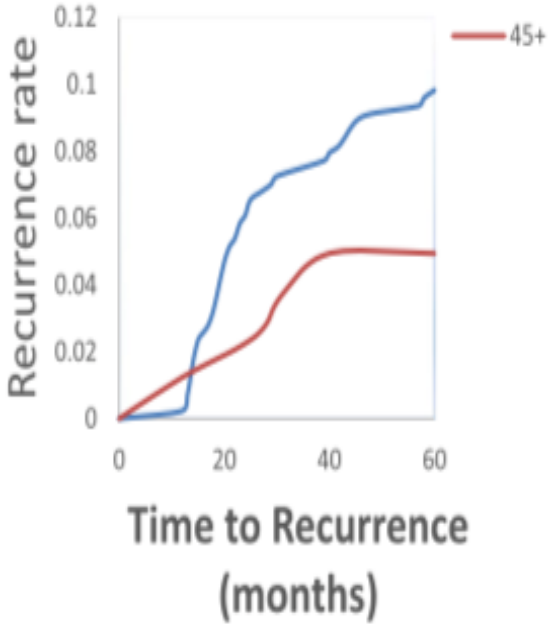
B



5 Year Recurrence

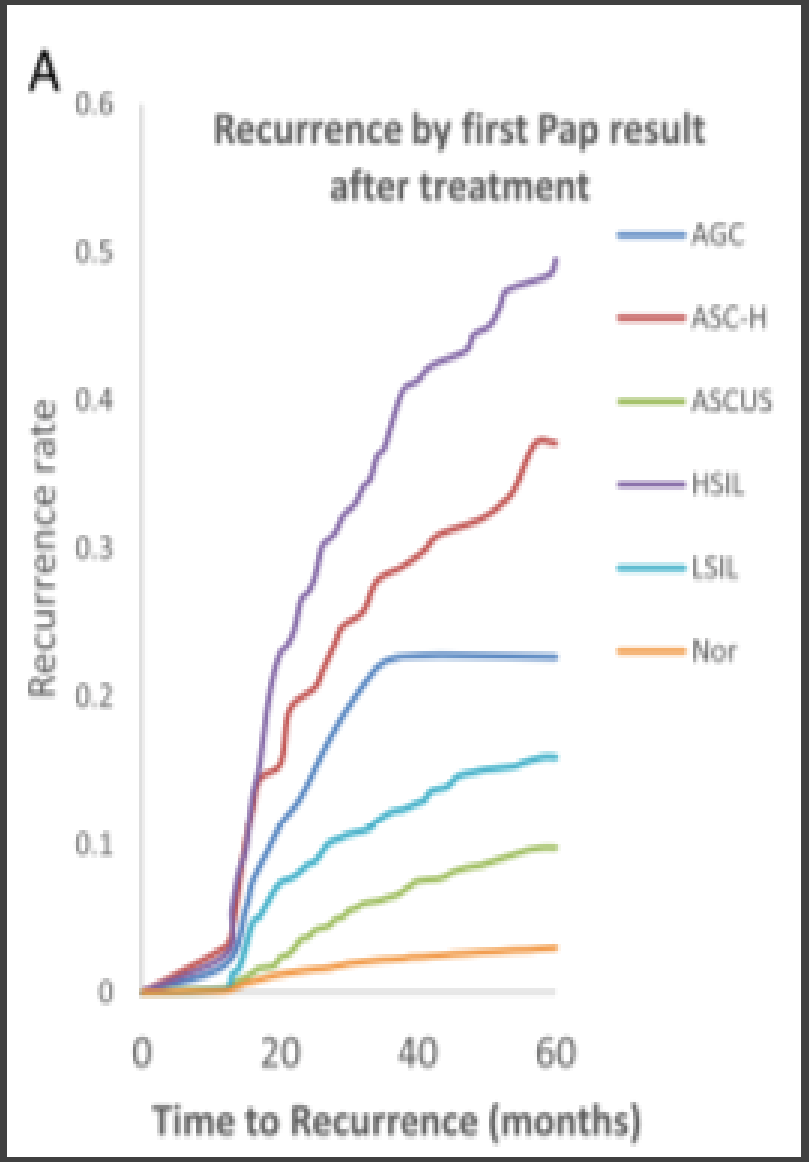
<45.....5.3%
45+.....11.2%
p=0.0001

C



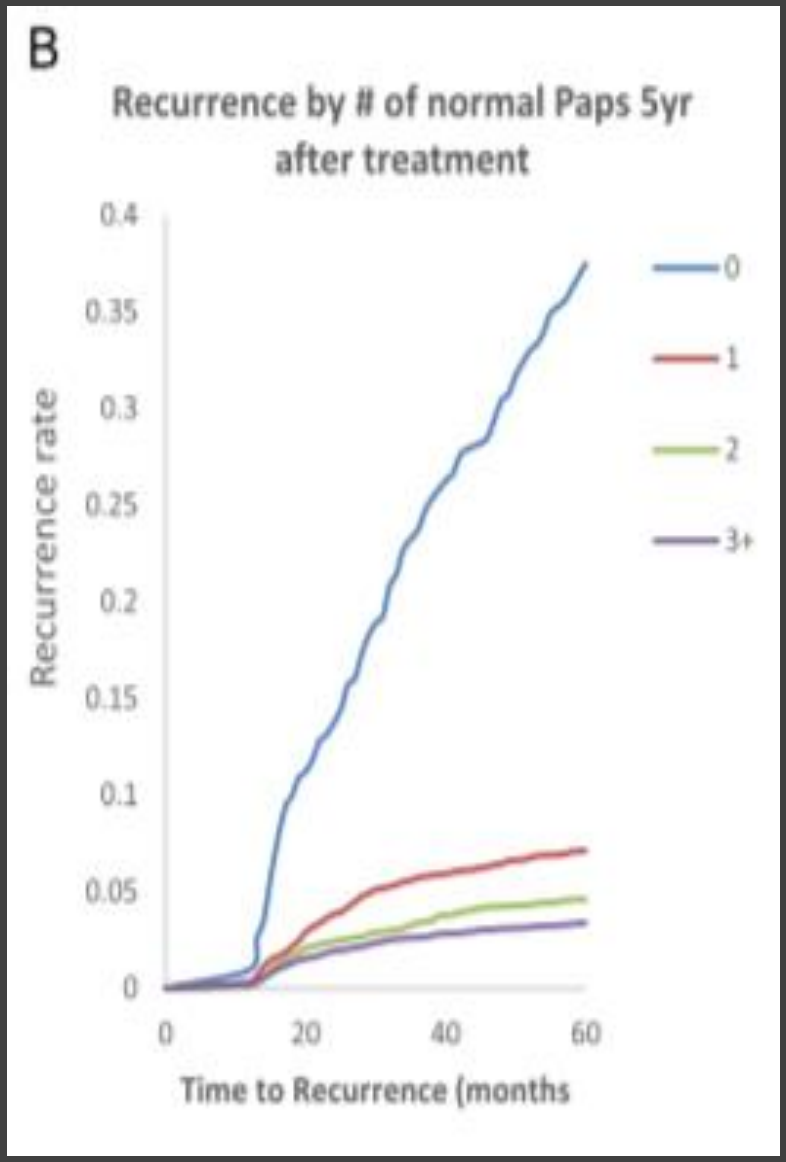
5 Year Recurrence

<45.....9.8%
45+.....4.9%
p=0.13



Recurrence

Normal.....3.1%
ASCUS.....9.8%
LSIL.....15.9%
AGC.....22.6%
ASC-H.....37.1%
HSIL.....49.5%
p=0.0001



5 Year Recurrence

0.....37.5%

1.....7.1%

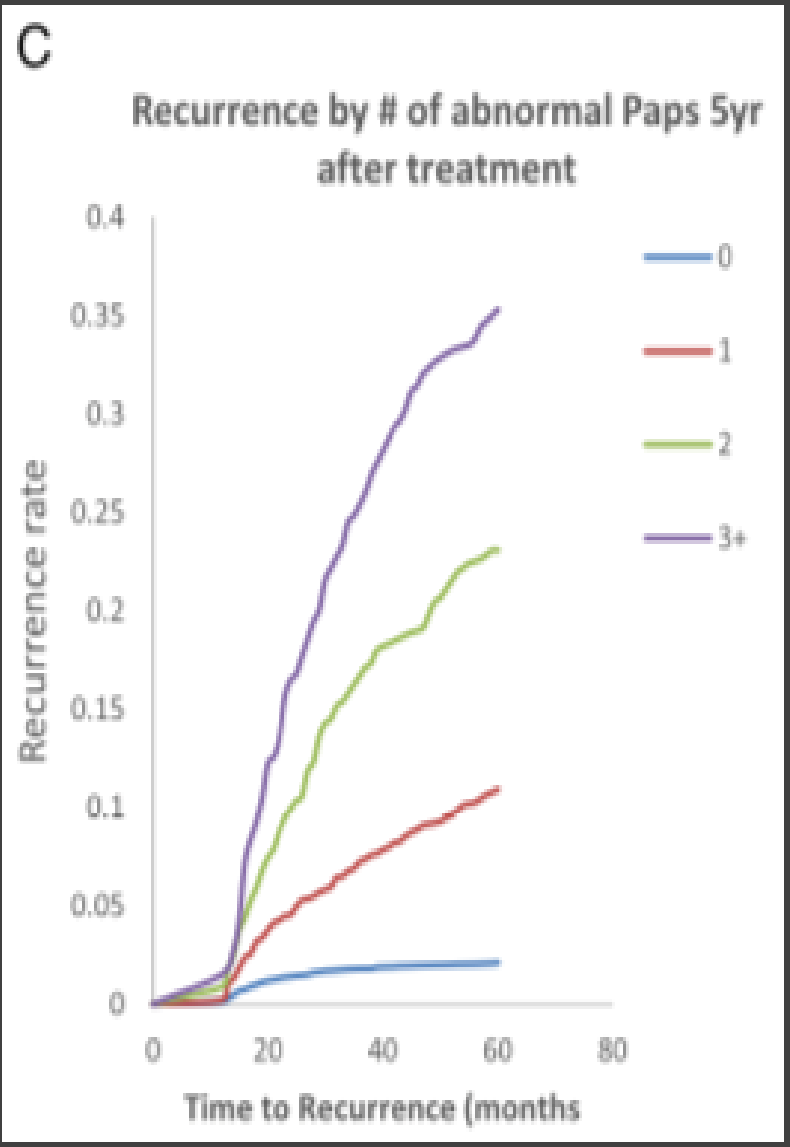
2.....4.6%

3+.....3.4%

p=0.0001

	Total # normal paps 5 years after treatment			
	0	1	2	3+
Mean total # of all paps 5 years after treatment	3.0	2.4	3.2	4.9

C



5 Year Recurrence

0.....2.1%

1.....10.9%

2.....23.1%

3+.....35.3%

p=0.0001

	Total # abnormal paps 5 years after treatment			
	0	1	2	3+
Mean total # number of all paps 5 years after treatment	3.5	4.4	5.1	7.0

Multivariable Analysis

TABLE 2. Multivariate Analysis of Patient Characteristics Comparing Recurrence Rate of CIN 3 and AIS for Patients Previously Treated for CIN 3 or AIS of the Cervix

Variables	HR	95% CI	*p*
Age			
<45	Ref		.01
45+	1.3	1.1–1.6	
First Pap result			
Normal	Ref		
High grade	12.4	9.7–15.7	<.0001
Low grade	3.5	2.8–4.4	
No. normal Pap after treat			
3+	Ref		<.0001
0	2.8	2.2–3.7	
1	2.0	1.6–2.5	
2	1.3	1.1–1.7	
Treatment			
LEEP	Ref		.8059
Cone	1.0	0.8–1.2	
Laser	1.1	0.8–1.4	
Histology			
CIN 3	Ref		<.0001
AIS	2.2	1.5–3.3	
Physician work load, no. procedures per surgeon per year			
<40	Ref		.2320
40+	1.1	0.9–1.3	

Risk of Cervical Cancer

- 31 cancers detected in the 1–5 years after treatment for pre-invasive lesions
  - **AIS:** 2 (0.39%) of 509 cases
  - **CIN3**: 29 (0.20%) of 14,668
  - **Median age:** 39, range 27–70 years
  - **Median time from treatment to cancer:** 35 months
  - **Median (range) follow-up time from treatment to first Pap test for women who subsequently developed cancer:** 10.5 months (3.1–60 months)
  - **First Pap test result after treatment:**
    - Normal in 35.5%
    - AGC/HSIL in 32.3%
    - ASCUS/LSIL/ASC-H in 9.7%
    - Unknown in 22.6%

Future Directions to Improve Risk Stratification

- Co-testing with HPV and cytology: exit testing has lowest recurrence rate of cervical dysplasia at 5 years after treatment for CIN 3 and AIS
  - 0.5%–3% and 1%–1.5% recurrence after 1 and 2 negative co-tests, respectively

- Dual staining with p16/Ki-67 in HPV positive patients: higher sensitivity, specificity, positive predictive and negative predictive value compared with cytology

- DNA methylation testing: identifies biomarker genes that are methylated in CIN 2/3 and cervical cancer, may identify subsets of CIN 2 and CIN 3 that are more likely to progress to invasive cancer

(Katki *et al.*, 2013; Kocken *et al.*, 2011; Gosvig *et al.*, 2015; Sun *et al.,* 2019; Lorincz *et al.,* 2016)

Key Take-aways

- Higher risk of recurrence of CIN3, AIS and invasive cancer in women previously treated for CIN3 and AIS

- Risk of recurrence higher with:
  - AIS
  - Over age 45 with CIN3; inconclusive for AIS
  - High-grade result on first cytology after treatment

Questions?

Thank you!

Implications for the program

- Colposcopy recommendations for the management of people with AIS is under review by the OCSP
- To finalize our recommendations, the OCSP will:
  - Review existing evidence, including Ontario-specific data
  - Seek advice by convening an expert panel
- Updated screening and colposcopy recommendations will be shared in advance of the implementation of HPV testing

Concluding remarks

Thank you!

CoP webinars have been recognized by the University of Toronto for winning the *Chair's Award for Excellence in Continuing Medical Education Course Coordination*

Accreditation

Royal College of Physicians and Surgeons of Canada – Section 1:

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, approved by Continuing Professional Development, Faculty of Medicine, University of Toronto. You may claim up to a maximum of 1.5 hours (credits are automatically calculated).

In order to obtain your certificate of participation, you must fill out our survey that will be emailed to you following this meeting.

What's next?

- Please ensure you fill out the post-webinar survey – survey link will be emailed to CoP webinar attendees
- Next CoP webinar: spring 2021 (dates TBD)
- Share your feedback and questions with us at ColposcopyCoP@ontariohealth.ca

Please note the NEW email address


Thank
You!

Appendix

References

Melnikow J, McGahan C, Sawaya GF, et al. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. J Natl Cancer Inst 2009;101:721–8.

Katki HA, Schiffman M, Castle PE, et al. Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. J Low Genit Tract Dis 2013;17:S78–84.

Kocken M, Helmerhorst TJ, Berkhof J, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol 2011;12:441–50.

Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer 2006;118:2048–55.

Coldman A, Phillips N, Kan L, et al. Risk of invasive cervical cancer after three consecutive negative Pap smears. J Med Screen 2003;10:196–200.

Gosvig CF, Huusom LD, Deltour I, et al. Role of human papillomavirus testing and cytology in follow-up after conization. Acta Obstet Gynecol Scand 2015;94:405–11.

Sun H, Shen K, Cao D. Progress in immunocytochemical staining for cervical cancer screening. Cancer Manag Res 2019;11:1817–27.

Lorincz AT. Virtues and weaknesses of dna methylation as a test for cervical cancer prevention. Acta Cytol 2016;60:501–12.

Methods: Study Design

- Population-based retrospective cohort study of Ontario women
- Women with diagnosis of CIN3 or AIS defined by ICD-O-3 code C53, in situ cervical cancer
- Index date defined as first date of treatment after diagnosis of CIN3 or AIS

Exclusion criteria:

- Women < age 21
- No follow up pap cytology within 5 years of treatment
- No treatment within 6 months of diagnosis
- Previous treatment for cervical abnormalities in the preceding 5 years
- Previous hysterectomy
- Previous cervical cancer
- In situ cervical cancer histology other than CIN3 or AIS
- Missing or invalid health card number
- Missing date of birth

Methods: Study Design

- Main study outcome: recurrent cervical dysplasia after local treatment with LEEP, laser or cone for CIN3 or AIS
  - Recurrence defined as:
    - Subsequent biopsy result of CIN3 or AIS

    OR
    - Retreatment with LEEP, laser, cone or hysterectomy in the period of 1-5 years after index treatment
      - Hysterectomy included if within 6 months of hysterectomy:
        - Abnormal pap
        - Colposcopy and biopsy
        - OR main diagnosis for hysterectomy was cervical dysplasia or malignancy

Additional Study Variables:

- Age
- Number of normal and abnormal Pap tests 5 years after treatment
- First Pap result after treatment,
- Treatment modality
- Histologic type
- Number of procedures per year/surgeon

Methods: Data Sources and Variables

- Administrative databases used to determine relevant study variables

OHIP database

- Contains healthcare billing services delivered by physicians to patients
  - Pap tests performed
  - Colposcopic care
  - Colposcopy–related treatments

Registered Persons database

- Age and other demographic variables

Canadian Institute for Health Information database

- indication for hysterectomy

Cytobase

- Used to identify Pap test cytology results

Ontario Cancer Registry

- Records all diagnosed cancer cases in Ontario since 1964

Methods: Statistical Analysis

- Descriptive statistics to analyze patient population stratified by CIN3 and AIS
- Survival analysis for recurrences using Kaplan-Meier method, compared by log rank test
- Multivariate analysis using Cox proportional hazards model to assess impact of covariates on recurrence risk
  - Statistical analyses were performed using SAS version 9.4

TABLE 1. Patient Characteristics Comparing Recurrence Rate of CIN 3 and AIS for Patients Previously Treated for CIN 3 or AIS of the Cervix

			AIS recurrence				CIN 3 recurrence		
Follow-up									
Total normal Pap 5 y after treat									
0	1857	85	12	87.63	12.37	1424	336	80.91	19.09
1	3131	93	13	87.74	12.26	2821	204	93.26	6.74
2	3366	69	4	94.52	5.48	3146	147	95.54	4.46
3+	6823	216	17	92.7	7.3	6386	204	96.9	3.1
Total abnormal Pap 5 y after treat									
0	12479	408	39	91.28	8.72	11593	439	96.35	3.65
1	1818	42	0	100	0	1561	215	87.89	12.11
2	525	8	5	61.54	38.46	397	115	77.54	22.46
3+	355	5	2	71.43	28.57	226	122	64.94	35.06
Total colpo 5 y after treat									
0	2694	120	2	98.36	1.64	2562	10	99.61	0.39
1	2667	57	3	95	5	2543	64	97.55	2.45
2	3526	58	3	95.08	4.92	3368	97	97.2	2.8
3+	6290	228	38	85.71	14.29	5304	720	88.05	11.95

Study Limitations

- Administrative data, not medical chart data
  - No documentation regarding transformation zone, margin status, HPV status
- Ontario Cancer Registry for biopsy pathology is a cancer database, may have had under reporting of precancerous specimens
- Pap tests or surgical pathology performed in hospital setting not captured in databases
  - Recurrence definition for retreatment procedure required previous biopsy, abnormal pap or diagnosis of cervical dysplasia or cancer for inclusion

Future Directions to Improve Risk Stratification: Other Jurisdictions

- HPV testing part of exit testing from colposcopy and screening after treatment for AIS and HSIL in the United States, Australia, New Zealand and the United Kingdom

	ASCCP/SGO	Australia/New Zealand	United Kingdom
After treatment for CIN3	Co-testing at 12 and 24 months, then at 3 years → all negative = routine screening	Co-testing at 12m months then annually until negative x 2 consecutive → routine screening	Cytology at 6 months with reflex HPV
After treatment for AIS	Hysterectomy recommended unless future fertility desired then co-test q6months x 3 yrs then q2 yrs until hysterectomy	Annual co-tests indefinitely	Co-testing at 6 and 18 months → all negative = routine screening

Summary

1. Higher risk of recurrence of CIN3, AIS and invasive cancer in women previously treated for CIN3 and AIS compared with the general population
    - Highest risk of recurrence:
        - AIS
        - Age > 45 years with CIN 3
        - First Pap smear after treatment showed high-grade cytology (HSIL, ASC-H, AGC)
    - Greater number of normal Pap smears after treatment associated with decreased risk of recurrence

2. Consideration of definitive management with hysterectomy is reasonable when fertility is not desired.
    - Guidelines from the ASCCP, NCCN, and ACOG support hysterectomy for women with AIS (20,25,26)
    - Australian guidelines do not recommend completion hysterectomy for AIS if margins negative (21)

3. Risk-based screening should also include HPV status at exit testing and follow-up screening after treatment for CIN 3 and AIS.
    - Future studies to consider co-testing with dual staining of p16/Ki-67 or DNA methylation