How can economic models inform decisions about screening?

Case study: choice of diagnostic test used in a population-based cervical screening program in Canada

23 September 2020

Dr Elisabeth Adams, Founder & Managing Director

Aquarius Population Health

Conflict of interest

- I am employed by Aquarius Population Health, an independent healthcare consultancy which conducts projects funded by government, academia, healthcare providers, charities and commercial companies.

- The research studies presented here were funded by Hologic; the results, interpretation and broader discussion are the authors' own.

Learning objectives

1. Understand how the choice and performance of diagnostic tools can have implications for resource use in screening programs

2. Explore the estimated costs and benefits of diagnostic test selection on a population-based screening program using economic modelling

3. Consider how to interpret economic model results to inform meaningful healthcare decisions

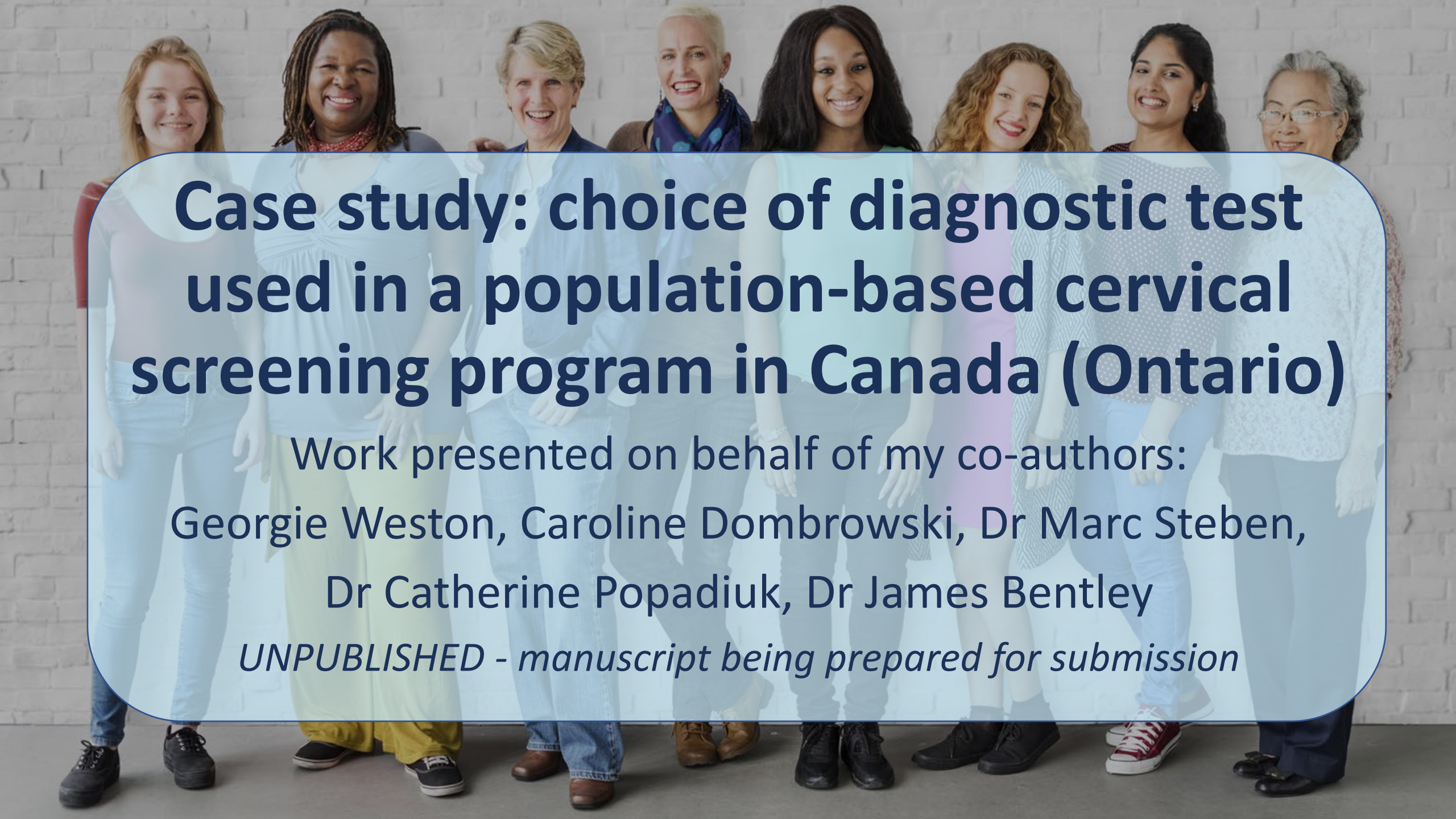
The tale of two presentations…

We want to do two things today:

- Discuss how health economics evidence can be developed to help policy decisions at local, regional, national and international levels
- Illustrate an example in which we explored how the choice of a screening test for human papillomavirus (HPV) can inform decision-making in cervical cancer screening programmes

What are the key questions when considering evidence for policy decisions?

- What is the specific question that needs to be answered?
- Who needs the evidence?
- How are they going to use the evidence?
- What output/format do they need it in to make the decision?
- When do they need it?
- Who needs to be involved in developing the evidence?



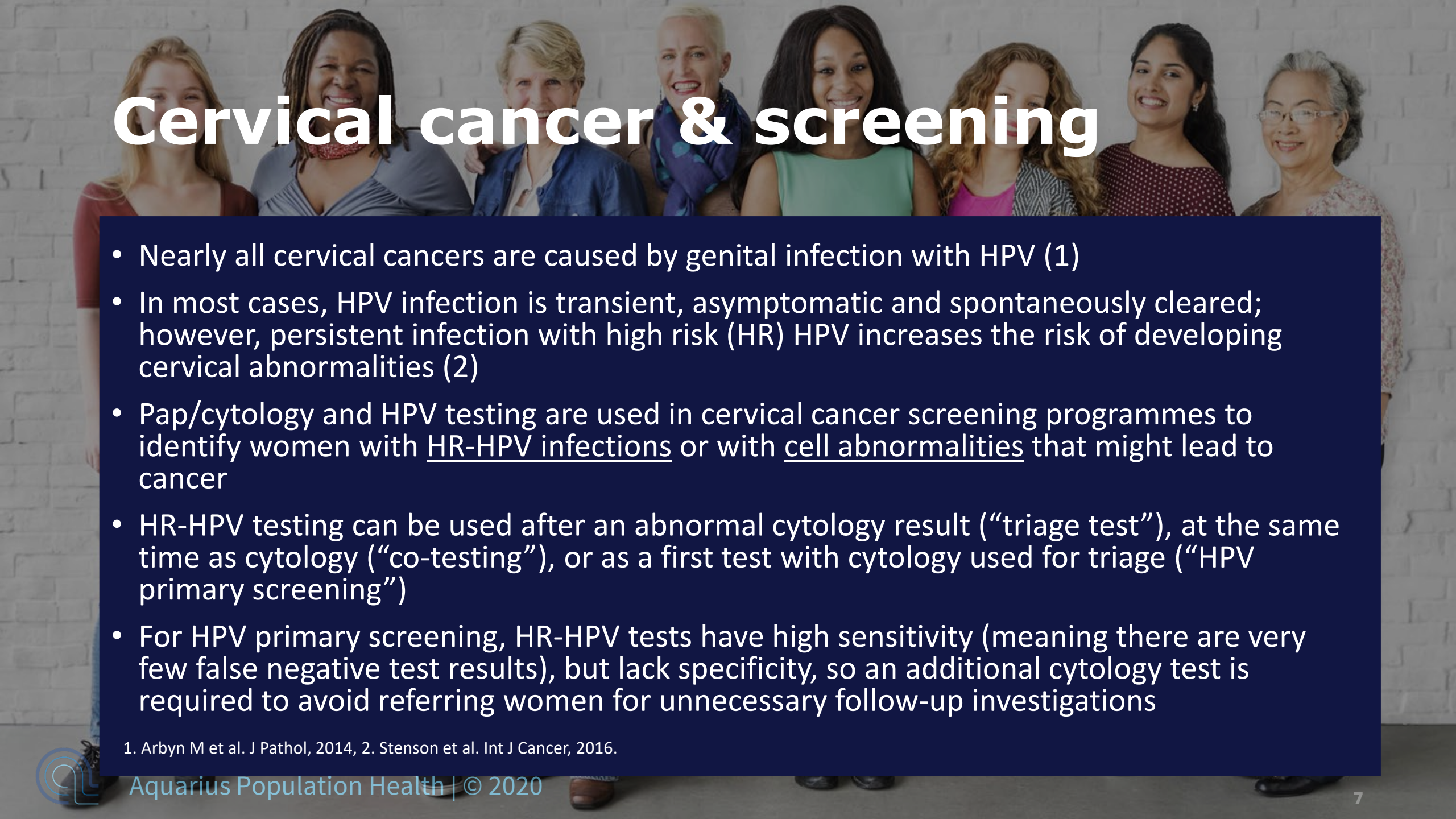
Case study: choice of diagnostic test used in a population-based cervical screening program in Canada (Ontario)

Work presented on behalf of my co-authors:

Georgie Weston, Caroline Dombrowski, Dr Marc Steben,

Dr Catherine Popadiuk, Dr James Bentley

UNPUBLISHED - manuscript being prepared for submission



Cervical cancer & screening

- Nearly all cervical cancers are caused by genital infection with HPV (1)
- In most cases, HPV infection is transient, asymptomatic and spontaneously cleared; however, persistent infection with high risk (HR) HPV increases the risk of developing cervical abnormalities (2)
- Pap/cytology and HPV testing are used in cervical cancer screening programmes to identify women with HR-HPV infections or with cell abnormalities that might lead to cancer
- HR-HPV testing can be used after an abnormal cytology result (“triage test”), at the same time as cytology (“co-testing”), or as a first test with cytology used for triage (“HPV primary screening”)
- For HPV primary screening, HR-HPV tests have high sensitivity (meaning there are very few false negative test results), but lack specificity, so an additional cytology test is required to avoid referring women for unnecessary follow-up investigations

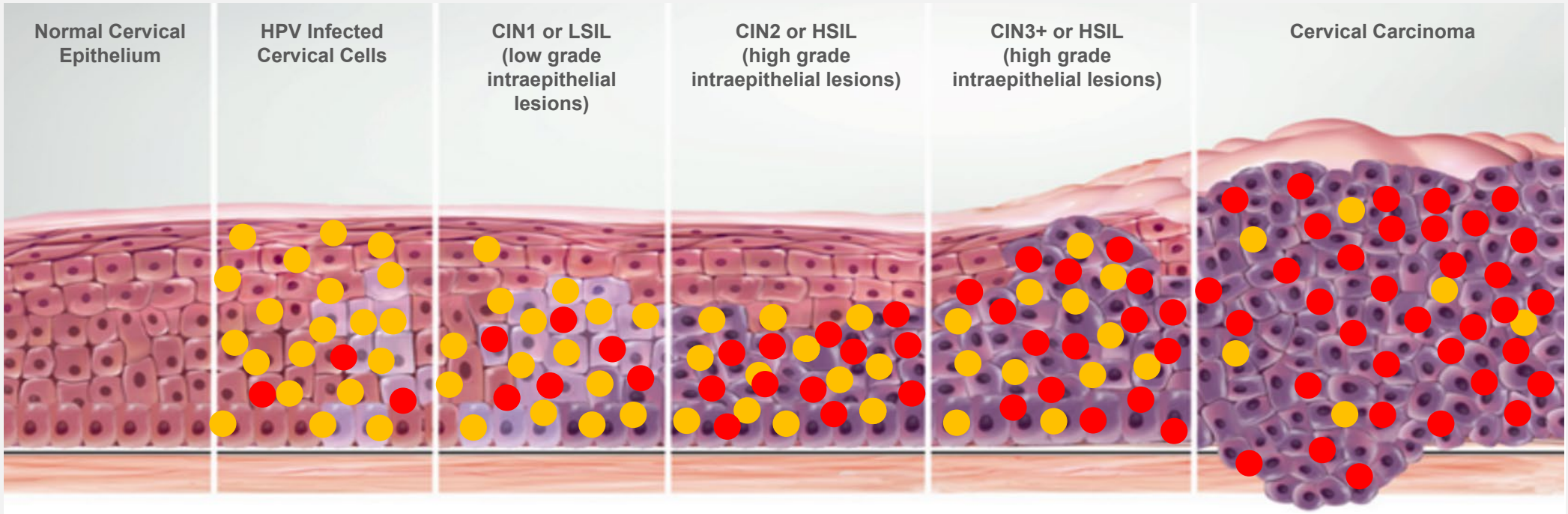
1. Arbyn M et al. J Pathol, 2014, 2. Stenson et al. Int J Cancer, 2016.

Months

Years

Decades

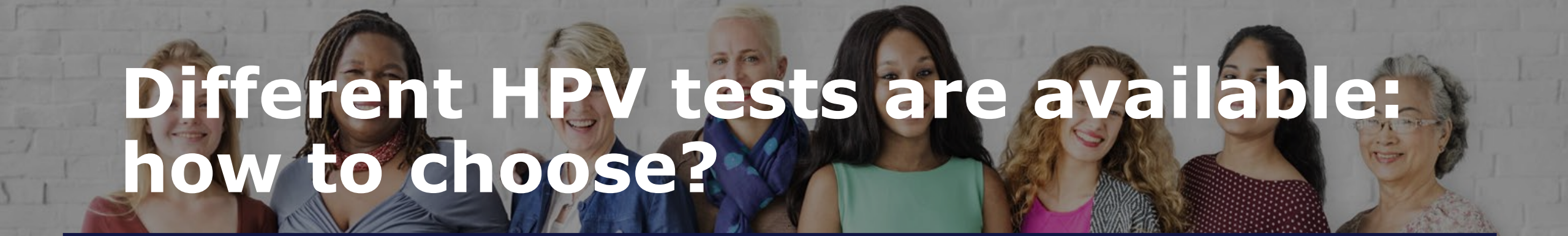
REGRESSION



HPV DNA Levels

HPV E6/E7 mRNA Levels

Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. Clinical Science 2006. 110(5):525-41



Different HPV tests are available: how to choose?

- Many approved HR-HPV tests on the market globally
- A positive HR-HPV DNA screening test indicates the presence of HR-HPV DNA in cervical screening samples (1)
- A positive mRNA test indicates that HPV E6/E7 oncoproteins are being expressed in the cell (1,2)
- Both mRNA and DNA tests have similarly high sensitivity for detecting cervical intraepithelial neoplasia (CIN), a precursor to cancer, meaning that few true positives are missed (1,3-6)
- mRNA has higher specificity for detecting CIN, than DNA and therefore reports fewer false positives (7)

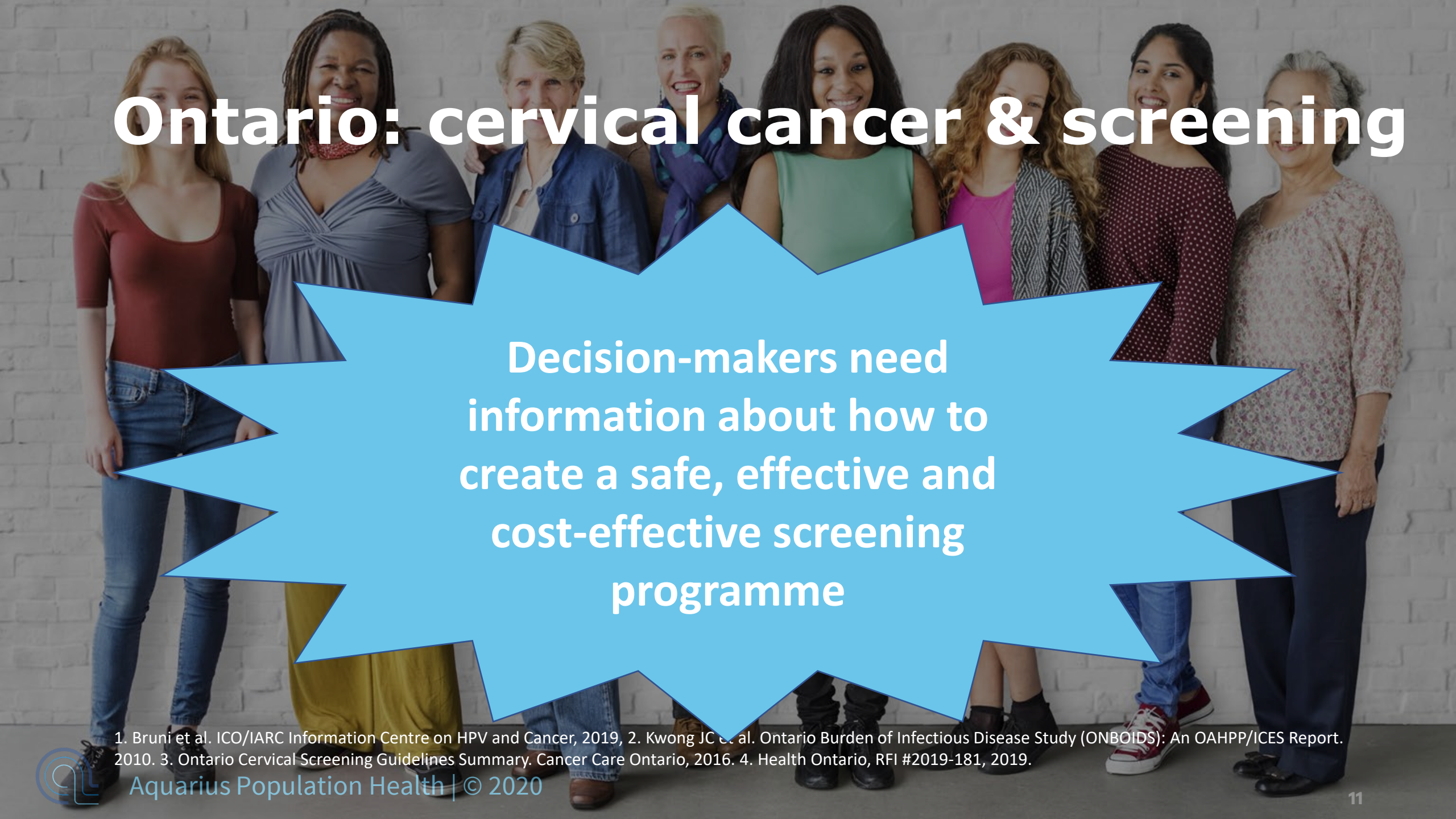
1. Cook et al. J Clin Virol. 2018. 2. Arbyn M et al. Cancer. 2013. 3. Arbyn M et al. Vaccine 2012. 4. Cuzick et al. Br J Cancer. 2013. 5. Cook et al. J Clin Virol. 2017. 6. Iftner T et al. J Clin Microbiol. 2015. 7. Haedicke J & Iftner T. Recent Adv Molec Detect Hum Papillomavirus Cerv Cancer Screen. 2016.

Ontario: cervical cancer & screening

- Some programmes in Canada are currently using HR-HPV testing for triage testing, with some provinces planning for HPV primary screening
- In Ontario, 2,822 cervical cancer cases were diagnosed in 2008-2012 (1) and an estimated 154 deaths from cervical cancer (2)
- Current cervical screening program guidelines for Ontario recommend cytology testing every 3 years to detect cervical abnormalities and prevent cervical cancer (3)
- Ontario has been in the process of changing to primary HPV based screening since 2012 and is currently assessing the most suitable algorithm (10)

1. Bruni et al. ICO/IARC Information Centre on HPV and Cancer, 2019, 2. Kwong JC et al. Ontario Burden of Infectious Disease Study (ONBOIDS): An OAHPP/ICES Report. 2010. 3. Ontario Cervical Screening Guidelines Summary. Cancer Care Ontario, 2016. 4. Health Ontario, RFI #2019-181, 2019.

Ontario: cervical cancer & screening



Decision-makers need information about how to create a safe, effective and cost-effective screening programme

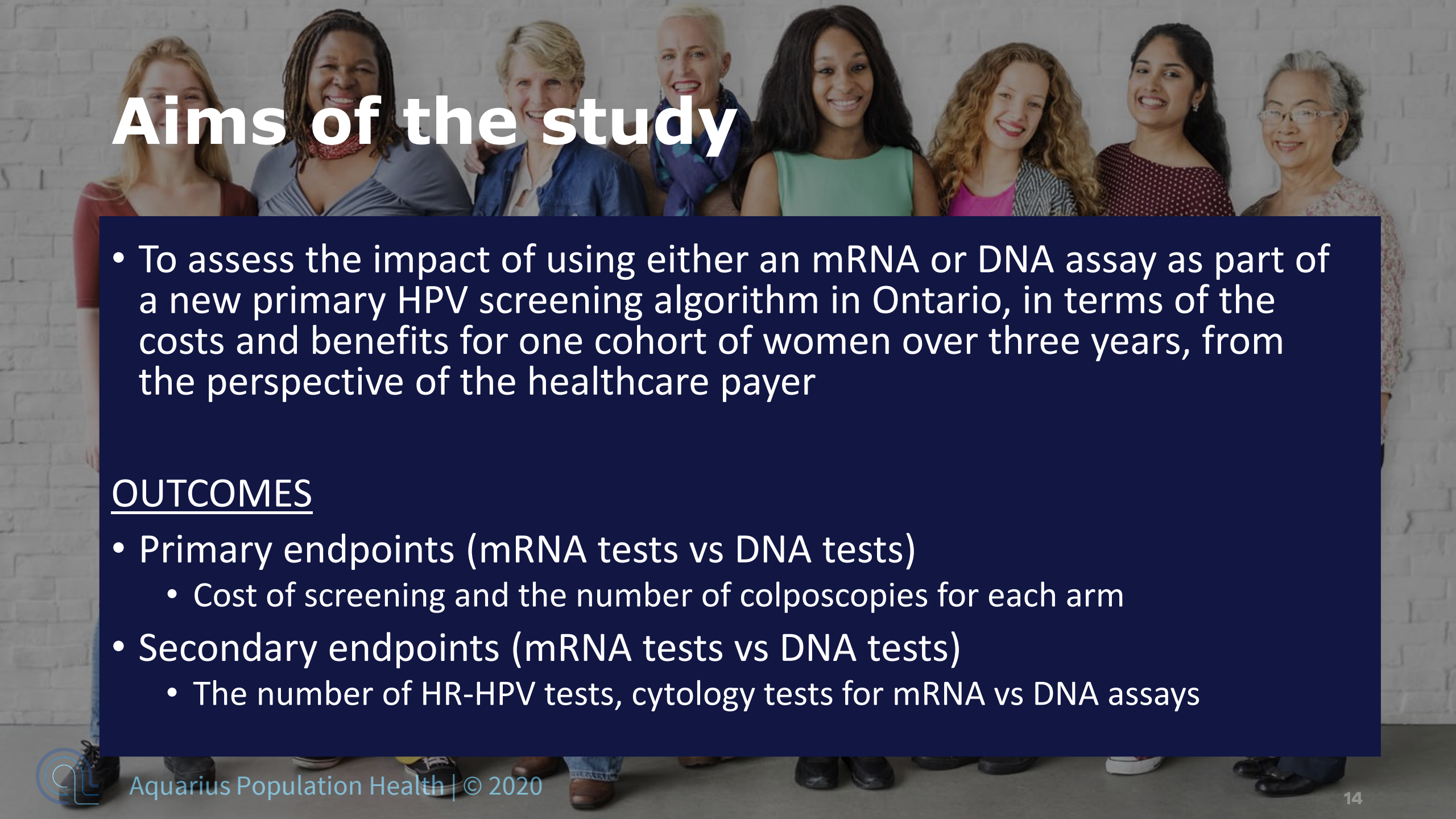
1. Bruni et al. ICO/IARC Information Centre on HPV and Cancer, 2019, 2. Kwong JC et al. Ontario Burden of Infectious Disease Study (ONBOIDS): An OAHPP/ICES Report. 2010. 3. Ontario Cervical Screening Guidelines Summary. Cancer Care Ontario, 2016. 4. Health Ontario, RFI #2019-181, 2019.

Economic evaluation & models: Key benefits

- Provides quantitative evidence to help inform decision-making
- Can consider a range of outcomes that are important to healthcare services, given stakeholders may be interested in different results
- Many methods are available to answer questions about making healthcare more efficient and better for patients, so economic evaluation can be tailored to the situation
- Reduces uncertainty and can represent yet simplify reality

Economic evaluation & models: Questions for a screening programme

- If we used a particular diagnostic test instead of current practice, could we estimate:
  - The change in costs/resources used or the change in clinical outcomes?
- What are the wider population level benefits or impact if different diagnostics are used?
- Can we increase capacity or decrease costs?
- Can we help budget holders prioritise/optimise their limited resources to maximise the health of the population?
- Is it safe?

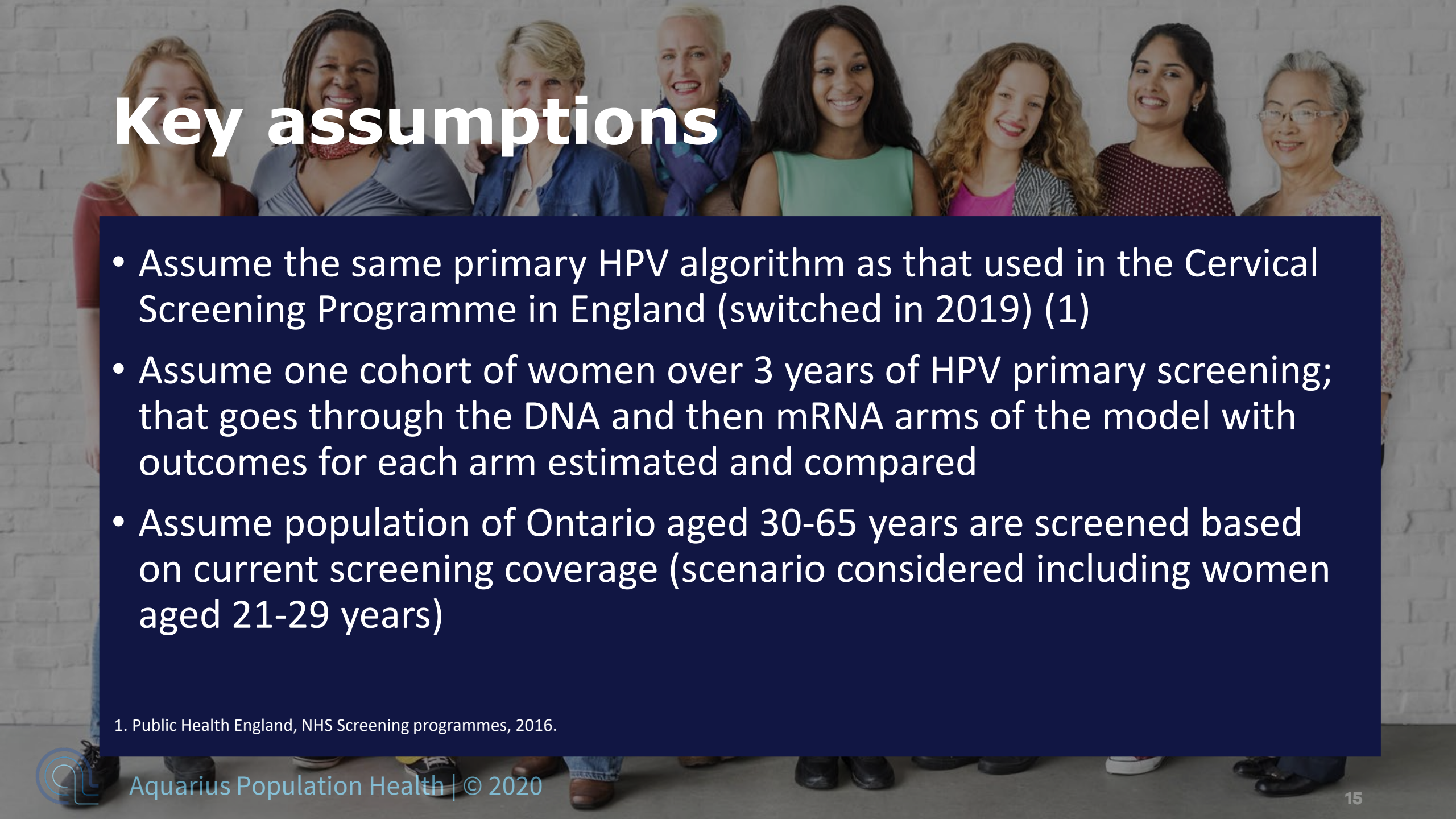


Aims of the study

- To assess the impact of using either an mRNA or DNA assay as part of a new primary HPV screening algorithm in Ontario, in terms of the costs and benefits for one cohort of women over three years, from the perspective of the healthcare payer

<u>OUTCOMES</u>

- Primary endpoints (mRNA tests vs DNA tests)
  - Cost of screening and the number of colposcopies for each arm
- Secondary endpoints (mRNA tests vs DNA tests)
  - The number of HR-HPV tests, cytology tests for mRNA vs DNA assays

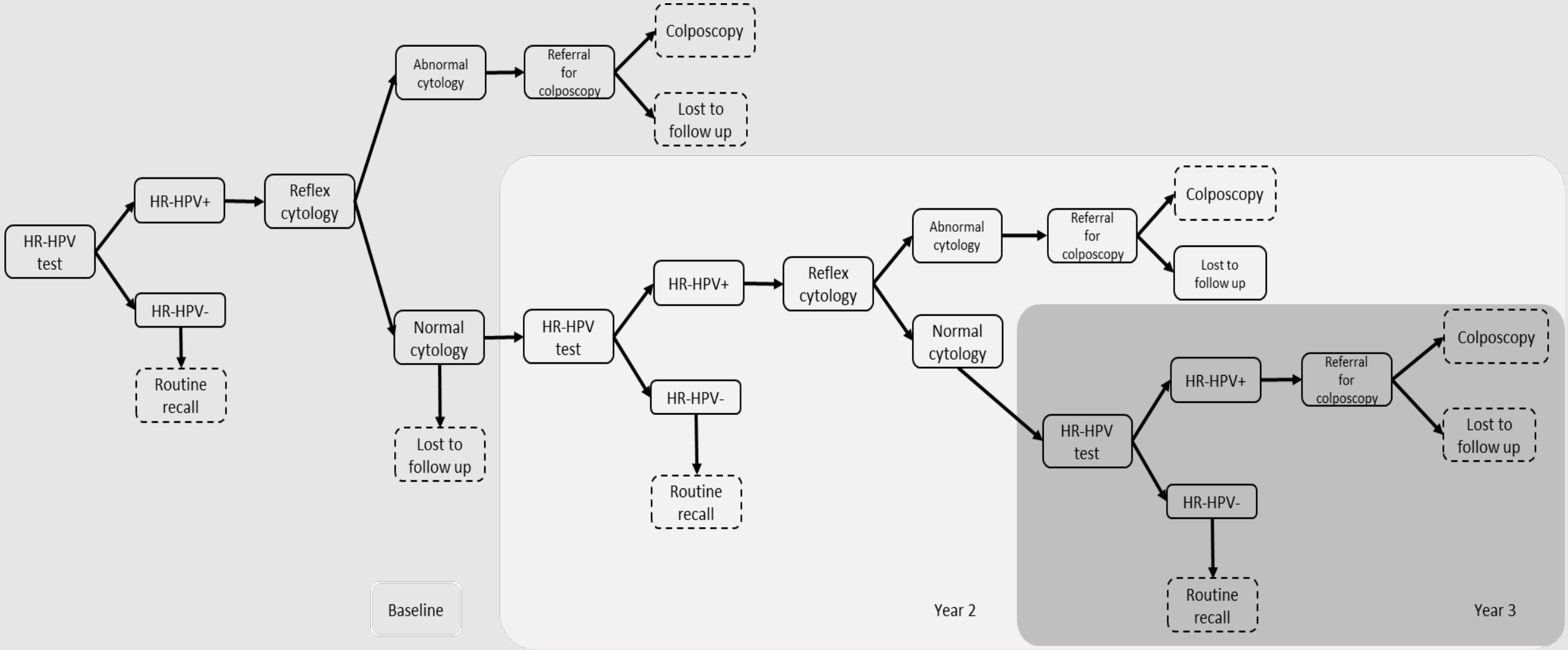


Key assumptions

- Assume the same primary HPV algorithm as that used in the Cervical Screening Programme in England (switched in 2019) (1)
- Assume one cohort of women over 3 years of HPV primary screening; that goes through the DNA and then mRNA arms of the model with outcomes for each arm estimated and compared
- Assume population of Ontario aged 30-65 years are screened based on current screening coverage (scenario considered including women aged 21-29 years)

1. Public Health England, NHS Screening programmes, 2016.

Primary HR-HPV cervical screening in Ontario



Head to head mRNA vs DNA HR-HPV studies

Study	Country	Summary
FOCAL (1)	Canada	mRNA assay compared to Hybrid Capture 2 (HC2, digene) DNA assay in women aged 25-65 at baseline and 48-month follow-up
HORIZON (2,3)	Denmark	Head to head comparison of mRNA assay to 3 DNA assays (HC2, cobas (Roche) and CLART (Genomica) in women aged 23-65
GAST (4)	Germany	Head to head comparison of mRNA assay to HC2 DNA assay in women aged 30-60 at baseline and follow-up
FASE (5)	France	Evaluation of mRNA compared to HC2 DNA assay in women aged 20-65 at baseline

1. Cook DA et al. J Clin Virol. 2017, 2. Rebolj M et al. Eur J Cancer. 2015. 3. Rebolj M et al. PLOS ONE. 2016, 4. Iftner T et al. J Clin Microbiol 2015, 5. Monsonego J et al. Int J Cancer 2010.

FOCAL (1)

The FOCAL RCT was conducted in British Columbia and recorded the results of liquid based cytology (LBC) and HR-HPV tests in a manner that could mimic HPV primary screening.

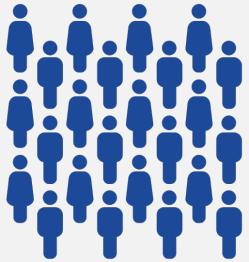
A cohort of FOCAL participants had an HR-HPV test at baseline and after 48 months using both HC2 (digene) and mRNA HPV tests (Aptima).

The FOCAL authors provided unpublished data including a breakdown of >= ASCUS cytology results to model the expected differences in the cytology arms in the model.

The results from baseline, 12-month follow up (with HC2) and 48-month follow up were adjusted to estimate 12 and 24 month results.

1. Cook DA et al. J Clin Virol. 2017.

Input parameters



Model population: 2,225,324
Assuming screening coverage 65% (1,2)

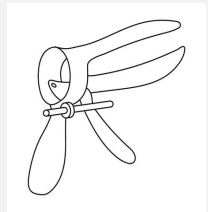
Probabilities: The probabilities were calculated using data from the FOCAL study (3); English data was used for loss to follow-up for HPV recall in the absence of Ontario data

Costs from the Ontario Health Insurance Plan (2016 & 2019) - *Note all costs presented in 2019 $CAD*

Consultation: $77.20
Sample collection: $18.30 (4)

LBC: $13.96 (5)

HPV test: $13.96 (5)



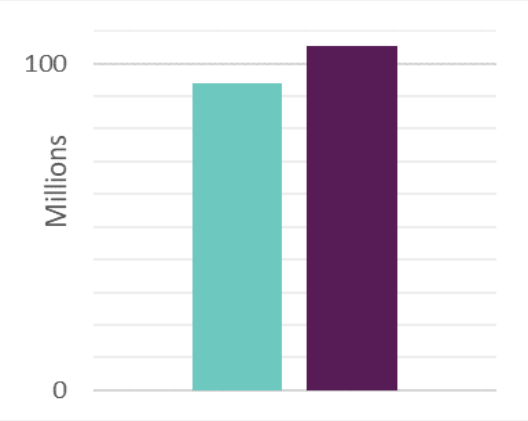
Colposcopy initial investigation: $50.90
Consultation: $101.70 (4)

1. Ontario Cervical Screening Program: 2012 Report. 2012. 2. Statistics Canada https://doi.org/10.25318/1710013401-eng. 3. Cook DA et al. J Clin Virol. 2017. 4. Ontario Ministry of Health, Ontario Health Insurance Plan Schedule of Benefits, 2020. 5. Schedule of benefits for Laboratory Services. Lab Med. 2019

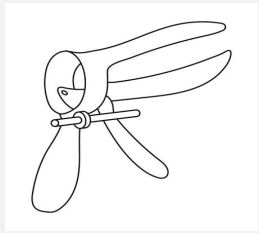
Baseline results

$

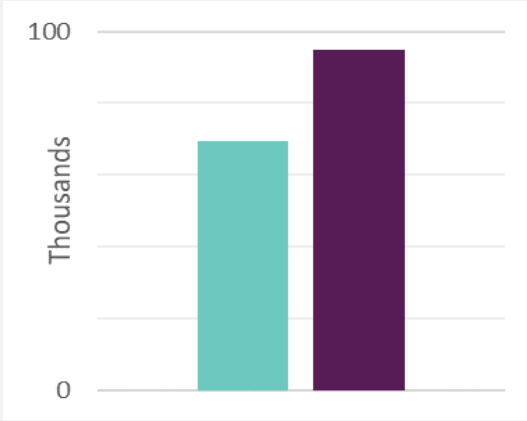
Total costs:
mRNA: $ 260,725,048
DNA: $ 264,777,822



Difference: $ 4,052,773 (1%)

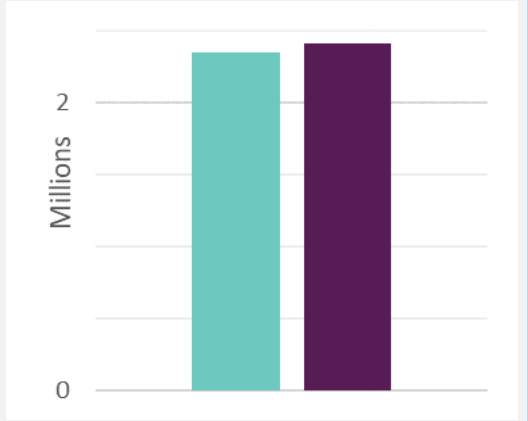


Colposcopies:
mRNA: 52,207
DNA: 63,173



Difference: 10,966 (21%)

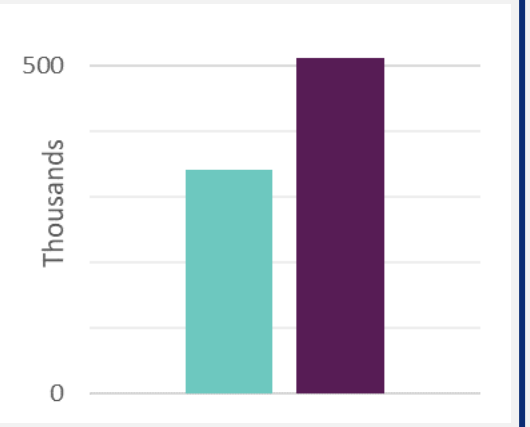
HPV tests:
mRNA: 2,289,999
DNA: 2,307,146



Difference: 17,147 (1%)

mRNA
DNA

Cytology tests:
mRNA: 160,968
DNA: 200,812

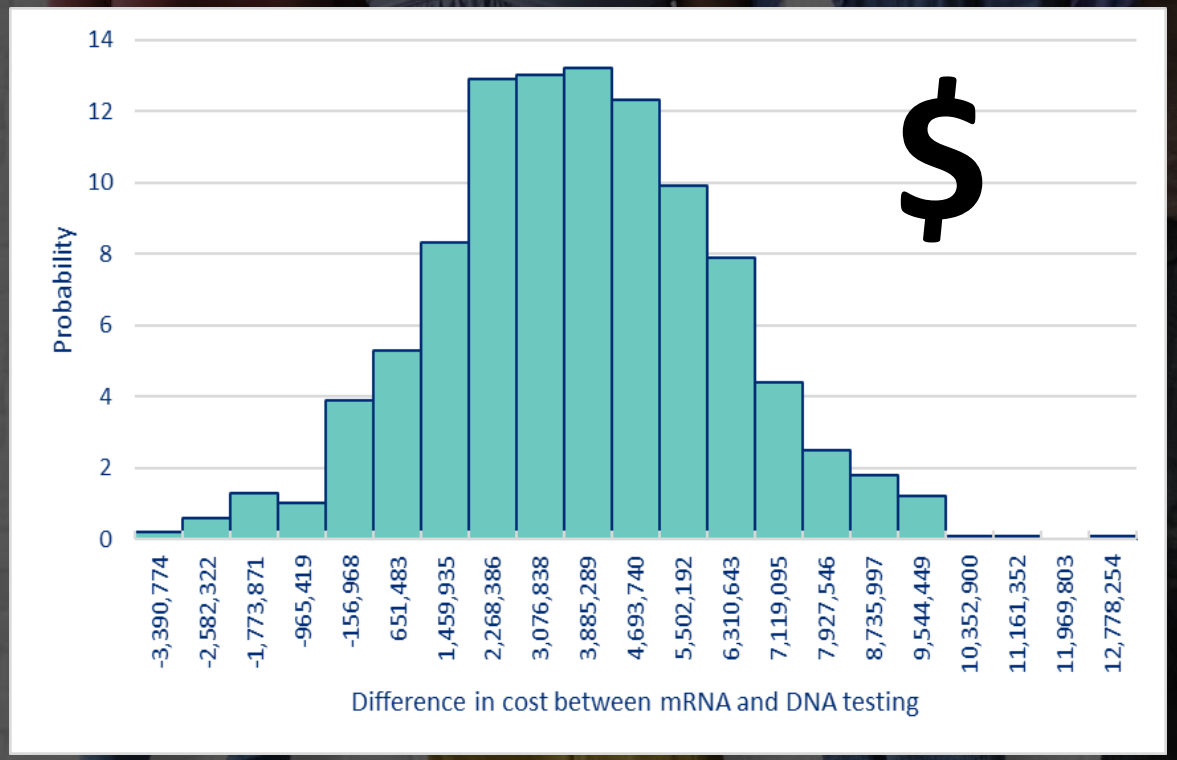


Difference: 39,844 (25%)

How do we deal with uncertainty in the data and assumptions?

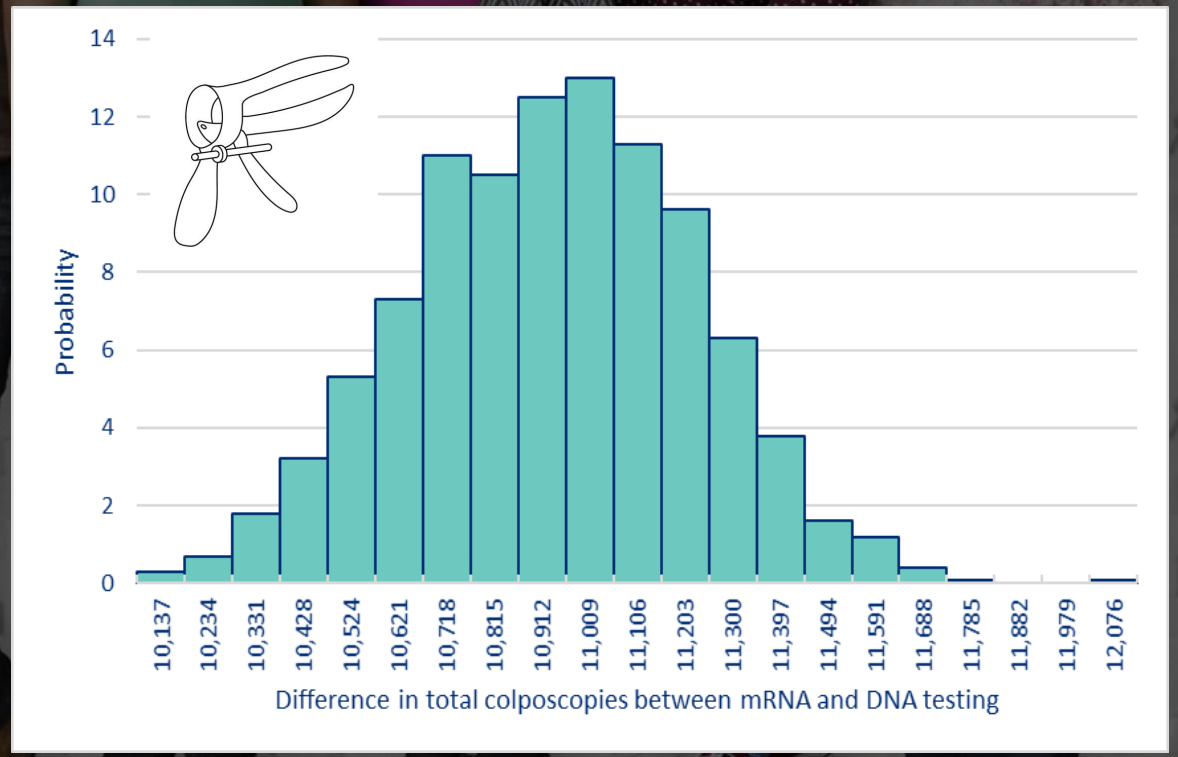
- We often have imperfect, incomplete or no data!
  - Run sensitivity analyses and vary the underlying data inputs
- Or, are unsure about certain assumptions
  - Part of the value of modelling is being able to run different “what-if” scenarios
  - Can deal with structural uncertainty, or changes in assumptions
- Uncertainty analyses helps understand how “robust” the results are, i.e. how confident you are in them based on the inputs and assumptions
- Modelling can also tell you what data should be prioritised for future studies

Probabilistic sensitivity analyses



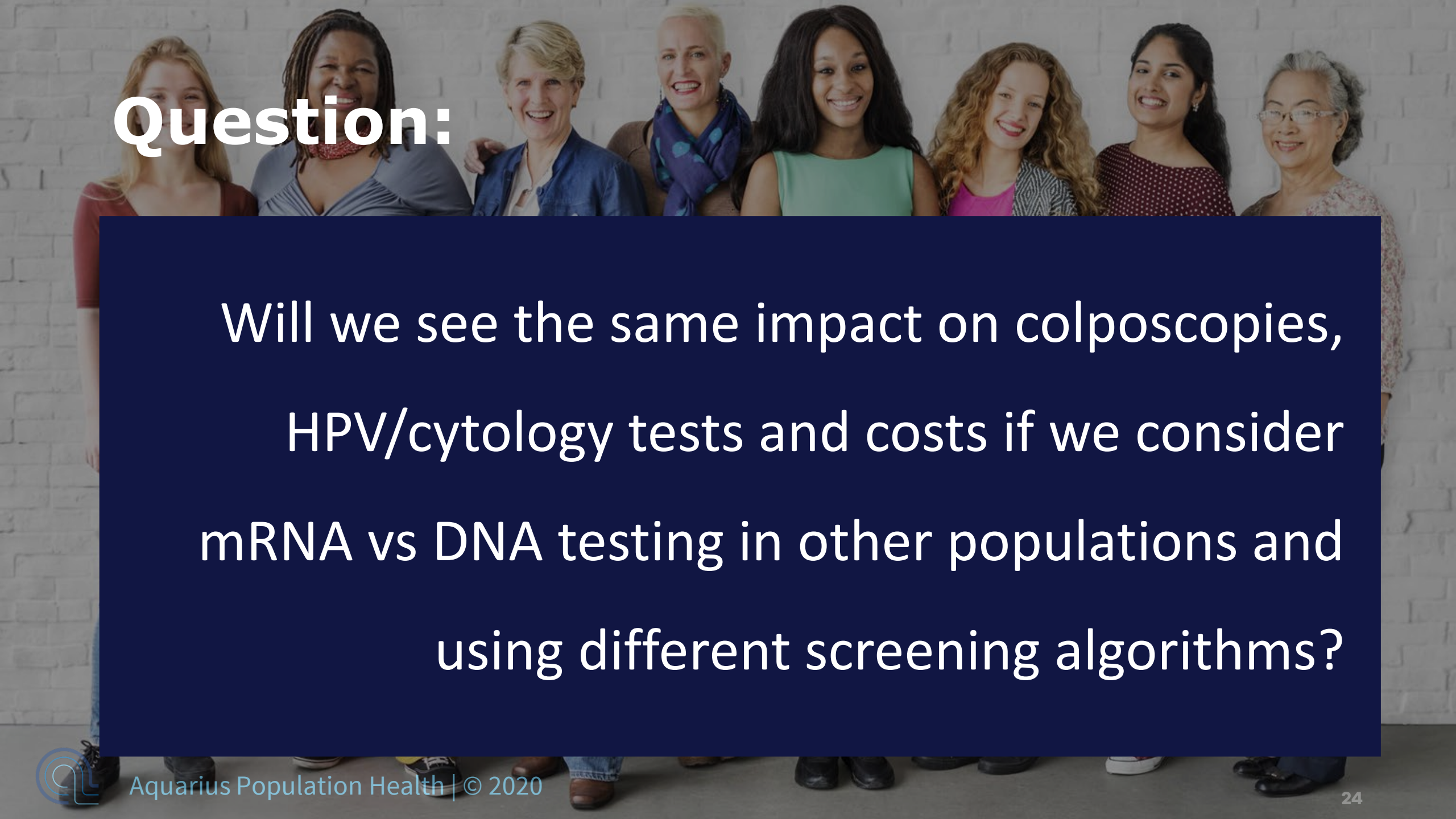
95% of results: $ 0.3 – $ 8.0 million cost savings

95% of results: 10,502 – 11,452 unnecessary colposcopies avoided



One-way & scenario analyses

- The probability of an HPV+ test at year 1 had the biggest impact on costs and number of colposcopies
- When the younger age group (21-24 year olds) are included, the cost savings for mRNA increases to $6.5 million, and 23k colposcopies averted
- If the HORIZON data are used, the cost savings increases by 6x using mRNA and the unnecessary colposcopies by 3x.



Question:

Will we see the same impact on colposcopies, HPV/cytology tests and costs if we consider mRNA vs DNA testing in other populations and using different screening algorithms?

Open access Original research

BMJ Open

Use of the Aptima mRNA high-risk human papillomavirus (HR-HPV) assay compared to a DNA HR-HPV assay in the English cervical screening programme: a decision tree model based economic evaluation

Georgie Weston ,[1] Caroline Dombrowski,[1] Michael J Harvey,[1] Thomas Iftner,[2] Maria Kyrgiou,[3,4] Christina Founta,[5] Elisabeth J Adams[1]

To cite: Weston G, Dombrowski C, Harvey MJ, *et al*. Use of the Aptima mRNA high-risk human papillomavirus (HR-HPV) assay compared to a DNA HR-HPV assay in the English cervical screening programme: a decision tree model based economic evaluation. *BMJ Open* 2020;**10**:e031303. doi:10.1136/bmjopen-2019-031303

► Prepublication history and

ABSTRACT

Objective To estimate the impact of using the Aptima messenger RNA (mRNA) high-risk human papilloma virus (HR-HPV) assay versus a DNA HR-HPV assay in a primary HPV cervical screening programme.

Design One hypothetical cohort followed for 3 years through HPV primary cervical screening.

Setting England.

Participants A hypothetical cohort of women aged 25–65 years tested in the National Health Service (NHS) Cervical Screening Programme (CSP) for first call or routine recall

Strengths and limitations of this study

- ► The first analysis of the estimated impact of using a messenger RNA (mRNA) versus DNA high-risk human papilloma virus (HPV) assay for primary HPV screening globally, in terms of the healthcare resources used and associated costs.
- ► Extensive sensitivity analyses generated understanding around the robustness of the results, and the impact of certain parameters on the results (particularly HPV positivity).

Weston *et al*. BMJ Open 2020;10:e031303. https://bmjopen.bmj.com/content/bmjopen/10/3/e031303.full.pdf

Robustness of results: changing input data for the English model (year 1)

HORIZON

Description	DNA	mRNA
Probability of positive HPV test	0.2026	0.1232
Probability of positive LBC test	0.1980	0.2529

4,128 women aged 23-64 yrs
Collection media: SurePath
DNA tests: HC2 and cobas
18 month follow up

FOCAL

Description	DNA	mRNA
Probability of positive HPV test	0.0935	0.0807
Probability of positive LBC test	0.4318	0.4260

3,473 women aged 25-65 yrs
Collection media: ThinPrep
DNA test: HC2
48 month follow up

GAST

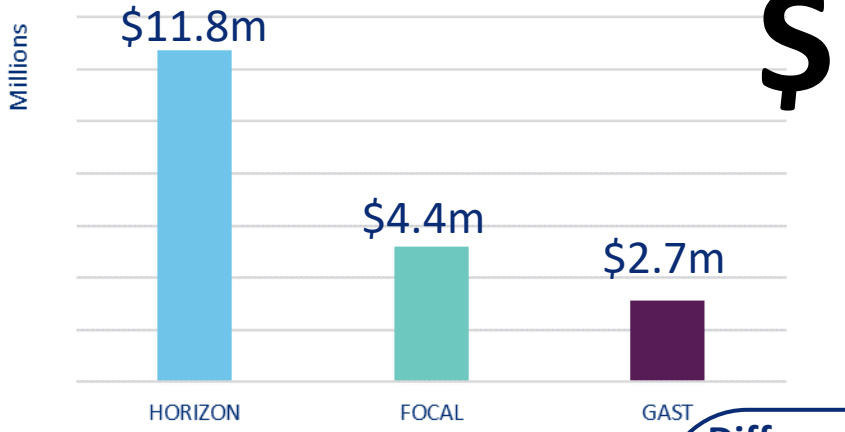
Description	DNA	mRNA
Probability of positive HPV test	0.0869	0.0727
Probability of positive LBC test	0.2224	0.2392

9,451 women aged 30-60 yrs
Collection media: ThinPrep
DNA test: HC2
No follow up

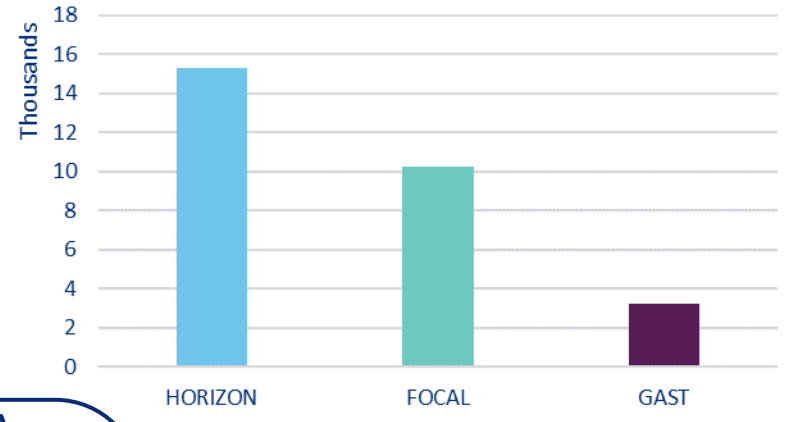
All costs, loss to follow-up probabilities and probability of a biopsy with a colposcopy were kept the same as in the baseline model

Comparison of HORIZON, FOCAL and GAST: year 1 results only

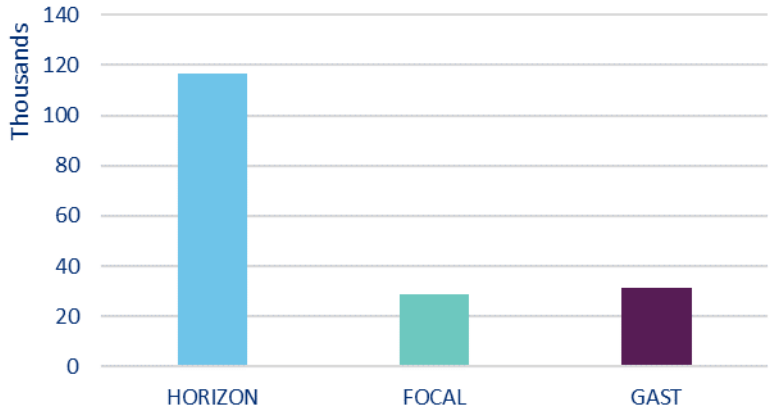
Difference in costs (DNA vs mRNA)



Difference in colposcopies (DNA vs mRNA)



Difference in cytology tests (DNA vs mRNA)



Cervical screening: pathway variations

Country	Pathway	Age groups	Source for HPV & cytology data	Type of DNA test
England	HPV primary screening	25+	HORIZON	cobas
Canada *	HPV primary screening	30-65	FOCAL	HC2
Sweden	HPV primary screening (18-month recall) Cytology primary screening (6/12-month recall)	30-60+ 23-29	HORIZON	Mean of HC2 and cobas
Denmark	HPV primary screening (18-month recall) 50% randomized to cytology primary, 50% randomized to HPV primary Cytology primary screening (6/12-month recall)	60+ 30-59 23-29	HORIZON	Mean of HC2 and cobas
France *	HPV primary screening Cytology primary screening	30-65 25-29	HORIZON	Cobas

** Canadian and French models and results in preparation for submission, Sweden and Denmark are unpublished*

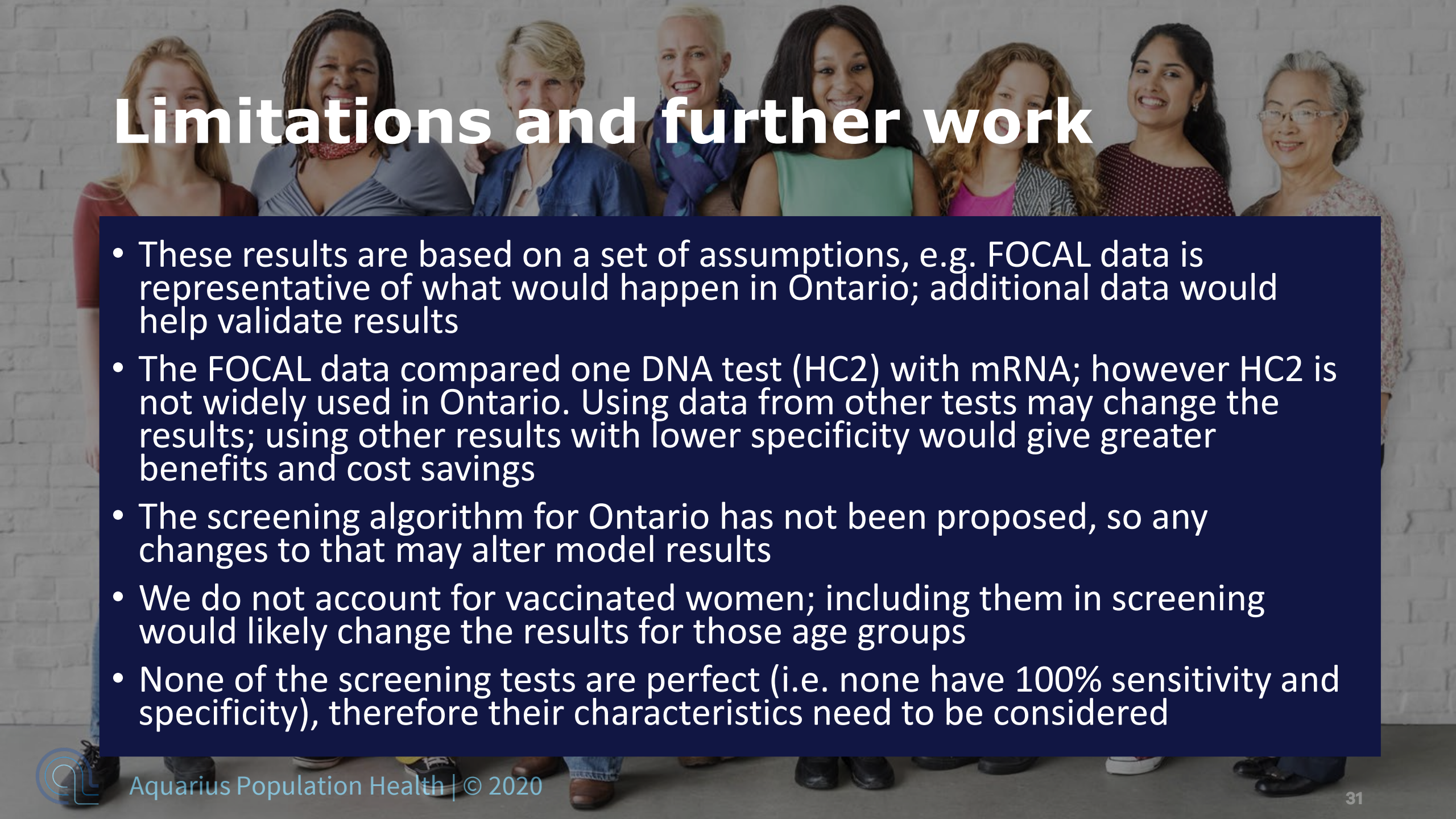
Results: Cost savings and reductions in tests & colposcopies

Country	Cost savings per 10,000 women screened (local currency)	Cost savings per 10,000 women screened ($ CAD)	Number of colposcopies saved per 10,000 women screened	Number of HPV tests saved per 10,000 women screened	Number of cytology tests saved per 10,000 women screened
England (1)	£ 68,562	$ 116,742	125	403	1,128
Canada (2)	$ 18,212	$ 18,212	49	77	179
Sweden (3)	882,136 kr	$ 132,469	238	267	382
Denmark (3)	210,393 kr	$ 44,231	159	167	234
France (4)	€ 30,750	$ 48,100	220	178	561

1. Weston et al. BMJ Open. 2019. 2. Canadian results are unpublished and being submitted for publication. 3. Swedish and Danish results are unpublished. 4. French results are preliminary and unpublished; costs are being confirmed with French co-authors.

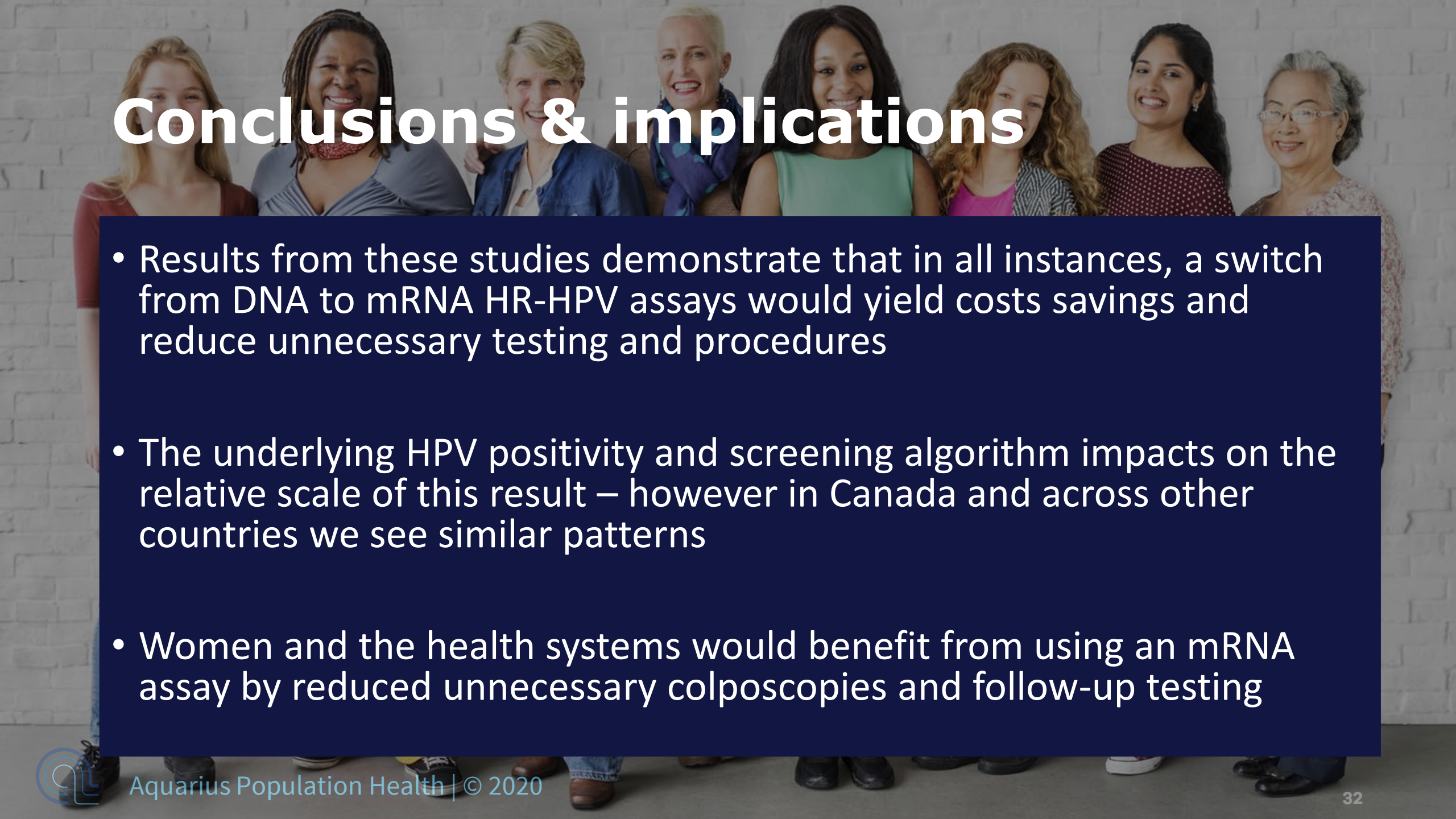
How to interpret model results?

- It is important to understand the model assumptions
- Are there any limitations in the structure/data?
  - Have these been discussed, clarified and mitigated?
- Can the results be applied to another population of interest?
- How much confidence do we have in the results?
- How do the results compare to other model results?



Limitations and further work

- These results are based on a set of assumptions, e.g. FOCAL data is representative of what would happen in Ontario; additional data would help validate results
- The FOCAL data compared one DNA test (HC2) with mRNA; however HC2 is not widely used in Ontario. Using data from other tests may change the results; using other results with lower specificity would give greater benefits and cost savings
- The screening algorithm for Ontario has not been proposed, so any changes to that may alter model results
- We do not account for vaccinated women; including them in screening would likely change the results for those age groups
- None of the screening tests are perfect (i.e. none have 100% sensitivity and specificity), therefore their characteristics need to be considered



Conclusions & implications

- Results from these studies demonstrate that in all instances, a switch from DNA to mRNA HR-HPV assays would yield costs savings and reduce unnecessary testing and procedures
- The underlying HPV positivity and screening algorithm impacts on the relative scale of this result – however in Canada and across other countries we see similar patterns
- Women and the health systems would benefit from using an mRNA assay by reduced unnecessary colposcopies and follow-up testing

Conclusions & implications

Theoretical evidence from health economic models can be hugely valuable and can inform decision-making in the absence of empirical data

Aquarius Population Health
Transforming health for everyone

What we do

- An independent healthcare consultancy based in London
- Passionate about enhancing people's health and wellbeing
- Flexible and responsive to our partners' needs
- Multidisciplinary team works across sectors and disease areas
- Use creative approaches in seeking solutions
- Champion collaborative working and close partnerships to deliver true value when exploring challenges

Our mission

- To generate evidence to inform and support rational decision-making and policy in healthcare
- To support the planning, evaluation and implementation of better and more efficient healthcare to improve patient care and outcomes
- Develop bespoke solutions to address our partners' needs and unique challenges
- To support innovation, adoption, and service change in healthcare
- To deliver the highest-quality work of any consultancy working in the healthcare sector, in a robust and timely way

If you have any questions, please get in touch
elisabeth.adams@aquariusph.com

Aquarius Population Health Limited

Unit 29 Tileyard Studios

London N7 9AH

+44 (0) 207 993 2930

www.aquariusph.com

info@aquariusph.com