A health economic model to estimate the costs and benefits of an mRNA vs DNA high-risk HPV assay in a hypothetical HPV primary screening algorithm in Ontario, Canada

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ABSTRACT

This study models the impact of using two different types of high-risk (HR) human papillomavirus (HPV) tests: mRNA (Aptima) and DNA (Hybrid Capture 2) as part of a hypothetical primary HPV screening program in Ontario, Canada. Outcomes were the costs of the screening program, and number of colposcopies, HPV tests and cytology tests. Results were estimated for one cohort going through the screening algorithm. A decision tree model was adapted from a published UK study, with inputs drawn from published Canadian data for the probabilities through the model, costs, demographic, and screening data from Ontario. Sensitivity and scenario analyses explored uncertainty in the model inputs and assumptions. Results indicated that screening using an mRNA test could yield cost savings of CAD $4,007,266 (95% credibility interval [CI]: −7,866,251 – 8,035) compared to using a DNA test, with 10,639 (95% CI: 10,170 – 11,094) fewer women undergoing unnecessary colposcopies, and reductions in unnecessary HR-HPV and cytology tests. The HR-HPV test comprised the largest percentage of the costs saved, and the probability of being HPV positive in the first year had the biggest impact on results. These results indicate that the choice of HR-HPV test is important when implementing a primary HPV screening program to avoid unnecessary resource use and cost, which will benefit both women and healthcare providers.

1. Introduction

Cervical cancer is primarily caused by persistent genital infection with high-risk (HR) human papillomaviruses (HPV) (Arbyn et al., 2014). Cases of cervical cancer in Canada have decreased recently as a result of implementing screening programs, (Vaccarella et al., 2013) however it remains a relatively common and preventable cause of cancer in women. In Ontario from 2008 to 2012, 2,822 cervical cancer cases were diagnosed (Bruni et al., 2019) and 154 deaths were recorded from cervical cancer (Kwong et al., 2010). Current cervical screening program guidelines for Ontario recommend cytology testing every 3 years to detect cervical abnormalities and prevent cervical cancer for ages 25–70 (Ontario Cervical Screening Program OCSP Screening Recommendations Summary, 2020).

New screening algorithms for cervical cancer, including primary HPV screening, are being implemented globally. Primary HPV screening in which a sample is tested first for HR-HPV, and positive samples are tested for cytology, has higher sensitivity than primary cytology testing in detecting precancerous cells (Mayrand et al., 2007). Long-term studies have shown that HPV screening detects high grade cervical intraepithelial neoplasia (CIN) before cytology-based screening (Ronco et al., 2014). A pilot study in England found that HPV testing as an initial screen was significantly more protective over 6 years than primary cytology screening done more frequently (Kitchener et al., 2014). A recent study in Canada comparing primary HPV testing to cytology testing showed a significantly lower likelihood of CIN3 + at 48 months in the HPV primary group as high grade lesions were detected sooner (Ogilvie et al., 2018). Since 2012, current guidance in Ontario has

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recommended cytology primary screening algorithm. However, Ontario Health has been evaluating HPV-based testing in cervical screening (Cervical Screening Guidelines Summary 2017), although no more recent guidance has been issued.

Two types of HR-HPV tests can be used in HPV primary screening. DNA tests, such as Hybrid Capture 2 (HC2, Digene), detect DNA presence of HR-HPV genotypes. mRNA tests, such as Aptima (Hologic), detect the downstream expression of the oncogenic E6/E7 mRNA from 14 high-risk HPV genotypes showing an active infection (Cook et al., 2018; Monsonego et al., 2012; Ratnam et al., 2011). The Aptima mRNA test has a non-inferior sensitivity compared to HC2 DNA tests for CIN2 + according to the Meijer criteria, with a pooled relative sensitivity of 0.98 (90% CI 0.95–1.01) for CIN2 + and 0.98 (90% CI 0.95–1.02) for CIN3 + in 6 cervical cancer screening studies as reported in Arbyn *et al* (Arbyn et al., 2015; Meijer et al., 2009). However, mRNA tests have a higher specificity compared to HC2 DNA, with a pooled relative specificity of 1.04 (CI 1.02–1.07) for detecting CIN2 + and CIN3+ (14). Due to its higher specificity, using an mRNA HR-HPV test in a cervical cancer screening program results in fewer false positive results, which subsequently reduces the number of unnecessary follow-up cytology tests and colposcopies, thereby saving costs (Weston et al., 2020).

When making the transition to HPV primary screening, it is important to consider both the change in effectiveness, in terms of detecting CIN2 + and minimizing harm from unnecessary tests, and the potential resource use and costs. This study explores the impact of using an mRNA versus DNA HR-HPV test on the costs, number of colposcopies, HPV and cytology tests in one cohort of women screened over a three-year interval in Ontario, assuming a hypothetical primary HPV screening algorithm similar to that implemented in England.

2. Methods

To model a hypothetical HPV primary algorithm in Ontario, an algorithm based on the Cervical Screening Programme (CSP) in England was selected (Public Health England, 2016), as it is similar to the primary HPV algorithm proposed by the Cervical Screening Guideline Working Group in Ontario (Murphy et al., 2011). Therefore, a published model that estimated the impact of DNA vs mRNA testing as part of the English primary HPV screening program was adapted for Ontario (Weston et al., 2020). In that model, a decision tree was developed in TreeAge (TreeAge Pro 2018); further details on the structure (Fig. 1) and assumptions in this model are found in that paper and summarized below.

In the hypothetical primary HPV screening model for Ontario, the two comparator arms (mRNA vs DNA HR-HPV testing) have the same structure. At baseline, women enter the screening algorithm and attend primary care to have a cervical sample taken as part of their first screen or routine recall. The sample is sent to a laboratory for HR-HPV testing. Those with a negative HR-HPV result are discharged to routine recall for repeat screening in 5 years. Women with a positive HPV result undergo reflex testing with cytology and referred for colposcopy if ≥ASCUS (atypical squamous cells of undetermined significance) cytology (including AGC, atypical glandular cells; LSIL, low grade squamous intraepithelial lesion; ASCH, atypical squamous cells; HSIL, high grade squamous intraepithelial lesion). A negative reflex cytology results in the women being recalled in 12 months for an HPV test and reflex cytology if HPV positive. If a woman is HPV positive but has normal cytology at the 12-month mark, they are recalled again in 12 months, and those with positive HPV results are referred directly to colposcopy (no reflex cytology is performed).

The model endpoint is at colposcopy, and treatment or longer-term outcomes are not included in the model. As mRNA and DNA tests are shown to have similar sensitivity, a similarly low number of false negative cases will be identified using both tests. Therefore, there will be no difference in the longer-term disease outcomes from false negative HPV results, and they do not need to be modelled. The number of true positives requiring treatment after colposcopy and treatment and follow up costs will not differ between the mRNA and DNA arms. The rationale for the model endpoint is discussed in more detail in Weston et al (Weston et al., 2020).

2.1. Population

Women in Ontario aged between 30 and 65 years undergoing cervical cancer screening were modeled. The latest data on the coverage of the cervical cancer screening program was applied (64.9%) (Cancer Care Ontario, 2014) to the number of women in Ontario aged 30–64 years (3,540,977) (Government of Canada SC. Estimates of population, 2016), giving a total screened population in the base case of 2,298,094 (Table 1). The population was varied in the scenario analysis to include women aged 21–29 years who were not included at baseline as, 1) they will likely not be included in an HPV primary screening as they have high HPV positivity and therefore there is less value in screening them for HPV, and 2) the FOCAL study did not include women aged 21–24 and hence direct data are unavailable.

2.2. Probability inputs

The probabilities used in the model are in Table 1. Probability data was taken from the FOCAL study (Cook et al., 2017). This randomized trial compared screening using HPV and liquid based cytology (LBC), using both DNA (HC2) and mRNA (Aptima) tests on 3,473 women in in
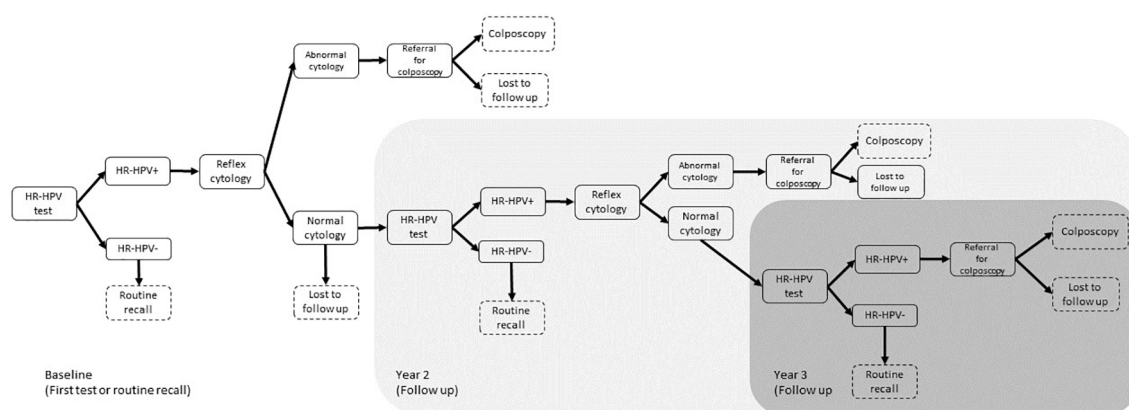

Figure 1: Structure of the decision tree model to simulate primary HR-HPV cervical screening in England; this structure was identical for both the mRNA and DNA testing arms.

Fig. 1. Structure of the decision tree to simulate primary HR-HPV cervical screening taken from Weston et al (Weston et al., 2020); **this structure was applied to Ontario for both the mRNA and DNA testing arms.**

Table 1
Baseline model and deterministic sensitivity analysis model input values.

Parameter	Type of HR-HPV test used	Baseline value	DSA[*] values Low	High
Discount rate (Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition). CADTH, 2017)		0.015	0	0.03
Total number of women in cohort (**women aged 30–65**) (Cancer Care Ontario, 2014; Government of Canada SC. Estimates of population, 2016)		2,298,094	–	–
Cost data				
Total cost of colposcopy		$162.60	–	–
Consultation (SoB code: A205) (Schedule of Benefits Physician Services, 2021)		$111.70	–	–
Initial investigation with colposcopy (SoB code: Z731) (Schedule of, 2021)		$50.90	–	–
Cost of LBC (SoB code: L733) (Schedule of Benefits for Laboratory Services, 2020)		$13.96	–	–
Total cost of HR-HPV test (sum of the 3 codes below)		$119.01	–	–
Consultation (SoB code: A003) (Schedule of Benefits Physician Services, 2021)		$84.45	–	–
Sample collection cost (outside of hospital) (SoB code: G365 + E430) (Schedule of Benefits Physician Services, 2021)		$20.60	–	–
Cost of HR-HPV test (assumed to be same cost as LBC) (Schedule of Benefits for Laboratory Services, 2020)		$13.96	$11.17	$16.75
Probability data (women aged 30–65)				
Probability of positive HPV test at year 1 (Cook et al., 2017)	DNA	0.0680	0.0510	0.0850
	mRNA	0.0571	0.0428	0.0714
Probability of positive cytology year 1, in those HPV + year 1 (Cook et al., 2017)	DNA	0.4245	0.3184	0.5307
	mRNA	0.4382	0.3287	0.5478
Probability of positive HPV test at year 2, in those HPV+/cytology normal year 1 (Cook et al., 2017)	DNA	0.5000	0.3750	0.6250
	mRNA	0.4198	0.3149	0.5248
Probability of positive cytology year 2, in those HPV + year 2 (Cook et al., 2017)	DNA	0.2951	0.2213	0.3689
	mRNA	0.3046	0.2284	0.3807
Probability of positive HPV test at year 3, in those HPV+/cytology normal year 2 (Cook et al., 2017)	DNA	0.2500	0.1875	0.3125
	mRNA	0.1762	0.1322	0.2203
Probability of loss to follow-up for colposcopy (Cancer Care Ontario, 2014)		0.1910	0.0	0.2388
Probability of loss to follow-up for HPV recall (Cervical Screening Programme, 2019)		0.3440	0.0	0.4300

[*] DSA – deterministic sensitivity analysis; all costs in 2020 Canadian dollars.

the Vancouver metro area and Vancouver island, Canada, and reported aggregated HPV and cytology results for ages 25–29 and ages 30–65 (Cook et al., 2017). The trial recorded the results of the LBC and HR-HPV tests in a manner which could mimic HPV primary screening, i.e., the management of the patient was not solely determined by the LBC results. The age range of the FOCAL population is representative of both the

larger Vancouver area and Ontario province (aged 25–29: 10.3%, 10.3%, 11.7% and aged 30–65: 88.3%, 89.7%, and 89.9% for FOCAL, Vancouver and Ontario, respectively) (Government of Canada SC, 2016).

The FOCAL study collected HPV results at baseline and after 48 months using both DNA and mRNA tests, and at 12 months using DNA tests only. The screening algorithm modeled in this study requires HPV positive/cytology normal results at baseline to be followed up at 12 months, for both the mRNA and DNA arms. As 12-month follow up data were not available for mRNA in FOCAL, the relative difference between baseline DNA and 12-month DNA positivity was applied to the mRNA baseline positivity to estimate HPV positivity in the mRNA arm at 12 months for those who are HPV positive with normal cytology at baseline. For the third year follow up data (24 months after baseline), the rate of decline in positivity was assumed to be linear from baseline.

The FOCAL authors provided unpublished data with a further breakdown of the published data to be used in this analysis. This included a breakdown of cytology results in year one and two for women who tested HR-HPV positive with the mRNA and DNA tests. (Supplementary Table A.5).

Probability of loss to follow up for colposcopy was sourced from the Ontario Cervical Screening Programme 2012 report (Cancer Care Ontario, 2014). Canadian data were not available for loss to follow up for HPV recall and data from England were used as a proxy (NHS Cervical Screening Pogramme 2013). These values were used in both arms.

2.3. Cost inputs

All costs were modeled from the perspective of the Ontario health system, and values from the most recent Ontario Health Insurance Plan (OHIP) schedule of benefits (SoB) were used (published in 2020 for physician and laboratory services) (Schedule of Benefits Physician Services, 2021; Schedule of Benefits for Laboratory Services, 2020). The cost of performing a HR-HPV test on the sample was assumed to be the same as performing an LBC as there is no code for an HPV test (expert opinion). Costs are reported in 2020 Canadian dollars, and no inflation was required as the costs from the SoB are for 2020.

The cost of a consultation, sample collection, and performing the HR-HPV test were included in the total cost of an HPV test, whereas the cost of reflex cytology only included the laboratory cost of performing the cytology test as it would be conducted on the same sample collected for the HPV test.

Costs occurring beyond one year were discounted at 1.5% per year according to CADTH guidelines for health economic evaluation (Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition). CADTH, 2017).

2.4. Outcomes

The model outcomes were the total costs, and total number of colposcopies, HR-HPV tests and cytology tests in both the mRNA and DNA arms, and the difference between them for one cohort of women aged 30–65 entering the screening algorithm for the first time or returning for routine recall.

2.5. Uncertainty analyses

A deterministic sensitivity analysis (DSA) was conducted to determine which parameters had the largest impact on the results of the model, with the high and low values parameter values shown in Table 1. The probabilities in the model were varied by 25% of the original values. Probability of loss to follow up was varied from 0% as the low value to represent perfect follow up to an additional 25% at the high value. Cost of the HR-HPV tests was varied in the DSA by 20%. Other costs were not varied, as reimbursement is fixed.

A probabilistic sensitivity analysis (PSA) was conducted with 1,000

independent iterations of the model, sampling the values for each input from their distribution, to ascertain the robustness of the results. All cost parameters were assigned a gamma distribution, and probabilities a beta distribution. Distributions for cost and probability parameters were taken from literature or a distribution was estimated using FOCAL trial data (Supplementary **Table A.1** and **Table A.2**). All inputs shared by the mRNA and DNA arms were assigned the same value and all other inputs were varied independently between arms. The outcomes were calculated for each iteration, and the 95% credibility intervals (CI) were estimated.

A scenario that included a younger screening population of 587,002 women In Ontario aged 21–29 years (the number of Ontario women aged 21–29 years, assuming screening coverage of 64.9%) (Government of Canada SC. Estimates of population, 2016) was run. FOCAL HPV positivity study data for women aged 25–29 years was used. HPV positivity using a DNA test in those aged 21–24 years (33.2% positivity) was taken from a study by Ogilvie *et al* (Supplementary **Table A.3)** (Ogilvie et al., 2013). The relative difference between DNA and mRNA positivity in the FOCAL study at baseline were applied to the Ogilvie DNA positivity, to estimate 29.9% mRNA positivity in women aged 21–24. Ogilvie *et al* did not report cytology results, therefore reflex cytology and follow up results from the FOCAL study were used.

3. Results

The model outcomes for the mRNA and DNA HR-HPV arms and the difference between the two arms are shown in Table 2. For women aged 30–65 years screened in Ontario in one year (2.3 million women), using an mRNA versus DNA test would save an estimated $4,007,266 CAD (95% CI: −7,866,251 – 8,035) with 10,639 (95% CI: 10,170– 11,094) fewer women undergoing colposcopies. There are also estimated reductions in the number of HR-HPV and cytology tests.

The breakdown of total costs is shown in Fig. 2, with nearly all costs incurred by the primary HPV test (94% both in the DNA and mRNA arms). The costs of colposcopies in the mRNA arm were $8,572,166 (2.9% of total costs), compared to $10,289,289 (3.5% of total costs) in the DNA arm.

A breakdown of the cytology results by year are available in Supplementary **Table A.5, Figure A.1 and Figure A.2**. The results in year 3 are not calculated as women with a positive HPV test are referred straight to colposcopy regardless of their cytology results in year 3. The mRNA arm showed 13.5% fewer abnormal results in year 1 and 31.2% in year 2. The absolute difference between mRNA and DNA was the largest in women with low-grade squamous intraepithelial lesions (LSIL).

3.1. Deterministic sensitivity analysis

The results of the DSA are in Supplementary **Figure A.3**. When the parameters were varied between their low and high values, the cost of the HPV test and probability of HPV positivity in year 1 had the biggest impact on the cost difference and probability of HPV positivity in year 1

Table 2
The baseline results for primary and secondary outcomes of the model in the mRNA and DNA arm and the difference between them: total costs, number of colposcopies, HR-HPV tests, and cytology tests.

	Cost ($)	Colposcopies	HR-HPV tests	Cytology tests
mRNA	291,048,945	52,865	2,355,741	160,854
DNA	295,056,211	63,504	2,370,766	199,513
Difference (DNA − mRNA) *	4,007,266	10,639	15,025	38,659
% reduction	1.4%	16.8%	0.6%	19.4%

* Note: a positive difference indicates that mRNA results in less cost or fewer tests/procedures compared to the DNA arm

had the biggest impact difference in numbers of colposcopies between the mRNA and DNA arm. The mRNA arm remained cost saving and had fewer unnecessary colposcopies in most instances.

3.2. Probabilistic sensitivity analysis

The impact on the outcomes of varying the parameter inputs in the PSA are shown in Fig. 3. In all instances, the number of colposcopies, HPV tests and cytology tests were lower when an mRNA test was used instead of the DNA test. In 94.8% of the 1,000 iterations, the mRNA pathway cost less than the DNA pathway (95% CI: −7,866,251 – 8,035).

3.3. Scenario analyses

Including 256,143 women aged 21–24 years and 330,859 women aged 25–29 into the model increased the cost savings of using mRNA testing over DNA testing to $6.76 million, with 23,203 unnecessary colposcopies avoided. Full results of this scenario can be found in Supplementary **Table A.4**.

4. Discussion

All provinces in Canada currently implement a cytology primary cervical cancer screening program and Ontario is one of the first regions considering HPV primary screening. This study explored the impact that the type of HPV test (mRNA versus DNA) could have within an HPV primary screening program. Study results indicate that the use of mRNA instead of DNA tests could save over $4 million annually, and avoid roughly 11,000 unnecessary colposcopies, 15,000 HPV tests and 40,000 cytology tests. Reducing unnecessary colposcopies and testing can reduce unnecessary anxiety in women around false positive test results (Waller and Marlow, 2007). Given the equivalent sensitivity of mRNA and DNA tests, no change in the longer-term outcomes such as disease and pre-cancerous states are anticipated by the choice of test.

4.1. Strengths and limitations

The strengths and limitations of the model structure have been previously discussed (Weston et al., 2020). As no HPV primary screening algorithm has been proposed yet for Ontario, it is unknown how closely the screening algorithm presented here would mirror that which is implemented. Therefore, it is recommended that this model is rerun with any algorithm changes.

Although HC2 testing is approved for use in Ontario, HC2 is infrequently used, and HPV tests are not used as the primary test in cervical screening at the present (Canadian Cancer Society, 2021). However, it is appropriate to use HC2 as the DNA comparator in this study as it was the DNA test used in the FOCAL trial (Cook et al., 2018). While different types of DNA HPV tests will return varied HPV positivity in the population, modeling the use of HC2 is likely to result in a conservative estimate for savings. In similar head-to-head studies, other DNA tests such as cobas have higher baseline positivity than HC2, which would result in higher costs due to more false positive women progressing through the pathway (e.g. HORIZON study reported initial positivity for women aged 30–65: HC2 = 11.7%, cobas = 16.2%, Aptima = 9.4%) (Rebolj et al., 2016).

HPV positivity for the youngest age group (21–24 years) was taken from Ogilvie *et al* (Ogilvie et al., 2013). The HPV positivity for the older ages reported by Ogilvie is similar to the positivity in the FOCAL study in the older age groups (Cook et al., 2018) (Supplementary Table A.3). If the younger ages are included in primary HPV screening, comparable savings would be expected to be seen as in this scenario.

There are similar numbers of women with HSIL in both arms; however, there are fewer women with ASCUS and LSIL results in the mRNA arm (Supplementary **Table A.5**). Those with borderline cytology results are more likely to have a transient HPV infection and a negative mRNA
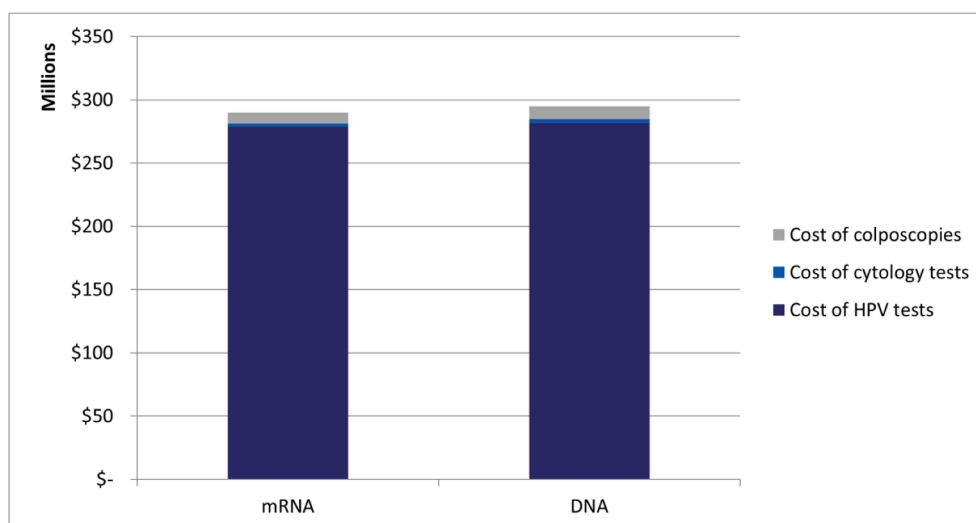
Fig. 2. A breakdown of the total costs in the mRNA and DNA pathways for one cohort of women aged 30–65.
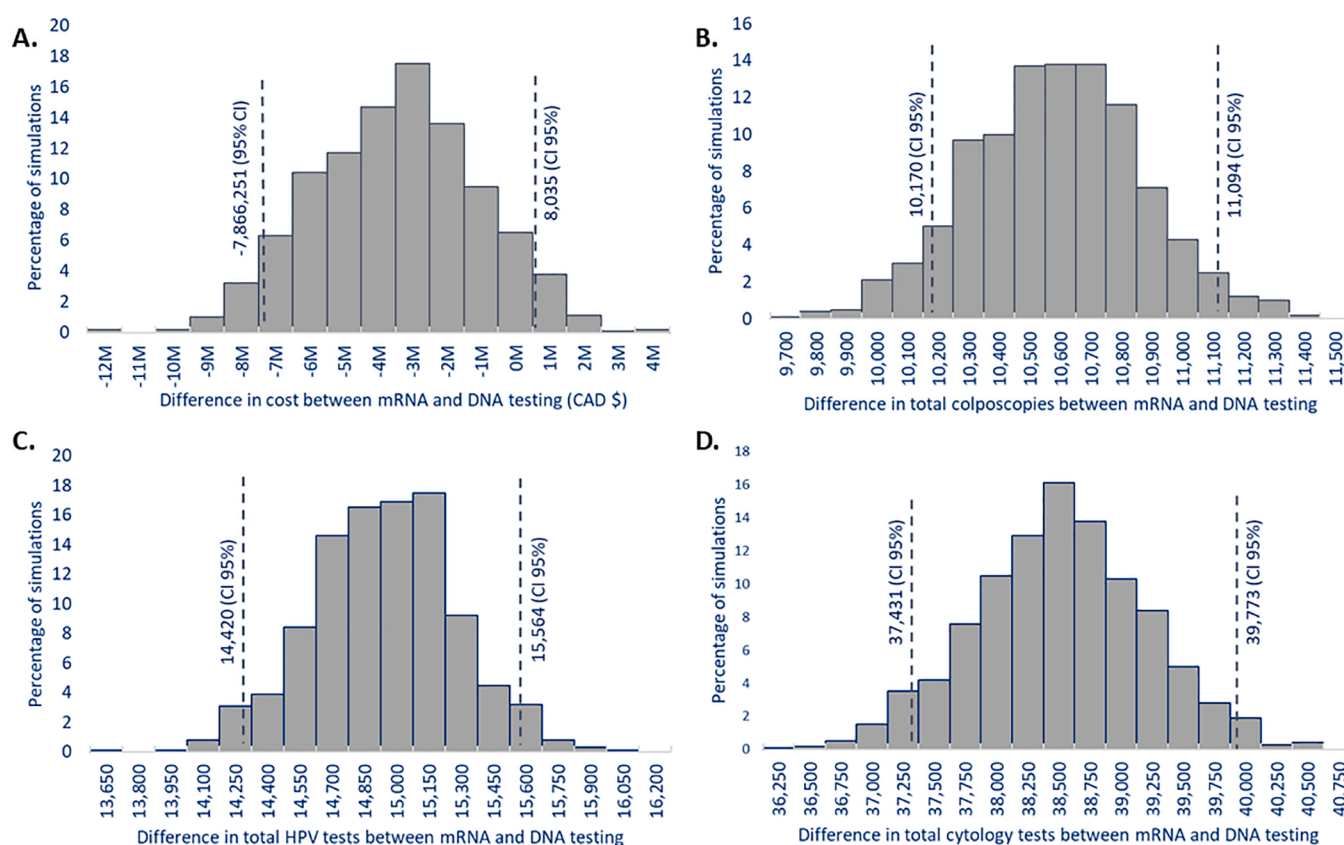

Fig. 3. Probabilistic sensitivity analysis results for A. costs, B. colposcopies, C. cytology, and D. HPV tests for a cohort of women aged 30–65.

test result (Ge et al., 2018).

4.2. Comparison to previous studies

The results of this study are similar to the previous model results of mRNA vs DNA testing in the English HPV primary screening algorithm, with cost savings and a decrease in unnecessary tests and colposcopies using mRNA vs DNA (Weston et al., 2020). The cost savings per 10,000 women screened is lower in Canada than in England ($17,437 vs $123,483 (inflated to 2020 CAD)), which reflects the lower HPV

positivity in part due to and older age group modelled in Canada, and different costs.

4.3. Implications

It is expected that in the short run, upon implementation of a HPV primary screening system, there would be an increase in the number of colposcopies (Rebolj et al., 2019). The unnecessary tests and colposcopies avoided using an mRNA test would ensure that the system is not overloaded.

In the base case, this model assumes women aged 30–65 years would undergo HPV primary screening. The CTFPH guidelines recommend that screening is started at age 25 and many experts support this (Popadiuk et al., 2019; CTFPHC Cervical Screening Guideline 2013). Other countries give different guidelines; for example, women entering the screening program aged 25 (Public Health England, 2016), women under 25 using a cytology primary algorithm (Screening for livmoderhalskræft: anbefalinger, 2018; Cervixcancerprevention, 2019) or using HPV primary and cytology primary algorithms concurrently for those over the age of 30 and varying the screening interval based on age (Livmoderhalskræft, 2021).

Other aspects of a primary HPV screening program will need to be assessed, such as the screening interval required. Recent studies have shown that a screening interval of up to 6 years would remain safe (Kitchener et al., 2014). With a longer screening interval, a higher positivity might be expected, which would increase the percentage of women progressing through the pathway, however fewer women would be screened annually. Even with a different screening interval, the cost or clinical outcomes in this study are not expected to be significantly different as this study models one screening iteration.

Some studies have evaluated using HPV 16/18 genotyping in the screening algorithm. The English pilot evaluated using genotyping to refer to 12 month recall (Rebolj et al., 2019). Australia has used 16/18 genotyping to refer women with negative cytology to colposcopy (Cancer Council Australia, 2021). As guidance for the screening algorithm in Canada has not yet been issued, further studies are needed to compare head-to-head mRNA to DNA performance using 16/18 genotyping and to support a cost-benefit analysis. At this time, it is unknown whether an evaluation will endorse the use of 16/18 genotyping in Ontario or other provinces in Canada.

Since 2007, the HPV vaccination has been offered to students in grade 7 in Ontario (Wilson et al., 2013). The first wave of women vaccinated against HPV will be turning 25 this year and will enter the screening program imminently. HPV vaccination will decrease population level HPV positivity significantly (Tabrizi et al., 2012), making it more viable to introduce HPV primary screening in the younger age group.

5. Conclusion

This study shows that if an HPV screening algorithm is implemented in Ontario, many unnecessary colposcopies, HPV tests and cytology tests could be avoided, and savings of around $4 million for one cohort of women over the three years would be generated if mRNA HPV testing were used instead of DNA testing. This will have a positive impact on healthcare providers and women.

CRediT authorship contribution statement

Georgie Weston: Conceptualization, Methodology, Formal analysis, Visualization, Writing - original draft. **Caroline Dombrowski:** Data curation, Validation, Writing - review & editing. **Marc Steben:** Validation. **Catherine Popadiuk:** Validation, Writing - review & editing. **James Bentley:** Validation, Writing - review & editing. **Elisabeth J. Adams:** Conceptualization, Supervision, Writing - review & editing.

Conflict of interest

GW, CD, and EA work for Aquarius Population Health, which has conducted work on HPV for several organizations, and diagnostic testing projects funded by other commercial companies, charities, grants and governmental agencies. MS has received grants from Abbott, BD, Bio-Fire, Hologic, Roche, GSK and Merck. CP has received travel funds for a conference from Hologic. JB has received research support from Merck Oncology and Clovis Oncology and is an advisor for NSV Tech.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2021.101448.

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