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Self-sampling for HPV testing: Increased cervical cancer screening participation and incorporation in international screening programs

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Keywords

human papillomavirus; HPV; cervical cancer; cancer screening; self-sampling; vaginal microbiome

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Abstract

In most industrialized countries, screening programs for cervical cancer have shifted from cytology (Pap smear or ThinPrep) alone on clinician-obtained samples to the addition of screening for human papillomavirus (HPV), its main causative agent. For HPV testing, self-sampling instead of clinician-sampling has proven to be equally accurate, in particular for assays that use nucleic acid amplification techniques. In addition, HPV testing of self-collected samples in combination with a follow-up Pap smear in case of a positive result is more effective in detecting precancerous lesions than a Pap smear alone. Self-sampling for HPV testing has already been adopted by some countries, while others have started trials to evaluate its incorporation into national cervical cancer screening programs. Self-sampling may result in more individuals willing to participate in cervical cancer screening, because it removes many of the barriers that prevent women, especially those in low socioeconomic and minority populations, from participating in regular screening programs. Several studies have shown that the majority of women who have been underscreened but who tested HPV-positive in a self-obtained sample, will visit a clinic for follow-up diagnosis and management. Additionally, a self-collected sample can also be used for vaginal microbiome analysis, which can provide additional information about HPV infection persistence as well as vaginal health in general.

Introduction

Cervical cancer takes the lives of about 250,000 women worldwide each year (Bray et al. 2013; Jemal et al. 2011; Ramzan et al. 2015). This statistic is even more tragic given the fact that most of these deaths could be prevented with proper screening for precancerous lesions or the presence of human papillomavirus (HPV) (Nour 2009) followed with standard clinical interventions. HPV DNA can be detected in the vast majority of cervical cancer tissue, and thus, HPV is considered the principal etiologic agent of cervical cancer (Bosch and Muñoz 2002; Walboomers et al. 1999). Of the over 170 HPV types known to date, only some are associated with cervical cancer; collectively, these are called high-risk HPV (hrHPV) types. The main carcinogenic hrHPV types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 (Bouvard et al. 2009; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012). Additionally, closely related HPV types such as 26, 53, 66, 67, 68, 70, 73 and 82 have been listed as possibly carcinogenic. Of these, hrHPV types 16 and 18 are detected in the majority (~70%) of cervical cancer samples worldwide (de Sanjose et al. 2010), and the detection of these HPV types is associated with a high probability of cancer development within 1 decade (Khan et al. 2005).

Cervical cancer screening programs

Given the limited HPV types that appear to be the etiologic agents of cervical cancer worldwide, cervical screening constitutes an unusually unique opportunity to examine the impact of resources and methodologies on cancer prevention programs (Schiffman 2017). Because the vast majority of cervical cancer is preventable after the detection of precancerous lesions or the presence of hrHPV, many countries have national cervical cancer screening programs in place, in which women are invited to undergo an in-clinic exam with follow-up visits and treatment in case of a positive finding. In countries where cervical cancer screening programs have been implemented, the incidence and mortality of this disease has shown a dramatic decrease over the past 20 years (Vaccarella et al. 2013). The majority of industrialized countries, including the United States, offer cervical cancer screening programs to women aged 21 years

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and older, where women are invited to visit their physician for a pelvic exam at regular intervals (Gakidou et al. 2008). Most of these tests involve a Pap smear (also called a Pap test), in which a physician obtains a cervical specimen for histological or cytological staining and analysis (Tambouret 2013). The test collects cells from the transformation zone of the cervix, using a small spatula and a brush, analyzing them under the microscope in search of abnormal morphology (Tambouret 2013). To classify lesions there are several nomenclature systems. Two of the most widespread are the cervical intraepithelial neoplasia (CIN) scale and the Bethesda system (Nayar and Wilbur 2017; Schiffman and Wentzensen 2013; Schiffman et al. 2016). The first distinguishes histological lesions by the fraction of epithelium replaced by undifferentiated cells into mild dysplasia (CIN 1), moderate dysplasia (CIN 2), and severe dysplasia and carcinoma *in situ* (CIN 3) (Nayar and Wilbur 2017; Schiffman and Wentzensen 2013; Schiffman et al. 2016). The Bethesda system is a cytological classification that describes abnormal findings as negative for intraepithelial lesion and malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSILs) or high-grade squamous intraepithelial lesions (HSILs) (Nayar and Wilbur 2017; Schiffman and Wentzensen 2013; Schiffman et al. 2016).

Because these classification systems are based on human evaluation via microscopic analysis, and because virtually all cervical cancers are caused by hrHPV (Bosch and Muñoz 2002; Walboomers et al. 1999), it has been proposed that molecular assays detecting DNA or RNA hrHPV markers might provide a better assessment of cancer risk than cytology (Schiffman et al. 2016; Schiffman 2017). Several hrHPV assays have been marketed, including Qiagen's hybrid capture signal-based Digene HC2 HPV assay, and several PCR amplification-based tests such as the Cobas test by Roche and the Xpert HPV test from Cepheid. Testing for the presence of hrHPV has proven to be more sensitive for cervical cancer precursors than the Pap test (Mayrand et al. 2007). In a large Kaiser Permanente study involving over 1 million women, three-year risks for CIN3 or worse (CIN3+) or cancer following an HPV-negative result were lower than those following a Pap-negative result, suggesting that testing for HPV is

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more predictive for the reduced three-year risk of developing cervical cancer and thus a better strategy for cervical cancer screening than a Pap smear (Gage et al. 2014).

These results support the use of hrHPV DNA testing for primary cervical screening, leading to recommendations from the United States, Australia, and Europe to implement HPV screening in nationwide programs (Bessell et al. 2014, Huh et al. 2015; Rijkaart et al. 2012). In the United States (US), screening guidelines provided by the American College of Obstetricians and Gynecologists (ACOG) (Committee on Practice Bulletins—Gynecology 2016) and the U.S. Preventive Services Task Force (USPSTF) (US Preventive Services Task Force 2016) recommend women visit their healthcare provider every three to five years, depending on age and risk factors, for a Pap smear, often with HPV co-testing. In September 2017, the USPSTF released new draft recommendations for average-risk women aged 30-65 year old, abandoning co-testing, but instead proposing either cervical cytology every 3 years or hrHPV testing alone every 5 years (US Preventive Services Task Force 2017). In both scenarios, samples are obtained by a physician during a pelvic exam. For women in high risk groups, such as those with HIV infection or a compromised immune system, more frequent screenings are recommended.

Barriers to cervical cancer screening

Although free or low-cost cervical cancer screening is available in the United States for women aged 21-64, not all women respond to these invitations. About 20% of women in the US eligible for cervical cancer screening have not been tested within the recommended timeframe (National Center for Health Statistics, 2017; Watson et al. 2017). This means that at least one in every five women in the US in the eligible age range, a group of at least 14 million women (Watson et al. 2017), have not been screened according to health guidelines. Screening participation is especially low among particular ethnic and socioeconomic groups within the US, including low-income groups, recent immigrants, and Native American, Native Hawaiian, Hispanic, and Asian populations (Crawford et al. 2016; Levinson et al. 2016; Musselwhite et al. 2016; National Center for Health Statistics. 2017; Watson et al. 2017). Similar poor responses

to invitations and reminders for cervical cancer screening have been found among certain population groups in other countries as well (Chorley et al. 2017). These disparities are likely to contribute to the higher invasive cervical cancer incidence and mortality rates found among certain ethnic groups (Benard et al. 2014; Musselwhite et al. 2016).

Multiple types of barriers preventing the participation in cervical cancer screening programs have been identified. First, subjective patient experience can decrease participation rates in conventional physician-performed cervical cancer screening (Marlow et al. 2015). Feelings of embarrassment and shame are often mentioned as reasons to not participate in cervical cancer screening (Chorley et al. 2017; Dzuba et al. 2002; Marlow et al. 2015; Waller et al. 2009). Women, in particular those of certain sociocultural groups, often report reluctance to having a physician see and touch their genital area (Marlow et al. 2015). Women who have been sexually abused or who have experienced intimate partner violence are often uncomfortable with a standard pelvic exam (Alcalá et al. 2017; Cadman et al, 2012). In addition, the experience of discomfort or pain at a past clinical visit can discourage women from visiting a health professional again (Chorley et al. 2017; Jia et al. 2013; Waller et al. 2009).

Secondly, lack of understanding about the importance of HPV or cervical cancer screening or underestimation of the risk of disease can also interfere with patient compliance. A study among 12,058 Norwegian women aged 25-45 showed that screening rates were highest among women who were aware of the recommended screening interval for cervical cancer (Hansen et al. 2011) and similar results were found in China (Jia et al. 2013) and the UK (Marlow et al. 2015). Additionally, a meta-analysis showed that cancer awareness education - either via printed material or face-to-face home visits - can increase the participation of women in screening programs (Everett et al. 2011).

Thirdly, practical challenges or socioeconomic barriers may also hinder patient compliance with recommended screening guidelines. In a 2014 study in the Netherlands among 10,000 women who answered a questionnaire about why they had not participated in past cervical screenings, most women answered that they had forgotten to schedule an appointment; other practical reasons were that they were pregnant,

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breastfeeding, or undergoing fertility treatment (Bosgraaf et al. 2014). Underestimation of the time elapsed since the previous screening has been identified as another factor associated with non-attendance (Eaker et al. 2001). In a study among First Nations women in Canada, women living in small rural communities indicated that the time it would take them to drive to clinic for a Pap smear provided a significant barrier to accessing care, because of the disruption to their daily lives and the resulting difficulties with transportation or child care services (Zehbe et al. 2017). In countries without nationwide health insurance (such as the United States), access to free or low-cost cervical cancer screening is not always readily available for the uninsured. In a National Health Interview Survey in 2013, it was found that only 60.6% of uninsured women in the US were compliant with their recommended Pap smear versus 85.2% of insured women (Sabatino et al. 2015; Smith et al. 2015). Even in countries with universal healthcare such as Canada and the UK, low socioeconomic status was associated with a lower compliance with cervical cancer screening. In a Canadian study, women in the lowest income neighborhoods were half as likely to be screened (Elit et al. 2012). Data from 2012-2013 obtained by the Primary Care Trust from the UK Health and Social Care Information Centre showed that women from the highest quintile of income deprivation had 4.9 percentage points less coverage for cervical screening than women from the lowest quintile (Douglas et al. 2016).

The socioeconomic and sociocultural barriers described above prevent many women from complying with recommendations for cervical cancer screening. Not surprisingly, cervical cancer rates are higher in women who have not been screened according to the recommended guidelines (Lam et al. 2017), with cervical cancer mortality rates being the highest in underscreened populations (Benard et al. 2014; Musselwhite et al. 2016).

Self-sampling may increase cervical cancer screening participation

Offering women the option to self-collect vaginal or cervical samples at home has been proposed as a means to increase participation in cervical cancer screening programs. Self-sampling reduces the potential financial and logistical burden for the

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patient, and allows for a greater initial sense of privacy and autonomy. A recent meta-analysis encompassing 37 studies with 18,516 women from 24 countries across five continents indicated strong acceptance of self-sampling and a preference for self-sampling over clinician sampling (Nelson et al. 2017).

Studies from a range of countries, both on the national level and on specific socioeconomic groups, have shown that offering self-sampling can lead to increased participation rates in cervical cancer screening (Table 1). In a study among 30,000 women in the Netherlands who had not responded to invitations and reminders for an in-clinic visit and Pap test, one third of the women did return a self-sampling device when provided with the option (Gök et al. 2010; Bosgraaf et al. 2014). In a study of over 3,000 Norwegian women, offering self-sampling materials instead of an invitation for a physician-sampling visit increased compliance to 33.4% from 23.2% (Enerly et al. 2016). Similarly, in a study performed amongst 4,060 Swedish women who had not been screened in at least 6 years, 39% accepted an invitation for self-sampling and HPV testing, while only 9% accepted an invitation for a Pap smear (Wikström et al. 2011). Another study among 8,800 Swedish women who had missed two previous screening rounds found the response rate was significantly higher when self-testing was offered (24.5%) compared to a standard screening invitation (10.6%) (Broberg et al. 2014). A large study among over 14,000 Italian women showed that 11.9% responded to an invitation to undergo an in-clinic Pap smear and 12.0% sent in a sample after having to pick up a kit at a pharmacy, compared with 21.6% who sent in a sample after receiving a self-sampling kit in the mail (Giorgi Rossi et al. 2015). A randomized controlled trial among 3,000 non-responder women in London showed that sending HPV self-sampling kits to persistent non-responders resulted in a 2.27-fold increased participation rate in cervical cancer screening in comparison with sending an invitation to attend for cervical cytology (Szarewski et al. 2011). Participation rates among a group of 8,000 under-screened Australian women were much higher when self-sampling was offered (20.3%) than when a Pap-smear reminder was sent (6.0%) (Sultana et al. 2016). An even more marked difference was obtained in a study of 7,650 women in Argentina, where 86% of women who were offered to self-collect responded for an HPV

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test, while only 20% of women who were invited to attend a health clinic responded, representing a four-fold increase in patient compliance (Arrossi et al. 2015).

A systematic review regarding different interventions to increase patient screening for various types of cancer combined 7 European studies on cervical cancer screening (several of which are mentioned above) and showed that mailing a self-sampling device for HPV testing directly to the patient resulted in an average 2.37-fold higher population participation in non-responder women when compared with a reminder for in-clinic Pap testing (Camilloni et al. 2013). In a meta-analysis of 10 studies, 8 from Europe and 2 from North America, the average compliance of HPV self-collected testing was 2.14 times higher compared to an invitation for a Pap smear. It was concluded that HPV self-sampling significantly improves the participation of women in cervical cancer screening (Racey et al. 2013). A more recent meta-analysis of 16 studies found similar results, with about 2.3 times more participants responding to a self-sampling kit sent to their homes, compared to an invitation for a clinician-obtained specimen (Verdoodt et al. 2015).

Self-collection might be of particular benefit for women of certain socioeconomic groups. In a study of 20,000 women from low-income communities in France, where low compliance with recommended Pap smear screening leads to 3,000 new cases of cervical cancer and 1,000 deaths each year, only 2% of women underwent Pap testing, while 18.3% of women responded to an invitation for a self-collected specimen for HPV testing (Sancho-Garnier et al. 2013). A study involving 346 women from underserved rural areas of Northern Greece, of whom only 17.1% had been regularly participating in Pap smear screening, found that 100% were willing to self-sample, with 90% willing to self-sample regularly if this option was available (Chatzistamatiou et al. 2017). First Nations women in Canada have a six-fold higher incidence of cervical cancer due to lower participation rates in cervical cancer programs; in a pilot program among 49 First Nations women, self-sampling was well received and the quality of samples was excellent (Zehbe et al. 2011). A second, larger study involving 834 First Nations women found an 1.3 higher response rate for self-sampling (Zehbe et al. 2016). In a study led by the University of Michigan, 93% of women from an indigenous community in

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Guatemala were willing to obtain a self-collected vaginal specimen, 88% provided a sample, and 79% found the test comfortable (Gottschlich et al. 2017).

Table 1: Summary of studies mentioned in this review comparing participation rates in underscreened women offered either the option to participate in conventional cervical cancer screening or self-sampling. NA, not available.

Study	Country	Type of study	Number of Women	Control group	Self-sampling group	Response to Pap-test invitation (%)	Response to self-sampling invitation (%)	Difference (% points)	*p*	Relative Risk (*, calculated)
Gök et al. 2010	The Netherlands	Randomized cohort	28,073	281	27,792	16.6	27.5	10.9	<0.001	1.66 *
Bosgraaf et al. 2014	The Netherlands	Questionnaire study	30,130	NA	30,130	-	33.3	-	NA	NA
Enerly et al. 2016	Norway	Randomized cohort	3,393	2,593	800	23.2	33.4	10.2	NA	1.44
Wikström et al. 2011	Sweden	Randomized cohort	4,060	2,060	2,000	9.0	39.0	30.0	<0.001	4.33 *
Broberg et al. 2014	Sweden	Randomized cohort	4,800	4,000	800	10.6	24.5	13.9	NA	2.32
Giorgi Rossi et al. 2015	Italy	Randomized cohort	9,528	5,012	4,516	11.9	21.6	9.7	NA	1.82
Szarewski et al. 2011	England	Randomized cohort	3,000	1,500	1,500	4.5	10.2	5.7	<0.0001	2.27 *
Sultana et al. 2016	Austalia	Randomized cohort	8,160	1,020	7,140	6.0	20.3	14.3	<0.001	3.38 *
Arrossi et al. 2015	Argentina	Randomized cohort	6,013	2,964	3,049	20.2	85.9	65.7	<0.0001	4.02

Women prefer self-sampling over sampling by a healthcare professional

Women participating in self-sampling trials for cervical cancer screening reported a positive experience. In a crossover trial in Hong Kong of self-sampling before undergoing a Pap smear, versus undergoing the Pap smear first, most women preferred self-sampling - in particular among women without previous experience of Pap smears. It was estimated that introducing self-sampling could increase participation rates of cervical cancer screening by 6.5% (Wong et al. 2016). In follow-up interviews with the First Nations study participants described above, many women stated that self-sampling removed key logistical barriers related to making a clinic visit, as well as removed the physical and emotional discomfort of a Pap test (Zehbe et al. 2017). A group of 746 Australian women who self-collected a vaginal sample and returned a questionnaire reported that the home-based test was less embarrassing, less uncomfortable, and more convenient than a clinician-performed Pap test (Sultana et al. 2015). In a study amongst 1,069 woman in Mexico, women reported that the Pap test caused more

discomfort, pain, and embarrassment than self-sampling (Dzuba et al. 2002). In a series of interviews with low-income indigenous Mexican women who were given self-sampling kits, most women identified the need to be screened for cervical cancer, but identified multiple barriers to making a clinic visit; the self-sampling kits were found less embarrassing and less painful than sampling by a healthcare professional (Allen-Leigh et al. 2017). In a questionnaire of 3049 women in Argentina who were invited to self-sample, most women preferred this method because it interfered much less with their daily responsibilities and was less time-consuming than a visit to a clinic (Arrossi et al. 2016). Similar results were found in a study in Santiago, Chile, where 86.5% of 1,254 women responded positively to an invitation to self-sample, and 91.6% of these reported self-sampling to be less uncomfortable than Pap testing (Léniz et al. 2013). German women aged 20 to 30 years, who participated in a study to self-sample by cervicovaginal lavage rated the user-friendliness of the self-sampling method as easy (Deleré et al. 2011). In a telephone survey of 199 low income women in North Carolina who had not had a Pap test in 4 years, HPV self-tests delivered by mail were perceived to be trustworthy (Galbraith et al. 2014). However, in a recent study among 1,769 women presenting to two University of Washington clinics for routine cervical cancer screening, about 40% of participants were concerned that self-sampling might be inferior to clinician-collected samples, although both patients as well as physicians were supportive of the concept of self-sampling for HPV testing (Mao et al. 2017). In some studies, women reported that they were afraid to hurt themselves during sampling (e.g., Allen-Leigh et al. 2017; Arrossi et al. 2016; Snijders et al. 2013).

Together, these studies show higher participation rates in self-sampling than physician-performed Pap smear and HPV co-testing. In addition, most women reported positive experiences with HPV self-sampling, which could lead to improved patient compliance.

Self-collected vaginal samples are comparable to clinician-collected cervical specimens for the detection of HPV

Both patients as well as physicians have raised concerns about whether self-sampling is comparable to clinician-sampling in detecting hrHPV. This agreement, often reported as kappa coefficient or concordance value, has been the topic of a large number of studies. Systematic reviews and meta-analyses from 2005 and 2007 found moderate to good HPV positivity agreement (kappa coefficient ranging from 0.24 to 0.96, overall sensitivity of 0.74 and specificity of 0.88) between these two sampling methods (Ogilvie et al. 2005; Petignat et al. 2007; Stewart et al. 2007), while more recent studies have shown an excellent performance of HPV infection diagnosis on self-sampled vaginal specimens. In a 2014 meta-analysis lead by Marc Arbyn and colleagues, data from 36 studies (on a total of 154,556 women) was used to assess the clinical accuracy of HPV detection on self-samples versus clinical-collected samples to detect CIN2 or worse (CIN2+) (Arbyn et al. 2014). The sensitivity for HPV detection on self-samples was no different than clinical-collected samples for the detection of CIN3+. For cytology, using low-grade squamous intraepithelial lesions (LSIL) as the threshold, self sampling was 14% more sensitive to detect CIN2+. For HPV detection, the authors found an overall 12% reduction in sensitivity for the detection of CIN2+ when compared to clinician-collected samples, but this reduced sensitivity was only associated with hybridization signal-based assays, such as used by the Digene HC2 assay. Of note, no reduced sensitivity was found if HPV screening was performed using amplification-based methods such as PCR. Overall, these results suggest that self-sampling is an equally good option for women who do not participate in screening programs involving physician-sampling, in particular if self-sampling is combined with DNA amplification, given its improved sensitivity compared against signal-based assays (Arbyn et al. 2014).

Other studies published after the meta-analysis by Arbyn and coworkers have confirmed agreement between self-obtained and clinician-obtained samples for the detection of hrHPV types. In a 2016 study using samples from 1,005 women in Papua New Guinea, 93.4% overall agreement was found between self-collected and clinician-collected samples using the PCR-based Xpert HPV test to detect hrHPV types (Toliman

et al. 2016). In a study among 194 women from Ghana, the overall HPV detection concordance of the two sampling techniques was 94.2% (Obiri-Yeboah et al. 2017). A comparison between two self-sampling devices (*Evalyn* brush versus *Qvintip* collection device) and clinician sampling on 136 German women showed no significant differences in CIN2+ or CIN+ and specificity of hrHPV testing between self-sampling in comparison with clinician sampling; in addition this same study showed agreement in the overall hrHPV detection rates between self-collected and clinician-collected specimens for both sampling devices, with a kappa of 0.82 for the *Evalyn* brush and a kappa of 0.78 for the *Qvintip* device (Jentschke et al. 2016).

HPV testing on self-collected samples with a follow-up Pap test is more sensitive than a Pap test alone

Combining HPV self-sampling with a follow-up clinic visit and Pap smear to address a positive hrHPV result has proven more sensitive than a Pap smear alone. A meta-analysis by Snijders et al. concluded that hrHPV testing is at least as, if not more, sensitive for CIN2+ as histology on clinician-obtained specimens (Snijders et al. 2013). Although hrHPV detection using self-sampling is less specific than clinician-collected samples exhibiting CIN2+ (i.e. hrHPV-positive specimens often show a less severe cytology), the increased sensitivity of self-sampling and HPV testing versus clinician-obtained Pap smear could potentially decrease morbidity and mortality associated with cervical cancer.

Other studies confirmed the high sensitivity of HPV testing from self-collected samples. For example, among a group of 615 women in Costa Rica, HPV testing of self-collected specimens was more sensitive for detecting CIN2+ than cytology. In addition, this study also showed that the proportion of women with initial normal baseline cytology that can develop CIN2+ during the follow up is three times higher than the proportion of women with HPV-negative results (obtained from self-collection) that can develop CIN2+ later (Porras et al. 2015); this suggests that HPV-screening may be more informative than cytology for predicting future cancer-related abnormalities. In a study performed amongst 2,000 Swedish women, women were sent an invitation for

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either self-sampling combined with an HPV test, or a Pap smear by a physician. Women who were HPV-positive after self-sampling were subsequently invited for further examination and histology. The odds ratio of finding histological CIN2 or CIN3 lesions with the self-sampling in comparison to the traditional Pap smear testing was 5.4 (Wikström et al. 2011). Another study among 8,800 Swedish women found similar higher response rates amongst women who were offered self-testing and an odds ratio of CIN2 cytopathology detection of 2.0 (Broberg et al. 2014). Additionally, the use of self-sampling for HPV screening can also help to capture more HPV-affected individuals in the population. A large study including 28,000 women in the Netherlands found an odds ratio of 2.1 for the detection of CIN2+ lesions in women who had participated in self-sampling screening versus those that did not participate (Gök et al. 2010). Another study, comprising over 22,000 low income women in Marseille, France, showed that detection of CIN2+ was higher among women offered self-sampling vs. women who received an invitation for a Pap smear (Sancho-Garnier et al. 2013). In a study of 100,000 self-sampled Mexican women, the prevalence of hrHPV was 10.8%, and women with a positive hrHPV test had a relative risk of 15.7 for CIN2+ (Lazcano-Ponce et al. 2013). Another large study including 13,140 Chinese women showed that HPV self-testing was more sensitive than cytology for the detection of CIN2+ (Zhao et al. 2012).

The results of these studies therefore strongly suggest that the use of self-sampling in HPV detection with a follow up Pap smear is a useful aid for the detection of abnormal cytologies, improving the detection when it is compared with the use of Pap smear alone.

Women who self-sample are motivated to undergo clinician-performed follow-up in case of a positive HPV test

In addition to increasing patient participation and compliance, HPV self-sampling is also useful in motivating under-screened or never-screened patients to engage with their physician for ongoing screening and cervical health care. For example, in a trial reported by Broberg and coworkers (Broberg et al. 2014), all nine women who tested

positive for hrHPV attended an exam for cytology and colposcopy, suggesting that women with hesitations to undergo screening might be motivated to visit a healthcare provider following a positive self-sampling result. Another study conducted in Chile showed that 106 of 124 (85%) women who had not been screened in the previous three years but who were identified as HPV-positive after self-sampling, attended a later colposcopy (Léniz et al. 2013). This number was even higher in the Norwegian study where 32 of 34 (94.1%) of the hrHPV-positive women in the self-sampling subgroup attended follow-up (Enerly et al. 2016). In the study that included 7,000 under-screened Australian women, 106 of the 140 women (75.7%) who tested positive for hrHPV had colposcopy or cytology within six months (Sultana et al. 2016), while in the Italian study mentioned above, 142 of the 168 women (84.5%) checked in at a clinic for follow-up examinations (Giorgi Rossi et al. 2015). The Dutch cohort involving 28,000 women mentioned above identified 757 HPV positive cases through self-sampling, 684 (90.4%) of whom presented for a follow-up with general practitioner (Gök et al. 2010). In what appeared to be an exception, the study among women in Marseille, France, had a self-sampling follow-up rate of only 41% (Sancho-Garnier et al. 2013).

More and more countries are accepting self-screening for HPV testing

Although self-sampling for the detection of hrHPV types is not currently recommended as part of the standard of care in the United States, it has already been implemented in many countries as a way to increase participation in cervical cancer screening and thus improve outcomes (Madzima et al. 2017). The Netherlands was the first country to offer women the possibility to self-collect samples for HPV testing instead of going to a clinic for a Pap smear (RIVM 2017; Rozemeijer et al. 2015). In 2017, the National Cervical Screening Program in Australia switched to a recommended HPV-screening every 5 years, with the ability to self-sample under medical/health care supervision (Smith et al. 2016). The Finnish Cancer Registry has also determined that self-sampling tests for HPV detection are reliable for cancer screening purposes (Karjalainen et al. 2016; Virtanen et al. 2015). Other countries have started trials with self-sampling to evaluate incorporation of this methodology in official national cervical

cancer programs, including the UK (Lim et al. 2017), Norway (Enerly et al. 2016), Denmark (Tranberg et al. 2016), and Switzerland (Viviano et al. 2017). In addition, trials have started that incorporate self-sampling amongst particular populations with low screening attendance, such as the Maori in New Zealand (Smith et al. 2017), Haitian, Hispanic, and African-American women in South Florida (Kobetz et al. 2017), low-income women from North Carolina (Anderson et al. 2017), and First Nations women in Canada (Zehbe et al. 2016). After the successful 2015 pilot study in Argentina by Arrossi et al. mentioned above, self-collection for HPV testing was scaled-up to include the complete Jujuy province (Arrossi et al. 2017). In addition, Romania will implement a new cervical screening system including HPV detection and self-sampling in order to help to increase participation rates (Vorsters et al. 2017).

In the US, a recent randomized controlled trial was started in which underscreened women were offered either patient clinic reminders or the usual care plus home delivered hrHPV self-sampling kits (Winer et al. 2017). This trial is the first within the US to evaluate if self-screening could increase cervical cancer participation and be a part of future preventive care. Although the outcomes, such as predictive value to detect precancerous states, have not been reported yet, this trial is timely and an indication that the US might follow in the steps of other countries.

The role of vaginal microbiome analysis in HPV diagnosis and monitoring

The associations between the vaginal microbiota and HPV acquisition, persistence, or progression is a growing area of research and potential treatment intervention. The vaginal microbiota may contribute to delayed HPV clearance, the triggering of carcinogenic pathways, and, thus, cervical cancer risk (Kyrgiou et al. 2017; Mitra et al. 2016). Self-sampling for HPV with the addition of associated microorganisms may provide patients and providers with increasingly relevant and actionable clinical information.

In most women, the healthy vaginal microbiota is characterized by the dominance of one or two members of the *Lactobacillus* genus, Gram-positive bacteria that are thought to play a key role in the maintenance of a healthy vaginal environment

(Smith and Ravel 2017; Younes et al. 2017). Several microbial community states have been described, with the *Lactobacillus*-dominated states associated with health, and the more diverse states associated with conditions such as bacterial vaginosis (BV) (Ling et al. 2010; Ravel et al. 2011; Ravel et al. 2013; Srinivasan et al. 2012; Younes et al. 2017). Specific vaginal microbiota signatures can also be seen during an HPV infection; including increased vaginal microbial diversity, decreased *Lactobacillus* spp. levels, and increased presence of specific microbes such as *Sneathia* spp. or *Gardnerella vaginalis* (Gao et al. 2013; Lee et al. 2013; Brotman et al. 2014; Reimers et al. 2016; Shannon et al. 2017). Certain *Lactobacillus* spp. may be protective, while other vaginal microorganisms may increase a woman's risk of HPV infection and cervical cancer (Mitra et al. 2016). In a study of 70 healthy women, the vaginal microbial diversity of HPV-positive women was higher than that of HPV-negative women, and *G. vaginalis* was found at a higher frequency in HPV-positive women (Gao et al. 2013). In a longitudinal study of 32 women, each self-collecting twice weekly for 16 weeks, microbiota dominated by certain *Lactobacillus* spp. were associated with the clearance of HPV levels, while communities with low *Lactobacillus* spp. and high *Atopobium* spp. had the slowest clearance rates (Brotman 2014). In a Korean twin cohort with 68 female twins, HPV-positivity was associated with a lower proportion of *Lactobacillus* spp., a higher microbial diversity, and higher counts of *Sneathia* spp. (Lee et al. 2013). In a study on 60 women from Chicago, certain *Lactobacillus* spp. abundance was inversely associated with HPV detection (Reimers et al. 2016). In another study of 65 women, HPV infection was associated with a more diverse microbiome and a lack of certain *Lactobacillus* spp. (Shannon et al. 2017).

Higher diversity of the vaginal microbiome and lower levels of *Lactobacillus* (particularly *L. jensenii)* are also associated with high-grade squamous intraepithelial lesions (HSIL) as compared to low-grade squamous intraepithelial lesions (LSIL) (Mitra et al. 2015). Additional associations with HSIL include higher levels of species of *Sneathia, Anaerococcus* and *Peptostreptococcus* (Mitra et al. 2015). Patients with cervical cancer have also been shown to have a vaginal microbiota dominated by certain cytokines and *Fusobacterium* (Audirac-Chalifour et al. 2016).

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The vaginal microbiome composition as found in BV is in particular associated with the presence or clearance of HPV. A meta-analysis covering 12 studies showed a positive correlation between BV and HPV infection (Gillet et al. 2011). Additionally, patients with persistent HPV infection showed a significantly higher prevalence of BV than patients with HPV clearance (Guo et al. 2012). Another study showed an association between cervical neoplasia (CIN2+) and the presence of BV (odds ratio: 3.90), providing additional support for the association between BV, HPV infection, and cervical cancer development (de Castro-Sobrinho et al. 2016).

The vaginal microbiome is an emerging treatment area; HPV self-sampling with vaginal microbial analysis can help provide patients with additional information related to HPV, cervical cancer, and their overall vaginal health (Bik et al. 2017). In addition to standard guidelines for monitoring and treatment of abnormal results, patients may also benefit from microbiome specific interventions including probiotics, prebiotics, dietary suggestions, hygiene and sexual practices, and contraceptive management (Kyrgiou et al. 2017; Mitra et al. 2016).

Discussion and conclusions

There is an international consensus that participation in cervical cancer screening programs remains a key factor in improving patient outcomes. However, many individuals do not comply with standard screening guidelines, often for a combination of reasons. For example, poor patient compliance may be caused by lack of time for a clinical visit, embarrassment related to the pelvic exam, and/or previous discomfort or pain during a Pap smear (Allen-Leigh et al. 2017; Dzuba et al. 2002; Sultana et al. 2015). Sociocultural and socioeconomic barriers may also cause women to postpone or decline regular cervical cancer screening. The percentage of women who have not had a Pap smear according to health care guidelines is higher among certain minority populations such as American Indians and Asians, as well as those who live below poverty level (National Center for Health Statistics, 2017). The use of self-collection for vaginal specimens for hrHPV screening has the potential to improve patient access to care, lead to higher patient compliance than current cervical cancer

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screening programs, and thus impact cervical cancer detection rates (Camilloni et al. 2013; Verdoodt et al. 2015; Wong et al. 2016).

High-risk HPV testing on self-collected specimens with subsequent follow-up visit to a physician and cytology on positive cases has also been shown to be more sensitive when compared to Pap smears taken by a health professional in detecting CIN2+ pathology (see e.g. Snijders et al. 2013, and other studies mentioned above). In addition, a negative HPV test is more predictive for a reduced three-year risk of developing cervical cancer than a negative Pap smear (Gage et al. 2014). Therefore, screening for hrHPV through self-sampling with appropriate follow-up for positive results may potentially be more effective than routine Pap smears (Schmeink et al. 2011).

Despite the advantages, self-sampling may also present new challenges for patient care. For example, self-sampling could conceivably decrease the opportunities for direct contact between the patient and the clinician, contributing to the possibility of decreased follow-up, as well as the potential for over-testing. Self-sampling without appropriate follow-up also has the potential to increase patient anxiety in the case of a positive result, especially given the likelihood of many HPV infections to clear spontaneously. In all of these cases, HPV education (see Everett et al. 2011) is important to ensure appropriate patient engagement. Moving forward, additional infrastructure and guidelines will be needed to support the use of HPV self-sampling; new processes are already in development in many countries currently implementing self-sampling as part of their national cervical cancer screening protocol.

An emerging area related to HPV screening is the role of vaginal microbiome analysis in detecting the presence of commensal and pathogenic bacteria that are positively or negatively associated with HPV infection. Self-sampling has the potential to encourage women to engage regularly with their physician for appropriate cervical cancer screening, while also providing unique insights into vaginal health. Recent developments in vaginal microbiome testing have now made detection of HPV and associated microorganisms readily accessible, providing additional information with the potential to complement and improve the diagnosis and control of HPV infection and cervical cancer (Bik et al. 2017).

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With the USPSTF now proposing a shift in cervical cancer screening for average-risk women aged 30-65 to hrHPV testing alone every 5 years (without cervical cytology), self-sampling may become an even more viable option for many women in the US. With appropriate patient education and access to follow-up, HPV self-sampling has the potential to improve participation in screening programs, to reduce socioeconomic barriers to care, to improve the subjective patient experience, and ultimately, to further reduce the continued morbidity and mortality related to HPV infection and cervical cancer.

Bibliography

1. Alcalá, H.E., Mitchell, E. and Keim-Malpass, J. 2017. Adverse childhood experiences and cervical cancer screening. *Journal of Women's Health* 26(1), pp. 58–63.
2. Allen-Leigh, B., Uribe-Zúñiga, P., León-Maldonado, L., Brown, B.J., Lörincz, A., Salmeron, J. and Lazcano-Ponce, E. 2017. Barriers to HPV self-sampling and cytology among low-income indigenous women in rural areas of a middle-income setting: a qualitative study. *BMC Cancer* 17(1), p. 734.
3. Anderson, C., Breithaupt, L., Des Marais, A., Rastas, C., Richman, A., Barclay, L., Brewer, N.T. and Smith, J.S. 2017. Acceptability and ease of use of mailed HPV self-collection among infrequently screened women in North Carolina. *Sexually Transmitted Infections*.
4. Arbyn, M., Verdoodt, F., Snijders, P.J.F., Verhoef, V.M.J., Suonio, E., Dillner, L., Minozzi, S., Bellisario, C., Banzi, R., Zhao, F.-H., Hillemanns, P. and Anttila, A. 2014. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *The Lancet Oncology* 15(2), pp. 172–183.
5. Arrossi, S., Paolino, M., Thouyaret, L., Laudi, R. and Campanera, A. 2017. Evaluation of scaling-up of HPV self-collection offered by community health workers at home visits to increase screening among socially vulnerable under-screened women in Jujuy Province, Argentina. *Implementation Science* 12(1), p. 17.

6. Arrossi, S., Ramos, S., Straw, C., Thouyaret, L. and Orellana, L. 2016. HPV testing: a mixed-method approach to understand why women prefer self-collection in a middle-income country. *BMC Public Health* 16, p. 832.
7. Arrossi, S., Thouyaret, L., Herrero, R., Campanera, A., Magdaleno, A., Cuberli, M., Barletta, P., Laudi, R. and Orellana, L. 2015. Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial. *The Lancet Global Health* 3(2), pp. e85–e94.
8. Audirac-Chalifour, A., Torres-Poveda, K., Bahena-Román, M., Téllez-Sosa, J., Martínez-Barnetche, J., Cortina-Ceballos, B., López-Estrada, G., Delgado-Romero, K., Burguete-García, A.I., Cantú, D., García-Carrancá, A. and Madrid-Marina, V. 2016. Cervical microbiome and cytokine profile at various stages of cervical cancer: A pilot study. *Plos One* 11(4), p. e0153274.
9. Benard, V.B., Thomas, C.C., King, J., Massetti, G.M., Doria-Rose, V.P., Saraiya, M. and Centers for Disease Control and Prevention (CDC) 2014. Vital signs: cervical cancer incidence, mortality, and screening - United States, 2007-2012. *MMWR. Morbidity and Mortality Weekly Report* 63(44), pp. 1004–1009.
10. Bessell, T., Lang, A., Creelman, A. and Hammond, I. 2014. Renewal Of The National Cervical Screening Program – From Evidence-based Recommendations To Policy And Practice: 369. *Asia-pacific Journal of Clinical Oncology* 10(S9), p. 20.
11. Bik, E.M., Bird, S.W., Bustamante, J.P., Leon, L.E., Nieto, P.A., Addae, K., Alegría-Mera, V., Bravo, C., Bravo, D., Cardenas, J.P., Caughey, A., Covarrubias, P.C., Pérez-Donoso, J., Gass, G., Gupta, S.L., Harman, K., Hongo, D.M.B., Jiménez, J.C., Kraal, L., Melis-Arcos, F., Morales, E.H., Morton, A., Navas, C.F., Nuñez, H., Olivares, E., Órdenes-Aenishanslins, N., Ossandon, F.J., Phan, R., Pino, R., Soto-Liebe, K., Varas, I., Walton, N.A., Vera-Wolf, P., Almonacid, D.E., Goddard, A.D., Ugalde, J.A., Richman, J. and Apte, Z.S. 2017. A new sequencing-based women's health assay combining self-sampling, HPV detection and genotyping, STI detection, and vaginal microbiome analysis. *bioRxiv* 217216..
12. Bosch, F.X. and Muñoz, N. 2002. The viral etiology of cervical cancer. *Virus Research* 89(2), pp. 183–190.
13. Bosgraaf, R.P., Ketelaars, P.J.W., Verhoef, V.M.J., Massuger, L.F.A.G., Meijer, C.J.L.M., Melchers, W.J.G. and Bekkers, R.L.M. 2014. Reasons for non-

attendance to cervical screening and preferences for HPV self-sampling in Dutch women. *Preventive Medicine* 64, pp. 108–113.

14. Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., Ghissassi, F. El, Benbrahim-Tallaa, L., Guha, N., Freeman, C., Galichet, L., Cogliano, V. and WHO International Agency for Research on Cancer Monograph Working Group 2009. A review of human carcinogens--Part B: biological agents. *The Lancet Oncology* 10(4), pp. 321–322.
15. Bray, F., Ren, J.-S., Masuyer, E. and Ferlay, J. 2013. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *International Journal of Cancer* 132(5), pp. 1133–1145.
16. Broberg, G., Gyrd-Hansen, D., Miao Jonasson, J., Ryd, M.-L., Holtenman, M., Milsom, I. and Strander, B. 2014. Increasing participation in cervical cancer screening: offering a HPV self-test to long-term non-attendees as part of RACOMIP, a Swedish randomized controlled trial. *International Journal of Cancer* 134(9), pp. 2223–2230.
17. Brotman, R.M., Shardell, M.D., Gajer, P., Tracy, J.K., Zenilman, J.M., Ravel, J. and Gravitt, P.E. 2014. Interplay between the temporal dynamics of the vaginal microbiota and human papillomavirus detection. *The Journal of Infectious Diseases* 210(11), pp. 1723–1733.
18. Cadman, L., Waller, J., Ashdown-Barr, L. and Szarewski, A. 2012. Barriers to cervical screening in women who have experienced sexual abuse: an exploratory study. *The Journal of Family Planning and Reproductive Health Care* 38(4), pp. 214–220.
19. Camilloni, L., Ferroni, E., Cendales, B.J., Pezzarossi, A., Furnari, G., Borgia, P., Guasticchi, G., Giorgi Rossi, P. and Methods to increase participation Working Group 2013. Methods to increase participation in organised screening programs: a systematic review. *BMC Public Health* 13, p. 464.
20. de Castro-Sobrinho, J.M., Rabelo-Santos, S.H., Fugueiredo-Alves, R.R., Derchain, S., Sarian, L.O.Z., Pitta, D.R., Campos, E.A. and Zeferino, L.C. 2016. Bacterial vaginosis and inflammatory response showed association with severity of cervical neoplasia in HPV-positive women. *Diagnostic Cytopathology* 44(2), pp. 80–86.
21. Chatzistamatiou, K., Chatzaki, E., Constantinidis, T., Nena, E., Tsertanidou, A. and Agorastos, T. 2017. Self-collected cervicovaginal sampling for site-of-care primary HPV-based cervical cancer screening: a pilot study in a rural

underserved Greek population. *Journal of Obstetrics and Gynaecology* 37(8), pp. 1059–1064.

22. Chorley, A.J., Marlow, L.A.V., Forster, A.S., Haddrell, J.B. and Waller, J. 2017. Experiences of cervical screening and barriers to participation in the context of an organised programme: a systematic review and thematic synthesis. *Psycho-Oncology* 26(2), pp. 161–172.
23. Committee on Practice Bulletins—Gynecology 2016. Practice bulletin no. 168: cervical cancer screening and prevention. *Obstetrics and Gynecology* 128(4), pp. e111–30.
24. Crawford, A., Benard, V., King, J. and Thomas, C.C. 2016. Understanding barriers to cervical cancer screening in women with access to care, behavioral risk factor surveillance system, 2014. *Preventing Chronic Disease* 13, p. E154.
25. Deleré, Y., Schuster, M., Vartazarowa, E., Hänsel, T., Hagemann, I., Borchardt, S., Perlitz, H., Schneider, A., Reiter, S. and Kaufmann, A.M. 2011. Cervicovaginal self-sampling is a reliable method for determination of prevalence of human papillomavirus genotypes in women aged 20 to 30 years. *Journal of Clinical Microbiology* 49(10), pp. 3519–3522.
26. Douglas, E., Waller, J., Duffy, S.W. and Wardle, J. 2016. Socioeconomic inequalities in breast and cervical screening coverage in England: are we closing the gap? *Journal of medical screening* 23(2), pp. 98–103.
27. Dzuba, I.G., Díaz, E.Y., Allen, B., Leonard, Y.F., Lazcano Ponce, E.C., Shah, K.V., Bishai, D., Lorincz, A., Ferris, D., Turnbull, B., Hernández Avila, M. and Salmerón, J. 2002. The acceptability of self-collected samples for HPV testing vs. the pap test as alternatives in cervical cancer screening. *Journal of women's health & gender-based medicine* 11(3), pp. 265–275.
28. Eaker, S., Adami, H.O. and Sparén, P. 2001. Reasons women do not attend screening for cervical cancer: a population-based study in Sweden. *Preventive Medicine* 32(6), pp. 482–491.
29. Elit, L., Krzyzanowska, M., Saskin, R., Barbera, L., Razzaq, A., Lofters, A., Yeritsyan, N. and Bierman, A. 2012. Sociodemographic factors associated with cervical cancer screening and follow-up of abnormal results. *Canadian Family Physician* 58(1), pp. e22–31.
30. Enerly, E., Bonde, J., Schee, K., Pedersen, H., Lönnberg, S. and Nygård, M. 2016. Self-Sampling for Human Papillomavirus Testing among Non-Attenders Increases Attendance to the Norwegian Cervical Cancer Screening Programme. *Plos One* 11(4), p. e0151978.

687 31. Everett, T., Bryant, A., Griffin, M.F., Martin-Hirsch, P.P., Forbes, C.A. and
688 Jepson, R.G. 2011. Interventions targeted at women to encourage the uptake of
689 cervical screening. *Cochrane Database of Systematic Reviews* (5), p.
690 CD002834.
691 32. Gage, J.C., Schiffman, M., Katki, H.A., Castle, P.E., Fetterman, B., Wentzensen,
692 N., Poitras, N.E., Lorey, T., Cheung, L.C. and Kinney, W.K. 2014. Reassurance
693 against future risk of precancer and cancer conferred by a negative human
694 papillomavirus test. *Journal of the National Cancer Institute* 106(8).
695 33. Gakidou, E., Nordhagen, S. and Obermeyer, Z. 2008. Coverage of cervical
696 cancer screening in 57 countries: low average levels and large inequalities. *PLoS*
697 *Medicine* 5(6), p. e132.
698 34. Galbraith, K.V., Gilkey, M.B., Smith, J.S., Richman, A.R., Barclay, L. and Brewer,
699 N.T. 2014. Perceptions of mailed HPV self-testing among women at higher risk
700 for cervical cancer. *Journal of Community Health* 39(5), pp. 849–856.
701 35. Gao, W., Weng, J., Gao, Y. and Chen, X. 2013. Comparison of the vaginal
702 microbiota diversity of women with and without human papillomavirus infection: a
703 cross-sectional study. *BMC Infectious Diseases* 13, p. 271.
704 36. Gillet, E., Meys, J.F., Verstraelen, H., Bosire, C., De Sutter, P., Temmerman, M.
705 and Broeck, D.V. 2011. Bacterial vaginosis is associated with uterine cervical
706 human papillomavirus infection: a meta-analysis. *BMC Infectious Diseases* 11, p.
707 10.
708 37. Giorgi Rossi, P., Fortunato, C., Barbarino, P., Boveri, S., Caroli, S., Del Mistro,
709 A., Ferro, A., Giammaria, C., Manfredi, M., Moretto, T., Pasquini, A., Sideri, M.,
710 Tufi, M.C., Cogo, C., Altobelli, E. and HPV Self-sampling Italian Working Group
711 2015. Self-sampling to increase participation in cervical cancer screening: an
712 RCT comparing home mailing, distribution in pharmacies, and recall letter. *British*
713 *Journal of Cancer* 112(4), pp. 667–675.
714 38. Gök, M., Heideman, D.A.M., van Kemenade, F.J., Berkhof, J., Rozendaal, L.,
715 Spruyt, J.W.M., Voorhorst, F., Beliën, J.A.M., Babovic, M., Snijders, P.J.F. and
716 Meijer, C.J.L.M. 2010. HPV testing on self collected cervicovaginal lavage
717 specimens as screening method for women who do not attend cervical
718 screening: cohort study. *BMJ (Clinical Research Ed.)* 340, p. c1040.
719 39. Gottschlich, A., Rivera-Andrade, A., Grajeda, E., Alvarez, C., Mendoza Montano,
720 C. and Meza, R. 2017. Acceptability of Human Papillomavirus Self-Sampling for
721 Cervical Cancer Screening in an Indigenous Community in Guatemala. *Journal*
722 *of Global Oncology*, p. JGO.2016.005629.

40. Guo, Y.L., You, K., Qiao, J., Zhao, Y. and Geng, L. 2012. Bacterial vaginosis is conducive to the persistence of HPV infection. *International Journal of STD & AIDS* 23(8), pp. 581–584.
41. Hansen, B.T., Hukkelberg, S.S., Haldorsen, T., Eriksen, T., Skare, G.B. and Nygård, M. 2011. Factors associated with non-attendance, opportunistic attendance and reminded attendance to cervical screening in an organized screening program: a cross-sectional study of 12,058 Norwegian women. *BMC Public Health* 11, p. 264.
42. Huh, W.K., Ault, K.A., Chelmow, D., Davey, D.D., Goulart, R.A., Garcia, F.A.R., Kinney, W.K., Massad, L.S., Mayeaux, E.J., Saslow, D., Schiffman, M., Wentzensen, N., Lawson, H.W. and Einstein, M.H. 2015. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. *Gynecologic Oncology* 136(2), pp. 178–182.
43. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012. Biological agents. Volume 100 B. A review of human carcinogens. *IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer* 100(Pt B), pp. 1–441.
44. Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E. and Forman, D. 2011. Global cancer statistics. *CA: A Cancer Journal for Clinicians* 61(2), pp. 69–90.
45. Jentschke, M., Chen, K., Arbyn, M., Hertel, B., Noskowicz, M., Soergel, P. and Hillemanns, P. 2016. Direct comparison of two vaginal self-sampling devices for the detection of human papillomavirus infections. *Journal of Clinical Virology* 82, pp. 46–50.
46. Jia, Y., Li, S., Yang, R., Zhou, H., Xiang, Q., Hu, T., Zhang, Q., Chen, Z., Ma, D. and Feng, L. 2013. Knowledge about cervical cancer and barriers of screening program among women in Wufeng County, a high-incidence region of cervical cancer in China. *Plos One* 8(7), p. e67005.
47. Karjalainen, L., Anttila, A., Nieminen, P., Luostarinen, T. and Virtanen, A. 2016. Self-sampling in cervical cancer screening: comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. *BMC Cancer* 16(1), p. 221.
48. Khan, M.J., Castle, P.E., Lorincz, A.T., Wacholder, S., Sherman, M., Scott, D.R., Rush, B.B., Glass, A.G. and Schiffman, M. 2005. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *Journal of the National Cancer Institute* 97(14), pp. 1072–1079.

759 49. Kobetz, E., Seay, J., Amofah, A., Pierre, L., Bispo, J.B., Trevil, D., Gonzalez, M.,
760 Poitevien, M., Koru-Sengul, T. and Carrasquillo, O. 2017. Mailed HPV self-
761 sampling for cervical cancer screening among underserved minority women:
762 study protocol for a randomized controlled trial. *Trials* 18(1), p. 19.
763 50. Kyrgiou, M., Mitra, A. and Moscicki, A.-B. 2017. Does the vaginal microbiota play
764 a role in the development of cervical cancer? *Translational Research* 179, pp.
765 168–182.
766 51. Lam, J.U.H., Elfström, K.M., Ejegod, D.M., Pedersen, H., Rygaard, C., Rebolj,
767 M., Lynge, E., Juul, K.E., Kjær, S.K., Dillner, J. and Bonde, J. 2017. High-grade
768 cervical intraepithelial neoplasia in human papillomavirus self-sampling of
769 screening non-attenders. *British Journal of Cancer*.
770 52. Lazcano-Ponce, E., Lőrincz, A.T., Torres, L., Salmerón, J., Cruz, A., Rojas, R.,
771 Hernández, P. and Hernández, M. 2014. Specimen self-collection and HPV DNA
772 screening in a pilot study of 100,242 women. *International Journal of Cancer*
773 135(1), pp. 109–116.
774 53. Lee, J.E., Lee, S., Lee, H., Song, Y.-M., Lee, K., Han, M.J., Sung, J. and Ko, G.
775 2013. Association of the vaginal microbiota with human papillomavirus infection
776 in a Korean twin cohort. *Plos One* 8(5), p. e63514.
777 54. Léniz, J., Barriga, M.I., Lagos, M., Ibáñez, C., Puschel, K. and Ferreccio, C.
778 2013. HPV vaginal self-sampling among women non-adherent to Papanicolaou
779 screening in Chile. *Salud Pública de México* 55(2), pp. 162–169.
780 55. Levinson, K.L., Jernigan, A.M., Flocke, S.A., Tergas, A.I., Gunderson, C.C., Huh,
781 W.K., Wilkinson-Ryan, I., Lawson, P.J., Fader, A.N. and Belinson, J.L. 2016.
782 Intimate partner violence and barriers to cervical cancer screening: A
783 gynecologic oncology fellow research network study. *Journal of Lower Genital*
784 *Tract Disease* 20(1), pp. 47–51.
785 56. Lim, A.W., Hollingworth, A., Kalwij, S., Curran, G. and Sasieni, P. 2017. Offering
786 self-sampling to cervical screening non-attenders in primary care. *Journal of*
787 *medical screening* 24(1), pp. 43–49.
788 57. Ling, Z., Kong, J., Liu, F., Zhu, H., Chen, X., Wang, Y., Li, L., Nelson, K.E., Xia,
789 Y. and Xiang, C. 2010. Molecular analysis of the diversity of vaginal microbiota
790 associated with bacterial vaginosis. *BMC Genomics* 11, p. 488.
791 58. Madzima, T.R., Vahabi, M. and Lofters, A. 2017. Emerging role of HPV self-
792 sampling in cervical cancer screening for hard-to-reach women: Focused
793 literature review. *Canadian Family Physician* 63(8), pp. 597–601.

794 59. Mao, C., Kulasingam, S.L., Whitham, H.K., Hawes, S.E., Lin, J. and Kiviat, N.B.
795 2017. Clinician and Patient Acceptability of Self-Collected Human Papillomavirus
796 Testing for Cervical Cancer Screening. *Journal of Women's Health* 26(6), pp.
797 609–615.
798 60. Marlow, L.A.V., Waller, J. and Wardle, J. 2015. Barriers to cervical cancer
799 screening among ethnic minority women: a qualitative study. *The Journal of*
800 *Family Planning and Reproductive Health Care* 41(4), pp. 248–254.
801 61. Mayrand, M.-H., Duarte-Franco, E., Rodrigues, I., Walter, S.D., Hanley, J.,
802 Ferenczy, A., Ratnam, S., Coutlée, F., Franco, E.L. and Canadian Cervical
803 Cancer Screening Trial Study Group 2007. Human papillomavirus DNA versus
804 Papanicolaou screening tests for cervical cancer. *The New England Journal of*
805 *Medicine* 357(16), pp. 1579–1588.
806 62. Mitra, A., MacIntyre, D.A., Lee, Y.S., Smith, A., Marchesi, J.R., Lehne, B., Bhatia,
807 R., Lyons, D., Paraskevaidis, E., Li, J.V., Holmes, E., Nicholson, J.K., Bennett,
808 P.R. and Kyrgiou, M. 2015. Cervical intraepithelial neoplasia disease progression
809 is associated with increased vaginal microbiome diversity. *Scientific reports* 5, p.
810 16865.
811 63. Mitra, A., MacIntyre, D.A., Marchesi, J.R., Lee, Y.S., Bennett, P.R. and Kyrgiou,
812 M. 2016. The vaginal microbiota, human papillomavirus infection and cervical
813 intraepithelial neoplasia: what do we know and where are we going next?
814 *Microbiome* 4(1), p. 58.
815 64. Musselwhite, L.W., Oliveira, C.M., Kwaramba, T., de Paula Pantano, N., Smith,
816 J.S., Fregnani, J.H., Reis, R.M., Mauad, E., Vazquez, F. de L. and Longatto-
817 Filho, A. 2016. Racial/ethnic disparities in cervical cancer screening and
818 outcomes. *Acta cytologica* 60(6), pp. 518–526.
819 65. National Center for Health Statistics. 2017. *Health, United States, 2016: With*
820 *Chartbook on Long-term Trends in Health.* Hyattsville, MD.
821 66. Nayar, R. and Wilbur, D.C. 2017. The bethesda system for reporting cervical
822 cytology: A historical perspective. *Acta cytologica* 61(4-5), pp. 359–372.
823 67. Nelson, E.J., Maynard, B.R., Loux, T., Fatla, J., Gordon, R. and Arnold, L.D.
824 2017. The acceptability of self-sampled screening for HPV DNA: a systematic
825 review and meta-analysis. *Sexually Transmitted Infections* 93(1), pp. 56–61.
826 68. Nour, N.M. 2009. Cervical cancer: a preventable death. *Reviews in obstetrics*
827 *and gynecology* 2(4), pp. 240–244.
828 69. Obiri-Yeboah, D., Adu-Sarkodie, Y., Djigma, F., Hayfron-Benjamin, A., Abdul, L.,
829 Simpore, J. and Mayaud, P. 2017. Self-collected vaginal sampling for the

detection of genital human papillomavirus (HPV) using careHPV among Ghanaian women. *BMC Women's Health* 17(1), p. 86.

70. Ogilvie, G.S., Patrick, D.M., Schulzer, M., Sellors, J.W., Petric, M., Chambers, K., White, R. and FitzGerald, J.M. 2005. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. *Sexually Transmitted Infections* 81(3), pp. 207–212.
71. Petignat, P., Faltin, D.L., Bruchim, I., Tramèr, M.R., Franco, E.L. and Coutlée, F. 2007. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. *Gynecologic Oncology* 105(2), pp. 530–535.
72. Porras, C., Hildesheim, A., González, P., Schiffman, M., Rodríguez, A.C., Wacholder, S., Jiménez, S., Quint, W., Guillen, D., Kreimer, A.R., Herrero, R. and CVT Vaccine Group 2015. Performance of self-collected cervical samples in screening for future precancer using human papillomavirus DNA testing. *Journal of the National Cancer Institute* 107(1), p. 400.
73. Racey, C.S., Withrow, D.R. and Gesink, D. 2013. Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis. *Canadian Journal of Public Health* 104(2), pp. e159–66.
74. Ramzan, M., Noor ul Ain, Ilyas, S., Umer, M., Bano, S., Sarwar, S., Shahzad, N. and Shakoori, A.R. 2015. A cornucopia of screening and diagnostic techniques for human papillomavirus associated cervical carcinomas. *Journal of Virological Methods* 222, pp. 192–201.
75. Ravel, J., Brotman, R.M., Gajer, P., Ma, B., Nandy, M., Fadrosh, D.W., Sakamoto, J., Koenig, S.S., Fu, L., Zhou, X., Hickey, R.J., Schwebke, J.R. and Forney, L.J. 2013. Daily temporal dynamics of vaginal microbiota before, during and after episodes of bacterial vaginosis. *Microbiome* 1(1), p. 29.
76. Ravel, J., Gajer, P., Abdo, Z., Schneider, G.M., Koenig, S.S.K., McCulle, S.L., Karlebach, S., Gorle, R., Russell, J., Tacket, C.O., Brotman, R.M., Davis, C.C., Ault, K., Peralta, L. and Forney, L.J. 2011. Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Sciences of the United States of America* 108 Suppl 1, pp. 4680–4687.
77. Reimers, L.L., Mehta, S.D., Massad, L.S., Burk, R.D., Xie, X., Ravel, J., Cohen, M.H., Palefsky, J.M., Weber, K.M., Xue, X., Anastos, K., Minkoff, H., Atrio, J., Souza, G. D', Ye, Q., Colie, C., Zolnik, C.P., Spear, G.T. and Strickler, H.D. 2016. The Cervicovaginal Microbiota and Its Associations With Human

Papillomavirus Detection in HIV-Infected and HIV-Uninfected Women. *The Journal of Infectious Diseases* 214(9), pp. 1361–1369.

78. Rijkaart, D.C., Berkhof, J., Rozendaal, L., van Kemenade, F.J., Bulkmans, N.W.J., Heideman, D.A.M., Kenter, G.G., Cuzick, J., Snijders, P.J.F. and Meijer, C.J.L.M. 2012. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *The Lancet Oncology* 13(1), pp. 78–88.
79. RIVM 2017. New population screening for cervical cancer is more effective and introduces self-collection of samples. In: *Annual Report RIVM 2016*.
80. Rozemeijer, K., de Kok, I.M.C.M., Naber, S.K., van Kemenade, F.J., Penning, C., van Rosmalen, J. and van Ballegooijen, M. 2015. Offering Self-Sampling to Non-Attendees of Organized Primary HPV Screening: When Do Harms Outweigh the Benefits? *Cancer Epidemiology, Biomarkers & Prevention* 24(5), pp. 773–782.
81. Sabatino, S.A., White, M.C., Thompson, T.D., Klabunde, C.N. and Centers for Disease Control and Prevention (CDC) 2015. Cancer screening test use - United States, 2013. *MMWR. Morbidity and Mortality Weekly Report* 64(17), pp. 464–468.
82. Sancho-Garnier, H., Tamalet, C., Halfon, P., Leandri, F.X., Le Retraite, L., Djoufelkit, K., Heid, P., Davies, P. and Piana, L. 2013. HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. *International Journal of Cancer* 133(11), pp. 2681–2687.
83. de Sanjose, S., Quint, W.G., Alemany, L., Geraets, D.T., Retrospective International Survey and HPV Time Trends Study Group, et al. 2010. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *The Lancet Oncology* 11(11), pp. 1048–1056.
84. Schiffman, M. 2017. Cervical cancer screening: Epidemiology as the necessary but not sufficient basis of public health practice. *Preventive Medicine* 98, pp. 3–4.
85. Schiffman, M., Doorbar, J., Wentzensen, N., de Sanjosé, S., Fakhry, C., Monk, B.J., Stanley, M.A. and Franceschi, S. 2016. Carcinogenic human papillomavirus infection. *Nature reviews. Disease primers* 2, p. 16086.
86. Schiffman, M. and Wentzensen, N. 2013. Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. *Cancer Epidemiology, Biomarkers & Prevention* 22(4), pp. 553–560.
87. Schmeink, C.E., Bekkers, R.L.M., Massuger, L.F.A.G. and Melchers, W.J.G. 2011. The potential role of self-sampling for high-risk human papillomavirus

902 detection in cervical cancer screening. *Reviews in medical virology* 21(3), pp.
903 139–153.
904 88. Shannon, B., Yi, T.J., Perusini, S., Gajer, P., Ma, B., Humphrys, M.S., Thomas-
905 Pavanel, J., Chieza, L., Janakiram, P., Saunders, M., Tharao, W., Huibner, S.,
906 Shahabi, K., Ravel, J., Rebbapragada, A. and Kaul, R. 2017. Association of HPV
907 infection and clearance with cervicovaginal immunology and the vaginal
908 microbiota. *Mucosal Immunology* 10(5), pp. 1310–1319.
909 89. Smith, M.A., Edwards, S. and Canfell, K. 2017. Impact of the National Cervical
910 Screening Programme in New Zealand by age: analysis of cervical cancer trends
911 1985-2013 in all women and in Māori women. *Cancer Causes & Control* 28(12),
912 pp. 1393–1404.
913 90. Smith, M., Lew, J.B., Simms, K. and Canfell, K. 2016. Impact of HPV sample
914 self-collection for underscreened women in the renewed Cervical Screening
915 Program. *The Medical Journal of Australia* 204(5), p. 1941e–7.
916 91. Smith, R.A., Manassaram-Baptiste, D., Brooks, D., Doroshenk, M., Fedewa, S.,
917 Saslow, D., Brawley, O.W. and Wender, R. 2015. Cancer screening in the United
918 States, 2015: a review of current American cancer society guidelines and current
919 issues in cancer screening. *CA: A Cancer Journal for Clinicians* 65(1), pp. 30–54.
920 92. Smith, S.B. and Ravel, J. 2017. The vaginal microbiota, host defence and
921 reproductive physiology. *The Journal of Physiology* 595(2), pp. 451–463.
922 93. Snijders, P.J.F., Verhoef, V.M.J., Arbyn, M., Ogilvie, G., Minozzi, S., Banzi, R.,
923 van Kemenade, F.J., Heideman, D.A.M. and Meijer, C.J.L.M. 2013. High-risk
924 HPV testing on self-sampled versus clinician-collected specimens: a review on
925 the clinical accuracy and impact on population attendance in cervical cancer
926 screening. *International Journal of Cancer* 132(10), pp. 2223–2236.
927 94. Srinivasan, S., Hoffman, N.G., Morgan, M.T., Matsen, F.A., Fiedler, T.L., Hall,
928 R.W., Ross, F.J., McCoy, C.O., Bumgarner, R., Marrazzo, J.M. and Fredricks,
929 D.N. 2012. Bacterial communities in women with bacterial vaginosis: high
930 resolution phylogenetic analyses reveal relationships of microbiota to clinical
931 criteria. *Plos One* 7(6), p. e37818.
932 95. Stewart, D.E., Gagliardi, A., Johnston, M., Howlett, R., Barata, P., Lewis, N.,
933 Oliver, T. and Mai, V. 2007. Self-Collected Samples for Testing of Oncogenic
934 Human Papillomavirus: A Systematic Review. *Journal of Obstetrics and*
935 *Gynaecology Canada* 29(10), pp. 817–828.
936 96. Sultana, F., English, D.R., Simpson, J.A., Drennan, K.T., Mullins, R., Brotherton,
937 J.M.L., Wrede, C.D., Heley, S., Saville, M. and Gertig, D.M. 2016. Home-based

HPV self-sampling improves participation by never-screened and under-screened women: Results from a large randomized trial (iPap) in Australia. *International Journal of Cancer* 139(2), pp. 281–290.

97. Sultana, F., Mullins, R., English, D.R., Simpson, J.A., Drennan, K.T., Heley, S., Wrede, C.D., Brotherton, J.M.L., Saville, M. and Gertig, D.M. 2015. Women's experience with home-based self-sampling for human papillomavirus testing. *BMC Cancer* 15(1), p. 849.

98. Szarewski, A., Cadman, L., Mesher, D., Austin, J., Ashdown-Barr, L., Edwards, R., Lyons, D., Walker, J., Christison, J., Frater, A. and Waller, J. 2011. HPV self-sampling as an alternative strategy in non-attenders for cervical screening - a randomised controlled trial. *British Journal of Cancer* 104(6), pp. 915–920.

99. Tambouret, R.H. 2013. The evolution of the Papanicolaou smear. *Clinical Obstetrics and Gynecology* 56(1), pp. 3–9.

100. Toliman, P., Badman, S.G., Gabuzzi, J., Silim, S., Forereme, L., Kumbia, A., Kombuk, B., Kombati, Z., Allan, J., Munnull, G., Ryan, C., Vallely, L.M., Kelly-Hanku, A., Wand, H., Mola, G.D.L., Guy, R., Siba, P., Kaldor, J.M., Tabrizi, S.N. and Vallely, A.J. 2016. Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens. *Journal of Clinical Microbiology* 54(7), pp. 1734–1737.

101. Tranberg, M., Bech, B.H., Blaakær, J., Jensen, J.S., Svanholm, H. and Andersen, B. 2016. Study protocol of the CHOiCE trial: a three-armed, randomized, controlled trial of home-based HPV self-sampling for non-participants in an organized cervical cancer screening program. *BMC Cancer* 16(1), p. 835.

102. U.S. Preventive Services Task Force. 2017. Draft Recommendation Statement: Cervical Cancer: Screening - US Preventive Services Task Force [Online]. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2 [Accessed: 19 November 2017].

103. US Preventive Services Task Force 2016. Final Update Summary: Cervical Cancer: Screening [Online]. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening [Accessed: 2 November 2017].

104. Vaccarella, S., Lortet-Tieulent, J., Plummer, M., Franceschi, S. and Bray, F. 2013. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. *European Journal of Cancer* 49(15), pp. 3262–3273.

105. Verdoodt, F., Jentschke, M., Hillemanns, P., Racey, C.S., Snijders, P.J.F. and Arbyn, M. 2015. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. *European Journal of Cancer* 51(16), pp. 2375–2385.

106. Virtanen, A., Anttila, A., Luostarinen, T., Malila, N. and Nieminen, P. 2015. Improving cervical cancer screening attendance in Finland. *International Journal of Cancer* 136(6), pp. E677–84.

107. Viviano, M., Catarino, R., Jeannot, E., Boulvain, M., Malinverno, M.U., Vassilakos, P. and Petignat, P. 2017. Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial. *British Journal of Cancer* 116(11), pp. 1382–1388.

108. Vorsters, A., Arbyn, M., Baay, M., Bosch, X., de Sanjosé, S., Hanley, S., Karafillakis, E., Lopalco, P.L., Pollock, K.G., Yarwood, J. and Van Damme, P. 2017. Overcoming barriers in HPV vaccination and screening programs. *Papillomavirus Research* 4, pp. 45–53.

109. Walboomers, J.M.M., Jacobs, M.V., Manos, M.M., Bosch, X.F., Kummer, A.J., Shah, K.V., Snijders, P.J., Peto, J., Meijer, C.J. and Muñoz, N. 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of Pathology* 189(1), pp. 12–19.

110. Waller, J., Bartoszek, M., Marlow, L. and Wardle, J. 2009. Barriers to cervical cancer screening attendance in England: a population-based survey. *Journal of medical screening* 16(4), pp. 199–204.

111. Watson, M., Benard, V., King, J., Crawford, A. and Saraiya, M. 2017. National assessment of HPV and Pap tests: Changes in cervical cancer screening, National Health Interview Survey. *Preventive Medicine* 100, pp. 243–247.

112. Wikström, I., Lindell, M., Sanner, K. and Wilander, E. 2011. Self-sampling and HPV testing or ordinary Pap-smear in women not regularly attending screening: a randomised study. *British Journal of Cancer* 105(3), pp. 337–339.

113. Winer, R.L., Tiro, J.A., Miglioretti, D.L., Thayer, C., Beatty, T., Lin, J., Gao, H., Kimbel, K. and Buist, D.S.M. 2017. Rationale and design of the HOME trial: A

pragmatic randomized controlled trial of home-based human papillomavirus (HPV) self-sampling for increasing cervical cancer screening uptake and effectiveness in a U.S. healthcare system. *Contemporary clinical trials* S1551-7144(17), pp. 30453–30456.

114. Wong, E.L.Y., Chan, P.K.S., Chor, J.S.Y., Cheung, A.W.L., Huang, F. and Wong, S.Y.S. 2016. Evaluation of the Impact of Human Papillomavirus DNA Self-sampling on the Uptake of Cervical Cancer Screening. *Cancer Nursing* 39(1), pp. E1–E11.

115. Younes, J.A., Lievens, E., Hummelen, R., van der Westen, R., Reid, G. and Petrova, M.I. 2017. Women and their microbes: the unexpected friendship. *Trends in Microbiology*.

116. Zehbe, I., Jackson, R., Wood, B., Weaver, B., Escott, N., Severini, A., Krajden, M., Bishop, L., Morrisseau, K., Ogilvie, G., Burchell, A.N. and Little, J. 2016. Community-randomised controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology. *BMJ open* 6(10), p. e011754.

117. Zehbe, I., Moeller, H., Severini, A., Weaver, B., Escott, N., Bell, C., Crawford, S., Bannon, D. and Paavola, N. 2011. Feasibility of self-sampling and human papillomavirus testing for cervical cancer screening in First Nation women from Northwest Ontario, Canada: a pilot study. *BMJ open* 1(1), p. e000030.

118. Zehbe, I., Wakewich, P., King, A.-D., Morrisseau, K. and Tuck, C. 2017. Self-administered versus provider-directed sampling in the Anishinaabek Cervical Cancer Screening Study (ACCSS): a qualitative investigation with Canadian First Nations women. *BMJ open* 7(8), p. e017384.

119. Zhao, F.-H., Lewkowitz, A.K., Chen, F., Lin, M.J., Hu, S.-Y., Zhang, X., Pan, Q.-J., Ma, J.-F., Niyazi, M., Li, C.-Q., Li, S.-M., Smith, J.S., Belinson, J.L., Qiao, Y.-L. and Castle, P.E. 2012. Pooled analysis of a self-sampling HPV DNA Test as a cervical cancer primary screening method. *Journal of the National Cancer Institute* 104(3), pp. 178–188.