Cervical cancer is the second most common cause of death in women worldwide, and is the leading cause of death among women in many developing countries. Facilitating our ability to prevent cervical cancer is our increasing understanding of the aetiology of the disease. Cervical cancer is invariably caused by infection with specific high-risk genotypes of HPV. Indeed, non-HPV infection accounts for <1-2% of all cervical cancers.

The problem with using HPV testing for screening for cervical cancer is that infection with HPV is very common. In the US, the Centers for Disease Control and Prevention estimates that most sexually-active women will acquire HPV at some point in their lifetime. However, only a few infected women will go on to develop cervical cancer. Moreover, HPV infection typically occurs in younger age groups whereas cervical cancer usually develops later in life. Hence, it takes many years before a precursor lesion becomes an invasive cervical cancer. This is reflected in the epidemiology of HPV infection and cervical cancer. Globally, 300 million women are infected with HPV of whom 30 million have low-grade cervical lesions, 10 million have high-grade lesions, and 528,000 have cervical cancer.

HPV are DNA tumour viruses that cause epithelial cell proliferation at the site of infection and are highly specific for their target epithelium. They are classified according to their degree of DNA relatedness, with there being approximately 100 different genotypes of HPV. Of these, about 40 genotypes specifically infect the anogenital tract. Fourteen of the anogenital tract types of HPV are classified as high risk (hrHPV) because they can infect the lower genitourinary tract epithelium of both men and women and cause cancer. The 14 hrHPV genotypes are: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. They are grouped into two clades: the A9 clade, which contains HPV 16, the most important HPV genotype for causing cancer in humans, and the A7 clade, which contains HPV18 and HPV45, the second and third most important HPV genotypes, respectively.

How important are the 14 hrHPV genotypes? Testing for specific hrHPV genotypes was performed in a pooled analysis of International Agency for Research on Cancer case-control studies of women with and without cervical cancer from nine countries. The analysis found extraordinarily high odds ratios for cervical cancer associated with hrHPV genotypes (Table 1). To place this degree of risk into perspective, the relative risk of cervical cancer associated with hrHPV is higher than the risk of lung cancer associated with smoking.

### Table 1. Risk of squamous-cell cervical cancer associated with specific hrHPV genotypes.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage Infection in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>HPV 16</td>
<td>3</td>
</tr>
<tr>
<td>HPV 18</td>
<td>1</td>
</tr>
<tr>
<td>HPV 45</td>
<td>0.7</td>
</tr>
<tr>
<td>HPV 31</td>
<td>0.6</td>
</tr>
<tr>
<td>HPV 52</td>
<td>0.3</td>
</tr>
<tr>
<td>HPV 33</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Although there is minimal geographical variation in the prevalence of the hrHPV genotypes, HPV58 is more common in Asia than in Europe or South America. HPV16 and HPV18 are the most common genotypes in all regions and account for 70% of all cervical cancers globally (Figure 1). In terms of the natural history of HPV infection, exposure to HPV results in a productive viral infection that causes mild cytological abnormalities, which are referred to as LSIL by cytologists or CIN1 lesions by pathologists. This is merely a marker of HPV infection. Most HPV infections are transient and cleared without need for any treatment. Persistent HPV infections are the only type of HPV infection that matter clinically since they can progress to high-grade precursor lesions (CIN2,3), which if left undetected and untreated have a risk of developing into invasive cervical cancer. Many high-grade precursors, however, will not progress to cancer even after protracted follow-up periods of up to 30 years. Hence, it is important to stress that HPV infection does not equate to cervical cancer.
What is the risk of progression with the different hrHPV genotypes? The risk of progression to a pre-cancerous lesion is considerably higher with an HPV16, 18 infection than with an infection with one of the other HPV genotypes. According to the well-controlled Seattle College Student Study in the US, the 3-year cumulative risk of developing a high-grade precursor in young women (aged 18-20 years) was 27% with incident HPV16 or 18 versus 11% with any incident HPV infection. An important finding of the study is that the median time to confirmation of CIN2, 3 was only 14 months after incident HPV16 or 18 infection. Previously, it was thought that it took many years to progress from HPV infection to a high-grade precursor lesion. It does, however, take many years to progress from a high-grade precursor to invasive cervical cancer. In another US cohort study, older women (aged ≥30 years) enrolled in the Kaiser Permanente health plan in Portland, Oregon who had negative cytology at study entry and proposed that future screening trials only compare cytology versus hrHPV testing alone. A 2011 systematic review of six cross-sectional screening studies that compared cytoscopy versus hrHPV testing for high-risk genotypes. There was no difference between conventional cytology and liquid-based cytology in terms of screening efficacy, so any benefit in the liquid-based cytology plus HPV test arm was due to the HPV test. After a single round of screening, 50% more cases of CIN2 or worse (75 vs 51) were detected in the liquid-based cytology plus HPV DNA testing arm versus the conventional cytology arm. The investigators were also able to show that in women with high-grade disease no benefit was gained from performing a Pap smear in HPV-positive women and proposed that future screening trials only compare cytology versus hrHPV testing alone. A 2011 systematic review of six cross-sectional screening studies that compared liquid-based cytology with hrHPV screening in women aged ≥30 years showed that HPV DNA testing was more sensitive for detecting high-grade disease (Figure 3), and was less variable between laboratories than cytology. hrHPV testing was less specific than cytology but not dramatically less specific.

Figure 1. High-risk human papillomavirus (HPV) genotypes (also categorised according to the clades A9, A7, and other) in cases of invasive cervical cancer that were positive for HPV DNA by geographical region. A Local and Global Perspective on Cervical Screening with HPV – An Educational Forum

How are we going to apply the powerful biology of HPV infection in a clinical setting? An HPV test (cobas HPV Test) received FDA approval for primary screening of cervical cancer in women aged ≥25 years in April 2014. The approval for marketing was primarily based on clinical evaluation of the new screening technology in the large ATHENA longitudinal study, but also on the results of many large cross-sectional screening studies, all of which have all uniformly demonstrated the utility of HPV testing.

The Italian New Technologies for Cervical Cancer (NTCC) Working Group screening trial is one of the more elegantly designed cross-sectional studies to have investigated the sensitivity and specificity of HPV testing for cervical cancer. In the first phase of this two-phase multicentre controlled study, a total of 33,364 women aged 35-60 years were randomly assigned to either conventional cytology (i.e. Pap smear) or liquid-based cytology plus HPV DNA testing for hrHPV genotypes. There was no difference between conventional cytology and liquid-based cytology in terms of screening efficacy, so any benefit in the liquid-based cytology plus HPV test arm was due to the HPV test. After a single round of screening, 50% more cases of CIN2 or worse (75 vs 51) were detected in the liquid-based cytology plus HPV DNA testing arm versus the conventional cytology arm. The investigators were also able to show that in women with high-grade disease no benefit was gained from performing a Pap smear in HPV-positive women and proposed that future screening trials only compare cytology versus hrHPV testing alone.

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CERVICAL SCREENING WITH HPV – INFORMATION LEARNED FROM LARGE TRIALS AND ATHENA

Prof. Thomas Wright

Figure 2. Twelve-year risk of developing CIN3+ in Danish women with persistent hrHPV (positive for HPV twice during a 2-year period). Abbreviations: 16 = HPV16; hc2 = hrHPV types as measured by the digene Hybrid Capture 2 HPV DNA test.

Collectively, the results of these studies emphasise the importance of identifying those women with HPV 16, 18 infections. Once a hrHPV infection has been established and is maintained for several years it is unlikely to be cleared and has a greater chance of producing invasive disease.

Figure 3. Review of six cross-sectional screening studies performed in developed countries in women aged ≥30 years to evaluate the sensitivity of cytology versus HPV DNA testing for detection of CIN2 or worse.

In 2012, new US guidelines for cervical cancer screening recommended Pap smear and hrHPV co-testing as the preferred approach in women aged ≥30 years. All of the screening studies conducted up to this point had been cross-sectional. However, screening is typically done multiple times in a woman’s lifetime so multiple rounds of screening are necessary in an evaluation setting for the benefits of HPV testing versus cytology to become evident.

In the Italian NTCC study, with the two separate recruitment phases combined, women aged 25-60 years were randomised to HPV testing (n=47,369) or conventional cytology (n=13,842), with the majority of women undergoing two rounds of screening.
over a 6-year period. After two rounds of screening, HPV testing had detected 60% more cases of CIN3 than Pap testing (106 vs 64) leading to half as many women (6 vs 15) developing invasive cervical cancer in the HPV arm versus the Pap test arm.16 This study was subsequently included in a follow-up analysis of four European randomised controlled longitudinal screening trials involving a total of 176,464 women aged 20-64 years and a median follow up of 6.5 years (>1 million person-years).17 The analysis showed a significantly lower occurrence of invasive cervical cancer in women screened using HPV testing versus cytology from 2.5 years after study entry (Figure 4), which translated to 60-70% higher protection against invasive cervical cancer with HPV testing as compared with cytology.17

**Figure 4.** HPV testing versus cytology for the prevention of cervical cancer in an analysis of four European randomised longitudinal screening trials.17

Cervical cytology is generally recognised as being highly subjective and there is considerable inter-laboratory variation in how slides are evaluated. However, little is known about how this impacts the performance of cytology. In a US study funded by the National Cancer Institute, nearly 5,000 liquid-based cytology slides obtained from women enrolled during 1996-1998 in the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) were interpreted by seven well-respected academic cytology centres and re-read by four Pathology Quality Control Group (QC) cytopathologists.18 Only 78% of the slides rated as NILM by the pathology centres were considered normal by the QC reviewers and only 47% of the slides considered HSIL by the pathology centres were considered HSIL by the QC reviewers. Hence, the interpretive variability was shown to be substantial for the reading of liquid cytology slides.18

Similar results were found in the ATHENA trial in which liquid-based cytology specimens obtained from 46,887 eligible women aged ≥21 years of age were evaluated at four large regional US laboratories. Review of these evaluations revealed considerable variability across the laboratories both in overall rates of cytological abnormality (ASCUS or higher), which ranged from 3.8 to 9.9%, and in the sensitivity of cytology to detect CIN2 or worse, from 42.0 to 73.0%. In comparison, the variation in rates of hrHPV test positivity was only 10.9 to 13.4%, and variation in the sensitivity of hrHPV testing was only 88.2 to 90.1%.20 Variability is removed because the HPV test is objective rather than subjective.

For the development of the 2012 US screening guidelines, the US government commissioned an evidence-based review to assess the performance of cytology versus HPV testing alone. The review identified six relevant high-quality cross-sectional studies. In all of these studies, HPV testing was more sensitive, affording an average 35.7% higher sensitivity versus cytology (Figure 3).15

Because of the poor sensitivity of cytology, the US adopted co-testing by adding HPV testing to cytology. The problem with this approach is that both an insensitive test, i.e. cytology, and a sensitive test, i.e. HPV testing, is used in all women, which is counterintuitive since the basic tenant of screening is to first use the most sensitive test and follow up the positive results with the most specific test, i.e. cytology.

In addition, there are a large number of cytology categories, e.g. NILM, ASCUS, LSIL, HSIL, etc., which were originally created for the purpose of risk stratification because at the time there was no tool capable of determining risk of high-grade disease. The problem with these being so many categories is that it is confusing, which makes it difficult for clinicians to work out how to best manage patients. For example, the 2013 American Society for Colposcopy and Cervical Pathology (ASCCP) Management Guidelines feature 12 different complex algorithms just for cytology results.

Hence, there is a need to simplify the process so that a family GP can work out how to screen a patient for cervical cancer.

The solution may be primary screening using hrHPV testing without cytology, not least because HPV testing alone requires a simple single algorithm for the screening test results. Using hrHPV testing with HPV16/18 genotyping and reflex cytology (Figure 5), women who are negative for HPV would go to routine screening while women testing positive for HPV 16/18 would proceed to colposcopy. Those positive for the 12 other hrHPV genotypes have sufficiently low risk to be referred to cytological triage. Women with the 12 other hrHPV types who are NILM go to follow up in 12 months to look for persistence and those who are cytology positive (i.e. ASCUS or higher) are referred to colposcopy.

**Figure 5.** Primary HPV screening algorithm, using hrHPV testing with partial genotyping and reflex cytology.

The ATHENA trial was designed to evaluate HPV screening strategies via the performance of the cobas HPV Test technology in three different populations: women aged ≥21 years with ASCUS cervical cytology, women aged ≥30 years with normal cervical cytology, and an overall screening population of women aged ≥25 years. The three different study populations in the ATHENA trial for which clinical validation of the hrHPV testing technology (cobas HPV Test) was obtained are depicted in Figure 6.21,22 Commenced in 2008, the ATHENA trial was a multicentre prospective study of more than 46,887 women aged ≥21 years of age undergoing routine cervical cancer screening (32,260 of whom were aged ≥30 years) in the US. All women had a gynaecological examination, a ThinPrep Pap test, and multiple hrHPV tests (including partial genotyping) using an analytically-sensitive HPV technology (cobas HPV Test). Women who were hrHPV(+) and/or Pap(+) underwent colposcopy as a subset who were hrHPV(+) or Pap(-) because it could not be assumed that every high-grade lesion would have either positive HPV or positive cytology, i.e. to ensure that women with double negative screens were evaluated for disease.23

**Figure 6.** Clinical validation of the HPV testing technology (cobas HPV Test) in women with ASCUS cytology (to get approval for ASC-US management), women negative for cytology (to get approval for co-testing), and in women aged ≥25 years (to get primary screening approval) in the ATHENA trial.20,22

The first aspect to consider with primary screening is at what age should primary HPV screening be initiated, which is a controversial issue. In an attempt to balance the harms and benefits of screening, current US screening guidelines do not recommend HPV testing for screening of women aged 25-29 years. The occurrence of transient...
HPV infections is very high in this age group and the guidelines committee wanted to avoid unnecessary follow-up examinations and colposcopy. However, there is evidence of a high burden of CIN3, which has a considerably lower rate of clearance than CIN2, in women aged 25-29 years. In addition, cytology generally performs poorly in younger women according to UK screening audits, which is the other reason why colposcopy was extended in the ATHENA trial to evaluate primary screening in women aged 25-29 years. Furthermore, after reviewing their registry data, Kaiser Permanente, Northern California commenced co-testing at age 25 years in 2013.

In terms of the evaluation of primary screening in the ATHENA trial, the relevant population is the overall population of nearly 42,000 women aged 25 years or older. A total of 274 cases of CIN3 or worse were detected in the overall population, with HPV testing detecting 92% (n=252) of these cases compared with 53% (n=146) detected by cytology.26 The end-of-study results from the ATHENA trial confirmed the following:

- the burden of CIN3+ in women aged 25-29 years is large and cytology performs very poorly in this age group
- HPV16 positive women have about a 25% risk of being diagnosed with CIN3 or worse over 3 years
- primary screening with HPV is more sensitive than cytology and is equivalent to co-testing
- managing HPV(+) women using HPV16/18 genotyping and reflex cytology is as sensitive and efficient as cytology in women aged >25 years.

Regarding resource utilisation, HPV testing as the primary screening test could also reduce the number of women referred to colposcopy compared with cytology and may allow the screening interval to be increased from three to five years. Hence, the results of the ATHENA trial support the case for using HPV testing for primary screening for cervical cancer. A limitation of using HPV testing for primary screening is that its specificity is lower than cytology. However, triage methods for HPV(+) women such as cytology and HPV 16/18 genotyping overcome this limitation and are already being used with co-testing.

COMPASS AUSTRALIA – A RANDOMISED CONTROLLED TRIAL OF PRIMARY HPV DNA TESTING FOR CERVICAL SCREENING IN AUSTRALIA
Assoc. Prof. Marion Saville

A systematic review of European screening studies and their longitudinal outcomes shows that a woman with a negative HPV test at six years is safer than a woman with a negative cytology test at three years, with a small additional benefit gained from co-testing.23 This is simply due to identifying women earlier in the process giving a much longer interval between testing negative and having a CIN3 lesion. The systematic review and other screening studies show a statistically significantly lower incidence of cervical cancer in the HPV versus cytology screening arms. So, why another primary randomised controlled trial of primary HPV testing?

COMPASS is a prospective clinical trial comparing 3-yearly Pap screening with 6-yearly HPV screening using the partial genotype and is the first large-scale clinical trial internationally to assess these screening strategies in an HPV-vaccinated population. The objectives of COMPASS are as follows:

- evaluate primary HPV in a partially vaccinated population using updated testing technology
- focus on optimal management of HPV positive women in the intermediate risk stratification group (i.e. those who are HPV16/18 negative but HPV other positive)
- distinct from the ATHENA study, COMPASS is an effectiveness trial and as such will specifically evaluate safety, effectiveness, and cost-effectiveness of primary HPV testing in an Australian context
- pragmatic trial/demonstration of concept.

Compass is a joint research initiative of the Victorian Cytology Service (VCS) and the University of New South Wales. Recruitment is taking place in selected general practices and other primary health care practices across the state of Victoria. Women aged 25-64 years attending for routine cervical screening at participating health practices are eligible to enrol.

Participants will be randomised (1:2:2) to either 3-yearly liquid-based cytology (ThinPrep) screening or 6-yearly HPV screening (partial genotyping) split into two arms with different follow-up for women who test positive for intermediate-risk HPV (Figure 7). Randomisation will occur in the laboratory on receipt of the first sample and participants will remain in their allocated study arm for the duration of the study. The primary effectiveness endpoint will be based on cumulative detection of confirmed CIN3 in screen-negative women at 6 years in each arm. Preliminary estimates suggest that 100,000 women will be required to compare dual staining with liquid-based cytology in the management of women with intermediate-risk HPV types.

Stratification of the data will be by birth cohort and vaccination status. Colposcopy will be performed in 5% of women whose results are negative or indicate immediate risk to determine what high-grade disease is being missed at the time of testing.

Before starting the main trial, a pilot study of 5000 women (1:2:2 randomisation allocation) is being conducted. The purpose of the pilot study is to:

- assess the recruitment rate (overall and by practice) and quantify participant and GP acceptance of the randomisation process and the use of longer routine screening intervals
- assess the feasibility for two primary screening laboratory technologies for testing samples (cobas HPV Test and digene Hybrid Capture 2 HPV DNA Test partial genotyping), including time and motion studies for each of the two technologies and to determine the ‘unsatisfactory rate’, which is the percentage of cases in which recollection of a sample is needed in order to complete all tests indicated by the protocol
- confirm the expected high standard of the tests that will be used in the trial.

To date, 24 clinics have enrolled 1500 eligible women. The screening frame-work used in COMPASS will generate a lot of data, allowing for many sub-studies. Some of the staged trial outcomes (from the pilot study, baseline round, sub-studies, and longitudinal follow-up) include:

- laboratory processing times/volumes and feasibility (from pilot study)
- unsatisfactory rate (from pilot study)
- impact on referral and treatment rates (from pilot study/baseline)
- cost/referral rates contribute to cost-effectiveness assessment (from pilot study)
- safety (3-yearly follow-up)
- effectiveness (including cross-sectional sensitivity/specificity from pilot study/baseline)
- organisation of screening (compliance with longer intervals)
- acceptability to women (from quality of life/utilities sub-studies)
- acceptability to practitioners (from focus groups).

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Cervical screening was established in New Zealand in 1990 in accordance with recommendations made following the Cartwright Enquiry (1987-88). Cervical screening is available to women aged 20-70 years, involving 3-yearly screening if smears are normal and follow-up with colposcopy and appropriate treatment in those with abnormal smears. The introduction of screening in New Zealand resulted in a dramatic reduction in both the incidence of and deaths from cervical cancer. From 1991 to 2008, the incidence of cervical cancer declined from 12 to 5.5 per 100,000 women and the rate of death from cervical cancer declined from 5 to 1.6 per 100,000 women.

However, Pap smear screening has its problems, including having low sensitivity and inadequate or obscured samples often being collected. Nonetheless, sensitivity increases cumulatively with regular screening and Pap smear screening has been for many decades the most successful cervical cancer screening test. It remained in place for about 50 years until the advent of liquid-based cytology, which addressed some of the technical and subjective problems of Pap smears.

Introduced in New Zealand in 2007, liquid-based cytology has many advantages over the Pap test. These include collecting the cells into a preservative, from which a homogeneous smear can be made and obscuring debris removed. In addition, multiple slides can be prepared from one sample and part of the sample can be used for ancillary tests, most importantly HPV testing. However, the subjective interpretive elements of cervical screening remain.

A need to increase the specificity and sensitivity of screening was the driver for the next advance in cervical screening, which arrived in the form of automation. Introduced in New Zealand in 2011, the Thin Prep Imaging System provided a standardised approach for cervical cytology and the benefits of increased specificity and sensitivity, a lower unsatisfactory rate, fewer false-negative results, and reduced turn-around time for results.

One of the most critical developments in cervical screening came with the 1991 mini-review by Herald our Hausen. He concluded that substantial experimental evidence accumulated over the previous eight years indicated an aetiologic role for HPV genotypes in anogenital cancers and its premalignant precursors, and even identified the genotypes HPV16 and 18 as carrying the highest risk of carcinogenesis. Publication of the mini-review prompted the development of technologies for HPV testing. This included a hrHPV testing technology (cobas HPV Test), which stains for the 14 hrHPV genotypes with a high negative predictive value (approximately 99%). A positive hrHPV test indicates increased risk of developing a high-grade lesion but does not indicate the presence of abnormal cell changes.

Testing for hrHPV, which can be requested with ThinPrep liquid-based cytology, was first introduced into New Zealand in 2009. Currently, it is used as an adjunctive test to cytology screening as the primary test and as such is used in the following settings:

- as a triage for low-grade smears
- as a test of cure
- discordant results between cytology and colposcopy.

Another development affecting cervical cancer screening was the launch of HPV immunisation (quadrivalent vaccine against HPV6, 11, 16, 18) in New Zealand in September 2008 for girls of ≤20 years of age. As a result, an increasing number of vaccinated women are starting to reach screening age. This vaccinated population will have a profound effect on the screening programme if it continues to use cytology as a primary screening tool. With the ATHENA trial having confirmed that identification of HPV16 and 18 identifies the majority of high-grade abnormalities in women, is it time for a change?

The opportunity to collaborate with the VCS on the COMPASS trial in the form of a service evaluation project will help to answer this question.
There has been a lot of discussion about using flow cytometry for dual staining. One of the problems is that when immunostaining is done on slides it is difficult to incorporate into the high-throughput capabilities of flow cytometry. However, in the US, flow cytometry is now being used for other aspects of cervical pathology, such as simultaneous detection of HPV E6/E7 gene expression levels. From an efficiency and results turn-around perspective, it is a good idea for dual staining to somehow also be built into flow cytometry and should be suggested to diagnostic technology manufacturers.

What is the best method for women to self-collect samples for HPV testing?

A lot of research has looked at various methods for self-collected samples but it has not shown that one method is better than any other, e.g. dry swabs versus cytofbrush collector. For the detection of high-grade disease, there does not appear to be any difference in the accuracy of HPV testing with PCR-based tests (e.g. cobas HPV Test, ampicor HPV Test) versus signal amplification tests (e.g. digene Hybrid Capture 2 HPV Test) for self-collected samples. However, a significant proportion of high-grade lesions is going to be missed with self-collected samples versus clinician-collected samples from the cervix.

There is evidence that self-collected chlamydia testing performs just as well as clinician-collected testing so why does self-collected HPV testing not perform as well as clinician-collected testing?

The analytical cut-off for chlamydia is a couple of organisms, with most of the chlamydia being excreted in the urine and chlamydia is a different organism from HPV. In addition, there is a lot of HPV colonisation of the vagina, which is very different from HPV colonisation of the cervix. The composition of HPV genotypes present in the cervix tends to differ from that in the vulva and vagina.

Why is it not possible for p16/Ki-67 dual staining to be included in flow cytometry?

There have been several studies using dual staining for cervical cancer. Estimated incidence, mortality and prevalence worldwide in 2012 Lyon, France: World Health Organisation. Available from: http://globocan.iarc.fr/Tools/Fact_sheets_cancer.aspx [Date accessed: 12/05/14].


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