It seems that the time is now mature for a generalized change in the cervical cancer prevention paradigm. How do you see the process and the milestones in the last decade?

I certainly agree that over the last decade or so, the maturation of the data we have for evaluating choices in cervical cancer screening demands that each society evaluate the data compared to historic norms. In the US, the process began in 2001 with the ASCUS LSIL Triage Study (ALTS) that clinically validated the concept of HPV testing for triage of equivocally abnormal cytology. The data from that study stimulated a global conversation about the relative performance of HPV testing versus cytology for screening. In parallel, the proof of efficacy in 2006 of HPV vaccines for the prevention of cervical cancer has led to the concept of potential cervical cancer eradication strategies using both vaccination and more optimized screening. The impact of vaccination and the improved screening sensitivity of HPV testing –including the US ATHENA trial and the large scale European experiences– dominates the conversation now with the recognition that screening must evolve to continue to be effective.

What is the importance of the FDA resolution on HPV primary screening?

If one follows current US news reporting, science or the lack of appreciation of science, even the repudiation of science, is constantly in the news. Climate change and vaccine safety versus medical policy are very hot topics. Medical policy in general continues to be of great national interest. In this context, the
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Federal Drug Administration (FDA) approval of an algorithm for cervical cancer screening that starts with HPV testing rather than traditional cytology is a true testimony to the fact that data driven science can actually produce a potential political or philosophical outcome that agrees with the data. But of course, not everyone agree...

**What should be the expected gains of the introduction of HPV testing into primary screening protocols?**

Simply put, the expected gains should be better health for women who are screened. Secondarily one might expect sufficient recovery of resources due to the efficiencies of the algorithm to actually be able to extend screening to populations who have not been screened. The push back to these ideas centers mainly on the concern for the potential harms of HPV screening by identifying women with precancer that may not progress over the screening interval to cancer, risking over-treatment. Yet, as should always be pointed out, HPV primary screening is always coupled to a triage test to focus treatment on those that need it most. Furthermore, screening for cervical cancer only has utility if one finds the precancer in the population and treats it to prevent cancer development. The focus of the current debates are how best to identify that population.

**The US is largely adopting a co testing strategy (cytology and HPV tests) for primary screening whereas Europe tends to favor HPV screening alone and cytology as one of the triage options. How do you interpret these different resolutions?**

I don’t think the distinctions are quite so clear. The US, unlike Europe has a long tradition of relative lack of cost-constraint and relative over-utilization of testing. But fundamentally, I think both European and US physicians as well as women, want the same thing, namely safety from cervical cancer. The difference is now we have an abundance of data to interpret and decide how best to achieve that goals while balancing the good with the bad. Furthermore, the conversation in the US has only just begun. No clinical practice in the US could even consider primary HPV testing until the interim guidance was published. In contrast, we have had “permission” to do co-testing for more than 10 years in US guidelines.

**Non participants in screening activities remain one of the most vexing population from which cervical cancer mortality persists. Any developments on the self-sampling front that may increase screening coverage in the US?**

As noted above, lack of screening is the major US risk factor for cervical cancer. More than half of the cancer in the US is found in unscreened or inadequately screened women. In some states and counties in the US, the incidence of cervical cancer is similar to that in Sub-Saharan Africa. The barriers to screening are manifold in the US especially in the absence of an organized screening program. Given recent published data, self-sampling approaches could well have a major impact on cervical cancer incidence in underscreened women. But that conversation has yet to be started in any meaningful way. The good news is the recent US health care policy (Obamacare), mandates access to free cervical cancer screening for all insured individuals in the US.

**The US is increasing HPV vaccination coverage. Do you anticipate any change in the screening protocols among vaccinated cohorts?**

The mathematics of screening is driven by prevalence. As vaccine coverage increases the prevalence of the targets of screening will decrease, demanding that more sensitive algorithms be applied. In this regard, the documentation of the ongoing Australian experience leads the way, with many European countries not
far behind. HPV vaccination is absolutely a primary driver for the necessary adoption of HPV primary screening. Let us not forget that these arguments will only be stronger once the just approved nonavalent HPV vaccine penetrates the market.

**Would you recommend integrated protocols of vaccination and screening for each age strata along women’s lifetime? If so what would they look like?**

Obviously, the HPV community has labored long and hard to try and bring primary prophylaxis and improved data driven secondary prevention through screening to the world’s women. The detail of how to best spread the fruits of these labors is unfortunately a complex economic and political question, less so a medical or scientific one except in how the science and political economics collide. That being said, I believe every population, male and female deserves protection from HPV-related disease. Universal and sustained prophylactic vaccination of our children, now with the nonavalent vaccine would drive HPV disease related prevalence rates down to a level where screening would mathematically be impossible. But for the next few decades, we need a transition strategy of screening all women in populations where the prevalence of disease still allows screening to work. We now have the technology to potentially bring affordable state of the art molecular screening at rational and infrequent intervals to populations where the economics and infrastructure of traditional cytology based screening would be impossible to implement and sustain. The details of any such integrated program really have to be determined on a regional or local basis. And of course screening must be coupled to treatment or screening is a waste of time.

**Any final comments?**

We are at the dawn of a new era in cervical cancer prevention, where we can now even talk about eradication, and the elimination of screening. In developed countries we are perhaps a bit too focused on the details of optimization or how to implement change. While the idea that screening requires a balancing of the benefits with the potential harms, in my opinion the biggest harm is not screening. I will also state it yet again, if we don’t treat precancer, screening will have no impact on women’s suffering from cervical cancer. Hence in my opinion the scales tip in favor of eradicating true precancer. The scientific community will work in the next decade to develop better biomarkers to better refine the target population needing treatment. Meanwhile, the HPV vaccination programs will continue to drive down the prevalence of precancer and cancer. We are beginning to realize our dreams…
Cervical cancer screening has been the most successful of all cancer screenings and in many ways remains the exception. The reasons for its success have been many-fold. Cervical cancer occurs in a highly localized region of the cervix, the squamocolumnar junction, and this zone is relatively accessible ( unlike for virtually all other cancers) making sampling and treatment relatively easy and accurate. And because invasive cervical cancer develops slowly from a precancerous lesion, on average over a time period of 1-2 decades, there are many opportunities to intervene ( screen, diagnose, and treat) prior to invasion.

"It is not hyperbole to say that Pap testing has saved millions of lives."

Papanicolaou or Pap testing, invented by Dr. George Papanicolaou in the mid-20th century, was the first cervical cancer screening test. Pap testing, or cervical cytology, is the process of microscopic assessment of exfoliated cervical cells for morphologic changes indicative of neoplastic alterations. Where cytology-based screening has been effectively implemented, e.g. United States;2 United Kingdom;3 Nordic countries;4 the Netherlands;2 New Zealand;4 and Australia4 to name a few, cervical cancer incidence and mortality have declined significantly because of the timely detection and treatment of cervical precancerous lesions and progressive down staging of invasive cervical cancer. It is not hyperbole to say that Pap testing has saved millions of lives.

Yet, despite its successes, Pap testing has a number of well-known limitations. Pap testing has only moderate one-time sensitivity for cervical precancer (cervical intraepithelial neoplasia grade 2 [CIN 2], grade 3 [CIN 3], and adenocarcinoma in situ [AIS]) and cancer. Thus, Pap testing requires many repeat screenings in a lifetime to achieve programmatic effectiveness. In particular, cytology has poor sensitivity for detection of adenocarcinoma precursors, e.g. AIS, perhaps because of poor sampling of the lesions higher in the endocervical canal. As a consequence, in the context of secular trends of increased exposure to HPV, annual rates of adenocarcinoma have not declined significantly in most countries and have even increased in some over the last few decades.2-6

Some of the limitations of Pap testing are due in part to its subjective and laborious nature. As a consequence, it has only fair-to-poor reproducibility ( inter-rater agreement).9 And because of its laborious nature, there is a limited number that any one reader can review per day so many readers are needed to meet the demands of a high-volume
clinical laboratory diagnostic, adding to overall variability in performance. Thus, in order to achieve high-quality Pap testing, significant investments in infrastructure and extensive quality assurance and control measures are required.

"As reported by Simonella and Canfell, greater reductions in the annual cervical cancer incidence and mortality were achieved in Australia, New Zealand, and England when each country switched from opportunistic screening to organized screening."

High-quality, high-throughput cytology-based screening is therefore best achieved through an organized screening program. As reported by Simonella and Canfell, greater reductions in the annual cervical cancer incidence and mortality were achieved in Australia, New Zealand, and England when each country switched from opportunistic screening to organized screening. In the US, where screening is opportunistic, the cervical cancer screening program is inefficient and costs more than $6 billion per annum. Comparing the US to the Netherlands, which have experienced comparable reductions in cervical cancer incidence and mortality, women from the US undergo 3- to 4-fold more Pap tests than women from the Netherlands. Therefore, women living in the US potentially experience a much greater burden of the harms of cervical cancer screening than those living in the Netherlands.

However, a new paradigm of targeting HPV, the obligate, viral cause of cervical cancer and its immediate precursor lesions, for cervical cancer prevention is emerging. Technical advances, including prophylactic vaccination against certain high-risk HPV (hr HPV) types for primary prevention and hrHPV testing for cervical cancer screening secondary prevention, are highly efficacious and when used in an age-appropriate manner, highly cost effective. Hr HPV testing is more sensitive and reliable than Pap testing for the detection of cervical precancer and cancer. Importantly, a negative hrHPV test provides greater reassurance against cervical precancer and cancer than Pap, safely permitting longer intervals between screens or increased safety for similar interval. A single round of hrHPV testing was more effective than Pap testing in reducing cervical cancer incidence in 6.5 years and in reducing mortality due to cervical cancer in 8 years.

High-risk HPV testing is best used only as the screening test, to rule-out disease, and clinical decisions should not be made based on a single hrHPV-positive result alone, since most hrHPV positive women do not have and will not develop cervical precancer or cancer. The application of Pap testing or potentially other markers, including biomarker-enhanced cytology using p16/Ki-67 immunocytochemistry, can be limited to the at-risk hrHPV positive group to “rule-in” i.e., to determine what kind of care is needed.

"A single round of hrHPV testing was more effective than Pap testing in reducing cervical cancer incidence in 6.5 years and in reducing mortality due to cervical cancer in 8 years."

Indeed, the Pap result, because of its inherent ability to grade cytologic severity, unlike the hrHPV result, can further stratify risk for clinical decision making on what kind of care is needed in HPV-positive women:

A) those with negative cytology are monitored closely until there is evidence of short-term hrHPV persistence, a strong risk factor for concomitant or future cervical precancer and cancer;
B) those with mild Pap abnormalities (e.g., atypical squamous cells of undetermined significance [ASC-US] or low-grade squamous intraepithelial lesion [LSIL]) are referred to colposcopy with the noted exception of young women, who are less likely to have cervical precancer and more likely to have a transient hrHPV infection, and
C) severe Pap abnormalities (e.g., high-grade squamous intraepithelial lesion [HSIL]) are
referred to colposcopy but might, with informed decision-making between patient and provider, lead to excisional treatment without histologic confirmation of cervical precancer.

**Shifting Pap testing from all women to the at-risk, hrHPV-positive women improves the performance of Pap testing in two ways:**

- First, enriching for (increasing prevalence of) cervical precancer and cancer algebraically results in a better positive predictive value.29
- Second, informing cytopathologists that the Pap is from hrHPV-positive women, “informed screening” or “screening with prejudice”, may increase sensitivity without significantly decreasing the specificity.30

The latter needs to be reproduced in other settings to show that it is a generalizable phenomenon. This approach, rule-out with hrHPV testing and rule-in with Pap testing (or another marker) or evidence of persistent hrHPV infection, is not only more efficient, but it becomes necessary in the context of secular trends of decreasing prevalence of cervical precancer and cancer due to screening and now HPV vaccination. Of the latter, HPV vaccination against HPV16 and HPV18 in HPV-naive populations is expected to reduce the prevalence of CIN 2/3 by ~50% and cervical cancer by 70%. Even in the US, where HPV vaccination coverage is embarrassingly low,31 there is already evidence of reduced prevalence of HPV16 and HPV18 infections52 and HPV16 and HPV18-related CIN 2/3.35

Table 1 presents the theoretical performance of Pap testing in the general population and in a vaccinated population, among all women and hrHPV-positive women, and the latter with or without screening with prejudice. The positive predictive value (PPV) of Pap testing at a positive cutpoint of ASC-US in a vaccinated population is 6.7% i.e. only 1 of 16 Pap-positive women will

### Table 1: Hypothetical positive predictive values (PPV) for cytology in HPV unvaccinated and vaccinated populations of women, as a general screen and as triage of high-risk HPV (hrHPV) positive women without and with a priori knowledge that the slides are from hrHPV-positive women.

<table>
<thead>
<tr>
<th>Pap Screening</th>
<th>Unvaccinated Populations</th>
<th>Vaccinated Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In all women</strong></td>
<td>CIN 2+ &lt; CIN 2 Total</td>
<td>CIN 2+ &lt; CIN 2 Total</td>
</tr>
<tr>
<td>Pap+</td>
<td>500 4,500 5,000</td>
<td>Pap+</td>
</tr>
<tr>
<td>Pap-</td>
<td>500 94,500 95,000</td>
<td>Pap-</td>
</tr>
<tr>
<td>Total</td>
<td>1,000 99,000 100,000</td>
<td>Total</td>
</tr>
<tr>
<td><strong>Triage of hrHPV Positives (cytology blinded)</strong></td>
<td>CIN 2+ &lt; CIN 2 Total</td>
<td>CIN 2+ &lt; CIN 2 Total</td>
</tr>
<tr>
<td>Pap+</td>
<td>450 2,050 2,500</td>
<td>Pap+</td>
</tr>
<tr>
<td>Pap-</td>
<td>450 7,050 7,500</td>
<td>Pap-</td>
</tr>
<tr>
<td>Total</td>
<td>900 9,100 100,000</td>
<td>Total</td>
</tr>
<tr>
<td><strong>Triage of hrHPV Positives (cytology informed)</strong></td>
<td>CIN 2+ &lt; CIN 2 Total</td>
<td>CIN 2+ &lt; CIN 2 Total</td>
</tr>
<tr>
<td>Pap+</td>
<td>720 1,905 2,625</td>
<td>Pap+</td>
</tr>
<tr>
<td>Pap-</td>
<td>180 7,195 7,375</td>
<td>Pap-</td>
</tr>
<tr>
<td>Total</td>
<td>900 9,100 10,000</td>
<td>Total</td>
</tr>
</tbody>
</table>

Pap sensitivity = 50% hrHPV testing sensitivity = 90%
Prevalence of CIN2+ in an unvaccinated population = 1%; Prevalence of CIN2+ in an HPV-naive population vaccinated against HPV16 and HPV18 = 1%
Prevalence of hrHPV in an unvaccinated population = 10%; Prevalence of hrHPV in an HPV-naive population vaccinated against HPV16 and HPV18 = 7.5%
Prevalence of ASC-US+ in an unvaccinated population = 5%; Prevalence of ASC-US+ in an HPV-naive population vaccinated against HPV16 and HPV18 = 3.75%
Informed screening or screening with prejudice increases sensitivity by 60% and decreases specificity by 5%.30

Table 1. Hypothetical positive predictive values (PPV) for cytology in HPV unvaccinated and vaccinated populations of women, as a general screen and as triage of high-risk HPV (hrHPV) positive women without and with a priori knowledge that the slides are from hrHPV-positive women.
References:


Dr. Castle has received commercial HPV tests for research at a reduced or no cost from Roche, Qiagen, Norchip, Arbor Vita Corporation, BD, and mtn. He has been compensated financially as a member of a Merck Data and Safety Monitoring Board for HPV vaccines. Dr. Castle has been a paid as consultant for BD, Gen-Probe/Hologic, Roche, Cephed, ClearPath, Guided Therapeutics, Teva Pharmaceuticals, Gentical, Inovio, and GE Healthcare. Dr. Castle has received honoraria as a speaker for Roche and Cepheid.

UNDERSTANDING THE LIMITATIONS OF CYTOLOGY FOR SCREENING

have CIN 2+ (and 1 of 32 will have CIN 3+). The PPV of Pap doubles when restricted to hrHPV-positive women and triples when slides from hrHPV-positive women are screened with prejudice.

The introduction of Pap testing in the mid-20th century was a major public health intervention and the first and most successful cancer screen. Pap testing led to the discovery of new and more effective prevention tools, HPV vaccination and hrHPV testing. These tools should and need to be deployed globally if we are to avert the unnecessary burden of cervical cancer, especially in populations living in low- and middle-income countries, where effective Pap programs were never established. Pap testing had its day and should be "celebrated" for all that it accomplished in cancer prevention. But "based on the weight of the current evidence", the Pap should no longer be the standard of care for cervical cancer prevention and its use should be limited to deciding what kind of care hrHPV-positive women need: increased surveillance, colposcopy, or possibly treatment.

Figure 1: A graphic representation of the positive predictive value (risks) for CIN2 or more severe diagnoses (CIN2+) as shown in Table 1. The risks are shown for Pap testing among the general population and as a triage test among HPV-positive women without and with informed screening.*

Risk of CIN 2+

Unvaccinated

Vaccinated

Pap

Triage

Triage*

0

5

10

15

20

25

30

%
Numerous large randomized studies\(^1,2\) and screening trials\(^3,4\) have established that high-risk HPV (hrHPV) testing can improve cervical cancer screening. Currently, the optimal screening strategy is uncertain with ongoing debates over primary hrHPV screening versus cotesting (hrHPV testing concurrently with Pap testing), the management of women screening positive, and the correct screening interval for women screening negative.

The most scientifically rigorous approach to resolve these debates would be randomized screening trials with head-to-head comparisons of candidate screening strategies. Such trials require many thousands of women followed for years to discern meaningful differences in risk of cervical cancer, which occurs very rarely in undeniably efficacious screening strategies such as primary hrHPV and cotesting at 3 or 5-year intervals. With so many options for screening and triage tests, and screening intervals, it is not possible to conduct randomized trials for each comparison of interest.

In the absence of randomized clinical trials, we turn to observational data produced as a matter of course from very large screening programs and registries, to glean the risks after one or multiple screening rounds using different testing strategies.\(^5,7\) In clinical programs, each woman is managed using a strategy; the statistical challenge is to estimate what would have happened had she been managed using alternative, “counterfactual” strategies. Key outcomes considered in the analysis of observational data used to decide whether to extend a screening interval or use a different screening test, are the extent and duration of protection against cervical cancer afforded by the negative screen. Cervical cancer is the optimal epidemiologic outcome because screening programs are intended to prevent cervical cancer mainly by identifying women at greatest risk of cervical cancer, namely those with precancer (best equated with histologically-diagnosed cervical intraepithelial neoplasia of grade 3 [CIN3]). Few cohorts are large enough with sufficient follow-up to estimate precisely the risk of prevalent and incident cancer among women screening negative. Thus, we are forced sometimes to estimate cancer risk by the use of surrogate endpoints, most commonly the detection of CIN3 (or rare cancers, CIN3+) at the first screen and risk of CIN3+ in subsequent screens. The use of CIN3 for screening studies is conceptually difficult, because finding CIN3 in time to avert cancer is a success of screening, and the concern regarding overdiagnosis (finding CIN3 cases that would not have become invasive cancer) is always present. Fortunately, data are now available that directly provide estimates of cancer risk after a negative screen from Kaiser Permanente Northern California (KPNC). KPNC is a large integrated health delivery system; since 2003 >1 million women age 30+ have been screened with cotesting, at approximate 3-year intervals. Using logistic-Weibull modeling, we have estimated the risks of cancer up to 5 years after a negative Pap, hrHPV and cotest (Figure 1). How to interpret and compare these risks is not straightforward, especially in the context of deciding screening guidelines.

"The risks following an HPV-negative and cotest negative test are definitely lower than those following a negative Pap test. Adding a Pap test to hrHPV testing (cotesting) confers only a very slight marginal gain in reassurance against cancer."
THE ROLE OF EPIDEMIOLOGY IN DISCERNING OPTIMAL CERVICAL CANCER SCREENING STRATEGIES

We use counterfactual reasoning to estimate risks for screening contexts that differ from actual clinical practice in an attempt to understand risks for screening strategies that did not actually occur (e.g., cotesting every 5 years or primary hrHPV testing every 3 years). This counterfactual reasoning is evident in several assumptions. We assume the estimated risk among women with a negative Pap in a cotesting screening program is similar to risk among women with a negative Pap in a primary Pap program. Because the vast majority of women at KPNC had cotesting, women testing Pap-negative are managed based upon their hrHPV result. Thus, in our recent screening analyses from KPNC, 3.7% of women testing Pap-negative were concurrently hrHPV-positive and had a repeat screen in 1 year with colposcopy referral if their repeat screen was positive. Cancer risk estimates for Pap-negative results are thereby likely overestimated slightly because of the higher cancer risk among women screening Pap-negative/hrHPV-positive versus Pap-negative.5

This challenge of counterfactual reasoning is also present when considering whether to extend screening intervals beyond standard practice, e.g., 5 instead of 3 years. Because women at KPNC typically return for screening 3 years after a negative cotest, some precancers destined to progress to cancer between 3 and 5 years are detected at the 3-year return and treated, thereby preventing cancer. The 5-year cancer risks are therefore slightly underestimated. Conversely, the 5-year risk of precancer is slightly overestimated because the precancer destined to regress between 3 and 5 years is detected and treated at the 3-year screen. This dilemma also exists for estimating risks that occur before returning for screening or during time points between screening visits, e.g., 1-year risks after a negative screen at KPNC. We are left to make careful assumptions regarding the natural history of cervical precancer and cancer between screening visits to permit risk modeling.

In spite of these challenges, the analytic approach of risk comparison from large clinical datasets has provided valuable evidence for decision-making with statistical power to quantify and distinguish risks that are extremely low and close to one another. Importantly, the same general trends observed with a surrogate endpoint (CIN3+) in other cohorts and in KPNC have been shown to hold true when we analyze invasive cancer outcomes in KPNC. Namely, the risks following an HPV-negative and cotest negative test are definitely lower than those following a negative Pap test.4,10,11 Adding a Pap test to hrHPV testing

Figure 1. Cumulative risks of cancer among women aged 30-64 at Kaiser Permanente Northern California by enrollment Pap and HPV test result, 2003-2012. Adapted from Gage, JC et al. JNCI 2014 8

![Figure 1. Cumulative risks of cancer among women aged 30-64 at Kaiser Permanente Northern California by enrollment Pap and HPV test result, 2003-2012. Adapted from Gage, JC et al. JNCI 2014 8](image)
(cotesting) confers only a very slight marginal gain in reassurance against cancer.

The choice of cotesting rather than primary HPV testing necessarily implies that the value of a very small reduction in cervical cancer is very high. A related and deeper question (which is societal, not statistical) is how much safety should screening provide. Assuming the risk models accurately measure risks that would be observed in their respective screening strategies, what risk threshold is appropriate for women to follow routine screening? In the US, the standard of care for many years was the annual Pap smear and therefore, it is argued that the threshold risk for evaluating other strategies should be the risk of cervical cancer within 1 year after a negative Pap.12

Public health policymakers in other settings have defined less stringent acceptable cancer risks for population-based screening programs.13,14 Fortunately, the majority of cervical cancer can be prevented through existing well-run screening programs. The debates now focus on relative minimal reductions in cervical cancer and how to fine-tune cervical cancer screening.

Importantly, the reassurance against cancer provided by a negative screening test is just the tip of the iceberg for evaluating a screening intervention. Risks are cumulative and extend over a lifetime of screening and they must be balanced with harms and financial costs. Mathematical decision modeling is currently the only approach that can incorporate the many factors influencing cervical cancer prevention in the context of repeated screening, changing screening intervals, treatment and vaccination. Such modeling provides projections of long-term population-based outcomes and cost-effectiveness. These analyses can be powerful tools for comparing screening strategies over time.15,16 Yet, they have their own inherent challenges and collaborative efforts to compare and standardize models are important (CISNET) to provide robustness and foster trust in their conclusions.

As epidemiologists, statisticians, or decision analysts, we are called upon because of our expertise in risk estimation. However, no discipline including clinical medicine can claim superiority in the act of balancing the harms and benefits of alternative cervical cancer screening programs. By nature, the debate is complicated for all but the simplest of questions (whether or not to screen). Many of the opinions are value-laden and philosophical, not necessarily scientific. In addition to the debates over screening test and interval, we can add the questions of age of first screen, age of last screen and screening among vaccinated women. It is useful to realize that formulating screening guidelines contains one part in which we are expert (risk estimation), and one part in which we provide just one voice (values regarding safety). With this realization, it becomes clear that variation in screening practices is inevitable and that international harmonization is highly unlikely. HPV is the universal cause of cervical cancer; what to do with that fact is not universal.
On April 24th 2014, the United States Food and Drug Administration (FDA) approved high risk HPV (hrHPV) testing for primary cervical cancer screening in the United States (US). This decision also reflected unanimous support (13-0) from the March 2014 FDA Medical Devices Advisory Committee Microbiology Panel Meeting, which included numerous US experts in the area of cervical cancer screening and prevention. This approval was based and supported from data derived from the ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial. ATHENA, the largest cervical cancer screening study conducted in the US, was a registration study sponsored by Roche Molecular Systems that utilized the cobas® 4800 system. Data from ATHENA was previously used for approval of hrHPV testing for ASC-US cytology and concurrent cytology and hrHPV screening (i.e., cotesting) in women 30 years and older. These two uses are widely recommended by numerous stakeholder societies and organizations, as well as the United States Preventive Services Task Force (USPSTF).

Furthermore, triage through identification of specific high-risk types of HPV, specifically types 16 and 18, is also an FDA approved use of hrHPV testing in selected settings. The FDA approved a specific primary HPV screening algorithm that utilized genotyping as well as cytology as triage tests in this new setting.

In 2011, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated screening guidelines for the early detection of cervical cancer and its precursors. These guidelines stated that there was insufficient evidence to use HPV testing alone as a screening mechanism. Specific reasons included lack of information regarding the specificity, potential harms including increased rates of colposcopy and treatment, appropriate screening intervals, and cost-effectiveness.

Since 2011, several additional randomized trials have been published in addition to ATHENA that have further informed us about the utility and benefit of primary HPV screening. The public announcement of an FDA application by Roche for a primary HPV screening claim triggered the creation of an interim guidance panel to review recent evidence and address specific questions and concerns regarding using a hrHPV test for primary screening, including ATHENA and data relevant to the primary HPV screening labeling. This panel was co-sponsored by the Society of Gynecologic Oncology and the American Society of Colposcopy and Cervical Pathology. The primary objective of the panel was to provide clinicians with a balanced overview of primary HPV screening including its benefits and potential harms. This process included an in depth literature review as well as a scientific summary presentation provided by Roche Molecular Systems of ATHENA including data and findings related to the primary HPV screening components of this trial. Panel members were allowed to submit questions both before and after the discussion.

Panel members were asked to address two primary questions:

1. Is HPV testing for primary screening as safe and effective as cytology-based screening?
2. Can primary HPV screening be considered as an alternative to current US cervical cancer screening methods?
There was considerable debate and discussion about initiating primary HPV screening at 25 years of age. Despite almost a third increased detection of CIN3+ in women 25-29 years of age and findings indicating that >50% of CIN3+ cases had preceding normal cytology, this screening algorithm would double the number of colposcopies performed in this age bracket. Although it’s unclear whether detection of CIN3+ in women 25-29 years of age would translate into a reduction in invasive cervical cancer, the panel did feel that this increased detection was clinically meaningful despite the increased rate of colposcopy. There was also considerable discussion comparing primary HPV to cotesting. Based on a recent paper by Gage et al in the Journal of the National Cancer Institute, which analyzed data from over 1 million women screened at Kaiser Permanente Northern California, it was evident that the reassurance of a negative cotest results was driven by the negative HPV test component and based on a 3 year screening interval, primary testing was as effective as 5 year cotesting. There continue to be multiple areas of future research and other considerations in the area of primary HPV screening. Some of these include the concern of false negative results, specimen adequacy, appropriate internal controls (since cytology might be viewed as a surrogate for this), and comparative effectiveness studies that address topics including cost and impact on lifetime screening. The panel also highlighted this algorithm is restricted to one assay at present and assumptions of comparability should not be made, and most importantly, expressed considerable concern about the confusion that a third recommendation might create for clinicians and the critical need for adequate provider education.

In the end, the panel felt that primary HPV testing was a highly important advance in cervical cancer screening (perhaps, one of the most important) based on the overwhelming supporting scientific data from numerous large clinical trials including ATHENA. But, these advances are meaningless if women are not screened and as such, it continues to be critically important for us to identify women who are unscreened or underscreened.

Dr. Warner K. Huh has been paid as a consultant for Merck and THEVAX. Dr. Huh also serves on the scientific advisory board for InCellDx but does not personally receive any fees (fees are paid to his institution).

References:
HPV TESTING IN THE UNITED STATES: PERSPECTIVES FROM SYSTEMS, PROVIDERS AND WOMEN

Vicki Benard and Mona Saraiya
Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta Georgia, USA.

Currently in the United States, two cervical cancer screening modalities are endorsed by all three major guideline organizations (American Cancer Society, American College of Obstetricians and Gynecologists, and the US Preventive Services Task Force).\(^1\)\(^-\)\(^3\)

The recommendations include:

1) screening with a Pap test every 3 years for women aged 21-65 or
2) screening with a Pap test combined with a test for high-risk types of human papillomavirus (hrHPV) every 5 years for women aged 30-65 (also known as co-testing).

In 2014, the Federal Drug Administration (FDA) approved high-risk HPV (hrHPV) testing for primary cervical cancer screening in women aged 25 and older. Shortly thereafter, the Society for Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology jointly published guidance recommending at least a 3-year interval after a negative test, with a proprietary algorithm for management of abnormal results.\(^4\)

"However, not many providers are willing to move to the new recommended interval of 5 years for co-testing, which may be expected given the recency of these guidelines. Barriers reported by providers include lack of knowledge of guidelines, patient demand or expectations of annual Pap tests, fear that patients will not come in for other preventive services, and concern about missing early cancers."
knowledge of guidelines, patient demand or expectations of annual Pap tests, fear that patients will not come in for other preventive services, and concern about missing early cancers.9,10,13

"In 2011 in the USA, over 12,000 women developed and over 4,000 women died of this highly preventable disease."

National surveys of women have shown a decrease in overall self-reported Pap tests from 2008 to 201014 and increases in Pap tests with longer intervals.15 When women were surveyed about their willingness to extend the screening interval to 3 years if their doctor recommended it, almost 70% agreed, but only 25% said they would extend screening to 5 years.16 When patients were surveyed about adherence to guidelines, they cited barriers such as lack of knowledge about cervical cancer screening, a desire for more frequent care, and a higher degree of perceived risk of cervical cancer.16,17 Most of the data collected come from self-reported surveys of providers and women; however, some of these practices are validated by other studies. New Mexico performs the only statewide systematic collection of cervical cancer screening records in the United States. This registry reported that screening intervals lengthened from annual screening to less frequent screening (but still not to the desired interval) from 2008 to 2011. Screening use decreased for all ages.18 In 2011, over 12,000 women developed and over 4,000 women died of this highly preventable disease.19 While 80% of women in the United States are screened according to guidelines, in 2012, approximately 8,000,000 women had not been screened for cervical cancer in the previous 5 years.19 The lack of an organized monitoring system for cervical cancer screening leads to unnecessary screening for some women and lack of screening for others. Prioritizing women who are rarely or never screened is essential in reducing the burden of cervical cancer because more than half of the cases were in women who had not been adequately screened (Figure 1)19

**MISSsed OPPORTUNITIES FOR CERVICAL CANCER SCREENING**

More than 50% all new cervical cancers are in women who have never been screened, or have not been screened in the last five years

**Figure 1.** Screening participation in the US in 2012. Source: Behavioral Risk Factor Surveillance System, 2012

In 2012, 8 million women were not screened in the last 5 years

7 out of 10 women who were not screened had a regular doctor and health insurance
As of today, few countries have introduced the HPV test as a primary screen into organized screening programs despite large-scale pilot studies.\textsuperscript{20,21} Australia recently adopted one national guideline for primary HPV testing every 5 years starting at age 25, which is a change after almost 20 years of recommending cytology-based screening every 2 years.\textsuperscript{22} This has occurred in the context of Australia's HPV vaccination campaign, which has resulted in high vaccination coverage among women now in their early 20s and promises to improve HPV screening efficiency by lowering the HPV burden among screened women. While primary HPV testing has a lot of promise for the United States, it is unclear how it compares to other screening strategies in terms of net benefit, acceptability and cost-effectiveness. Indeed, more information is needed to identify which strategies constitute "high-value" care. Guidelines for the use of HPV tests for primary screening among women under age 30 are now conflicting, with some authors expressing concern about overtreatment in young women in whom the prevalence of HPV is relatively high and where treatment may be of lesions that would never progress to cancer.\textsuperscript{24}

In addition, some women will be unable to end screening at age 65 due to persistently positive HPV tests. In a review by Giorgi-Rossi et al, there was caution and concern about increased disparities related to communications about HPV positivity in than women who were disadvantaged and lower educated had higher anxiety that higher educated women.

Finally, in all of the excitement about new technologies, we must remember to focus on improving coverage to women who are not getting screened at all or not getting screened regularly, to ensure followup for abnormal results, and to be clear about how these new technologies translate into actionable steps for systems and providers, and improved outcomes for women.

"Australia recently adopted one national guideline for primary HPV testing every 5 years starting at age 25, which is a change after almost 20 years of recommending cytology-based screening every 2 years."

The authors declare no conflict of interest.
In 2014, Australia became the first country to announce large scale changes to cervical screening as a direct response to the successful and widespread national implementation of HPV vaccination. The rollout of the Australian National HPV Vaccination Program from 2007, with routine vaccination in 12-13 year old girls and an initial two-year catch-up to age 26 years, has already reduced confirmed high grade cervical abnormalities in young women. This, together with an accumulation of international evidence on primary HPV testing, has led to the development of new recommendations for cervical screening in Australia. These recommendations, which have emerged out of a structured and evidence-based process of review (the ‘Renewal’), propose that primary HPV screening be conducted every 5 years in women 25 years and older, and that women are discharged from screening in their early seventies.

Australia is thus now transitioning from cytology screening to an HPV-based cervical screening program which will be specifically tailored to interface with HPV vaccination by incorporating partial genotyping for the vaccine-included oncogenic types, HPV 16 and 18. From 2017, all women, whether unvaccinated or vaccinated, will be offered HPV screening and those found to have HPV16/18 infections will be classified as higher risk for development of cervical intraepithelial neoplasia grade 3 or invasive cervical cancer (CIN 3+) and referred directly to colposcopy for further evaluation. Those with other oncogenic type infections will be classified as intermediate risk and undergo triage testing, and HPV negative women will be returned to routine recall at five years. Because all women in Australia aged 35 years or younger have now been offered vaccination and coverage rates have been relatively high, infection rates with HPV16/18 in the population are expected to be relatively low and thus colposcopy referral rates are expected to be lower than, or comparable to, current rates in the program. Australia will thus be the first country to implement a population risk assessment approach to screening in the context of vaccination, using the screen-positive partially genotyped HPV results to determine a woman’s longitudinal risk of developing CIN 3+ and thus to determine her optimal management, without needing to know her individual vaccination status at the time of screening.

“These recommendations, which have emerged out of a structured and evidence-based process of review (the ‘Renewal’), propose that primary HPV screening be conducted every 5 years in women 25 years and older, and that women are discharged from screening in their early seventies.”

As part of the transitional process, a major randomised controlled trial of 121,000 women randomised to HPV versus cytology screening is currently ongoing. This trial, known as Compass, is stratifying enrollment by whether women are in birth cohorts offered vaccination, and will thus provide key information on cervical screening in a vaccinated population. Compass has already facilitated the development of systems for primary HPV screening with partial genotyping, and the trial will continue to act as a sentinel experience for the transition of the National Cervical Screening Program in Australia.

**BACKGROUND: CERVICAL SCREENING IN AUSTRALIA**

Australia’s organised National Cervical Screening Program, which was established in 1991, recommends 2-yearly conventional cytology (Pap smear) screening in sexually active women aged 18-20 to 69 years. Participation rates over 2 years are 58%, with 83% of eligible women being...
screened every 5 years. The program has been very successful in reducing the incidence and mortality from cervical cancer, which fell by ~50% in the first decade, although it is notable that similar falls were also achieved in countries with longer screening intervals for cervical cytology.

"It is notable that the relative proportion of adenocarcinomas compared to squamous cancers diagnosed has grown from 11% in 1982 to 26% in 2008 as the incidence of invasive squamous cervical cancer has reduced due to the effect of screening."

In the second decade of the cytology screening program, rates of cervical cancer incidence and mortality appear to have plateaued, and at the present time, although Australia is one of the countries with the lowest incidence of cervical cancer, it is likely that the cytology screening program has ‘reached its limits’ due to the continuing difficulties of reaching some groups of women (including those in remote and rural communities) for regular 2-yearly screening and also due to the limitations of cervical cytology in detection of adenocarcinoma. It is notable that the relative proportion of adenocarcinomas compared to squamous cancers diagnosed has grown from 11% in 1982 to 26% in 2008 as the incidence of invasive squamous cervical cancer has reduced due to the effect of screening.

Whilst successful, the National Cervical Screening Program is associated with substantial ongoing costs. The direct program costs have been estimated as A$195M in 2010 (projected to grow to $215M in 2015); this is equivalent to a cost of A$23 per adult woman in 2010, whether actually screened or not. Approximately half of these costs are being spent on frequent ‘front-end’ cytology tests.

Although liquid-based cytology (LBC) was evaluated for use in the program (most recently in 2009) it has not been adopted, in part because the cost-effectiveness of LBC was adversely impacted by the frequent screening interval and the consequent need to apply an incremental cost for LBC for a large number of screening tests (26 recommended screens per lifetime).

**IMPACT OF HPV VACCINATION IN AUSTRALIA**

Australia was the first country to initiate a national publically-funded HPV vaccination program in 2007. Female vaccination uptake is approximately 71-72% for 3 dose coverage in 12-13 year old females; catch-up in 18-26 year old females achieved coverage rates of the order of 30-50%. From 2013, males aged 12-13 have also been vaccinated at school with a two-year catch-up to Year 9 (~15 years). Via herd immunity, male vaccination will also provide incremental benefits to females, and is expected to lead to further reductions in vaccine-included types infections and high grade cervical abnormalities in females.

"From 2004-6 to 2012, for women aged < 20 years, rates of CIN 2/3 decreased by 53%; for women aged 20-24 years, rates of confirmed CIN 2/3 were stable until 2010, then decreased by 21% in the following year."

Several factors have come together to lead to a more rapid impact of vaccination on cervical screening in Australia compared to many other countries – these include the early introduction of HPV vaccination, the extended catch-up to age 26 years, the early age of starting screening at 18-20 years, and the consequent overlap of vaccinated and screened populations from the inception of the vaccination program, and relatively high vaccination and cervical screening coverage rates. After the introduction of vaccination, Australia experienced rapid falls in
vaccine-included HPV type infections, in anogenital warts and in histologically confirmed cervical high grade precancerous abnormalities (CIN 2/3). These have now been documented extensively in young females and also in heterosexual males due to herd immunity effects. From 2004-6 to 2012, for women aged < 20 years, rates of CIN 2/3 decreased by 53%; for women aged 20-24 years, rates of confirmed CIN 2/3 were stable until 2010, then decreased by 21% in the following year. It is expected that rates of high grade abnormalities will continue to decline in these age groups and that the declines will extend to older age groups as the cohorts offered vaccination continue to age.

THE AUSTRALIAN EXAMPLE: AN INTEGRATED APPROACH TO HPV VACCINATION AND CERVICAL SCREENING

"The Renewal modelling predicted that 5-yearly HPV screening with partial genotyping from age 25 would be both life year and (potentially) cost saving, and that this would be the most favourable screening approach overall for both unvaccinated and for cohorts offered vaccination."

A modelling approach was used to combine the international evidence on vaccine efficacy and screening and diagnostic test accuracy with local information on vaccination and screening costs i.e. an explicitly linked evidence approach to guide decision making was taken. The process was guided by an expert reference group, the Renewal Steering Committee. A large number of options were considered for the future screening program, based on six main primary screening approaches – conventional cytology, manually-read LBC, image-read LBC, HPV screening for a pool of oncogenic types with cytology triage of HPV positive women, HPV screening with partial genotyping for HPV 16/18, and adjunctive co-testing using both cytology and HPV testing (Table 1).

"The Renewal modelling predicted that 5-yearly HPV screening with partial genotyping from age 25 would be both life year and (potentially) cost saving, and that this would be the most favourable screening approach overall for both unvaccinated and for cohorts offered vaccination."

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<table>
<thead>
<tr>
<th>Primary screening test</th>
<th>Age range</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT PRACTICE: Conventional cytology</td>
<td>18-20 to 69 years</td>
<td>2</td>
</tr>
<tr>
<td>1 Conventional cytology</td>
<td>25-65 years</td>
<td>IARC intervals (3-yearly &lt; 50; 5-yrly 50+ years)</td>
</tr>
<tr>
<td>2 Manually-read LBC+/HPV triage of LSIL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Image-read LBC +/-HPV triage of LSIL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 HPV with LBC triage of pooled oncogenic types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 HPV with partial genotyping for HPV 16/18 &amp; direct referral to colposcopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Co-testing with both HPV and LBC</td>
<td></td>
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Table 1. Options considered in the Renewal (review) of the Australian National Cervical Screening Program.
behaviour and to simulate future outcomes for the screening program.

The simulation incorporated a dynamic model of sexual behaviour and HPV transmission, natural history and screening which was extensively validated including against post-vaccination outcomes for infections and CIN 2/3. The Renewal modelling predicted that 5-yearly HPV screening with partial genotyping from age 25 would be both life year and (potentially) cost saving, and that this would be the most favourable screening approach overall for both unvaccinated and for cohorts offered vaccination. It was predicted that the use of partial genotyping would result in further improvements in cervical cancer incidence and mortality compared to the current screening program of at least 13-15%, and up to 22%, if retaining a screening end-age of 70 years. Although partial genotyping strategies were predicted to increase colposcopies in an unvaccinated population, in Australia a large increase in colposcopies was not predicted because by 2016, women aged ≤35 years will have been offered vaccination.

The MSAC evidence review report was released on April 28th 2014, with the recommendations based on the above modelled findings (Figure 1). A ‘preferred pathway’ or management algorithm for HPV-positive women was also identified (Figure 2), but this is yet to be supported by the development of professional clinical practice guidelines, which will be occurring as part of the implementation phase. The Australian Health Ministers’ Advisory Council has now endorsed an Interim Implementation Plan and the transition from evidence to practice will be guided by a Steering Committee for the Renewal Implementation Project, and a Quality and Safety Monitoring Committee has also been configured. The target implementation date for the Renewed National Cervical Screening program is May 2017.

THE DRAFT RENEWED NATIONAL POLICY FOR CERVICAL SCREENING IN AUSTRALIA

1. Australian women should start having HPV tests at 25 years.
2. HPV tests should be undertaken every 5 years until 74 years.
3. Women with positive HPV tests results should be followed up in accordance with cervical screening pathway*.
4. Women 70 to 74 years of age, with a negative HPV test result may exit the cervical screening program.
5. Women 74 years of age and older who have never had, or who request a HPV test at least 5 years after their last cervical screening test, should be screened.
6. HPV an cytology co-testing is not recommended.

*Management Guidance to be updated following development clinical practice guidelines.

Source: National Screening Program Australia, Partner Reference Group E-newsletter. September 2014

Figure 1.

COMPASS TRIAL: A SENTINEL EXPERIENCE

Compass [Clinicaltrials.gov NCT02328872] is a large scale randomised controlled trial of 5-yearly HPV versus 2.5 yearly image read LBC cytology screening in women aged 25–69 years. Compass is one of the first large scale cervical screening experiences in a population of women who have been offered HPV vaccination, and it is being conducted in the state of Victoria by the Victorian Cytology Service. Women presenting for screening are consented by the primary practitioner and an LBC sample taken with randomisation applied in the laboratory. HPV screening in the trial incorporates...
the use of partial genotyping. Recruitment is stratified according to whether women are in age cohorts that were offered vaccination (i.e. whether aged ~35 years or less in 2015). Compass is a pragmatic trial which has allowed the development of new systems for HPV screening, including the implementation of ‘call-and-recall’, whereby women are proactively issued an invitation to attend screening when their test is due. Compass is being performed in two phases – Phase I (the pilot) has involved recruiting 5,000 women, and Phase 2 (the main trial) involves the ongoing recruitment of 121,000 women. The trial is designed not only to assess comparative performance of HPV and LBC screening in both unvaccinated and vaccinated women, but also to assess optimal triage strategies for HPV-positive women in both groups. In HPV-screened women, a secondary randomisation process for intermediate risk women with other oncogenic HPV infections (i.e. not HPV16/18) is implemented, these women are randomised to be triaged either with LBC or with dual-stained p16/Ki67 cytology (CINtec PLUS, Roche/Ventana). The sample size of 121,000 incorporates 114,000 women presenting for screening or follow-up and

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**Figure 2. Preferred pathway for cervical screening in Australian: primary HPV screening with partial genotyping.**

(This preferred pathway was identified as a result of the Medical Services Committee Evidence Review and modelled analysis; clinical guidelines development to underpin this management algorithm is ongoing as part of the implementation phase of Renewal.)

**HPV TEST WITH PARTIAL GENOTYPING**

<table>
<thead>
<tr>
<th>Test was negative (normal)</th>
<th>Test was negative (normal)</th>
<th>Test was negative (normal)</th>
<th>Test was negative (normal)</th>
<th>Test was negative (normal)</th>
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<tr>
<td>HPV other onco types</td>
<td>Reflex LBC</td>
<td>Reflex LBC to assist management at colposcopy</td>
<td></td>
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<tr>
<td>Negative Cytology</td>
<td>ASC-US/LSIL Cytology</td>
<td>ASC-H/HSIL cytology</td>
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<tr>
<td>Repeat HPV test in 12 months</td>
<td>Repeat HPV test in 12 months</td>
<td>May require treatment</td>
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<td></td>
</tr>
<tr>
<td>Negative HPV</td>
<td>Any positive HPV</td>
<td>May require treatment</td>
<td></td>
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</tr>
<tr>
<td>Indicate HPV infection</td>
<td>Test was positive (normal)</td>
<td>High-risk HPV infection</td>
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<tr>
<td>present</td>
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<td>present</td>
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</tr>
<tr>
<td>Track HPV</td>
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<td>Unsatisfactory test</td>
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<td>for technical reasons</td>
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</table>

Risk of cervical cancer precursors:
- Lower
- Intermediate
- Higher

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21
Karen Canfell is a co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia (‘Compass’), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However neither Karen Canfell nor her institution on her behalf (Cancer Council NSW) receives direct funding from industry for this trial or any other project.


THE AUSTRALIAN EXAMPLE: AN INTEGRATED APPROACH TO HPV VACCINATION AND CERVICAL SCREENING

CONCLUSION

Australia was the first country to implement a free public HPV vaccination program in young females. The successful rollout of the vaccination program and its rapid impact to reduce high grade cervical abnormalities in young women has prompted a major review of cervical screening. The Renewed cervical screening program will be directly tailored to work with vaccination via specific detection and management of women with vaccine-included type infections. HPV16/18 positive women may, for example, have been in older age cohorts not offered vaccination, or they may have been infected prior to vaccination, or they may not have completed the vaccination course and were subsequently HPV-infected - in any case they will be managed as higher risk women. Women positive for other oncogenic type infections will be managed as intermediate risk via triage testing, and HPV-negative women will be referred to 5-yearly screening, which will reflect a low level of risk even for unvaccinated women. In the Renewed screening program, therefore, whether offered vaccination or not, women will be managed according to their HPV status and thus their level of risk. Australia is thus the first country to move to a truly population-based risk assessment approach to cervical screening in the context of HPV vaccination.
Greetings to PVR

A new scientific Journal devoted to HPV and other small DNA tumor viruses and the official journal of the International Papillomavirus Society

www.journals.elsevier.com/papillomavirus-research
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