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 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

(cont. page 3)
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

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**Mark H. Stoler**

Professor (Emeritus) of Pathology and Clinical Gynecology. Associate Director of Surgical and Cytopathology. Department of Pathology. University of Virginia Health System. Charlottesville, USA

"The 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."
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…

Dr. Mark H. Stoler has served as a consultant in clinical trial design and as an expert pathologist for HPV vaccine and/or diagnostic trials for Roche, Ventana Medical Systems, Hologic/Gen-Probe, Becton Dickinson, Cepheid, Qiagen, Inovio and Merck.
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.

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, United Kingdom, Nordic countries, the Netherlands, New Zealand, and Australia 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.

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). 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. 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) cer-
vical precancer and cancer algebraically results
in a better positive predictive value.29
• Second, informing cytologists that the Pap is
from hrHPV-positive women, “informed screen-
ing” 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 vac-
cination against HPV16 and HPV18 in HPV-naïve
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 embarrassing low,31 there is already evidence of
reduced prevalence of HPV16 and HPV18 infec-
tions52 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

<table>
<thead>
<tr>
<th>Pap Screening</th>
<th>Unvaccinated Populations</th>
<th>Vaccinated Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN 2+ &lt; CIN 2</td>
<td>Total</td>
</tr>
<tr>
<td>In all women</td>
<td>Pap+ 500 4,500 5,000</td>
<td>Sp= 95.5%</td>
</tr>
<tr>
<td></td>
<td>Pap- 94,500 95,000</td>
<td>PPV= 10.0%</td>
</tr>
<tr>
<td></td>
<td>Total 1,000 99,000 100,000</td>
<td>NPV= 99.5%</td>
</tr>
<tr>
<td>Triage of hrHPV Positives (cytology blinded)</td>
<td>CIN 2+ &lt; CIN 2</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Pap+ 450 2,050 2,500</td>
<td>Sp= 77.5%</td>
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<td></td>
<td>Pap- 7,050 7,500</td>
<td>PPV= 18.0%</td>
</tr>
<tr>
<td></td>
<td>Total 900 9,100 100,000</td>
<td>NPV= 94.0%</td>
</tr>
<tr>
<td>Triage of hrHPV Positives (cytology informed)</td>
<td>CIN 2+ &lt; CIN 2</td>
<td>Total</td>
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<tr>
<td></td>
<td>Pap+ 720 1,905 2,625</td>
<td>Sp= 79.1%</td>
</tr>
<tr>
<td></td>
<td>Pap- 180 7,195 7,375</td>
<td>PPV= 27.4%</td>
</tr>
<tr>
<td></td>
<td>Total 900 9,100 100,000</td>
<td>NPV= 97.6%</td>
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</table>

Pap sensitivity = 50% hrHPV testing sensitivity = 90%
Prevalence of CIN2+ in an unvaccinated population = 1%; Prevalence of CIN2+ in an HPV-naïve population vaccinated against HPV16 and HPV18 = 1%
Prevalence of hrHPV in an unvaccinated population = 10%; Prevalence of hrHPV in an HPV-naïve population vaccinated against HPV16 and HPV18 = 7.5%
Prevalence of ASC-US+ in an unvaccinated population = 5%; Prevalence of ASC-US+ in an HPV-naïve 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.
cutpoint of ASC-US in a vaccinated population is 6.7% i.e. only 1 of 16 Pap-positive women will 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.*

Dr. Castle has received commercial HPV tests for research at a reduced or no cost from Roche, Qiagen, Arbor Vita Corporation, BD, and mtm. 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, Cepheid, ClearPath, Guided Therapeutics, Teva Pharmaceuticals, Gentecel, Inovio, and GE Healthcare. Dr. Castle has received honoraria as a speaker for Roche and Cepheid.
The ATHENA (Addressing the Need for Advanced HPV Diagnostics) study is the US registrational study that has been used to obtain Federal Drug Administration (FDA) approval of the Roche cobas HPV Test for use in the US. The ATHENA study was begun in 2008 and consisted of two distinct phases. The Baseline Phase was cross-sectional and enrolled 46,887 eligible non-pregnant women ≥21 years undergoing routine cervical cancer screening at 61 clinical centers in 23 states across the United States. At enrollment all women had a ThinPrep liquid-based cytology (LBC) sample and HPV testing with multiple high-risk HPV DNA assays (AMPLICOR HPV Test, LINEAR ARRAY High Risk HPV Genotyping Test, cobas HPV Test—all manufactured by Roche Molecular Systems, Pleasanton, CA). All women with either an abnormal cytology result or who were HPV positive were referred to colposcopy. In addition, a random subsample of cytology and HPV negative women were referred to colposcopy (n=886) to allow for verification bias adjustment.

"Data obtained from the Baseline Phase of ATHENA were used to obtain FDA-approval for use of cobas HPV Test in women ≥21 years with ASC-US and for cotesting using both cytology and HPV testing in women ≥30 years."

"Data from the Baseline Phase were also used to obtain FDA-approval for HPV 16/18 genotyping in both ASC-US patients and when cotesting."

Athena was the Greek virgin goddess of reason, intelligent activity, arts and literature. She became the patron goddess of Athens after winning a contest against Poseidon by offering the olive tree to the Athenians.
All women who underwent colposcopy during the Baseline Phase of ATHENA and found not to have cervical intraepithelial neoplasia of grade 2 (CIN 2+), were eligible for enrollment into a 3 year Follow-up Phase. During the Follow-up Phase, women had yearly gynecological exams and both liquid based cytology (LBC) and HPV testing and were referred to colposcopy if found to have ≥ ASC-US. At the 3 year visit, women were offered an exit colposcopy. Data from both the Baseline and the Follow-up Phases were subsequently used to obtain FDA-approval in April of 2014 of the cobas HPV Test with HPV 16/18 genotyping for primary screening in women ≥25 years.5

**WHAT WE LEARNED FROM ATHENA REGARDING THE ROLE OF HPV GENOTYPING IN COTESTING.**

The prevalence of HPV in women with negative for intraepithelial lesion or malignancy (NILM) results decreased with increasing age, however most of the decrease occurred between the 30-39 and the 40-49 age groups, Table 1. Only small decreases were observed for HPV (14 pooled types), HPV 16, HPV 18, and 12 “other” high-risk HPV genotypes between the other age groups. Although the overall prevalence of HPV in women ≥ 30 yrs with NILM was 6.7%, the majority of this was due to positivity for the 12 “other” high-risk HPV genotypes. Positivity for HPV 16/18 was relatively uncommon, 1.5%. Verification bias-adjusted estimates for relative risk of CIN 3+ in women with NILM cytology by HPV genotypes status clearly demonstrates the importance of a woman’s HPV 16/18 status. Women with NILM cytology who were HPV negative had an estimated absolute risk of CIN 3+ of only 0.3, which is low enough to allow interval screening at 3 to 5 years. Women with NILM cytology who were high-risk HPV positive (for any of the 14 high-risk HPV genotypes combined) have an absolute risk of 4.1 and those with one of the 12 "other" high-risk HPV genotypes have a risk of 2.4. Since their risk of CIN 3+ is < 5.0, it is generally accepted that these women can be followed up at 12 months with repeat co-testing and only need colposcopy if found to have persistently HPV positive or have a repeat cytology of equal or greater than low-grade squamous intraepithelial lesions (LSIL) with a negative HPV result. In contrast, women positive for either HPV 16 or HPV 18 have an estimated absolute risk of CIN 3+ of 9.8 and would clearly benefit from a referral to immediate colposcopy. Risk for all combinations of genotypes was highest in women 30-39 years of age and lowest in women ≥50 years. Thus the results from ATHENA clearly demonstrate the usefulness of being able to genotype for HPV 16 and HPV 18 when cotesting.

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>HPV (+)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>prevalence</td>
<td>9.0</td>
<td>5.7</td>
<td>5.3</td>
<td>4.9</td>
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<td>1.1</td>
<td>2.7</td>
<td>4.1</td>
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<tr>
<td>HPV 16 (+) / 18 (+)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prevalence</td>
<td>2.3</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
<td>1.5</td>
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<td>6.6</td>
<td>4.4</td>
<td>0.0</td>
<td>9.8</td>
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<tr>
<td>HPV 16 (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prevalence</td>
<td>1.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.7</td>
<td>1.0</td>
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<td>risk of CIN 3+</td>
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<td>7.5</td>
<td>2.4</td>
<td>0.0</td>
<td>11.7</td>
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<td>HPV 18 (+)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>prevalence</td>
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<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.5</td>
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<tr>
<td>risk of CIN 3+</td>
<td>7.1</td>
<td>2.4</td>
<td>3.7</td>
<td>0.0</td>
<td>5.7</td>
</tr>
<tr>
<td>HPV 12 other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prevalence</td>
<td>6.7</td>
<td>4.6</td>
<td>4.4</td>
<td>4.0</td>
<td>5.2</td>
</tr>
<tr>
<td>risk of CIN 3+</td>
<td>3.0</td>
<td>2.8</td>
<td>0.3</td>
<td>3.3</td>
<td>2.4</td>
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<tr>
<td>HPV (-)</td>
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<td></td>
</tr>
<tr>
<td>risk of CIN 3+</td>
<td>0.0</td>
<td>0.4</td>
<td>0.0</td>
<td>1.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 1. Impact of age on prevalence of HPV and estimated absolute risk of CIN 3+ (in % over the 3-year follow up period) by HPV status in women with NILM cytology.

KEY FINDINGS OF THE ATHENA STUDY

WHAT WE LEARNED FROM ATHENA REGARDING THE SAFETY OF HPV PRIMARY SCREENING.

At Baseline, 10.5% of the 40,901 women ≥25 years were HPV positive and 6.4% had an abnormal cervical cytology. During the course of the 3-year study, a total of 319 CIN 3 lesions, 20 adenocarcinoma in-situ, and 8 invasive cervical cancer cases were detected. Figure 1 shows the 3-year cumulative incidence rate (CIR) of CIN 3+ adjusted for sampling fraction and follow-up. A negative cytology result at Baseline conferred a lower level of protection against the subsequent identification of CIN 3+ than does a negative HPV test result. Of the CIN 3+ identified after 3 years 47.3% had a NILM cytology result at Baseline whereas only 9.8% were HPV negative. A negative cotest at Baseline offered minimal additional protection compared to a negative HPV test alone. HPV genotype status was also highly predictive of CIN 3+ over the course of the study. The highest 3-year CIR of CIN 3+ was 25.2% (95% CI, 21.7-28.7%) in HPV 16 positive women and the lowest was 0.3% (95% CI, 0.1-0.6%) in HPV negative women, Figure 2. Women positive for HPV 18 had a 3-year CIR for CIN 3+ that was intermediate between HPV 16 positive women and those positive for the 12 “other” high-risk HPV genotypes. The high prevalence of HPV positivity (10.5%) in women ≥25 years means that some form of triage is required to identify those women who should undergo immediate colposcopy and those who can be followed without immediate colposcopy. The HPV primary screening algorithm that was approved by the FDA for use in the U.S is a combination of genotyping for HPV 16/18 and reflex cytology for women positive for the 12 other high-risk HPV genotypes, Figure 3. This is also the strategy that the recent Society of Gynecologic Oncology (SGO) / American Society for Colposcopy and Cervical Pathology (ASCCP) Interim Guidance adopted for HPV primary screening.6

We compared the FDA approved strategy to a strategy of either cytology alone (with reflex HPV testing for women with ASC-US) for women

"Of the CIN 3+ identified after 3 years 47.3% had a NILM cytology result at Baseline whereas only 9.8% were HPV negative."
KEY FINDINGS OF THE ATHENA STUDY

≥ 25 years or a hybrid strategy that uses cytology in women 25-29 years and cotesting with cytology and HPV testing in women ≥ 30 years. The HPV primary screening strategy detected the most cases of CIN 3+ over the 3 years (n=294) and had the highest adjusted sensitivity (76.1%) for CIN 3+, Table 2. For comparison, cytology detected only 179 cases of CIN 3+ and had an adjusted sensitivity of 47.8% whereas the hybrid strategy detected 240 cases of CIN 3+ and had an adjusted sensitivity of 61.7%. Specificity for CIN 3+ was highest for the cytology strategy (97.1%) and lowest for the HPV primary screening strategy (93.5%). The efficiency of a given strategy can be estimated by determining the number of colposcopies that are required to detect a single case of CIN 3+. Cytology was the most efficient strategy requiring only 10.8 colposcopy exams per CIN 3+. The hybrid strategy and HPV primary screening had similar efficiencies, 12.8 and 12.9 colposcopy exams per CIN 3+, respectively.

These data clearly demonstrate that HPV primary screening using the FDA-approved screening strategy is as safe as cervical cytology over a 3-year screening interval in women > 25 years and that it is as efficient as using cytology in women 25-29 years and cotesting in women ≥ 30 years.

"The HPV primary screening algorithm that was approved by the FDA for use in the U.S is a combination of genotyping for HPV 16/18 and reflex cytology for women positive for the 12 other high-risk HPV genotypes."

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Nº. CIN 3+ detected</th>
<th>Nº. Colposcopy Exams</th>
<th>Nº. Colpo per case of CIN 3+</th>
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</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>47.8</td>
<td>97.1</td>
<td>179</td>
<td>1,934</td>
<td>10.8</td>
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<tr>
<td>Hybrid strategy*</td>
<td>61.7</td>
<td>94.6</td>
<td>240</td>
<td>3,097</td>
<td>12.9</td>
</tr>
<tr>
<td>HPV primary</td>
<td>76.1</td>
<td>93.5</td>
<td>294</td>
<td>3,769</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Table 2. Performance of different screening strategies for detection of CIN 3+ in women ≥ 25 years.*

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Dr. Thomas C. Wright is a consultant and speaker for Roche, BD Diagnostics and Cepheid. Dr. Catherine M. Behrens was previously employed by Roche Molecular Systems and now serves as a consultant for Roche and other women’s health care entities.

References:

HPV testing for cervical cancer screening provides high sensitivity for detection of cervical precancers, allowing extended screening intervals compared to cytology in women who test negative. However, most HPV infections are cleared and do not progress to cervical cancer. HPV testing can double the number of screen-positive women compared to cytology and it is neither feasible, nor effective to send all HPV-positive women to colposcopy. Therefore, additional tests are needed to identify women at highest risk of cervical cancer that require immediate colposcopy and biopsy. An ideal test should identify the small group of women at highest risk for treatable cervical precancers needing colposcopy referral, while reassuring the majority of women that their risk is low. In other words, an optimal strategy should identify as much disease as possible, while leading to as little colposcopy referral as possible. Several strategies for triage of HPV-positive women have been evaluated, and some have already been introduced in screening practice. In addition to the different characteristics of currently available triage tests, their use may vary substantially between different regions. Importantly, the perception of risk may differ in different situations and societies.

An ideal test should identify the small group of women at highest risk for treatable cervical precancers needing colposcopy referral, while reassuring the majority of women that their risk is low. In other words, an optimal strategy should identify as much disease as possible, while leading to as little colposcopy referral as possible.

Figure 1 shows the principle of risk-based management in cervical cancer screening. The risk of cervical cancer and

![Figure 1. Risk based management.](image-url)
CIN3 in the general population is low (a) HPV primary screening changes the prior, baseline risk estimate to a higher risk in test-positive women (b) and to an even lower risk than baseline in those who test negative (c). The absolute risk of disease in test-positives is equal to the positive predictive value, while the absolute risk of disease in test-negatives is equal to the complement of the negative predictive value (cNPV or 1-NPV).5 However, in the example given from US management guidelines, the risk in HPV-positives does not cross the threshold for referral to colposcopy (d). A useful triage marker applied to the HPV-positive population should change the risk estimate to a risk in triage-positive women above the colposcopy referral threshold (e) and to a lower risk in those who test-negative for the triage marker (f).

The operational characteristics of a triage test are important for designing a screening program. Some triage tests are based on detection of nucleic acids from lysed specimens (e.g. HPV genotyping, methylation markers) while others require intact cells (e.g. cytology, p16/Ki-67 dual stain). Depending on the primary test and the organization of the screening program, some triage tests may require an additional specimen type for the triage test or even an additional visit for collection following a positive screening test result. It is obviously preferable to run the triage test from the specimen collected for primary HPV testing (reflex triage).

"The risk of cervical precancer and cancer differs considerably by HPV genotype, with HPV16 being by far the most carcinogenic type, followed by HPV18. Because of this remarkable risk stratification, HPV genotyping for HPV16 and HPV18 has been evaluated for triage of HPV-positive women."

Proposed markers for triage of HPV-positive women are summarized in table 1. Cytology has been evaluated as a triage test for primary HPV testing in several studies and is the triage strategy in the proposed organized Dutch cervical cancer screening program. Women who are HPV-positive in primary screening can have reflex cytology testing and are referred to immediate colposcopy when cytology is positive (the thresholds for cytology

<table>
<thead>
<tr>
<th>Assay</th>
<th>Examples</th>
<th>Validation</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>HPV genotyping</td>
<td>Cobas 4800 (Roche); Cervista (Hologic); Onclarity (BD)</td>
<td>Large screening and triage studies</td>
<td>Type-restriction</td>
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<td>Oncogene mRNA</td>
<td>Aptima HPV (Genprobe); Proofer (NorChip); HPV Oncotec (InCell Dx)</td>
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<td>E6 detection</td>
<td>OncoE6 (Arbor Vita)</td>
<td>Limited data available</td>
<td>Type-dependent</td>
</tr>
<tr>
<td>p16/Ki-67 cytology</td>
<td>CINtec PLUS (Roche Ventana)</td>
<td>Large observational studies</td>
<td>Not type-dependent; slide-based</td>
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<tr>
<td>MCM2/ Top2A cytology</td>
<td>ProExC (BD)</td>
<td>Limited data available</td>
<td>Not type-dependent; slide-based</td>
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<tr>
<td>3q</td>
<td>Oncofish (Ikonisy); FHACT (Cancer Genetics)</td>
<td>Limited data available</td>
<td>Not type-dependent; slide-based</td>
</tr>
<tr>
<td>Host and viral methylation</td>
<td>Host markers: CADM1, MAL, mir-124, EPB41L3, LMX1 Viral markers: L2, L1</td>
<td>Some large observational studies and trials</td>
<td>Host: not type dependent Viral: type-dependent</td>
</tr>
</tbody>
</table>

Table 1. Triage marker candidates
positivity differ between studies and healthcare settings). HPV-positive, cytology-negative women undergo retesting after at least 6-12 months, to allow a proportion of the transient HPV infections to clear. While there is concern that the limited sensitivity of cytology cancels out some of the advantages of primary HPV screening, there is evidence suggesting that the sensitivity of cervical cytology is increased when it is conducted with knowledge of HPV status, or when it is restricted to HPV-positive women only.6

The risk of cervical precancer and cancer differs considerably by HPV genotype, with HPV16 being by far the most carcinogenic type, followed by HPV18.7 Because of this remarkable risk stratification, HPV genotyping for HPV16 and HPV18 has been evaluated for triage of HPV-positive women. Several HPV assays now provide separate results for HPV16 and HPV18, or for more HPV genotypes, either as a second test or integrating this triage approach into the primary screening test. Women who test positive for HPV16 or HPV18 have high enough risk for referral to colposcopy, while women testing positive for the other carcinogenic types typically have a repeat test after 12 months. There is an ongoing debate about whether other carcinogenic types should be included for triage to immediate colposcopy. While adding more types increases the sensitivity of the approach somewhat, the absolute risk is reduced since all other types are associated with a much lower risk compared to HPV16.

In the US, primary HPV testing with the cobas assay was approved with a combination of HPV genotyping and cytology for triage of HPV-positive women. According to the approved algorithm, all women testing positive for HPV16 or HPV18 should be referred to immediate colposcopy. Women testing positive for the other 12 high-risk types have cytology testing and should be referred to colposcopy when cytology shows ASC-US or greater. Women positive for HPV types other than HPV16/18 and with normal cytology undergo repeat testing after 12 months.8

Several other possible markers for triage of HPV-positive women have been evaluated. The p16/Ki-67 dual stain is a cytology-based assay that indicates overexpression of two cellular proteins altered in cervical precancers.9 The detection of cells stained for both p16 and Ki-67 is considered a positive result. A previous version of the assay was based on p16 staining alone followed by morphological evaluation of p16-stained cells. In a study using the p16 assay nested in the Italian cervical cancer screening trial, p16 showed good risk stratification for triage of HPV-positive women.10 p16-positive women had high enough risk for referral to colposcopy, while the repeat testing interval could be extended to at least two years among p16-negative women according to these data. Similar results were observed in smaller studies using the dual stain, and several large studies are now underway to confirm these results.11 It has been demonstrated that the p16/Ki-67 dual stain assay can be implemented with limited training while achieving high reproducibility and accuracy and that automated evaluation of dual stained slides is feasible.12

Recently, there has been a lot of focus on developing DNA methylation markers for triage of HPV-positive women. Marker panels including the cellular genes CADM1, MAL, and miR-124-2 in various combinations have been evaluated in Dutch
cervical cancer screening studies and have shown comparable performance to cytology-based triage. This approach is particularly appealing for primary screening based on self-sampling, since the test can be run from the screening sample and does not require an additional collection for a cytology specimen. Beyond host methylation, it has also been demonstrated that methylation of the HPV genome, especially in the L2 and L1 regions, is associated with prevalent and future precancer and cancer. Initial studies have shown that measuring HPV methylation could provide sufficient risk stratification for triage of HPV-positive women and development of HPV methylation assays is currently underway. Other approaches that have been proposed to triage HPV-positive women include measuring HPV oncogene mRNA or protein expression, detection of recurrent chromosomal changes at 3q and other sites, and staining for other cellular proteins that are associated with HPV-related transformation, such as mcm2 and Top2a.

"It has been demonstrated that the p16/Ki-67 dual stain assay can be implemented with limited training while achieving high reproducibility and accuracy and that automated evaluation of dual stained slides is feasible."

The number of triage assay candidates is steadily increasing and choosing the optimal triage strategy is becoming increasingly a challenge. The evaluation of screening and triage strategies needs to be conducted on a program level, since different assays have very different implications on management procedures. For example, a certain triage assay could have a low immediate colposcopy referral rate, but still send the majority of women to colposcopy after the repeat test, e.g., a year later. It is already now apparent that some triage strategies have similar performance, and other factors may be important to decide which test to use, such as the sampling buffer, assay throughput, and ultimately cost. A theoretical optimal triage strategy may combine assays from different manufacturers that are not compatible or cannot be combined because of commercial concerns. Furthermore, different population characteristics, screening and management procedures can influence performance estimates for individual assays, making comparisons across studies difficult for the small differences expected for some of the strategies. It is not possible to conduct randomized controlled trials for every strategy comparison. Therefore, it is necessary to evaluate triage options in large head-to-head observational comparisons that allow evaluating disease detection and management prospectively over multiple years, by multiple testing of aliquots of the same clinical specimens. Defining an acceptable, management set of triage strategies for women that screen HPV-positive is one of the major ongoing tasks we face in the introduction of HPV-based screening.

Dr. Nicolas Wentzensen is employed at the National Cancer Institute (NCI). The NCI has received commercial HPV tests for research at a reduced or no cost from BD, Cepheid, Hologic, and Roche.

Numerous large randomized studies\textsuperscript{1,2} and screening trials\textsuperscript{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.\textsuperscript{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).

“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.”

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We use counterfactual reasoning to estimate risks for screening contexts 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
(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.

Public health policymakers in other settings have defined less stringent acceptable cancer risks for population-based screening programs. 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. 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?
The panel also made the following additional recommendations:
- Based on limited data, triage of hrHPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women. (Figure 1)
- Re-screening after a negative primary HPV screen should occur no sooner than every 3 years.
- Primary HPV screening should not be initiated prior to 25 years of age.

The panel also made the following additional recommendations:
- Based on limited data, triage of hrHPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women. (Figure 1)
- Re-screening after a negative primary HPV screen should occur no sooner than every 3 years.
- Primary HPV screening should not be initiated prior to 25 years of age.

Figure 1. Candidate Screening Algorithm. HPV with 16/18 Genotyping and Reflex Cytology.

There was considerable debate and discussion about initiating primary HPV screening at 25 years of age. Despite almost a one 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:
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).\textsuperscript{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.\textsuperscript{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."

At this time, the three national screening organizations with most influence on clinical practice and reimbursement have not updated their guidelines to include primary HPV testing as an option for screening. Until the first half of the 20\textsuperscript{th} century, the United States had a high burden of cervical cancer that was similar to the current burden seen in many low- and middle-income countries. Doctors began to use the Papanicolaou (Pap) test in the 1950s, when annual testing was heavily promoted.\textsuperscript{1} Although clinical trials to assess its potential effectiveness were never performed before implementation, Pap testing in both opportunistic and organized systems has accompanied large decreases in cervical cancer mortality and incidence.\textsuperscript{5,6}

The United States does not have a universal, nationally organized cervical cancer screening program with a mechanism that can systematically collect information on cervical cancer screening or generate reminders or recalls. Therefore, we must rely on special studies that provide details about provider and patient practices. Through the years, expert groups have made changes to the US guidelines, often causing confusion among health care providers about screening methods, intervals, and target age groups. Guidelines have shifted over a decade to include longer intervals.\textsuperscript{7} However, providers have been very slow to adopt these longer intervals, and surveys and anecdotal reports show that some/many providers are conducting co-testing annually.\textsuperscript{8} Provider surveys have shown reluctance to extend the screening interval beyond annual screening until very recently.\textsuperscript{8,11}

Clinicians in managed care organizations have been the most successful at increasing intervals.\textsuperscript{12} With all national organizations reporting consistent recommendations since 2012, the linking of reimbursement for clinical preventive services to one particular guideline (the US Preventive Services Task Force), and over a decade of co-testing use, more providers have reported moving towards longer intervals.\textsuperscript{13} 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.\textsuperscript{13} 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.9,10,15

"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

**MISSED 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

**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**

*Figure 1. Screening participation in the US in 2012.*

Source: Behavioral Risk Factor Surveillance System, 2012
As of today, few countries have introduced the HPV test as a primary screen into organized screening programs despite large-scale pilot studies. 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. 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.

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 that women who were disadvantaged and lower educated had higher anxiety that higher educated 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."

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.
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.

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 recruitment 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...
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. 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.

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.

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 RENEWAL OF AUSTRALIA’S NATIONAL CERVICAL SCREENING PROGRAM

A major review, known as Renewal, of Australia’s cervical screening program, was announced in November 2011. Its aim is “to ensure that all Australian women, HPV vaccinated and unvaccinated, have access to a cervical screening program that is acceptable, effective, efficient and based on current evidence.” In the first phase of Renewal, the Australian government’s Medical Services Advisory Committee (MSAC) commissioned a systematic review of the international evidence and modelled evaluation of health outcomes and 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."

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

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<tr>
<th>Primary screening test</th>
<th>Age range</th>
<th>Interval</th>
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<tr>
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<td>18-20 to 69 years</td>
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<tr>
<td>1 Conventional cytology</td>
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<td>IARC intervals</td>
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<tr>
<td>2 Manually-read LBC +/- HPV triage of LSIL</td>
<td>25-65 years</td>
<td>(3-yearly &lt; 50; 5-yrly 50+ years)</td>
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<tr>
<td>3 Image-read LBC +/- HPV triage of LSIL</td>
<td></td>
<td>5-yearly</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>
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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

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

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...
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.


an additional 7,300 recruited to allow for 10% of HPV negative women to be assigned to early recall for safety monitoring. The primary outcome will be cumulative CIN 3+ at 5 years, assessed on an intention-to-treat basis, following 5 year HPV exit testing round in both arms. Key secondary outcomes will include cross-sectional baseline confirmed CIN 2+ and CIN 3+ detection rates, and the rates of cumulative CIN 3+ in baseline screen-negative women at 5 years.

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.

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

VACCINATION

+ SCREENING

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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

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