



# Risk in Perspective

## NEW TECHNOLOGY PROVIDES ADDITIONAL OPTION FOR WOMEN WITH EQUIVOCAL PAP SMEAR RESULTS



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*“Compared with current practice of annual conventional Pap smear screening, shifting women to liquid-based Pap smears every 3 years and performing HPV DNA testing for women with ASC-US results will provide similar protection against cervical cancer and save the health care system more than \$20 billion dollars over the lifetime of a typical group of 18-24 year old women.”*



Jane Kim, M.Sc.

### Overview

In the U.S. mortality from cervical cancer has been reduced as a result of regular screening with Papanicolaou (Pap) smears. A Pap smear detects early precancerous abnormalities in cervical cells allowing a woman to be treated and cured before she develops full blown cancer. Currently, the 2 – 3 million Americans who receive an “equivocal or indeterminate” result on their Pap smear each year are followed in a variety of ways. Some are asked to return for repeat Pap tests twice within the following year. Others are advised to return for colposcopy, an invasive procedure in which a special magnifying scope is used to view the cervix and biopsy abnormal areas. Recent studies have suggested that a third strategy,

DNA testing to detect high-risk strains of human papillomavirus (HPV), the virus that causes cervical cancer, can more accurately identify those women in need of colposcopy and biopsy. This analysis was done to inform the development of national guidelines for how doctors should advise women who get abnormal Pap results. The key findings suggest that an automatic follow-up DNA test for HPV is a cost-effective way of reducing risk of cervical cancer, decreasing anxiety in women, and minimizing health care costs.

### Cervical Cancer is a Preventable Disease

Cervical cancer is a highly preventable disease. Like many other cancers, cervical cancer appears to evolve through a series of “steps” so that the earliest stage is not actually true cancer but a warning sign of possible cancer in the future. The terms “precancer”, “dysplasia”, and “squamous intraepithelial lesions” (SIL) all refer to the earliest changes that occur in cervical tissue prior to development of cancer.

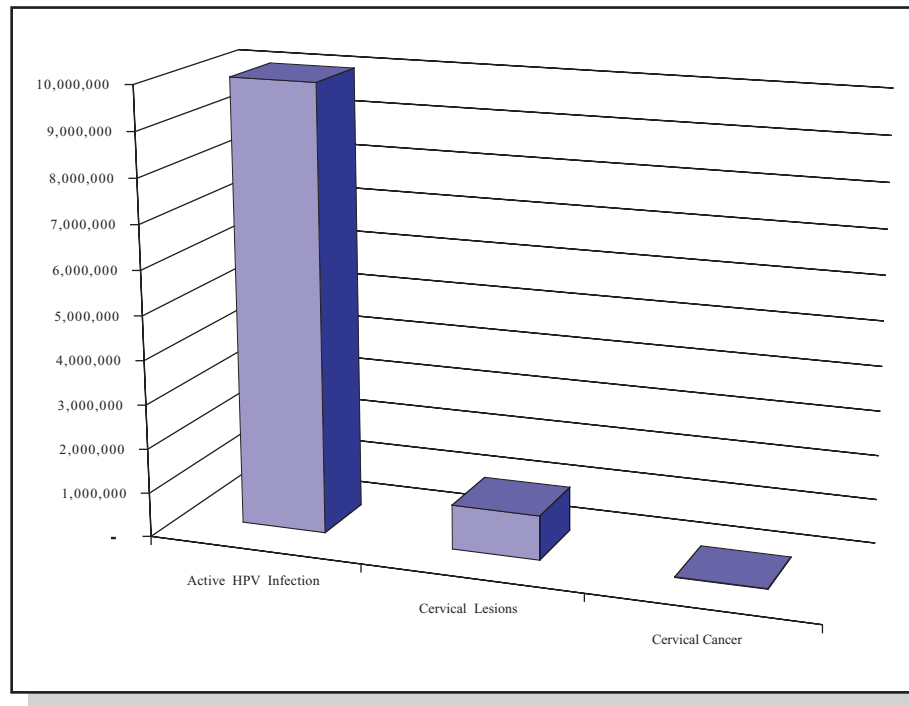
Cervical cancer is now known to be caused by high-risk types of HPV, a sexually transmitted virus that infects the

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## 2 New Technology Provides Additional Option for Women with Equivocal Pap Smear Results — continued

cells of the cervix. The vast majority of HPV infections are short-lived (e.g., 8 to 12 months) and do not result in precancerous lesions. In a very small number of women, the viral infection persists and can lead to the development of precancerous lesions. A very important fact is

that only a small proportion of precancerous lesions will progress to cancer, and the process can take up to 20 years. (Figure 1) This long lag period gives us ample opportunity to screen, detect, and remove the lesions, thereby preventing invasive cervical cancer.



### Cervical Cancer screening with Pap Smears

When a woman gets screened for cervical cancer, she undergoes a pelvic exam in which a sample of cells is obtained from her cervix. Her doctor may use a **conventional Pap smear** (cells are smeared onto a glass slide and immediately sprayed with alcohol fixative) or a **liquid-based Pap smear** (cells are dropped into a small vial of clear liquid preservative which eliminates some of the artifacts that may occur with the conventional method). The samples are then sent to a special laboratory where they are examined under a microscope. Laboratories in the U.S. use

a standardized nomenclature (known as the Bethesda System) to report results of abnormal Pap smears. When it is not possible to tell whether abnormal cells indicate precursors to cancer, or instead are caused by an infection or another cause of irritation, a diagnosis of “atypical cells of undetermined significance” (ASC-US) is made. We conducted a cost-effective analysis of different strategies to manage women with this equivocal result on their Pap smear.

### Decision Science and Cost-Effectiveness Analysis to Evaluate New Technology

How to invest health resources wisely, such that clinical benefits are maximized and opportunity costs are minimized, is a critical question in the context of new technology. In

addition to an intervention’s effectiveness, public health decision-making requires consideration of its feasibility, sustainability and affordability. No clinical trial or single

cohort study will be able to simultaneously consider all of these components. Decision analytic techniques using mathematical simulation models can be useful tools in evaluating alternative cervical cancer control strategies by extending the knowledge from empirical studies to real-world situations.

A cost-effectiveness analysis evaluates an intervention (e.g., cervical cancer screening

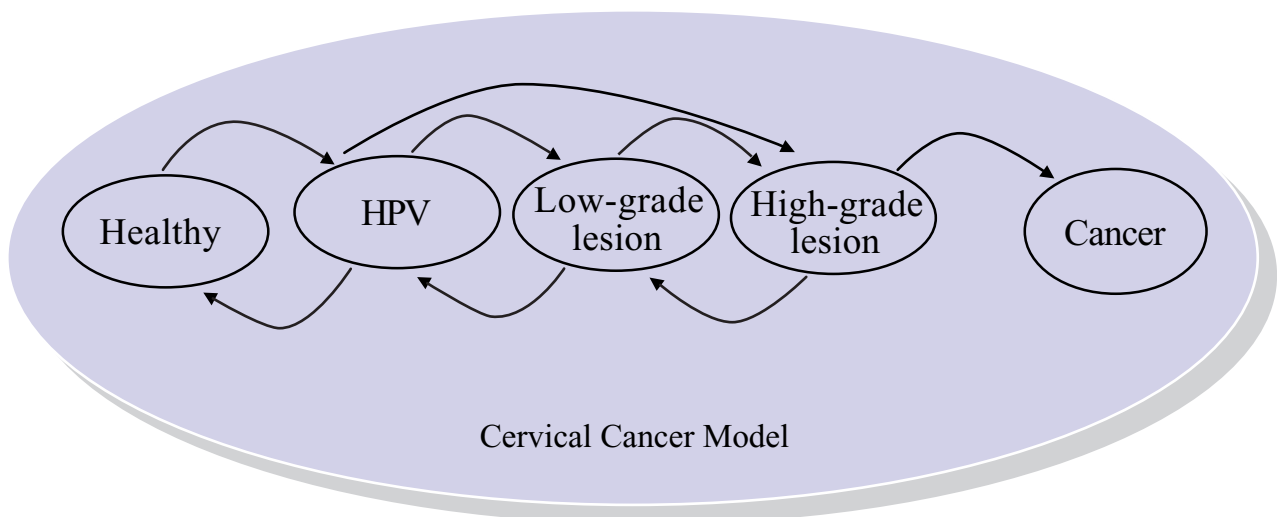
strategy) through the use of an incremental cost-effectiveness ratio. In this ratio, all health outcomes (compared to an alternative) are included in the denominator, and all costs or changes in resource use (compared to an alternative) are included in the numerator. This type of analysis defines the “opportunity cost” of choosing one strategy over another, and provides useful data to a wide range of policy makers in different settings.

### Cervical Cancer Model

We developed a computer-based model to compare the costs and benefits of different strategies to manage equivocal results (i.e., ASC-US) on Pap smears. The model uses information from a wide variety of scientific studies on the epidemiology of HPV and cervical cancer, the burden of other diseases in the population, the performance of different screening tests, and the

effectiveness of treatment. Many different kinds of costs are also included - direct medical costs (e.g., office visit, screening test), direct nonmedical costs (e.g., transportation costs) and patient time costs (e.g., work missed to get screened). Finally, the model also considers clinical information such as the likelihood of compliance with screening.

In the model, the natural history of cervical cancer is represented as a sequence of transitions among “health states”.



(Figure 2)

Health states are defined to describe each woman’s clinical condition, quality of life, prognosis, and resource utilization. The time horizon of the analysis incorporates each woman’s entire lifetime and is divided into equal monthly increments, during which women “transition” from one health state to another. For example, in each month, a woman may become infected with HPV, develop precancerous

cervical lesions, or progress to cancer. The model can be used to evaluate alternative screening strategies and takes into account how well each test works, how often they are done, and what happens after an abnormal test result. In our analysis, we assume that women with confirmed high-grade lesions are treated with standard procedures that are approximately 95% to 98% effective at preventing cancer.

### Follow-up Strategies

We evaluated three main options for women who receive an ASC-US result.

<p><b>1. Repeat Pap smears:</b> Women are asked to return for repeat Pap tests twice within the following year. Only those who continue to have equivocal results will be advised to undergo colposcopy.</p> <p><b>2. Immediate colposcopy:</b> Women are advised to return immediately for colposcopy, an invasive procedure in which a special magnifying scope is used to view the cervix and biopsy abnormal areas.</p>	<p><b>3. Reflex HPV testing:</b> The term “reflex” refers to the immediate availability of a cervical sample for HPV testing should an ASC-US result arise. As a result, women would not need to return to the office. If using liquid-based Pap smears part of the original sample obtained for the Pap smear can be used, if needed, for HPV testing. If using a conventional Pap smear, an HPV sample may be co-collected at the time of the initial screening.</p>
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Some advantages and disadvantages of each are shown in the table below.

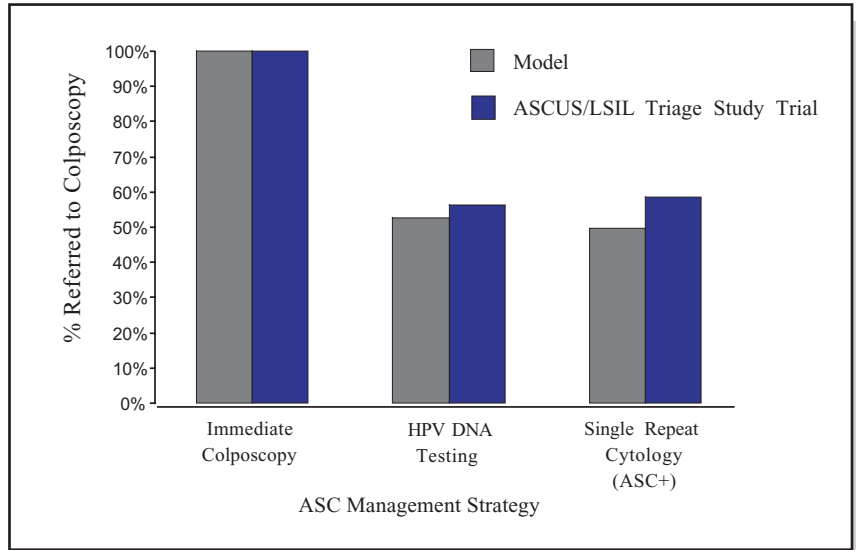
Strategy	Advantages	Disadvantages	costs*
<b>Repeat Pap Smear</b>	Avoid colposcopy	Prolonged period of worry and anxiety	\$146
<b>Immediate Colposcopy</b>	Result within one to two weeks	Invasive procedure, possible discomfort and bleeding, cost	\$436
<b>Reflex HPV testing</b>	Rapid reassurance if negative. Avoid Colposcopy.	Anxiety about having an infection with HPV, cost	\$100

\* Includes direct medical costs, transportation costs, and cost of a woman’s time.

### Face Validity of the Model

We used the model to project the age-specific prevalence of HPV, cervical precancerous lesions, and invasive cancer. We also used the model to predict the proportion of women who would require an invasive colposcopy with each of our screening strategies. These estimates were

then compared to the actual proportion of women referred to colposcopy in the ASCUS/LSIL Triage Study (ALTS), the largest randomized controlled trial of strategies for equivocal Pap results. **(Figure 3)**

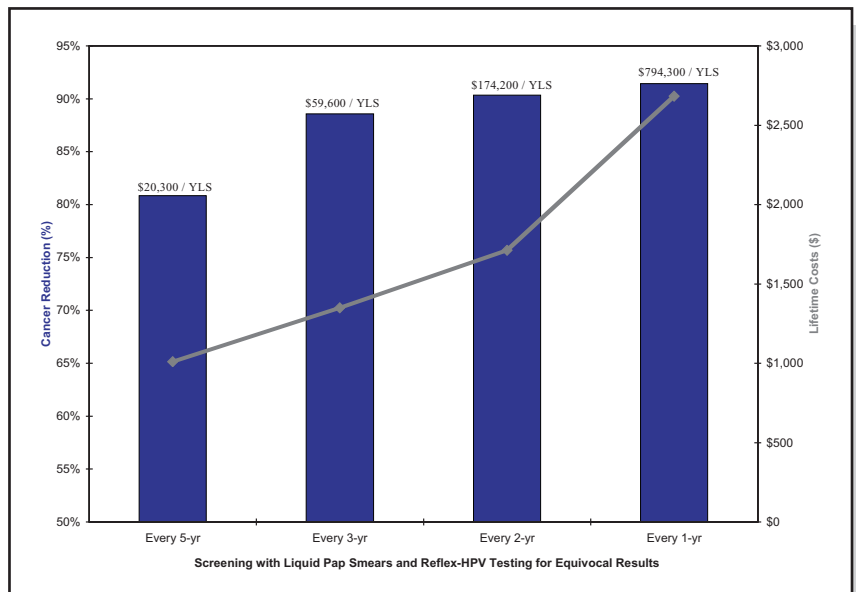


(Figure 3)

**Results**

Our results confirmed that some follow-up strategy for an ASC-US result is important. For example, if women are screened every 2 years but ASC-US results are ignored, (since many precancerous lesions resolve on their own) their lifetime risk of cancer is reduced by 79%. If these same women are screened every 2 years but ASC-US results are managed using either HPV testing, colposcopy, or repeat Pap testing, their lifetime risk of cancer is reduced by 86%, 87%, and 85%, respectively. While all three ASC-US follow-up strategies provide similar

clinical benefits, their costs vary substantially. Immediate colposcopy and repeat cytology are always more expensive than HPV testing. The HPV testing strategy eliminates the need for a repeat clinical visit and reduces the number of colposcopies by 40% to 60%, compared to immediate colposcopy. Regardless of whether liquid-based or conventional cytology was used, our results were stable even when we varied the baseline estimates of test performance, treatment effectiveness, and costs.



(Figure 4)

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**FOR FURTHER READING:**

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From the broad health policy perspective, an important question is how often a woman should get a Pap smear. **Figure 4** shows the relationship between the benefits (reduction of cancer incidence) and lifetime costs associated with different Pap smear screening frequencies. We assumed reflex HPV testing would be conducted for all ASC-US results. The graph shows that while reduction in cancer incidence (vertical bars, left axis) is similar with 1-, 2- and 3-year screening intervals, the total lifetime costs (horizontal line, right axis) increase dramatically with more frequent screening. The relationship between the incremental benefits and costs is formally described using an **incremental cost-effectiveness (CE) ratio** (shown on the graph above each strategy). The CE ratio for every 1-year screening exceeds \$500,000 per year of life gained, reflecting the dramatic increase in costs associated with increasing screening frequency

from every 2-years to every 1-year for an additional gain of only 4 hours of average life expectancy. In contrast, screening every 3 years has a cost-effectiveness ratio of \$60,000 per year of life gained, compared to the next best strategy.

While there is no consensus on the “acceptable cost per year of life gained,” cost-effectiveness ratios are often placed in context by comparing them to interventions that are considered well-accepted in the U.S. For example, annual breast cancer screening for women over 50 years of age costs between \$32,000 and \$120,000 per YLS, and hemodialysis for end-stage renal disease costs between \$60,000 and \$128,000 per YLS. Compared with well-accepted medical interventions, every 3-year screening, using liquid-based Pap and reflex HPV testing for ASC-US, appears to be a cost-effective approach to cervical cancer screening in the U.S.

## Conclusions

The 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities provide recommendations for evaluation and treatment that can prevent precancerous changes in the cervix from developing into invasive cancer. This past year, more than 100 experts in diagnosis and treatment of precancerous cervical lesions, including members from 29 professional organizations, were brought together by the American Society of Colposcopy and Cervical Pathology (ASCCP) to develop evidence-based recommendations. The results of this policy analysis contributed to the development of these national guidelines.

Compared with current practice of annual conventional Pap smear screening, shifting women to liquid-based Pap smears every 3 years and performing HPV DNA testing for women with ASC-US results will provide similar protection against cervical cancer and save the health care system more than \$20 billion dollars over the lifetime of a typical group of 18-24 year old women. Most importantly, HPV DNA testing can reduce the anxiety associated with returning for Pap smears every few months by providing women with rapid and accurate information about their current risk of invasive cervical cancer.

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