

New, molecular cervical cancer screening technologies: Results from PATH's START-UP project

Cervical cancer is a preventable disease affecting an estimated 530,000 women each year and leading to nearly 275,000 deaths.¹ If current trends continue, by the year 2050 there will be more than 1 million new cases annually.

Research conducted over the past 30 years established that human papillomavirus, or HPV, is the primary cause of cervical cancer. HPV infection is very common; the majority of men and women become infected within a few years after becoming sexually active.²

About 88 percent of women who die from cervical cancer live in developing countries.¹ The lack of effective screening and treatment programs in these countries is the main cause of this tragic health inequity.

HPV infection rates for women tend to be high during their teens and 20s. Most women spontaneously clear infections within a year or two, but in about 10 percent of women the infection persists, causing precancerous lesions to develop. If not detected through screening programs (and then treated), precancer develops into invasive cancer in about 10 percent of women with lesions (about 1 percent of all infected women).³

Ideally, all women over the age of 30 should be routinely screened for precancerous lesions of the cervix, but in reality only a small percentage of them are.⁴

Fortunately, cervical cancer does not develop quickly. The progression from infection to precancer takes 10 to 20 years, and from precancer to cancer another 10 to 20 years. Therefore there are many opportunities to stop the disease before it becomes fatal.

Wealthier countries have used Pap smears (cytology) for many decades to screen adult women for cervical precancer, and low mortality rates in those parts of the world support the value of regular screening. Many organizations have tried to introduce Pap in low-resource settings, but without good results. Unfortunately, to work well, Pap testing



PATH/R. Lord

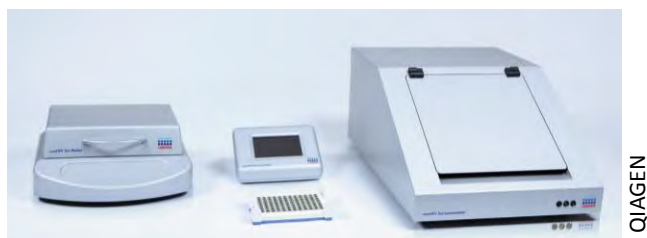
All women over the age of 30 should be routinely screened for precancerous lesions of the cervix, but in reality only a small percentage of them are. New screening and treatment options—like the **careHPV™ DNA Test** and the **OncoE6™ Cervical Test**—can help.

requires a good laboratory with highly trained cytotechnicians and other specialized staff, and because sensitivity of Pap is low (only about 50 percent), each woman must be retested regularly to increase screening impact. This creates a heavy screening burden for the country. Furthermore, Pap test results tend to be slow in coming; women often wait weeks or months to learn the results of their exam and this can result in “drop out”—when women who screened positive do not return for treatment (and who may succumb years later to invasive cervical cancer).

START AND START-UP: DEVELOPING OBJECTIVE, SENSITIVE SCREENING TESTS FOR CERVICAL CANCER

Over the past decade, several alternatives to Pap have been field tested and validated. One of the simplest and most affordable is visual inspection with acetic acid, or VIA. Studies have shown that VIA is in most cases more

sensitive than Pap. But like Pap, it is a subjective test and exam quality depends in large measure on the skill of the provider conducting the exam. That said, VIA is an excellent option for many low-resource settings.



The careHPV™ DNA test was designed especially for use in low-resource settings.

HPV testing is another of the new alternatives. It detects the presence of HPV DNA in a woman's cervical or vaginal mucus. Global health experts recommend use of HPV DNA testing for primary cervical cancer screening, noting that it is much more sensitive than either cytology or VIA. Unfortunately, until recently HPV testing was too expensive and the equipment too unwieldy and fragile for most low-resource settings.

PATH, working with private companies, decided to change that.

In 2003, PATH launched the Screening Technologies to Advance Rapid Testing (START) project with support from the Bill & Melinda Gates Foundation. The project sought to develop two different HPV screening methods appropriate for use in the developing world. It was important that the tests be acceptable to women and their health care providers, relatively simple to use, accurate, affordable, and rapid, to allow for single-visit efficiencies.

By the time the project ended in 2008, START had developed a test based on the more complex Hybrid Capture II HPV DNA test, produced by QIAGEN. Most HPV tests are not suitable for low-resource settings because of the requirement for sophisticated laboratory equipment, refrigeration, and other resources. But the new *careHPV™* test is compact (the full set of instruments fits on a desktop), it does not require running water or a controlled-temperature environment, its reagents do not require refrigeration, it detects 14 oncogenic (cancer-causing) HPV types, and results are available in less than three hours. Test results are easy to read and, unlike Pap and VIA, are not vulnerable to misinterpretation.

The second test developed under the START project—called the OncoE6™ cervical test—does not look for HPV DNA; rather it detects the E6 protein associated with the

three most common oncogenic HPV types. E6 signals that cells have actually become precancerous (or cancerous). A test for E6 is particularly useful because it allows clinical staff to identify and treat women at highest risk of disease.

PATH recognizes that challenges exist to widespread adoption of new technologies. Before incorporating tests into national cervical cancer prevention strategies and plans, ministries of health need evidence that the tests are feasible and appropriate for their health-system infrastructure and their geographic, cultural, and economic circumstances.

To address these challenges, in November 2007 PATH inaugurated a follow-up project to START, called START-UP (also with support from the Bill & Melinda Gates Foundation). START-UP focused on conducting field assessments of *careHPV™* in India, Nicaragua, and Uganda, examining the potential for using vaginal, rather than cervical, sampling (thereby eliminating the need for a pelvic examination—which can be difficult to obtain in some settings—and offering the option for women to self-sample). START-UP also assessed the clinical performance of the OncoE6 test.

CareHPV™ AND ONCOE6 TEST RESULTS

The START-UP studies concluded that, using either cervical or self-collected vaginal specimens, *careHPV™* (an objective test) had better clinical performance than the subjective tests it was compared against: VIA and Pap. While using *careHPV™* with cervical samples offered the best performance (sensitivity of 81.5 percent), using *careHPV™* with vaginal samples can increase access to services because it does not require a pelvic examination. However, vaginal sampling results in somewhat lower sensitivity (about 10 percent less than using a cervical sample).

VIA and Pap sensitivity were considerably lower than *careHPV™* sensitivity—59.8 percent and 58.4 percent, respectively.

The OncoE6 test results from China also were encouraging, showing 53.5 percent sensitivity for precancerous lesions with the current version, which tests for HPV types 16, 18, and 45.

While *careHPV™* is currently being sold by QIAGEN, the OncoE6 test is not yet on the market (April 2013).

THE PROMISE OF VAGINAL SAMPLING

Vaginal self-sampling and assisted vaginal sampling have important implications for future programming because they

could dramatically increase access to screening for many women worldwide. For example, field outreach teams could give self-sampling kits to women when visiting villages and ask them to return the samples to the clinic later (or the team could pick them up on a return visit). Even in a clinical setting, women could be trained to sample correctly and be given a private place to do so, speeding sample collection. And if a woman did not feel comfortable collecting the sample herself, a nurse, nurse’s assistant, or female “health helper” could be trained to collect vaginal samples from the women without a speculum or pelvic evaluation (this is called “assisted vaginal sampling”), freeing up the time of higher-level clinic staff and increasing screening rates.

It is easy to imagine teams of trained, lay village health assistants gathering hundreds of vaginal samples in a day, with clinic staff processing the samples overnight and returning the following day to seek out women who had tested positive. Such strategies could have a major impact on finally achieving national-scale screening coverage in low-resource settings.

Vaginal self-sampling and assisted vaginal sampling...could dramatically increase access to screening for many women worldwide.

KEY LESSONS LEARNED THROUGH START-UP

- Both providers and clients valued the fact that HPV DNA testing is much more sensitive than VIA or Pap.
- *CareHPV™* provides good results with either cervical or vaginal specimens in low-resource settings (though sensitivity when using cervical samples is higher).
- HPV DNA and other molecular tests are more objective than VIA or Pap and therefore less vulnerable to user error.
- *CareHPV™* results are available much more rapidly than Pap results, but because *careHPV™* requires two to three hours to produce results, and because samples likely will be batched for testing to save money, HPV DNA is less amenable than VIA to same-day screen and treat strategies.
- Because the evidence supporting HPV DNA testing is relatively new, health professionals in lower-resource settings may not be aware of the data and may not readily accept it. They may perceive HPV DNA testing as inappropriate or as too high-tech for their setting.
- Countries should consider developing a VIA-based screening platform now. Later they can introduce HPV DNA or other molecular tests and then use VIA for treatment selection.
- In cases where it would be culturally appropriate, clients can be taught to collect a vaginal sample themselves, in a private space at the clinic or at home. Assisted vaginal sampling is also a good option.
- Vaginal sampling is rapid and convenient, both for women and for providers. It avoids the discomfort associated with pelvic exams.
- Many women report that self-sampling was less embarrassing than exposing themselves during a pelvic exam. However, some patients reported that they did not like touching their genital area.
- In general, patients felt that self-sampling was easy to do once it had been explained to them clearly. Most said it was not painful. Some—a minority—said that they were concerned about hurting themselves.
- Some women had concerns about not sampling correctly. They were afraid that the sample might become contaminated or otherwise unsuitable. They worried that they “could not see down there” and they felt that a trained provider could collect a sample more reliably. They accepted self-sampling when they were reassured that the sample they collected would suffice for the test.
- Obese women may have trouble reaching their genital regions and may need the provider to obtain a sample (either cervical or vaginal).
- Some women worried about pushing the sample collection brush in too far. And when some women heard the word “brush,” they assumed that the sample collection brush is coarse or stiff like a toothbrush or hairbrush. To reduce concerns about hurting themselves during self-sampling, PATH staff showed women the brush ahead of time and let them feel how soft it was on their arms.

EXPANDING SCREENING SERVICES

While VIA and *careHPV*TM provide exciting alternatives to Pap, very few low-resource countries have trained sufficient staff to roll out screening programs at national scale. Considerably more training needs to be done, along with continuing supportive supervision in the field.

To help meet this need, in 2009 PATH and Jhpiego teamed with the National Cancer Institute of Peru (INEN) to create a “Training Excellence Center” (TEC) for VIA and cryotherapy. A TEC can serve as a resource for governments and ministries of health ready to scale-up services. TECs not only provide structured, competency-based training, but also support all aspects of a cervical cancer screening and treatment program to ensure quality and sustainability. They show tremendous promise for the development of quality cervical cancer prevention programming in the settings that need it most. The first TEC was designed to serve Peru and other countries in the region. Clinicians and trainers from Bolivia, Colombia, Nicaragua, and Peru received classroom and field training from INEN, and spin-off training centers have been inaugurated in two of the countries.

Currently, PATH is working with the Uganda Cancer Institute in Kampala to create a similar TEC for Africa.

CONCLUSION

Data generated over the past decade by PATH and other partners clearly demonstrate that alternatives to Pap, such as VIA and HPV DNA testing, work well and are acceptable to providers, female patients, and their families.

Ministries of health and NGOs should add VIA and precancer treatment to their clinical offerings as soon as possible—the program will begin saving lives immediately. And once *careHPV*TM and the OncoE6 test become broadly available, those tools can replace VIA for primary screening (because they are more sensitive). At that point, VIA can be used for cervical visualization and treatment selection for women who received positive results from the molecular tests. In this way, ministries can “work smarter” and more efficiently by allocating VIA pelvic exam resources to the women who need them most.

PATH and the START-UP team are proud of our contributions to the evolving science of improved cervical cancer prevention.

We look forward to the day when every woman, no matter where she lives, has access to high-quality cervical cancer screening and treatment services.

For more information:

- START and START-UP have published a number of scientific papers detailing study methods and results. Search the PubMed database or Google to find the papers.
- PATH’s RHO Cervical Cancer Library gathers the best global resources on cervical screening and HPV vaccination. Visit the library at www.rho.org.
- Contact PATH at info@path.org.

- ¹ Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. *Cancer Incidence and Mortality Worldwide*. . GLOBOCAN 2008 V1.2, International Agency for Research on Cancer; 2010. Available at: <http://globocan.iarc.fr/>.
- ² World Health Organization. *Comprehensive Cervical Cancer Control: A Guide to Essential Practice*. Geneva: World Health Organization; 2006.
- ³ PATH. *Progress in Preventing Cervical Cancer: Updated Evidence on Vaccination and Screening*. May 2010. Report No. 27.
- ⁴ Sherris J, Wittet S, Kleine A, et al. Evidence-based, alternative cervical cancer screening approaches in low-resource settings. *International Perspectives on Sexual and Reproductive Health*. 2009;35(3):147–154.



PATH is an international nonprofit organization that transforms global health through innovation. We take an entrepreneurial approach to developing and delivering high-impact, low-cost solutions, from lifesaving vaccines and devices to collaborative programs with communities. Through our work in more than 70 countries, PATH and our partners empower people to achieve their full potential.

MAILING ADDRESS
PO Box 900922
Seattle, WA 98109 USA

info@path.org
www.path.org

STREET ADDRESS
2201 Westlake Avenue
Suite 200
Seattle, WA 98121 USA