Investing in Cervical Cancer Screening:
A Point of Care HPV Diagnostic Test to Reduce
Cervical Cancer Deaths in Developing Countries

Prepared for Global Good
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Acronyms

AIDS       Acquired Immune Deficiency Syndrome
DALY       Disability-Adjusted Life Years
GSK        GlaxoSmithKline
HICs       High Income Countries
HIV        Human Immunodeficiency Virus
HPV        Human Papillomavirus
HR-HPV     High-Risk HPV
HRS        High Resource Settings
LBC        Liquid Based Cytology
LMICs      Low and Middle Income Countries
LRS        Low Resource Settings
LTFU       Loss to Follow-Up
NIH        National Institutes of Health (U.S.)
PAHO       Pan American Health Organization (WHO Regional Office)
POC        Point of Care
STIs       Sexually Transmitted Infections
TPP        Target Product Profile
VIA        Visualization of the cervix using Acetic Acid
WHO        World Health Organization
Executive Summary
No woman should die of cervical cancer; it is one of the most preventable diseases in the world. Globally, about one billion women are 30-49 years old, the target age group for cervical cancer screening and at highest risk for cervical cancer, yet it is estimated that over one million women worldwide have undiagnosed cervical cancer. This disease is deadly, particularly for women in low-resource settings (LRS), because Human Papilloma Virus (HPV), a sexually transmitted infection (STI), often goes undetected and progresses into precancer and, if left untreated, ultimately into invasive cancer. The impact of cervical cancer affects women, their families, and communities, disrupting the economic and social stability that women as heads of households, economic contributors, and caretakers often provide. Another 550 million women are 20-29 years old and will be of screening age in the next two decades. Without adequate attention and investment in appropriate screening and treatment approaches, deaths due to cervical cancer are projected to rise by approximately 25% over the next decade, highlighting the need for improved HPV diagnostics and better treatment options.

Cervical cancer mortality rates have fallen in many higher income countries (HICs) during the past 30 years, largely due to widespread screening and treatment services. Over this same time period, rates in low and middle income countries (LMICs) have risen or stagnated. This is primarily due to limited access to health services, low coverage of screening and treatment programs, high HIV/AIDS burden, and lack of awareness of the disease and how to prevent it. Invasive cervical cancer is an AIDS defining illness; cervical cancer is the most common cause of cancer death among women in sub-Saharan Africa, home to the majority of HIV infections. Despite the large burden of disease, only 20–40% of HIV-infected women are screened for cervical cancer; 10–30% of HIV positive women are found to have lesions requiring treatment, and less than 10% receive appropriate therapy.

In high-resource settings (HRS), the standard approach for cervical cancer screening is through routine cytology (Pap smear) or, increasingly, HPV diagnostic testing followed by colposcopy and close monitoring of women to ensure their disease does not progress, and provision of treatment as appropriate. Cytology-dependent services are not pragmatic in LRS, where loss to follow up (LTFU) is more challenging, trained pathologists are scarce, and service quality is problematic. The alternative recommended for LRS by the World Health Organization (WHO) is to use a ‘screen-and-treat’ approach in which, ideally during a single visit, a woman is screened for cervical cancer, and treatment is provided after a positive result. Achieving adequate
coverage of screen-and-treat programs in LRS is heavily dependent upon an accurate and affordable diagnostic, in which there is a considerable gap.

The landscape of technology focused on cervical cancer is emerging and is indeed promising, with some diagnostic tests for HPV gaining footholds in LMICs, and the potential of new treatment technologies to accompany better diagnostics. However, the widespread availability of an affordable HPV test remains low. Existing diagnostics are either difficult to use or too expensive to procure for most LMICs.

**Global Good** is a collaborative effort between Bill Gates and Intellectual Ventures focused on inventing, developing, and deploying commercially-viable technologies that improve health and quality of life in developing countries. Global Good and **QuantuMDx**, one of the world’s most innovative companies dedicated to improving and democratizing global health by providing transformative diagnostics to overburdened healthcare systems, have joined forces to develop a point of care (POC) HPV test to address these rural and low-throughput needs in LRS, focusing on a short time to result and simplified platform technology. The goal of this partnership is to create a solution that can integrate into cervical cancer screen-and-treat programs in a manner that is both cost-effective and scalable in LRS.

Global Good and QuantuMDx share a commitment to achieve a clinically relevant POC HPV solution specifically for LRS and to generate sufficient evidence for the scalability of the solution within a variety of health care environments. They will conduct phased field trials and research activities to demonstrate the following:

- The new testing option will increase the coverage of women screened for HPV, which causes virtually all cases of cervical cancer;
- The clinical and technical performance of the Global Good/QuantuMDx solution is superior to those that currently exist; and
- The health system requirements for adoption and sustainability of such a solution are well defined.

Global Good and QuantuMDx seek collaboration and investment support from donors and governments committed to scaling up the critical intervention of screen-and-treat programs for cervical cancer in LMICs. This would require adequate funding to ensure that, in addition to the procurement of the technology for use in LRS, there would be commensurate investment into expanding the knowledge and awareness of HPV testing generally – and the new POC HPV test specifically – among different cadres of health care providers, administrative workers, and community leaders engaged in HPV screen-and-treat services.
Despite being one of the most addressable diseases and cancers, cervical cancer programs have been underrepresented in the global discussions about women’s health, and diluted in the agenda for reproductive health. Women are pillars of communities and economies, yet are vulnerable to the silent killer of cervical cancer in the absence of life-saving screening and treatment interventions. There is tremendous opportunity to positively impact the burden of cervical cancer in LRS by continuing to support clinical, scientific, and technological advances that can improve prevention and detection and treatment.
The Global Disparity in Cervical Cancer

The Burden of a Preventable Disease
Cervical cancer is the fourth most common cancer affecting women globally. In 2015, nearly 300,000 women died of cervical cancer, and mortality is increasing. The World Health Organization (WHO) estimates that, by 2030, about 443,000 women will die each year from cervical cancer. Though one of the most preventable cancers and diseases in the world, cervical cancer is also one of the most fatal for women living in LRS; it is estimated that 80% of cervical cancer cases and 95% of cervical cancer deaths occur in LRS. In high HIV burden areas, the magnitude of the problem is much higher. HIV positive women are about 5 times more likely to develop cervical cancer because their low immune resistance prevents them from fighting off the virus. They also progress more quickly to invasive cancer, making cervical cancer screening for HIV positive women more urgent.

Figure 1: Estimated Age Standardized Mortality Rate for Cervical Cancer-Global 2012

The stark contrast in disease mortality between LMICs and HICs (Figure 1) highlights that cervical cancer is indeed a preventable, addressable disease. The success of screen-and-treat programs in HRS demonstrates that the disease can be controlled. However, the diagnostic strategies utilized in such settings are not suitable for more resource-constrained settings that have struggled to develop quality, sustainable screen-and-treat programs.
A closer look at select representative countries and regions (Figure 2) further underscores the urgency of addressing cervical cancer more effectively, with LMICs showing higher rates of prevalence (except in China) and higher rates of mortality, suggesting that the disease is going undiagnosed and/or untreated.

**Figure 2: Cervical Cancer Incidence, Prevalence, and Mortality in Select LMICs**

![Graph showing cervical cancer incidence, prevalence, and mortality in select countries.](image)


### Cervical Cancer Concentration in High HIV Burden Settings

Cervical cancer is the most common cause of cancer-related death among women in sub-Saharan Africa, home to the majority of HIV infections, accounting for 71% of the people living with HIV worldwide. HIV is associated with a higher prevalence of persistent infection with high-risk human papillomavirus (HR-HPV) subtypes – some subtypes of HPV are more oncogenic, or cancer-causing, than others. High burden HIV areas compound the risk and the burden of higher cervical cancer incidence and related mortality. HIV infection is also associated with a higher incidence of precancerous cervical lesions and accelerated progression of these lesions to invasive forms of cervical cancer. In spite of the large burden of disease, only 20–40% of HIV-infected women are screened for cervical cancer, 10–30% of HIV positive women are found to have lesions requiring treatment, and less than 10% receive appropriate therapy.
Investing in HIV prevention and treatment therefore must incorporate cervical cancer screening as a resource-effective way to minimize this compound effect. Cervical cancer prevention programs targeting HIV-infected women have a dual challenge to identify and treat a disease that progresses more rapidly and recurs more frequently than in the general population."

"Today women are surviving an HIV diagnosis only to succumb to avoidable cervical cancer. The need for concerted efforts in responding to the ‘double burden’ of HIV and cervical cancer is warranted now more than ever! We need to increase the coverage of cervical cancer screening services, especially for women living with HIV, link eligible women to early treatment, and make the HPV vaccine accessible to all eligible girls. Let us all do our part and humanity will thrive."

- Gertrude Mutharika
  First Lady of Malawi and Vice-President of the Organisation of African First Ladies Against HIV/AIDS

**Disease Pathway of HPV**

Ninety-nine percent of cervical cancer cases are caused by HPV infection, which is the most common sexually transmitted infection (STI) worldwide. Most sexually active persons acquire HPV, but the majority of HPV cases clear without clinical complications or intervention. A much smaller proportion of cases progress to cervical cancer within 10-15 years, although progression is faster in HIV positive women. HPV vaccines have been available for nearly a decade, but they have only recently begun to reach LRS and do not protect women who are currently infected with HPV and at risk for developing cervical cancer.

Abnormal cell morphology, classified by cervical intraepithelial neoplasia (CIN) grade, and the progression to cervical cancer, result from infection with specific HR-HPV subtypes. There are specific HPV subtypes, about 15 of which are classified as oncogenic HR-HPV. These HR-HPV subtypes account for about 98% of all cervical cancers worldwide, three of which are the most common – subtypes 16, 18, and 45 even with some regional variation. CIN is a premalignant lesion that may exist at any one of three stages: CIN1, CIN2, or CIN3. If left untreated, these lesions may continue to develop and can progress to cervical cancer. HPV infection can linger over many years and may eventually lead to cervical and other cancers. As depicted in Figure 3, there are crucial windows of opportunity between HPV infection and CIN 1 through CIN 2, in which HPV detection can avert progression into severe cervical dysplasia and invasive cancer.
Figure 3: Overview of Programmatic Interventions Over the Life Course to Prevent HPV Infection and Cervical Cancer


(More detail about the HPV genome as it relates to diagnostic targets is available in Appendix 1.)

Continuum of Interventions for Addressing Cervical Cancer in LRS
The ability for any country to reduce the burden of cervical cancer mortality and morbidity relies on four key interventions:
(1) Primary prevention through HPV vaccination and prevention of STIs;
(2) Screening (secondary prevention), either with HPV testing, Visual Inspection of the cervix with Acetic acid (VIA), or, where available, cytology (Pap smear);
(3) Visualization of the cervix (which can be also be done through VIA) to determine treatment options; and
(4) Treatment with ablative therapy such as cryotherapy, or cold coagulation or excision using Loop Electrosurgical Excision Procedure (LEEP) and referral for more invasive cancers.

While appropriate integration of these four interventions is critical, there are important factors related to primary prevention (vaccination) and visualization and treatment that highlight the significance and urgency of screening (secondary prevention), which will be discussed in greater detail in the following section.

**Primary Prevention: HPV Vaccines and the Long-Term Promise**
Since 2006, vaccines to prevent HPV infection have been available from Merck (Gardasil and Gardasil 9) and GSK (Cervarix). In LMICs, however, these HPV vaccines still are not widely available. Primary challenges in scaling up HPV vaccination in LMICs are the cost of programmatic implementation, and issues within the supply chain and health system planning. WHO updated their HPV vaccine position paper in October 2014, and now it recommends a 2- dose vaccine schedule for girls between 9 and 15 years old. Gavi, the Vaccine Alliance, is aiming to fund vaccination of over 30 million girls in more than 40 LMICs by 2020. If and when LRS are able to achieve comparable HPV vaccination coverage, they could potentially see reductions in the incidence and prevalence of cervical cancer comparable to those found in HRS, but that coverage is decades away. Importantly, broader STI prevention interventions which include abstinence, partner reduction, male circumcision, and appropriate use of condoms can also reduce HPV infection but perhaps only marginally without concurrent efforts in increasing HPV vaccination coverage.

**Secondary Prevention: Screening through HPV Testing or Visual Inspection of Cervix using Acetic Acid (VIA)**
The two predominant ways to screen for cervical cancer are by HPV testing or by VIA. A key innovation for addressing cervical cancer in low resource settings has been the use of acetic acid (or Lugol’s Iodine) for visual inspection of the cervix. This has wide coverage in LRS in part due to the low cost of acetic acid, and in part due to the absence of a more scalable HPV test suitable for rural and low-volume health settings. (Further detail provided in following section about cervical cancer screening generally, and HPV testing specifically.)
Visualization of the Cervix Using Acetic Acid (VIA) for Treatment Decision-Making

Once a screening test is positive, the woman’s cervix should be visualized prior to treatment to identify and assess lesion(s) to determine the best course of treatment. VIA is used for screening and also used for visual inspection of lesions to determine treatment. Visual inspection for treatment decisions can be further enhanced through better optics, and is critical to differentiate precancerous lesions from more invasive cancers and to triage the appropriate treatment or referral algorithms. In LRS, VIA has been an important approach for detection of cervical precancerous lesions and for visualization for treatment decisions, but has significant shortcomings as a highly impactful approach to cervical cancer screening in LRS. HPV testing offers an important alternative to VIA to the extent such a test can be affordable and scalable even at lower levels of healthcare systems.

Treatment: Emerging Technologies Only as Impactful as Effective Screening

Screening and treatment are mutually dependent, both only as impactful as the effectiveness and availability of the other. Scaling up screening is critical to the extent that there are reliable and accessible treatment modalities for those identified with precancerous lesions, and there are referral systems for more invasive cancers. Conversely, improving treatment technology and availability must be paired with reliable screening programs. For precancerous lesions visible to the health worker, ablation using cryotherapy is the standard treatment recommended by WHO to necrotize the cancerous tissue. There are emerging improvements in treatment technology, including in cryotherapy, thermal coagulation, and even topical ointments and antivirals that may prove effective and more affordable. For more advanced lesions, loop electrosurgical excision procedure (LEEP) is the most effective treatment to excise the cancerous tissue, but it requires a trained physician and surgical facilities. The global health community anxiously awaits improved and affordable cervical cancer treatment technologies, and should make commensurate investments in HPV screening to maximize coverage and impact.

All interventions described above are essential, and dependent on the effectiveness and scalability of the others in order to stall the disproportionate effect of cervical cancer in LRS. The epidemiology and quiet disease progression from HPV to precancer and more invasive cancer is important when considering the returns on investments in addressing cervical cancer, for which primary and secondary prevention have the potential for high yield if paired with effective treatment.
The Opportunity to Make an Impact through Cervical Cancer Screening

Experts estimate that there are one billion adult women today who have not received the HPV vaccine and have not been screened for cervical cancer. WHO recommends that women in LRS should be screened at least once from 30 to 49 years, but ideally every 5 to 10 years for women starting at age 30. HIV positive women should be screened every three years according to WHO. In a seminal study of HPV screening in 57 developing countries, the percentage of women screened in LMICs, was 19 percent compared to 63 percent in HICs. Accelerating the coverage of the HPV vaccine and the availability of affordable and effective treatments are critical, but in the absence of improved HPV screening and detection, it will remain difficult to bend the curve in the cervical cancer burden.

WHO Recommended Approach: Screen-and-Treat

Screening is the critical anchor of successful cervical cancer management due to the silent nature of HPV and the slow progression of precancerous lesions. Cervical cancer screening is testing for precancerous lesions and cancer among women, including those who may have no symptoms and feel perfectly healthy. The approach recommended by WHO for LRS is to use a ‘screen-and-treat’ approach in which, ideally during a single visit, the treatment decision is based on a cervical cancer screening test and treatment is provided after a positive result. Screening for HPV infection provides a secondary level of prevention, giving effective treatment a window to halt progression of precancer to more invasive cancer. Early stage cancer is easier, cheaper, and more effective to treat than later stage cancer, so routine screening increases the likelihood of “downstaging” disease identification, or decreasing extent of a tumor.

There are three different types of screening tests currently available, with unique characteristics and inherent challenges for LRS: (1) conventional (Pap smear) test and liquid-based cytology (LBC); (2) VIA to visualize precancerous lesions and determine appropriate treatment modalities, and (3) diagnostic testing for HR-HPV. In LMICs, cytology-dependent services are very difficult to implement, and programs tend to have low sensitivity, high costs, and long wait times. WHO recommends that countries that do not have an effective cytology program in place not start one.
The current standard of care in most LRS is VIA, where the health worker applies diluted acid (table vinegar) onto the cervix during a pelvic exam and, within a few minutes, precancerous and cancerous lesions will turn white. This is a cost-effective alternative to more expansive screening options, particularly where countries cannot afford HPV tests, because the components and consumables for VIA are very inexpensive and readily available, and the test can be performed proficiently by nurses. There is some disagreement among experts about sensitivity and specificity of VIA programs; sensitivity is usually moderate and specificity tends to be low relative to HPV diagnostics. In the absence of a higher performing and more affordable HPV test, screening with VIA remains an essential intervention within screen-and-treat programs, and the only option for many LRS. Hence this underscores the importance of innovation in low-cost HPV diagnostics.

Loss to Follow-Up (LTFU)- A Pragmatic Consideration in Screen-and-Treat Programs for Cervical Cancer

Screening programs that require women to return multiple times for results of tests are impediments to effectiveness of screening, regardless of type. The primary benefit of screening is derived when women with positive test results and precancerous lesions are identified and treated in a single visit. In LRS, where follow-up visits were scheduled for more than four weeks after initial visit, LTFU can range up to 80%. (Gaffikin, Blumenthal et al 2003 and Doh AS et al, 2005, Goldfaber et al 2005).

Efforts to reduce LTFU and to maintain it at an acceptably low level thus are a key part of cervical cancer screening programs and drivers of developing an effective POC diagnostic for HR-HPV that can be used in screening (secondary prevention). Many existing diagnostics require batch processing or long run times, which preclude WHO’s recommendation for a single visit approach and lead to more LTFU.

Unmet Need in Cervical Cancer Screening: The Imperative for an Improved HPV Diagnostic

There are significant societal costs associated with women dying of a preventable disease like cervical cancer, including loss of economic productivity and shifting economic burden of childcare to other family members and society. The biggest impacts of cervical cancer are on poverty, education, and gender equity – the first three United Nations Millennium Development Goals (MDGs). Many of the women who die of cervical cancer play a significant economic and caretaking role of children and elders; women are heads of household in one-third of all households in sub-Saharan Africa. xii Though not all women who die of cervical cancer are mothers or mothers of
newborns, the loss of a female head of household can cause a “chain of disruption” in a household. This generates increased demands of household work and childcare that interrupt others’ time on economic activities, not to mention the emotional trauma. Cervical cancer screening is one of many public health issues competing for resources in developing countries. Cost-effectiveness thresholds vary by setting, and traditional measures of life expectancy and DALYs (disability-adjusted life years) from cervical cancer screening have inherent limitations given the target population of women of reproductive age who tend to die of cervical cancer later in life. The consequences of female mortality, particularly of mothers, span from newborn and infant survival, to childcare and schooling, and disruption of daily household activities and emotional burden borne by loved ones and extended family.

Figure 4 shows countries in which screening has been implemented at the national level, revealing a wide disparity in the current coverage percentage (i.e., the number of eligible women who are screened). Only 5% of eligible women are screened in India, while China screens approximately 40% of eligible women. In Central America, Honduras has the lowest cervical cancer screening coverage at 26% whereas El Salvador has a coverage rate of 67%. In South America, a similar range exists, with Brazil screening 80%, and Ecuador screening only 24% of eligible women. Very few LMICs achieve coverage rates comparable to or higher than OECD countries.

Figure 4: Cervical Cancer Screening Coverage in LMICs

The maps below show the discrepancy between the introduction of VIA programs and the introduction of HPV testing programs, with LMICs (particularly in sub-Saharan Africa) having very low HPV testing penetration relative to HICs, especially in Latin America.
America. Better HPV testing will enable health systems to identify and shift the focus and resources to the population infected with HR-HPV, while providing greater reassurance for those who test negative. Achieving this requires a more affordable POC HPV test to integrate into their screen-and-treat programs.

Introduction of VIA programs and HPV programs in Low Resource Settings

VIA Screening Programs

Many countries in Latin America, Africa, and South Asia have introduced VIA screening as the approach for cervical cancer screening, likely due to resource constraints and the availability of an HPV test that is both affordable and suitable for LMICs. HPV screening, as shown below, has gained some traction in HICs but at a slower pace among LMICs.

Source: Cervical Cancer Action: Progress report card 2015
Several clinical and economic studies have suggested that one- and two-visit screen-and-treat approaches using VIA or HPV DNA testing can be feasible, beneficial, and cost-effective in low-resource settings.\textsuperscript{xiv} HPV diagnostic testing is associated with higher sensitivity than VIA to detect precancer,\textsuperscript{xix}xvi yet VIA is associated with programmatic advantages, including lower costs and the ability to screen-and-treat within a single visit. For countries that have sufficient resources, WHO recommends HPV testing over any other cervical cancer screening method.

The Enabling Environment: Important Programming Considerations
Despite being one of the most addressable diseases and cancers, cervical cancer programs have been underrepresented in the global discussions about women’s health, and diluted in the agenda for reproductive health. The cervical cancer community is mostly comprised of advocates and implementers from the cancer and non-communicable diseases (NCDs) arenas. This can misrepresent the compelling need and opportunity to frame HPV as a preventable and treatable sexually transmitted infection before it becomes cancer. Unless donors and governments support integrating cervical cancer screen-and-treat programs into other vertical programs, it becomes a separate program that is difficult to “add-on” to existing services, even though it is potentially very cost-effective to do so. There are some...
opportunities to better position cervical cancer screening, particularly in high-prevalence HIV areas\textsuperscript{xvii}, and in HPV vaccination efforts, moving the needle of HPV and cervical cancer more central to a comprehensive reproductive health agenda. Some awareness and action to integrate HPV/cervical cancer programs into reproductive health programs has begun in a few countries, such as Tanzania and Zambia, and countries in Latin America are paving the way for greater coverage and integration of cervical cancer into other health services.

There is a significant gap in reliable funding sources to support the implementation and scale up of cervical cancer screen-and-treat programs. Traditionally, donors have either not understood the scale of the problem, or been reluctant to fund cancer programs. Many donors are concerned that funding programs targeting NCDs, even those like cervical cancer caused by an infectious agent, will increase their obligations beyond their abilities. Cervical cancer tends to kill when women are in their 30s and 40s in sub-Saharan Africa, and later in HRS but the ripple effect reaches families and communities in magnitude. There is an increasing awareness about the potential of screen-and-treat programs to prevent cancer, as well as to protect the gains in HIV/AIDS treatment and care programs. The prevention or treatment paradigm in public health applies here: Investing billions of dollars to address HIV, but then have a subset die of cervical cancer, a preventable disease, does not maximize program effectiveness.

**Context Matters: Service Delivery Models for an Improved Screening Test**

Based on the summary of existing HPV diagnostics and their limitations for LRS, it is evident that the context in which the HPV test will be utilized is important in terms of practical considerations of deployment in LRS settings, and cost-effectiveness and accuracy depending on throughput. There are several ways, individually and collectively, in which screen-and-treat programs are implemented in LRS, depending on the resources and priorities of the health system, and each with inherent advantages and disadvantages. Campaigns, low-volume clinical settings, and high-volume clinical...
settings have implications for selecting the most appropriate screening and treatment interventions.

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<td><strong>Campaign</strong></td>
<td>Through ad hoc clinics or pop-up mobile services, services reach women closer to where they live. Can also reach a large number of women in a short amount of time.</td>
<td>- Most convenient for women, particularly in remote and rural areas &lt;br&gt;- High throughput in short amount of time can increase coverage quickly</td>
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<td><strong>Low-Volume</strong> (low throughput)</td>
<td>Women can attend clinic where they are already receiving other routine screening or care, women with lesions can be immediately treated and can accommodate self-collection (swabs)</td>
<td>- Most typical health care service model to which women are already accustomed &lt;br&gt;- Integrates HPV services into broader reproductive health, HIV and primary care, making it more routine and less stigmatized</td>
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<td><strong>High-Volume</strong> (High Throughput)</td>
<td>Women visit a busier health center and provide a sample (or self-collect) which then goes to centralized lab and then results are sent back to health center where women are then notified to return for results and treatment</td>
<td>- Volume drives cost effectiveness &lt;br&gt;- Tests more likely to have higher sensitivity and specificity &lt;br&gt;- More appropriate and convenient in urban areas</td>
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An Improved HPV Test Could Reduce Cancer Incidence and be Cost-Effective: Lessons from the Field

Data from demonstration projects in three LMICs (Uganda, India, and Nicaragua) showed that HPV testing is both effective in reducing cervical cancer and is cost effective. This research presents compelling evidence of value for money in investing in HPV testing from both impact and cost perspectives. The HPV diagnostic used in this research was careHPV™, which along with GeneXpert are the two HPV diagnostics currently being most used within LRS and the best available at present. Extending the value of these diagnostics through a complementary POC test optimized for scalability and affordability in LRS (for certain conditions with low-throughput and rural needs) can only enhance the global effort to reduce cervical cancer incidence and its resulting impact on women and their communities. In response to the potential value of a POC HPV test and the limitations within existing HPV diagnostics, WHO published updated target product profiles (TPPs) for HPV diagnostic tests for use in LMICs, following a discussion with the Pan American Health Organization (PAHO) and National Institutes of Health (NIH) in June 2014. The specifications within these TPPs are guiding the HR-HPV diagnostic development work of Global Good and QuantuMDx.

Global Good and QuantuMDx: Collaborating to Develop an Improved POC HR-HPV Test for Low Resource Settings

Global Good and QuantuMDx entered into a formal partnership to develop a better HR-HPV diagnostic for LRS. The goal of this partnership is to produce a low cost, rapid and easy to use POC diagnostic test to screen women for HR-HPV infection. The test can be easily integrated into screen-and-treat programs in both high and low throughput environments. Leveraging their respective core competencies, Global Good and QuantuMDx are designing and validating a test with the capability to detect the 13 oncogenic HPV subtypes.

This diagnostic will improve on the existing HPV tests described below, through improved sensitivity, low-throughput, shorter time to result, and affordability, all of which will facilitate greater scale and coverage of cervical cancer screen-and-treat programs.

Limitations in Existing HPV Diagnostics

Pairing available and effective treatments for precancerous lesions with effective HPV diagnostics that are low cost, rapid, and easy-to-use would enable the scaling of
screen-and-treat programs as a high value and cost-effective priority for health systems in LRS. There are a number of HPV tests designed for HRS that are FDA approved, but few of these tests are suitable for use in LRS, where HPV prevalence and cervical cancer-related mortality are the highest. There are cost constraints and technology characteristics that render these diagnostics less relevant for, or accessible to, LRS. Some HPV tests have gained a small foothold in LMICs at private hospitals in urban areas, or in large referral hospitals with high patient volumes. But penetration of HPV testing at the outlying health clinics remains low, and reaching rural populations, which exceed 60% in some LMICs, is both a priority and a challenge. In rural areas, cervical cancer screening is likely to be with VIA, which remains the least expensive and most widely available at all levels of the health system. Even so, in most sub-Saharan countries, fewer than 5% of eligible women have ever been screened.

Broadly speaking, HPV diagnostic tests for LMICs should achieve the following characteristics:
- detect highest risk HPV DNA or RNA in women aged 30-64 (and all HIV-positive women)
- accuracy of clinical sensitivity of 90-95% and a clinical specificity of 90-98%
- applicable in a Level 1 or higher health care system to reach rural and low-throughput environments
- not require a cold chain or clean water; if clean water is required it must be contained in the kit
- simple enough for a healthcare worker with minimal training (four hours to one day maximum) to administer and interpret
- results should be able to be read with the naked eye or with an easy pictorial display (e.g. reactive, non-reactive, invalid)
- a target price of US$5 or less and cost of goods under US $3
- operate on a multi-analyte platform to maximize efficiency
- time to result less than 2 hours
- compatible with provider collected specimen or self-collected cervicovaginal specimen

Though the existing diagnostics perform well and meet many needs of LRS, there is room for more innovation in a true POC HPV testing platform that can be used in either high-throughput or low-throughput settings.

Among the existing HPV tests, there are varying degrees of sensitivity and specificity. This may result in some degree of overtreatment that can have implications in childbirth following treatment. With screening once or twice over a 10- to 15-year period, some level of overtreatment should be acceptable, especially if compared to...
high numbers of undiagnosed precancerous lesions and undertreatment that characterizes the current situation relating to cervical cancer in LRS.

A critical decision point for diagnostics developers is deciding whether to pursue low-throughput or high-throughput testing. To achieve high coverage in LRS, both approaches will be necessary, but must be suitable for the level of the health system in which they will be utilized. Many of the existing solutions cost US $10-20 per test and higher, and many of those also rely on high throughput (higher number of samples) or expensive platform technologies. Those may be more cost-effective in larger facilities with higher patient volumes, but can be a challenge in LRS because running tests in batches generally delays results to the patients, making these tests incompatible with single visit approach programs and risking LTFU. Recalling that more than 85% of cervical cancer cases occur in LMICsxx, there is a great need for increased access to affordable testing in these markets. Many LMICs have a large rural population, where high throughput may be difficult.xxi The rural population has different needs than the urban population that few molecular diagnostic companies have prioritized.

**Conclusion: Critical Success Factors for Cervical Cancer Screening with an Improved POC HR-HPV Test**

The case for improving the coverage, quality, and impact of cervical cancer screening is clear, and will rely on the scalability of HPV diagnosis as a viable if not dramatic improvement over VIA. Such a test, as described above, must meet critical performance requirements and address gaps that exist among the current HPV diagnostics. This is the driver behind the Global Good and QuantuMDx partnership, which reflects a joint commitment to help reduce the burden of cervical cancer in LRS. In addition to improving an HR-HPV test from a technology vantage point, Global Good and QuantuMDx seek to find partnerships and resources to ensure that the POC HR-HPV diagnostic will be adapted, utilized, and scaled even in the world’s lowest resource settings. This goal, which is to deliver a solution and not only a technology, will be dependent on other key success factors which meet local needs in terms of resources, infrastructure, and capacities within the health systems, societal norms and patient acceptability and the desired level of cervical cancer risk reduction.xxii

Arguably, there are some likely success factors that would transcend some of those differences and also common barriers that many LRS would encounter beyond the introduction of a better POC HPV diagnostic. Additional success factors will include:
1) **Leveraging existing women’s health and HIV initiatives.** Many LRS have established women’s health programs with varying degrees of emphasis on family planning, reproductive health, and prenatal services, among others. There are efficiencies to be gained by integrating HPV and cervical cancer into those programs, which also have created an environment in which women’s health is a priority.

2) **High-level government support.** Governments have both the financial and legal power to support screening programs, but also the stature to influence the country’s culture toward women’s health and screening. Given the stigma towards women with cervical cancer, it is especially helpful to earn the support of high profile leaders. In several countries in Africa – including Mozambique, Kenya, and Ethiopia – the First Ladies have helped to advance cervical cancer screening by speaking out in support of women’s health initiatives.

3) **Increased focus on cancer.** Cervical cancer screening is still emerging in most LRS. The epidemiological transition and double burden are increasing the awareness of other diseases when many LRS have been overwhelmed by HIV, malaria, and TB and childhood diseases. But as many LMICs confront the dual epidemiologic burden of infectious diseases and NCDs, cervical cancer has a unique profile of transcending both, with detrimental effects on women, their families, and their communities.

The societal costs associated with women dying of a preventable disease like cervical cancer on poverty, education, and gender equity – the first three MDGs, should speak for themselves when considering investing in improved HR-HPV diagnostic tests for LRS.
Appendix 1: Additional Detail on Disease Pathway and HPV Diagnostic Targets

HPV is a double stranded DNA virus. Its genome consists of 8,000 base pairs that encode early and late expressed genes. The “early” region of the genome encodes proteins E1, E2, E4, E5, E6, and E7, which are expressed to drive viral genome replication, regulation, and modification of host proteins to promote viral production. The “late” region of the genome encodes the capsid proteins L1 and L2 that enclose virions. (See Figure below.)

Early and Late Stage Genes in HPV Genome

![HPV Genome Diagram](image.png)

The increased risk associated with high risk (HR-HPV) oncogenic types is in part due to the expression of two early genes, E6 and E7. E6 and E7 levels increase with disease progression and harbor immortalization and transformation functions that dysregulate cell growth. With repeated dysregulation, cervical cells generate genomic mutations that facilitate persistent infection and progression to cervical cancer. This progression drives changes in cellular proteins, including p16 and Ki-67. p16 is a human cyclin-dependent kinase inhibitor that regulates cell growth. It is significantly overexpressed in cancerous and precancerous cervical tissue and correlates with an increase in the viral oncoprotein E7. E7 disrupts a key cell regulator, pRb, and this disruption leads to overexpression of p16. Ki-67 is a nuclear protein that is expressed during all active phases of the cell cycle and is a marker of cell growth. In normal cells, the expression of p16 and Ki-67 is mutually exclusive, but cells displaying unregulated growth will express both p16 and Ki-67 concurrently. Because of the association of E6 and E7 with disease progression, E6 and E7 are used as biomarkers for molecular and antigen diagnostic screening assays. In addition, there are new efforts to develop screening assays using the cellular markers p16 and Ki-67. There are two commercial cytology-
based tests that currently use p16 and Ki-67 – CINtec and CINtec Plus, both from Roche.

References


Quiao et al. Int. J. Cancer: 00, 00-00 (2013)