Molecular diagnostic assays for cervical neoplasia: emerging markers for the detection of high-grade cervical disease

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The accurate detection and diagnosis of cervical carcinoma and its malignant precursors (collectively referred to as high-grade cervical disease) represents one of the current challenges in clinical medicine and cytopathology. The advent of molecular diagnostics and the use of whole-genome profiling using DNA microarrays promises to yield improved understanding of the disease process with the subsequent development of more accurate diagnostic procedures based upon these discoveries. Recent reports describing a variety of experimental approaches have identified a series of candidate genes that are overexpressed in cervical carcinoma. In this article, representative examples of these markers and the resulting translational research will be reviewed within the context of improved cervical disease detection. An emerging class of markers, the minichromosome maintenance protein family of DNA licensing factors (MCM-2, MCM-6, MCM-7), shows promise for the specific detection of high-grade cervical disease using simple antibody-based immunochemistry formats. These proteins are overexpressed in cervical disease as a result of infection by oncogenic strains of human papillomavirus (HPV) and subsequent uncontrolled activation of gene transcription and aberrant S-phase induction, mediated through the E2F transcription factor pathway. This behavior appears to be a hallmark of high-grade cervical disease and provides the link between oncogenic HPV infections and the molecular behavior of cervical neoplasia (CN). The use of these molecular descriptors of CN in simple immunochemistry formats compatible with conventional cytology preparations is anticipated to improve the screening and detection of cervical disease within the healthcare system.

INTRODUCTION

Cervical neoplasia (CN), which includes squamous cell carcinoma arising from cells lining the exterior of the uterus cervix, adenocarcinoma arising from cells lining the endocervical canal, and their malignant high-grade dysplastic precursors, represent a significant issue in women’s health on a world-wide basis. Each year in the U.S., approximately 14,000 new cases of cervical cancer and approximately 500,000 cases of high-grade malignant precursors to cervical cancer are detected in 50 million women who are screened annually with a Papanicolaou (Pap) smear. Outside the U.S., cervical cancer represents a significant cause of mortality in women with an estimated 470,000 new cases of cervical cancer diagnosed annually. The detection and diagnosis of CN is accomplished through the morphological assessment of cervical cells obtained during an annual Pap screen examination. In this procedure, scrapings of both endocervical and ectocervical cells from the cervix are collected, deposited on a microscope slide, stained with the Pap stain, and then examined microscopically for the presence of neoplastic cells as determined by abnormal morphology.

Within the morphologic classification of CN, the malignant precursors of squamous cervical carcinoma include severe and moderate dysplasia that are defined respectively as cervical intraepithelial neoplasia grade 3 (CIN3) and grade 2 (CIN2) in histology and as high-grade squamous intraepithelial lesions (HSIL) in cytology. Mild dysplasia is defined as CIN1 on histology and low-grade squamous intraepithelial lesion (LSIL) on cytology and generally represents the morphologic abnormality associated with transient human papillomavirus (HPV) infections. However, underlying cervical disease can still be present within these LSIL or CIN1 specimens. Finally, suspicious cells that appear can be categorized either as atypical squamous cells in which HSIL cannot be ruled out (ASC-H) or atypical squamous cells of uncertain significance (ASC-US). Appropriate clinical management guidelines exist to manage patients across this spectrum of morphological classifications of cervical abnormalities (1–3). For the purposes of this article, high-grade cervical disease is defined as the detection of a CIN2 lesion or higher following colposcopy examination and tissue biopsy confirmation. A typical high-grade HSIL cell within a cervical cytology specimen is shown in Figure 1.

The use of morphology-based classification for cervical neoplasia presents a number of dilemmas for the accurate diagnosis of this disease. Factors that compromise the diagnostic accuracy of Pap screening and cytology diagnosis include rare event detection, sample adequacy, obscuring features such as blood, mucus, inflammation, and the appearance of suspicious appearing cells that appear malignant yet are the result of benign cellular changes arising from inflammation, repair processes, etc. In addition, the diagnosis of cervical disease based upon cellular morphology is inherently a subjective analysis that is highly dependent upon the skills and experience of the cytopathologist and the cytotechnologist, which can lead to variability in diagnoses. Hence there is a recognized need within the medical community to utilize supplemental diagnostic markers to improve the sensitivity, specificity, reproducibility, and utility of current morphology-based diagnostics for the detection of high-grade cervical disease.

Figure 1. The presence of cervical high-grade squamous intraepithelial lesion (HSIL) cells within a cervical cytology specimen. The HSIL cells are characterized by a smaller cell size and an enlarged nucleus in comparison to the larger normal cervical keratinocytes shown in the figure. Also shown in the figure are small inflammatory leukocytes. The cervical cytology specimen was collected in SurePath™ liquid-based fluid (Tripath Imaging, Burlington, NC, USA).
Table 1. Human Papillomavirus Open Reading Frame Genes

<table>
<thead>
<tr>
<th>HPV Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCR</td>
<td>Regulatory control of transcription, replication, and host interactions.</td>
</tr>
<tr>
<td>L1</td>
<td>Major capsid protein.</td>
</tr>
<tr>
<td>L2</td>
<td>Minor capsid protein.</td>
</tr>
<tr>
<td>E1</td>
<td>Viral replication and maintenance of viral episome.</td>
</tr>
<tr>
<td>E2</td>
<td>Transcriptional regulation and cofactor for replication.</td>
</tr>
<tr>
<td>E4</td>
<td>Keratin interactions and viral shedding.</td>
</tr>
<tr>
<td>E5</td>
<td>Growth factor receptor interactions and signal transduction.</td>
</tr>
<tr>
<td>E6 and E7</td>
<td>Prolongs division phase of the cell cycle to promote replication. Responsible for malignant transformation of the cervical keratinocyte following infection with oncogenic subtypes of HPV.</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus.

HPV IN THE PATHOGENESIS OF CERVICAL NEOPLASIA

HPV is recognized as the etiologic agent responsible for the initiation of CN. Within the HPV family of viruses, there are both non-oncogenic and oncogenic forms of the virus. The non-oncogenic forms of the virus (including HPV types 6 and 11) are associated with common warts and condyloma. The oncogenic forms of HPV (including types 16 and 18) are associated with cervical carcinoma. The oncogenic forms of HPV can be classified into high-risk and intermediate-risk viral subtypes. The high-risk HPV viral subtypes include HPV types 16, 18, 45, and 58, and the intermediate-risk HPV viral subtypes include HPV types 31, 33, 35, 39, 51, 52, and 69 (4). The genome of HPV consists of a double-stranded circular DNA molecule with eight open reading frames encoding the genes shown in Table 1. Within the context of CN development, the genes E6 and E7 from the oncogenic forms of HPV encode two distinct oncoproteins that are the major determinants in cellular transformation as discussed in more detail below.

Current literature suggests that HPV infects the basal stem cells within the underlying tissue of the uterus cervix. Differentiation of the stem cells into mature keratinocytes, with resulting migration of the cells to the stratified cervical epithelium, is associated with HPV viral replication and reinfection of cells. During this viral replication process, a number of cellular changes occur that include cell cycle deregulation, active proliferation, DNA replication, transcriptional activation, and genomic instability (5–7). These changes are diagramed in Figure 2.

Most HPV infections are transient in nature, with the viral infection resolving itself within a 12-month period. For those individuals who develop persistent infections with one or more oncogenic subtypes of HPV, there is a risk for the development of neoplasia in comparison to patients without an HPV infection. Given the importance of HPV in the development of CN, the clinical detection of HPV has become an important diagnostic tool in the identification of patients at risk for developing CN. Both the high-risk and the intermediate-risk HPV viral subtypes are detectable through the use of the DiGene Hybrid Capture II assay (DiGene Corporation, Gaithersburg, MD, USA). The National Cancer Institute (NCI) ASCUS LSIL Triage Study (ALTS) clinical trial helped define the clinical utility of HPV testing in combination with annual Pap screening. Within the ASCUS patient population, 50%–60% of these patients harbored HPV infections with 7% of patients presenting high-grade disease upon colposcopy and biopsy confirmation. The ALTS trial concluded that HPV triage of ASCUS patients was more effective for disease detection upon referral to colposcopy than repeat cytology or direct referral to colposcopy. However, HPV testing of LSIL patients was not useful as a triage for colposcopy because of their high prevalence of HPV infection (8–12). The use of HPV testing has been approved by the Food and Drug Administration (FDA) in combination with Pap screening as both a reflex test within the ASCUS patient population and as a primary screen for cervical disease (13). The utility for HPV testing in a primary diagnostic setting has been recommended in recent guidelines from the American College of Obstetrics and Gynecology (ACOG) (14). In addition to the Hybrid Capture II assay, a number of PCR-based methods have been shown to support HPV detection and viral genotyping using liquid-based cervical cytology specimens (15–19).

The clinical utility of HPV-based screening for cervical disease is in its negative predictive value. An HPV negative result in combination with a history of normal Pap smears is an excellent indicator of a disease-free condition and a low risk of CN during the subsequent 1–3 years. However, a positive HPV result is not diagnostic of cervical disease; rather it is an indication of infection. Although the majority of HPV infections are transient and will spontaneously clear within a 12-month period, a persistent infection with a high-risk HPV viral subtype indicates a higher risk for the development of CN. To supplement HPV testing, a number of molecular markers associated with CN have been evaluated in order to improve the clinical specificity for cervical disease diagnosis.

HPV-INDUCED ALTERATIONS OF THE CELL CYCLE AND CELLULAR PROLIFERATION

HPV infection within cervical keratinocytes results in a number of alterations that disrupt the activities within the cell cycle. The cell cycle normally represents a series of coordinated activities within the cell that insures DNA integrity prior to replication of the genome, the separation of duplicated chromosomes and final cell

![Figure 2. The pathogenesis of cervical neoplasia (CN).](Image)
division. Key proteins that coordinate these activities include the tumor suppressor protein p53, a series of serine/threonine protein kinases (i.e., the cyclin-dependent kinases or CDKs) that control the passage of the cell through the various phases of the cell cycle, the regulatory subunits (cyclins) that control CDK activity, and the corresponding CDK inhibitors (p16INK4, p21-Waf-1, and p27KIP). A detailed review of the cell cycle is beyond the scope of this article, and the reader is directed to the appropriate references for a detailed description (20,21).

The E6 and E7 oncoproteins of the high-risk HPV subtypes have been implicated in a number of cellular processes related to increased proliferation and neoplastic transformation of the infected keratinocytes. The E6 protein has been implicated in two critical processes. The first is the degradation of the p53 tumor suppressor protein through ubiquitin-mediated proteolysis. Removal of functional p53 eliminates a major cell cycle checkpoint responsible for DNA repair prior to entry into DNA replication and mitosis (22). In addition, E6 has been shown to interact with the c-myc protein and is responsible for direct transcriptional activation of the hTERT gene with subsequent expression of telomerase (23,24). Activation of telomerase is a key step in cancer biology, responsible for the maintenance of telomere length on replicating chromosomes, and this enzyme ensures functionally intact chromosomes during cellular immortalization. The HPV oncoprotein E7 is known to contribute to cellular proliferation through two independent mechanisms. The first is the inactivation of the transforming growth factor-β (TGF-β) tumor suppressor pathway responsible for cell cycle arrest at the G1 phase through direct interaction of E7 with the Smad proteins (Smad 2, 3, and 4), thereby inhibiting their ability to bind to DNA (25). Likewise, E7 is known to specifically interact with the Rb tumor suppressor protein. Within the G1 phase of the cell cycle, Rb forms a complex with the E2F transcription factor and prevents E2F from activating gene transcription. At the G1/S boundary, the Rb protein is phosphorylated with release of the E2F transcription factor—thereby initiating E2F gene transcription and entry into the S phase of the cell cycle. The HPV E7 oncoprotein abrogates this control mechanism by directly binding with Rb and displacing E2F from the complex. This results in E2F-driven gene transcription independent of normal cell cycle control (22). This release of E2F un couples gene transcription from cell cycle control and results in prolonged and aberrant transcription of S-phase genes responsible for DNA synthesis and cellular proliferation. In addition, the combined actions of both E6 and E7 have been shown to contribute to centrosomal abnormalities and subsequent genomic instability in CN (26). These effects are summarized in Figure 3.

**CYCLINS AND CN**

In CN, numerous alterations in the cell cycle have been identified as a result of HPV infection. These alterations include abnormal overexpression of various cyclins (including cyclins A, B1, and E) and overexpression of various CDK inhibitors (e.g., p16INK4A). The general alterations in the cell cycle that accompany CN are shown in Figure 3. These alterations have been investigated for potential

![Cell Cycle Alterations Diagram](image-url)
utility in the clinical diagnosis of high-grade cervical disease. Cyclin E, A, and B have all been shown to be overexpressed in squamous cell cervical neoplasia as well as in LSIL and HSIL lesions (26–32). Likewise, cyclins A and B have been shown to be overexpressed in cervical adenocarcinoma and its malignant precursors (33). To date, none of the cyclins that are overexpressed in HPV-induced neoplasia display sufficient sensitivity or specificity for the accurate detection of high-grade cervical disease (either for CIN2+ lesions in histology or HSIL+ cells in cytology) to be useful as independent molecular markers in a clinical diagnostic assay. Moreover, overexpression of cyclin E appears to be a surrogate marker for HPV (28). These published observations are summarized in Table 2.

**Table 2. Cyclins in Cervical Neoplasia**

<table>
<thead>
<tr>
<th>Cyclin Protein</th>
<th>Cell Cycle Phase</th>
<th>Function</th>
<th>Expression Status in CN</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin D1 and D3</td>
<td>G1</td>
<td>CDK4 and CDK6 regulatory subunits. Links mitogenic stimuli to cell cycle progression.</td>
<td>Cyclin D1 decreased in 97% of HSIL and 72% of invasive cervical cancer. Cyclin D3 decreased in 51% of squamous cell carcinoma. Increased expression within cervical carcinoma associated with poor disease-free survival.</td>
<td>27,30–32</td>
</tr>
<tr>
<td>Cyclin E</td>
<td>G1</td>
<td>CDK2 regulatory subunit.</td>
<td>Increased in 97% of LSIL, 92% of HSIL, and 82% of squamous cell carcinoma.</td>
<td>27–29</td>
</tr>
<tr>
<td>Cyclin A</td>
<td>S and M</td>
<td>CDK2 regulatory subunit in the S-phase and CDK1 in the M-phase. Links anchorage-dependent cell growth to cell cycle progression.</td>
<td>Increased in 35% of squamous cell carcinoma and adenocarcinoma.</td>
<td>27,33</td>
</tr>
<tr>
<td>Cyclin B</td>
<td>G2 and M</td>
<td>CDK1 regulatory subunit.</td>
<td>Increased in CN, squamous cell carcinoma, and adenocarcinoma.</td>
<td>27,33</td>
</tr>
</tbody>
</table>

CN, cervical neoplasia; CDK, cyclin-dependent kinases; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion.

**Table 3. Characteristics of p16INK4A and MCM-5 Staining of Cervical Neoplasia**

<table>
<thead>
<tr>
<th>Features</th>
<th>Characteristics of p16 Staining</th>
<th>Characteristics of MCM-5 Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for HSIL detection</td>
<td>70%–100%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity for HSIL detection</td>
<td>Low and inconsistent: 25%–75%</td>
<td>67%</td>
</tr>
<tr>
<td>Scoring criteria</td>
<td>Variable across studies with a minimum of 10+ positive cells per slide</td>
<td>Percent positive cells detected in tissue biopsy specimens.</td>
</tr>
<tr>
<td>Staining localization</td>
<td>Overexpression in both the nucleus and the cytoplasm.</td>
<td>Staining localized to nucleus.</td>
</tr>
<tr>
<td>Specificity of staining</td>
<td>Expression in both nucleus and cytoplasm makes immunocytochemistry interpretation difficult. Expression detected in both LSIL and HSIL lesions.</td>
<td>Nuclear localization makes immunocytochemistry interpretation easy.</td>
</tr>
</tbody>
</table>

MCM-5, minichromosome maintenance 5; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion.

p16INK4A AND CN

p16INK4A (p16) is an inhibitor of CDKs 4 and 6 and functions in the progression from G1 to S phase of the cell cycle. In response to infection by high-risk HPV infections, p16 is overexpressed in CN including HSIL lesions and carcinoma (34). Overexpression of p16 has been shown to correlate with HPV type 16 and 18 infections and can be detected in both squamous cell carcinoma and adenocarcinoma (35–40). The specificity of p16 overexpression has been examined and is associated with carcinoma, biopsy confirmed CIN 2+ lesions, and a significant number of LSIL—CIN 1 lesions (41–44). The p16 protein can be detected in both histology specimens as well as liquid-based cytology (39–41). Characteristics of p16 detection of cervical disease are summarized in Table 3, and the clinical performance of p16 detection of HSIL specimens within cytology specimens is shown in Table 4.

MINICHROMOSOME MAINTENANCE PROTEINS AS MARKERS OF CELLULAR PROLIFERATION

The minichromosome maintenance (MCM) proteins function in the early stages of DNA replication through loading of the pre-replication complex onto DNA and functioning as a helicase to help unwind the duplex DNA during de novo synthesis of the duplicate DNA strand. Early publications have shown that the MCM proteins, and in particular, MCM-5, are useful for the detection of cervical disease (45) as well as other cancers (46). The published literature indicates that antibodies to MCM-5 are capable of detecting CN cells. The specificity for detection of high-grade cervical disease has not been demonstrated for MCM-5 (45). The detection of MCM-5 expression is not restricted to high-grade cervical disease but is...
MCM-5 overexpression is detected in both tissue and cytology specimens using specific monoclonal antibodies in an immunohistochemistry format (48,49). The overexpressed MCM-5 protein is localized to the nucleus of the neoplastic cells. CIN3, cervical intraepithelial neoplasia grade 3.

![Image](306x94 to 555x281)

**Figure 4.** The detection of minichromosome maintenance 5 (MCM-5) overexpression in cervical high-grade intraepithelial neoplasia using specific monoclonal antibodies in an immunohistochemistry format. MCM-5 overexpression is detected in both tissue (left panel) and cytology specimens (right panel) using a molecular immunocytochemistry assay in a routine SurePath liquid-based cytology specimen. Overexpressed proteins are detected using monoclonal antibodies and TOP2A have been identified as overexpressed genes in CN (50–52). In addition, other promising candidates have been identified by DNA microarray profiling, including IGFBP-3 and claudins 1 and 7. Translational research on the genes identified using these approaches has yielded interesting advances in both the understanding and the application of these disease-specific markers for the detection of cervical disease (48,49,53–55). Preliminary results have shown that the genes identified from the microarray analysis, such as MCM-6 and TOP2A, encode proteins that are overexpressed in cervical disease (48,49). These proteins have been used to develop molecular immunohistochemistry and immunocytochemistry assays for the detection of high-grade cervical disease. These markers have been reported to detect cervical disease with a higher level of specificity and positive predictive value over current methods of HPV detection or cytology-based diagnosis (48,49).

**EMERGING MARKERS AND THE MOLECULAR DESCRIPTION OF CN**

Molecular markers such as MCM-2, MCM-7, and MCM-6 hold promise for the development of more specific assays to detect cervical disease. In addition to these markers, topoisomerase I-α (TOP2A) has been shown to be overexpressed in cervical disease and to correlate with the detection of aberrant S-phase induction and transcriptional activation present within CN (48,50). As shown in Figure 3, the action of the HPV oncoproteins E6 and E7 abrogate the critical cell cycle checkpoints and induce expression of S-phase genes through the constitutive action of the E2F transcription factor. This results in prolonged and active induction of S-phase genes and DNA replication outside the normal control mechanisms of the cell cycle. Key proteins such as the MCM proteins and TOP2A are expressed during this aberrant gene transcriptional activation. This behavior appears to be a hallmark within high-grade cervical disease and provides the link between infections with oncogenic HPV viral subtypes and the molecular behavior of cervical disease. Furthermore, overexpression of the MCM proteins is not restricted to cervical carcinoma, but is known to be a characteristic of other neoplasias (46). As such, this aberrant expression of genes controlled by E2F and the resulting increase in S-phase induction appears to be a common characteristic of many cancers.

**EMERGING DIAGNOSTIC ASSAYS FOR THE DETECTION OF CERVICAL DISEASE**

The application of transcriptional profiling using DNA microarrays has identified a number of genes that are overexpressed within cervical disease samples. Genes overexpressed in cervical carcinoma and in response to HPV infections have been described in the literature (50–52). Using this approach, MCM-6, MCM-4, and TOP2A have been identified as overexpressed genes in CN (50–52). In addition, other promising candidates have been identified by DNA microarray profiling, including IGFBP-3 and claudins 1 and 7. Translational research on the genes identified using these approaches has yielded interesting advances in both the understanding and the application of these disease-specific markers for the detection of cervical disease (48,49,53–55). Preliminary results have shown that the genes identified from the microarray analysis, such as MCM-6 and TOP2A, encode proteins that are overexpressed in cervical disease (48,49). These proteins have been used to develop molecular immunohistochemistry and immunocytochemistry assays for the detection of high-grade cervical disease. These markers have been reported to detect cervical disease with a higher level of specificity and positive predictive value over current methods of HPV detection or cytology-based diagnosis (48,49).

**Table 4. Performance of p16<sup>INK4a</sup> and MCM-5 Detection of HSIL in Cervical Cytology Applications**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Specificity&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16&lt;sup&gt;INK4a&lt;/sup&gt;</td>
<td>96</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>p16&lt;sup&gt;INK4a&lt;/sup&gt;</td>
<td>92</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>p16&lt;sup&gt;INK4a&lt;/sup&gt;</td>
<td>97</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>MCM-5</td>
<td>100</td>
<td>67</td>
<td>43</td>
</tr>
</tbody>
</table>

Sensitivities and specificities for the detection for HSIL in cervical cytology calculated from the data in the referenced literature. MCM-5, minichromosome maintenance 5; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; TP, true positive (HSIL stained with biomarker); FP, false positive (LSIL stained with biomarker); TN, true negative (LSIL not stained with biomarker); FN, false negative (HSIL not stained with biomarker).  
*<sup>a</sup>Sensitivity = TP/TP + FN.  
*<sup>b</sup>Specificity = TN/TN + FP.

![Image](54x574 to 65x689)

**Figure 5.** The detection of an invasive cervical cancer cell using a molecular immunocytochemistry assay in a routine SurePath liquid-based cytology specimen. Overexpressed proteins are detected using monoclonal antibodies and TOP2A have been identified as overexpressed genes in CN (50–52). In addition, other promising candidates have been identified by DNA microarray profiling, including IGFBP-3 and claudins 1 and 7. Translational research on the genes identified using these approaches has yielded interesting advances in both the understanding and the application of these disease-specific markers for the detection of cervical disease (48,49,53–55). Preliminary results have shown that the genes identified from the microarray analysis, such as MCM-6 and TOP2A, encode proteins that are overexpressed in cervical disease (48,49). These proteins have been used to develop molecular immunohistochemistry and immunocytochemistry assays for the detection of high-grade cervical disease. These markers have been reported to detect cervical disease with a higher level of specificity and positive predictive value over current methods of HPV detection or cytology-based diagnosis (48,49). The detection of cervical cancer in a cytology specimen using one such prototype molecular immunocytochemistry assay is shown in Figure 5.

It is anticipated that further development and investigation of molecular assays employing markers such as the MCM proteins and TOP2A within clinical settings will define the clinical utility of these molecular-based diagnostics for the specific improvement in the detection of cervical disease. As stated previously in this article, the dilemmas of morphology-based diagnosis will benefit from the development and use of more objective molecular diagnostic assays based upon discrete molecular changes in response to HPV infection and subsequent neoplastic transformation. The use of...
these molecular descriptors of CN is anticipated to permit the development of objective molecular assays to detect high-grade cervical disease. The development of such objective clinical diagnostics that specifically detect cervical disease without relying on the subjective interpretation of an individual cytopathologist will represent a significant advancement in the clinical detection of cervical disease. Furthermore, the ability to use currently available and standardized liquid-based cytology specimens in conjunction with emerging molecular diagnostics promises to improve the screening and detection of cervical disease and to significantly improve the current state of cervical disease screening and diagnosis within the healthcare system.

HPV VACCINE DEVELOPMENT

Recent work in the development of vaccines for the prevention of HPV infection in young patients has been demonstrated for HPV types 16 and 18 (56–58). The efficacy of such vaccinations is anticipated to significantly improve public health with the ultimate goal of eliminating cervical cancer on a global basis. The implementation of such a vaccination program will require measurement of both effective clinical end points for vaccine efficacy as well as an active monitoring program post-vaccine introduction to insure that the vaccination program is working. The use of highly sensitive analytical methods for the detection of HPV, such as PCR-based detection and genotyping methods, as well as emerging molecular diagnostics for the detection of active CN would be useful clinical tools in the monitoring of HPV vaccination programs on a global basis. The markers discussed in this article and the emerging molecular diagnostic assays utilizing these markers are expected to become important clinical tools in patient monitoring and surveillance programs related to a global HPV immunization effort.

ACKNOWLEDGMENTS

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COMPETING INTERESTS STATEMENT

The author is employed by Tripath Imaging, Inc., which manufactures and sells medical devices, instruments, and diagnostic assays related to cancer screening, detection, and diagnosis. Dr. Malinowski has stock/stock options in Tripath Imaging, Inc.

REFERENCES


